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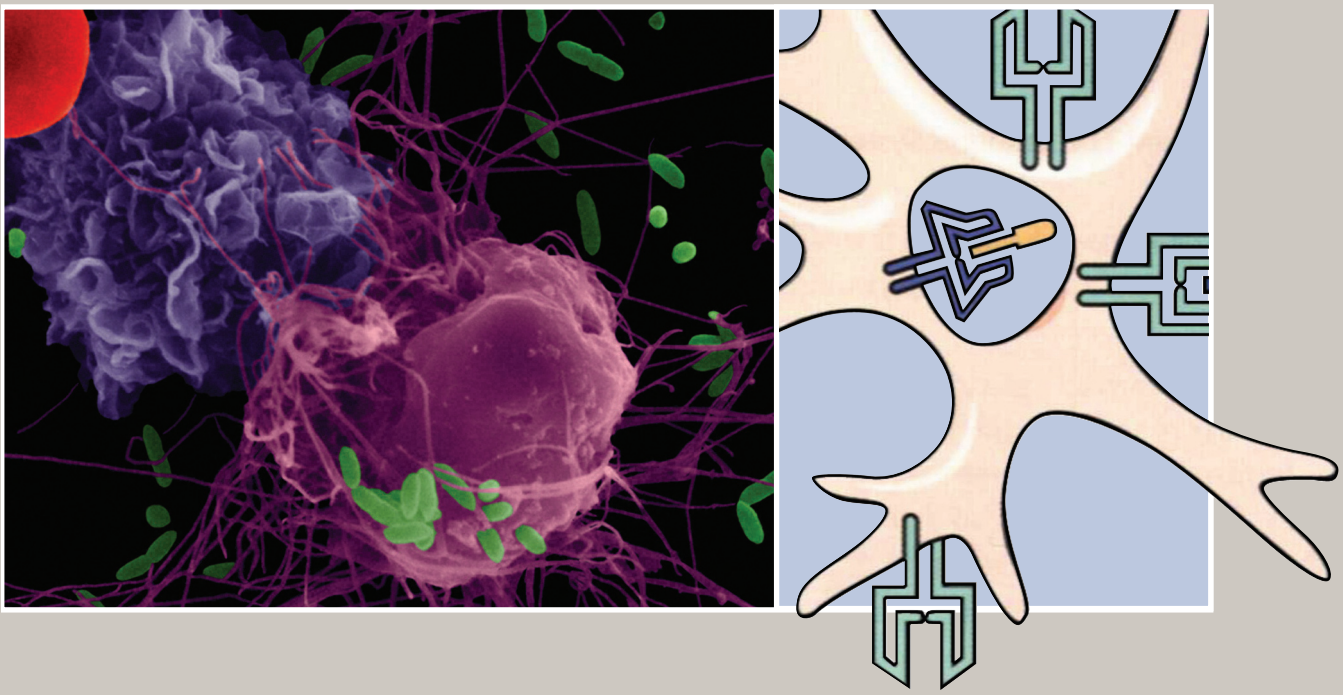

Selected Abstracts from the 2024 Clinical Immunology Society Annual Meeting:
Immune Deficiency and Dysregulation North American Conference
May 1–4, 2024
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CONTENTS

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Selected Abstracts from the 2024 Clinical Immunology Society Annual Meeting: Immune Deficiency and Dysregulation North American Conference May 1–4, 2024 Minneapolis, Minnesota, USA

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Late-Breaking Oral Abstracts

(210)

A multimorphic variant in ThPOK causes a novel human disease characterized by T cell immune developmental abnormalities, immunodysregulation, atopy, and organ fibrosis

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The role of the transcription factor ThPOK has not been formally established in humans since individuals with ThPOK deficiency or other damaging variants in ThPOK have not yet been identified. Recent research highlights the critical role of ThPOK in modulating T cell differentiation by promoting CD4 T cell development and suppressing CD8 T cell differentiation. Here, we report the first case of a human with a damaging variant in ThPOK causing a syndrome encompassing CD4 T cell deficiency, allergic disease, severe fibrotic interstitial lung disease, global developmental delay, and growth failure.

Trio whole-genome sequencing revealed a de novo variant (NM_001256455.2:c.1080A>C, p.K360N) in ZBTB7B, encoding ThPOK. The expression of ThPOKK360N remained unaffected but functional investigations demonstrated multimorphic activity of ThPOKK360N. Specifically, ThPOKK360N showed dominant-negative activity, interfering with the ability of ThPOKWT to drive the expression of its known targets, SOCS1 and COL2A1 (antimorph). Assays assessing protein-DNA interactions revealed that ThPOKK360N lacked the ability to bind WT consensus sequences in an EMSA (hypomorph). ThPOKK360N also demonstrated neomorphic properties in its DNA-binding specificity confirmed by HT-SELEX, ChIP-seq, and RNA-seq (neomorph). Single-cell seq confirmed patient's CD4 T cell deficiency, also showing that the majority of the T cells remained at an early differentiation stage compared to healthy controls. In addition, naive CD4 and CD8 T cells exhibited reduced activation response following stimulation. The causal relationship between ThPOKK360N and patient's phenotype was established through lentiviral transduction of healthy control T cells and pulmonary fibroblasts. T cells transduced with ThPOKWT showed upregulation of genes in activation, proliferation, and interferon effector pathways, a response largely absent in cells transduced with ThPOKK360N. Overexpression of ThPOKWT and ThPOKK360N in fibroblasts revealed distinct gene expression profiles, with ThPOKK360N upregulating pro-fibrotic genes implicated in pulmonary fibrosis (ACTA2, TGFB1, LTBP2, BDNF, and COL1A1).

This description of a novel IEI caused by a multimorphic variant in ThPOK confirms its role in CD4 T cell development in an intact human context, while also revealing an unanticipated role for ThPOK in fibrosis. We anticipate this discovery will accelerate the diagnosis of additional affected individuals, helping to reveal the full spectrum of human ThPOK-related disorders.

Keywords: Inborn error of immunity, Primary atopic disorder, CD4 T cell deficiency, Allergy, Transcription factor, Combined immunodeficiency, Fibrosis, Interstitial lung disease, ThPOK, T cell development

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(211)

Biallelic null mutations in PPM1D cause a novel combined immunodeficiency with severe neurodevelopmental defects

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PPM1D is a phosphatase that regulates the DNA damage response pathway by inhibiting p53 and other proteins through dephosphorylation. Human germline heterozygous variants have been identified as causative of Jansen de Vries (JdV) syndrome, which presents with behavior-related neurodevelopmental/autistic spectrum disorders without immunodeficiency. Here, we present a novel syndromic inborn error of immunity caused by a biallelic PPM1D null mutation.

We describe two siblings with progressive B and NK-cell lymphopenia, agammaglobulinemia, non-infectious colitis and severe neurodevelopmental defects including microcephaly. Both carry a homozygous N-terminal truncating variant in PPM1D (p.Thr174fs*6), inherited from their healthy heterozygous consanguineous parents. This variant leads to no endogenous protein detection with a PPM1D-null phenotype. We also evaluated a JdV-causing PPM1D variant (p.S403fs*), observing an over-accumulation of the truncated protein with conserved phosphatase activity, resulting in a gain of function (GOF) effect.

Further in vitro testing revealed that PPM1D inhibition in healthy control lymphocytes caused a dramatic decrease in B-cell viability and reduced plasmablast formation, showing the relevance of PPM1D in mature B-cell survival and maturation. B-cell development was evaluated in Ppm1d-knock-out (KO) mice, showing a partial arrest in bone marrow B-cell development at the precursor stage, with decreased B-cell frequency in the bone marrow and spleen, supporting the patients' B-cell lymphopenia phenotype.

In addition, Ppm1d-KO mice revealed increased embryonic and perinatal lethality with increased apoptosis in the neural tissue; however, surviving mice did not show gross neurodevelopment defects. Artificial cerebral organoids (ACO) were generated from patient-derived induced pluripotent stem cells (iPSC). The PPM1D-null patient-derived ACO were markedly smaller than the control ACOs, accompanied by reduced cell numbers and a more immature phenotype, supporting the patients' phenotype. These effects were rescued after pharmacological intervention with pifithrin-a (p53 inhibitor). Contrarily, organoids derived from the PPM1D-GOF patient had conserved cell numbers and a more mature phenotype, in agreement with previously reported results in autistic spectrum disorder patients.

Here we describe a biallelic PPM1D-null deficiency causing a novel syndromic disease characterized by B and NK-cell lymphopenia and a severe neurodevelopmental alteration. We also provide proof-of-principle that pharmacological compensation of the defect can modify the neurodevelopmental defects observed in the patients.

Keywords: Immunodeficiency, Neurodevelopment, Cerebral organoids, iPS cells, Murine model

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(212)

Human ASXL1 Deficiency Causes Epigenetic Dysfunction, Combined Immunodeficiency and EBV–Associated Hodgkin Lymphoma

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Inborn errors of immunity (IEI) are a group of disorders caused by deleterious variants in immune-related genes, including some that function as epigenetic regulators. Additional sex combs-like 1 (ASXL1) is an epigenetic modifier that has not previously been linked to an IEI. Somatic ASXL1 variants are found in clonal hematopoiesis and hematologic neoplasms, while heterozygous germline variants cause Bohring–Opitz syndrome. We present a new IEI caused by biallelic germline variants in ASXL1. The patient had a complex and unusual history of disease progression notable for severe and persistent cutaneous vaccine-strain

rubella granulomas initially manifesting at age 3 years, chronic macrocytosis and mild bone marrow cellular hypoplasia, and Epstein Barr virus–associated Hodgkin lymphoma in adolescence. Detailed immunophenotyping revealed progressive loss of B-cells, hypogammaglobinemia, and T-cell lymphopenia with severe skewing toward a memory phenotype and elevated expression of T-cell exhaustion and senescence markers. Molecular investigations confirmed ASXL1 protein deficiency in the patient's T-cells and fibroblasts. The T-cells exhibited marked loss of DNA methylation, increased epigenetic aging, and CD8 T-cell dysfunction. These aberrations were ameliorated by lentivirus-mediated transduction with wild-type ASXL1, confirming the pathogenicity of ASXL1 variants. This study defined a novel human IEI caused by ASXL1 deficiency, a diagnosis that should be considered in individuals with chronic viral infections, virus-associated hematologic malignancies, and combined immunodeficiency. Furthermore, our findings provide fresh insights into the mechanisms underlying the roles of human ASXL1 in T-cell function as well as in the development and maintenance of lymphomas.

Keywords: Inborn error of immunity, ASXL1, Combined immunodeficiency, Hodgkin lymphoma, Epigenetics

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(213)

IKAROS negatively regulate memory T cell formation in humans

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IKAROS, is a zinc finger (ZF) transcription factor encoded by IKZF1, expressed throughout hematopoiesis. Patients with heterozygous germline IKZF1 mutations have progressive B cell deficiency and impaired immune functions, leading to recurrent infections, immune dysregulation, and an increased risk of malignancies. However, the role of IKAROS in T cell maturation and differentiation is not fully understood. In this study, we discovered that patients with mutations in IKAROS have defects, particularly affecting the generation of naive (CD45RA+) and memory (CD45RO+) T cell phenotypes. Remarkably, patients with loss-of-function (LOF) variants (N159K, H167R and Y503*) mainly presented with increased memory T cells, skewed towards Th1 subset, and markedly decreased naive T cells. However, the dominant negative variant (N159S) manifests mainly with naive T cells, which is due to impairment in T cell activation and proliferation. Unlike the LOF variants, the IKAROS gain-of-function (GOF) variant R183C primarily manifests with naive T cells. Additionally, to mimic the LOF mutations in vitro, we degraded IKAROS through lenalidomide or knocked-down IKZF1 by lentiviral shRNA, resulting in a significant increase in memory T cell formation from naive T cells. To further study the role of IKAROS in early T cell maturation and differentiation in the thymus, artificial thymic organoids were generated from patient CD34+ cells, which clearly revealed that IKAROS LOF variants induce generation of CD45RO+ T cells even at the early stages of T cell development in thymus, when T cell progenitors normally have a CD45RA+ phenotype. Mechanistically, splicing of CD45RA in to CD45RO in activating T cells is mediated by heterogeneous nuclear ribonucleoprotein L-like (hnRNPLL), here we demonstrated that IKAROS inhibits the expression of hnRNPLL and LOF mutations or degradation of IKAROS by lenalidomide releases this inhibition. Altogether, here we illustrate that IKAROS negatively regulates hnRNPLL there by memory T cell generation. Importantly, these insights suggest that targeted degradation of IKAROS could be exploited to generate robust homogenic memory T cells, which is one of the challenges in CAR T cell generation.

Keywords: IKAROS, CD45RA, CD45RO, hnRNPLL, Artificial thymic organoids, Memory T cells, CAR T cells

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(214)

ICOS Agonist Vopratelimab Modulates Follicular Helper T Cells and Improves B Cell Function in Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is an immune defect characterized by hypogammaglobulinemia and impaired development of B cells into antibody-secreting memory B cells and plasma cells. As follicular helper T cells (TFH) play a central role in humoral immunity, we examined TFH cells in CVID, and investigated whether an ICOS agonist, vopratelimab, could modulate TFH, B cell interactions and enhance immunoglobulin production. CVID subjects had decreased TFH17 and increased TFH1 subsets; this was associated with increased transitional B cells and decreased IgG+ B and IgD- CD27+ memory B cells. ICOS expression in CVID CD4+ T cells was also decreased. However, ICOS activation of CD4+ T cells by vopratelimab significantly increased total CVID TFH, TFH2, cell numbers, IL-4, IL-10 and IL-21 secretion in vitro. Vopratelimab treatment also increased plasma cells, IgG+ B cells, reduced naïve & transitional B cells and significantly increased IgG1 secretion by CVID B cells. Interestingly,

vopratelimab treatment also restored IgA secretion in PBMCs from several CVID patients who had a complete lack of endogenous serum IgA. Our data demonstrate the potential of TFH modulation in restoring TFH and enhancing B cell maturation in CVID. The effects of an ICOS agonist in primary antibody defects warrants further investigation; this biologic may also be of therapeutic interest in other clinical settings of antibody deficiency.

Keywords: Common variable immune deficiency, Inducible T cell co-stimulator (ICOS) activation, Follicular helper T cells, IL-10 and IL-21 secretion, IgG1 production, Follicular helper T cell modulation

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Friday Poster Abstracts

(1)

A novel CARD9-deficiency mouse model recapitulates chronic CNS candidiasis and identifies defective monocytic-cell responses in immunopathogenesis

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Human CARD9 deficiency is a recessive inborn error of immunity that manifests with susceptibility to invasive fungal disease. Enigmatically, it often presents as an adult-onset, indolent disease with candidal brain abscess/meningo-encephalitis, what we have previously termed "spontaneous central nervous system candidiasis (sCNSc)". The immunopathogenic basis for this manifestation is poorly understood. While CARD9-null mouse platforms have unambiguously shown that CARD9 influences disease susceptibility and severity to Candida, this approach is not an accurate model of disease in that mice die of fulminant multi-organ dysfunction, of which the brain is one of many organs infected. This course does not mirror the human disease, imploring the need for a more accurate model to study immunopathogenesis. Here, we generated a mouse homozygous for the recurring human p.Y91H mutation; using it and the null mouse, we titrated the candidal challenge to the CARD9 genotype. Through clinical, radiological, and histological analyses, we show that this approach creates mouse models that phenocopy the human disease. We then used this model to demonstrate that monocytic-cells (Ly6C+ monocytes and bone-marrow derived macrophages) are aberrant in anti-candidal responses. We also identify subtle immunologic disturbances between the hypomorphic (p.Y91H) and null mice, which we believe may shed light on some of the clinical variability seen in CARD9-deficient humans. This clinically-accurate, CARD9-deficient mouse model will enable a better understanding of fungal disease pathogenesis and the rational development of therapeutic interventions.

Keywords: CARD9, Candidiasis, Fungal, Mouse model

Disclosures: Donald Vinh: I have relevant financial relationships with proprietary interests: AstraZeneca (Advisory Board); GSK (Advisory Board); Moderna (Advisory Board); Takeda (Advisory Board). The other authors have no financial relationships or conflicts of interest to report.

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(2)

Maternal and neonate outcomes following exposure to hyaluronidase-facilitated subcutaneous immunoglobulin 10% during pregnancy: a retrospective case series based on US claims data

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The efficacy and safety of hyaluronidase-facilitated subcutaneous immunoglobulin 10% (fSCIG 10%; HYQVIA) in primary immunodeficiency diseases are well documented in the general population. However, data are limited on the safety of fSCIG 10% during pregnancy. In this retrospective, noninterventional, administrative claims database study, we sought to describe maternal and neonate characteristics and outcomes following exposure to fSCIG 10% during pregnancy. De-identified data from the US MarketScan Research Database between January 1, 2014 and December 31, 2021 were used to identify all women (ages 16–44 years) exposed to fSCIG 10% during pregnancy. Pregnancy losses and livebirths were identified using inpatient and outpatient fetal loss or delivery-related diagnostic and procedure codes. Exposure was defined based on filled prescriptions or infusion of fSCIG 10% from 90 days before the last menstrual period until the end of pregnancy. Among approximately 1.9 million pregnancies recorded in the database during the study period, seven pregnancies (6 patients with immunodeficiency diseases aged between 24 and 40 years) were exposed to fSCIG 10%. Five pregnancies were exposed to fSCIG 10% throughout pregnancy; one pregnancy was exposed during the first trimester only and one pregnancy during the second and third trimesters only. For all patients, there was evidence of multiple infections and concomitant medication use during pregnancy. Out of the seven pregnancies identified, six ended in a single livebirth at term (38–40 weeks). One pregnancy ended in spontaneous abortion at 9 gestational weeks in a patient with a history of recurrent pregnancy loss. No unusual pattern of complications or adverse events was identified. Of the six newborns, four were linked to maternal records and were followed for 3 months. In these four neonatal records, there were no codes for major congenital

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abnormalities, small size for gestational age, or admission to the neonatal intensive care unit. This clinical case series, extracted from a large claims database, does not raise concerns regarding the safety of fSCIG 10% use during pregnancy. However, more evidence is needed to narrow the uncertainty around these initial observations.

Study funder: Takeda Development Center Americas, Inc. Writing support funder: Takeda Pharmaceuticals International AG.

Keywords: Database, fSCIG, Hyaluronidase, Immunoglobulin G, Inborn errors of immunity, Immunodeficiencies

Disclosures: Krista Huybrechts: I have relevant financial relationships with proprietary interests: Takeda (Grants/Research Support Recipient). Jin Xia: I have relevant financial relationships with proprietary interests: Takeda Development Center Americas, Inc. (Employee); Takeda Development Center Asia (Employee). William Spalding: I have relevant financial relationships with proprietary interests: Takeda Development Center Americas, Inc. (Employee). Sonia Hernández-Díaz: I have relevant financial relationships with proprietary interests: Johnson & Johnson (Consultant); Moderna (Consultant); Takeda (Grants/Research Support Recipient); UCB (Consultant).

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(3)

Development of the Canadian Inborn Errors of Immunity National Registry (CIEINR)

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Introduction: It is estimated that 29,000 Canadians live with monogenic or polygenic inborn errors of immunity (IEI). Canada has a unique IEI population with specific founder mutations including those in First Nations, Métis, Inuit (FNMI), and Mennonites as well as diverse immigrant communities. As has been highlighted as a major deficiency by patient organizations, there is no comprehensive portrait of patients with IEI in Canada. Our aim is to develop the Canadian IEI National Registry (CIEINR) to standardize data collection to better understand the landscape of IEI in Canada.

Methods: The Registry Working Group (RWG) of the Clinical Immunology Network - Canada (CINC), with input from the national patient organization 'ImmUnity Canada', organized registry development into 7 phases (Fig. 1). Consensus was reached on a longitudinal, patient-focused study design and the protocol was externally peer-reviewed. Multi-level data collection tools, with annual updates on demographics, infectious and non-infectious manifestations, laboratory values, treatment, quality of life (PROMIS survey), and patient-reported outcomes have been developed. Data forms were based on those developed by the Collaborative Immunology Program, Southern Alberta, and align with the United States Immunodeficiency Network (USIDNET) and European Society for Immunodeficiencies (ESID) registry forms. Adolescents will complete an 'Adolescent- ready to Transition Questionnaire' created by the University of British Columbia team. De-identified data will be collected in RedCap, with the data center housed at the University of Calgary. Sites will be able to query the data via request submitted to the Working Group.

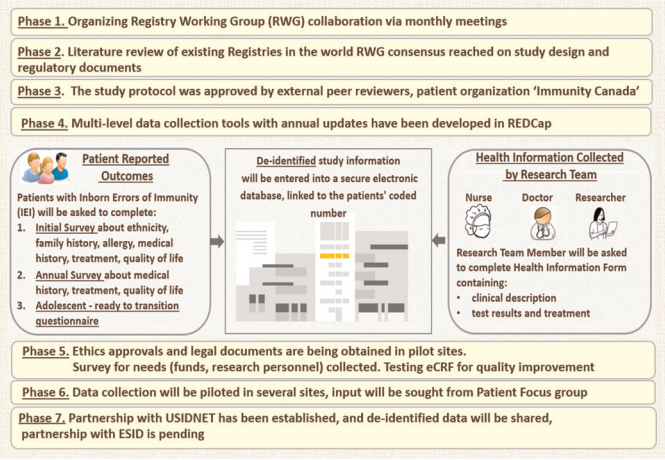

Figure 1. Development phases of the Canadian Inborn Errors of Immunity National Registry (CIEIN).

Results: Ethics approval has been obtained or is in process at several sites and legal agreements are in process. Data collection is being piloted at several sites with a variety of pediatric and adult cases; initial data is included in Table 1.

Table 1.
Canadian Inborn Errors of Immunity National Registry Pilot Data.

Characteristics	Pediatric Cohort*	Adult Cohort**
Recruited participants	20	42
Sex	n (%)	n (%)
Male	12 (60)	10 (24)
Female	8 (40)	32 (76)
	Median (range)	Median
Age at the time of symptom onset (years)	1 (0.08–4)	n/a
Age at the time of diagnosis (years)	5 (1–15)	n/a
	Mean (SD)	Median (range)
Age at last visit (years)	11 (5.1)	63 (18–77)
Diagnosis (IUIS classification)	n (%)	n (%)
1. Predominantly antibody deficiency	***15 (75)***	***30 (71)***
CVID with no gene defect specified	10 (50)	17 (40)
Selective antibody deficiency (IgA/IgM deficiency)	1 (5)	9 (21)
X-linked agammaglobulinemia with an associated BTK mutation	2 (10)	n/a
Hypogammaglobulinemia with absent B cells, no genetic evaluation	n/a	3 (7)
TACI deficiency	2 (10)	n/a
APDS	n/a	(2)
2. Immunodeficiencies affecting cellular and humoral immunity	***n/a***	***2 (5)***
Low CD4 count	n/a	2 (5)
3. CID with associated syndromic features	***1 (5)***	***4 (9.5)***
SPNS2 deficiency	1 (5)	n/a
Hyper-IgE syndrome	n/a	4 (9.5)
4. Auto-inflammatory disorders	***1 (5)***	***n/a***
ADA2 deficiency	1 (5)	n/a
5. Diseases of immune dysregulation	***3 (15)***	***n/a***
XMEN	2 (10)	n/a
LRBA deficiency	1 (5)	n/a
6. Phenocopies of PID	***n/a***	***2 (5)***
Good's syndrome	n/a	2. (5)
7. Secondary immune deficiencies	***n/a***	***3 (9.5)***
Immunoglobulin replacement therapy	n (%)	n (%)
IVIG	9 (45)	7 (17)
SCIG	11 (55)	21 (50)
Infections in the last 12 months	n (%)	n (%)
Respiratory tract infections (sinusitis, pneumonia)	11 (55)	26 (62)
Gastrointestinal infections	2 (10)	19 (45)
Ear infections	9 (45)	5 (12)
Skin infections	n/a	3 (7)
Abscess	n/a	5 (12)

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ADA2 deficiency- adenosine deaminase 2 deficiency, APDS-activated p110δ syndrome, CID -combined immune deficiency, CVID -common variable immune deficiency, IVIG – intravenous immunoglobulin, LRBA deficiency - lipopolysaccharide-responsive and beige-like anchor protein deficiency, PID -primary immune deficiency, SCIG – subcutaneous immunoglobulin, SPNS2 deficiency- Spinster homolog 2 deficiency, TACI deficiency - hypogammaglobulinemia due to TNFRSF13B mutation, XMEN-X-linked immunodeficiency and magnesium defect, EBV and neoplasia.

Conclusion: The information collected in the CIEINR will be essential to analyze unique features of IEI in Canada and will provide a strategic method to optimize patient care and improve access to novel therapies and clinical trials. Registry data will provide a tool to assess barriers to medical care, particularly for those in rural/remote regions, and will be vital to support advocacy for resource allocation.

Keywords: Registry, Inborn Errors of Immunity, Canada

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(4)

A novel BNLK mutation presenting with hepatopathy and rickets

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BLNK represents a central linker protein that bridges the B cell receptor–associated kinases with a multitude of signaling pathways and may regulate the biologic outcomes of B cell function and development. Blnk deficiency is a type of autosomal recessive immune disorder that involves the absence of B cells, agammaglobulinemia, and recurrent infections. Only ten patients with BLNK deficiency have ever been identified.
We present a 29-year-old Turkish female with BLNK deficiency with a novel homozygous CGA > TGA codon123, exon6) mutation in the BLNK gene. She developed severe liver failure and rickets at the age of 12. Although BLNK mutations are rare causes of agammaglobulinemia, it is important to consider them in patients with B cell deficiency.
She is the first to be described with hepatopathy and bone metabolism disorder in BLNK deficiency in the literature. Hepatopathy and rickets, seen in this case, are clinical conditions that should be considered in BLNK deficiency.

Keywords: BLNK deficiency, Inborn errors of Immunity, Liver failure, Rickets, Hepatopathy

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(5)

How do non-infectious presentations begin in patients with Inborn Errors of Immunity?

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Background: Non-infectious presentations may be the first data for the clinical suspicious of Inborn Errors of Immunity (IEI) and their recognition may contribute to an early diagnosis. We aim to describe the non-infectious presentations in patients with diagnosis of IEI.

Methods: We analyze medical records of patients with diagnosis of IEI followed at a Tertiary Pediatric Hospital between 2018–23. Patients were included if they had only initial non-infectious presentations related to the disease. We divided these presentations in 5 groups:

1. Syndromic Presentations (such as heart disease and facial abnormalities).
2. Immune Dysregulation Presentations (such as lymphoproliferation and autoimmune cytopenias).
3. Blood Count Changes (such as pancytopenia and isolated cytopenia).
4. Family History of IEI (reported before any clinical manifestation).
5. Changes in T-Cell Receptor Excision Circles (TRECs).

We then describe the specific initial presentations in each group and the ages at which they began.

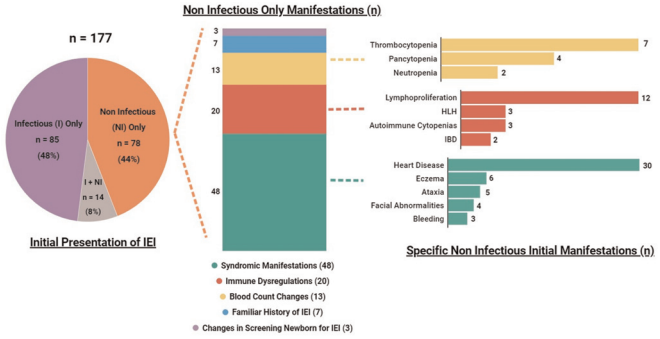

Chart 1: Initial presentation of Inborn Errors of Immunity (IEI) specified by groups of non-infectious only manifestations and these specific initial manifestations. ***I (Infectious); NI (Non Infectious); IEI (Inborn Error of Immunity); HLH (Hemophagocytic Lymphohistiocytosis); IBD (Inflammatory Bowel Disease).***

Figure 1.

Results: Of the 177 patients (45M) with diagnose of IEI, 78 patients (44%) were included. 53 presented before 1yo and 25 between 1 and 5yo.
91 non-infectious initial presentations were reported in these 78 patients (due to overlapping) as follow:

- Syndromic Presentations (48): [Heart disease (30), eczema (6), ataxia (5), facial abnormalities (4) and bleeding (3)].
- Immune Dysregulations (20): [Lymphoproliferation (12), autoimmune cytopenias (3), hemophagocytic lymphohistiocytosis (3) and inflammatory bowel disease (2)].
- Blood Count Changes (13): [Thrombocytopenia (7), pancytopenia (4) and neutropenia (2)].
- Family History (7).
- Changes in TRECs (3).

The distribution of age at onset of presentations in each group was: Syndromic Manifestations (38 before 1yo and 10 between 1 and 5yo); Immune Dysregulation (5 before 1yo and 15 between 1 and 5yo); Blood Count Changes (8 before 1yo and 5 between 1 and 5yo); Family History of IEI (7 before 1yo) and Changes in TRECs (3 before 1yo).

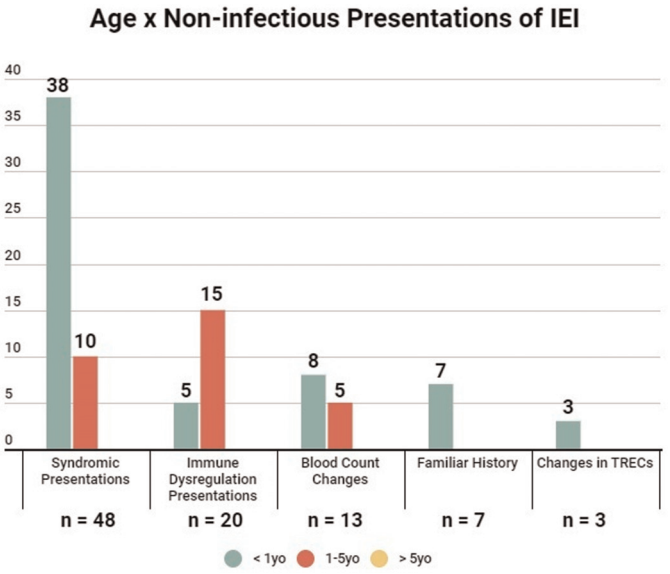

Figure 2.

Conclusion: The initial non-infectious presentations of IEI were frequent and early (mainly in the first year of life). Knowledge of the different clinical features and laboratory findings is essential for improve the suspicious and make and early diagnosis, enabling strategies to improve the prognosis of patients.

Keywords: Immunodeficiency, Noninfectious, Immune dysregulation, TRECs

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(6)

A Case of CGD Colitis: Sparing Steroids and Colectomy

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Introduction: Chronic granulomatous disease (CGD) is a rare immunodeficiency resulting in inability of phagocytes to kill ingested catalase-positive organisms, predisposing patients to recurrent bacterial and fungal infections. X-linked CGD is associated with at least a 50% risk of developing bowel inflammation resembling inflammatory bowel disease (IBD). Tumor necrosis factor (TNF) inhibitors, when used for CGD colitis, have been associated with increased mortality related to severe infection susceptibility, which limits treatment options. We present a case of a patient with CGD colitis that achieved remission with the addition of high dose vedolizumab.

Case Description: We present a case of a 22-year-old male diagnosed with X-linked CGD at age 4 months after presenting with cervical lymphadenitis. He developed CGD colitis with perirectal abscess requiring diverting

ileostomy at age 4. Over the ensuing 14 years his colitis was controlled reasonably well on mesalamine and azathioprine, with infrequent flares that improved on antibiotics and steroid bursts. At age 19, he experienced three severe flares requiring hospitalization in a 6 month period and steroid dependence. CT imaging demonstrated pancolitis with diffuse colonic wall thickening with "acute appendicitis." Appendectomy and colectomy for refractory colitis was considered. Capsule endoscopy demonstrated sparing of the small bowel but confirmed active diffuse colonic disease. Mesalamine dosing was maximized, metronidazole was added and vedolizumab, which blocks the action of α4β7 integrin, was initiated at every 8 weeks but required shorter dosing intervals due to pre-dose recurrence of symptoms. Partial remission with no prednisone use or hospitalizations continues after 2 years. Azathioprine dosing was decreased but continued in order to reduce risk of developing anti-vedolizumab antibodies.

Discussion: Treatment of CGD colitis can be challenging given baseline immunocompromised state and risk of severe infections with TNF inhibitors and steroids. This case highlights that newer agents such as vedolizumab may be steroid sparing and reduce the need for colectomy in patients with CGD colitis. Alternatively, ustekinumab may be the preferred treatment when small bowel involvement is demonstrated. Capsule endoscopy can help guide treatment choice in these cases. This case also supports that maximizing dosing can be effective for achieving remission.

Keywords: Chronic granulomatous disease, CGD, Colitis, Vedolizumab

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(7)

Phase 3 Trial of an Oral CXCR4 Antagonist, Mavorixafor, for Treatment of Patients With WHIM Syndrome: Preliminary Results From Ongoing Open-Label Extension Period of Continuous Mavorixafor Treatment

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Background: WHIM syndrome is a rare, combined immunodeficiency disease resulting from impaired leukocyte trafficking and characterized by neutropenia, lymphopenia, infections with variable hypogammaglobulinemia and warts. It is predominantly caused by gain-of-function variants in CXCR4. In a 52-week randomized placebo-controlled period (RCP) of a phase 3 trial of participants aged ≥12 years with WHIM syndrome (NCT03995108), treatment with mavorixafor, an oral CXCR4 antagonist, was well tolerated, led to sustained increases in neutrophils and lymphocytes, and reduction in infections. Here, we present safety and efficacy results from participants continuously treated with mavorixafor in the ongoing open-label extension (OLE).

Methods: All participants from the RCP who entered the OLE, received mavorixafor (Figure). Assessments included safety, tolerability, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and infection rate.

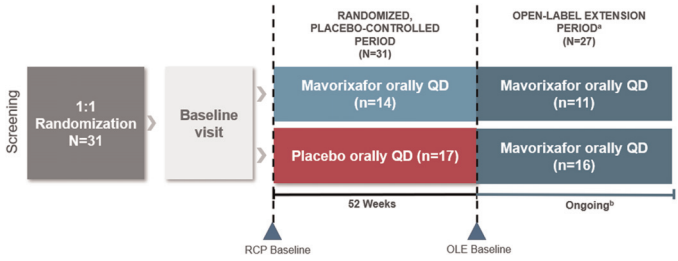

Figure. WHIM phase 3 study design: RCP and OLE.
OLE, open-label extension; QD, once daily; RCP, randomized placebo-controlled period.
[a]Early release participants may roll over from the randomized placebo-controlled period to the open-label period.
[b]Until commercial availability, study termination by sponsor, or discontinuation for any reason.
NOTE: Age- and weight-based dosing of mavorixafor: adults and adolescents (aged 12 to <18 y) weighing >50 kg, 400 mg QD orally; adolescents weighing ≤50 kg, 200 mg QD orally.

Results: Twenty-seven of 31 participants from the RCP entered the OLE. Median age was 18 years (range, 13–73 years). Maximum drug exposure was ≈37.6 months among the 11 participants who received mavorixafor in the RCP and OLE. Participants who received ongoing mavorixafor during the RCP and OLE had sustained ANC and ALC levels (mean changes from OLE baseline, – 0.09 × 10e9/L and – 0.01 × 10e9/L, respectively, based on samples collected at single timepoints) and maintained reduction in infection rate. As demonstrated in the Phase 3 registration study, the 16 patients who initiated mavorixafor in the OLE (after receiving placebo during the RCP) experienced an increase in ANC and improvement in infection rate.

During continued mavorixafor treatment in the OLE, no notable increase in the number of participants with serious adverse events (SAEs) was observed. All treatment emergent AEs (TEAEs) were mild to moderate, and none was grade ≥3.

Further analysis is ongoing.

Conclusions: The safety profile of mavorixafor in the OLE was consistent with RCP results. No new safety signals were observed. This analysis of long-term preliminary data supports sustained ANC and ALC improvements and infection rate reduction in participants chronically treated with mavorixafor beyond 52 weeks. Overall, these data confirm the positive risk-benefit profile of mavorixafor therapy for the long-term treatment of patients with WHIM syndrome.

Keywords: WHIM syndrome, Combined immunodeficiency, CXCR4 antagonist, Mavorixafor, Phase 3 clinical trial, Neutropenia, Lymphopenia, Neutrophil, Rare disease, Primary immunodeficiency

Disclosures: Teresa Tarrant: I have relevant financial relationships with proprietary interests: AbbVie (Grants/Research Support Recipient); ThermoFisher Scientific (Consultant); Viela Bio (Grants/Research Support Recipient); X4 Pharmaceuticals, Inc. (Consultant, Grants/Research Support Recipient). Raffaele Badolato: I have relevant financial relationships with proprietary interests: Angelini (Consultant); Janssen (Consultant); X4

Pharmaceuticals, Inc. (Consultant). Jean Donadieu: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Consultant). Susan Dubuc: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Employee, Equity ownership in X4 Pharmaceuticals, Inc.). Yanping Hu: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Employee, Equity ownership in X4 Pharmaceuticals, Inc.). Honghua Jiang: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Employee, Equity ownership in X4 Pharmaceuticals, Inc.). Sunny Li: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Employee, Equity ownership in X4 Pharmaceuticals, Inc.). Deborah Steiner: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Employee). Tina Yan: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals, Inc. (Employee, Equity ownership in X4 Pharmaceuticals, Inc.). Christophe Arbet-Engels: I have relevant financial relationships with proprietary interests: Harvard University (Board Member, Employee); X4 Pharmaceuticals, Inc. (Employee).

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(8)

Impact of plasma collection date on antibodies to SARS-CoV-2 in intravenous immunoglobulin

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In order to provide an efficacious treatment for patients with primary immune deficiency, intravenous immunoglobulin products need to contain an antibody profile aligned with the potential exposure of the patient to pathogens circulating in the community.

Following the COVID-19 pandemic, levels of antibodies to SARS-CoV-2 isotypes have previously been reported in a number of different different IVIG products. We present a longitudinal review of SARS-CoV-2 antibody levels in Kedrion's IVIG product Gammaplex with the aim of establishing functional antibody levels in the product and assessing how these levels change over time.

Testing was carried out on representative Gammaplex 5% and Gammaplex 10% batches manufactured in 2021, 2022 and 2023. Tests were carried out on the finished product using a neutralizing antibody detection assay (GenScript c-Pass kit) which measures the antibodies in a sample able to bind to the SARS-CoV-2 spike protein and prevent it binding to immobilized host-cell ACE-2 receptors.

The results show detectable levels of antibodies to SARS-CoV-2 in Gammaplex batches tested across all three years.

Levels of antibodies are shown to increase significantly from 2021 to 2022 ($p < 0.01$) but no significant difference was observed between levels in 2022 and 2023 ($p = 0.53$). The potency distribution of batches is also shown to change with non-normal distribution in 2021 and 2022 but a normal distribution in 2023 suggesting antibody levels in Gammaplex have stabilized in this period. This shows that Gammaplex continues to provide antibodies against COVID in the post-pandemic period.

The results from the longitudinal study show a good correlation between the proportion of plasma donations collected following widespread exposure to SARS-CoV-2 in the USA and the antibody levels in intravenous immunoglobulin finished product ($p = 0.64$).

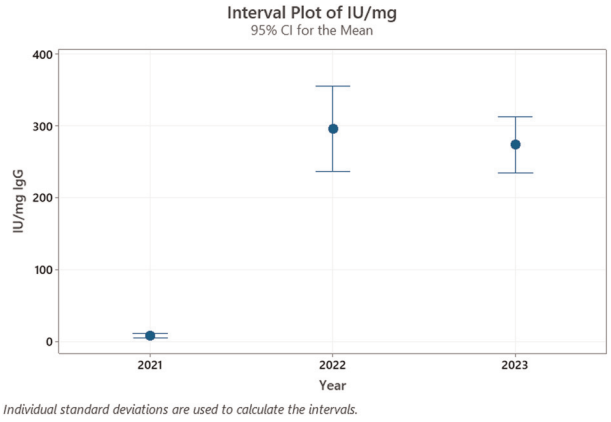

Figure 1. SARS-CoV-2 antibodies in Gammaplex expressed as IU/mg IgG in batches manufactured from 2021 to 2023.

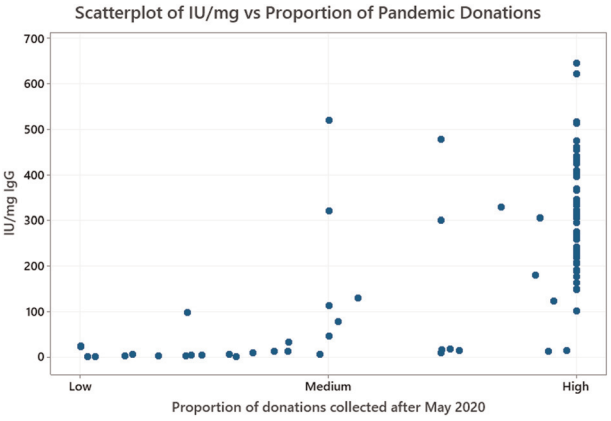

Figure 2. SARS-CoV-2 antibodies in Gammaplex expressed as IU/mg IgG versus proportion of donations collected post May 2020.

The timing of the pandemic and the detection of widespread stable antibody levels in intravenous immunoglobulin products has implications for future pandemics and for the level of protection afforded to immune deficient patients. Ensuring measures are in place to allow safe plasma collection and processing from the start of a pandemic allows IVIG batches containing protective antibodies to be made available to immune-deficient patients as soon as possible.

Keywords: IVIG, COVID, PID

Disclosures: Martyn Paddick: I have relevant financial relationships with proprietary interests: Kedrion Biopharma (Employee). Kim Clark: I have relevant financial relationships with proprietary interests: Kedrion Biopharma (Employee). Ramesh Pun: No financial relationships or conflicts of interest.

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(9)

Emergence of γδ+ T-cell Acute Leukemia Following Hematopoietic Stem Cell Transplant in a Patient with Nijmegen Breakage Syndrome

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Introduction: Nijmegen breakage syndrome (NBS) is a DNA repair defect characterized by growth deficiencies, immunodeficiency, and predisposition to cancer. Recent data suggests that 40% of NBS patients experience malignancy under age 10 and over 70% by age 20. Hematopoietic stem cell transplant (HSCT) is the primary approach to reduce the risk of late malignancy and definitively treat immunodeficiency; however, myeloablative conditioning pre-HSCT poses the risk of severe toxicity.
Case Presentation: A 7-week-old male presented with an abnormal SCID newborn screen; follow-up testing was concerning for T-B-NK+ SCID (CD3+ 635 cells/μL, CD4+: 401 cells/μL, CD8+: 132 cells/μL, CD19+ 84 cells/uL, CD3-/CD56+: 146 cells/μL). Whole exome sequencing revealed classic homozygous deletions in NBN (c.657_661delACAAA: p.Lys219AsnfsX16), leading to a diagnosis of NBS. He was treated with immunoglobulin replacement therapy and was clinically well without significant infections or autoimmunity. A matched sibling donor bone marrow transplant was performed at age five. His conditioning regimen was based on published international recommendations and included low-dose cyclophosphamide (40 mg/kg), fludarabine (150 mg/m2), and anti-thymocyte globulin (9 mg/kg). This reduced-intensity transplant was well tolerated; however, total donor chimerism remained low throughout the post-transplant course, reflected in myeloid chimerism <10%. While T-cell donor chimerism rose to as high as 44%, it declined in parallel to his overall T-cell numbers rising exponentially. The CD3+ T-cell absolute count exceeded the sum of his CD8 + and CD4+ cells, leading to quantitative tests for a γδ+ T-cell population. Eight months post-transplant, his engraftment and flow cytometry confirmed autologous reconstitution of γδ+ T-cells, which were monoclonal, and he was subsequently diagnosed with γδ+ T-cell acute lymphoblastic leukemia (T-ALL). He has since undergone ALL-directed chemotherapy, achieving complete remission. A second HSCT is currently being planned.

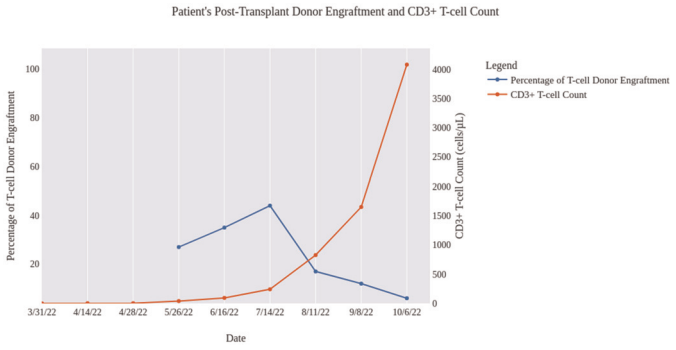

Figure 1. Post-transplant donor chimerism compared to total CD3+ T-cells of the patient. The numbers revealed that T-cell reconstitution was occurring even though donor engraftment was declining, leading to further testing.

Conclusion: In NBS patients, the choice of a pre-transplant conditioning regimen is challenging due to the heightened risk of acute complications and long-term late effects from alkylator-based myeloablative conditioning. Regardless, without sufficient donor engraftment, T-ALL may still occur. Clinicians should be wary of declining donor T-cell chimerism and increasing T-cell numbers in patients with NBS, as this could signify the emergence of a monoclonal T-cell population in post-transplant patients.

Keywords: γδ+ T-cell acute leukemia, Nijmegen breakage syndrome, Hematopoietic stem cell transplant, Alkylator-based myeloablative conditioning

Disclosures: Timothy Olson: I have relevant financial relationships with proprietary interests: Bluebird bio (Consultant); Pfizer (Advisory Board); Vertex pharmaceuticals (Consultant). Jennifer Heimall: I have relevant financial relationships with proprietary interests: CIRM (Scientific Advisory Board); CSL Behring (Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Health Economics & Outcomes Research Ltd (Consultant); Jobs Research Foundation (Scientific Advisory Board); Regeneron (Clinical Trial Investigator); Sumitomo (Consultant, Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); UpToDate (Royalties) Jane Cai: No financial relationships or conflicts of interest.

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(10)

Replacement therapy with subcutaneous immunoglobulin in 25 patients with humoral immunodeficiencies: adverse effects and evaluation of quality of life

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Introduction: Human immunoglobulin replacement therapy is considered a very important arm in the treatment of patients with humoral immunodeficiencies. The use of Subcutaneous Immunoglobulin (SCIg) maintains stable Immunoglobulin G (IgG) levels, reduces systemic adverse effects, and improves quality of life.
Method: Descriptive, cross-sectional, ambispective study. Patients with a diagnosis of a predominant antibody defect were included, according to IUIS 2020 who are being managed with SCIg at replacement doses from 2017 to 2023. Local and systemic adverse effects were evaluated, as well as their severity. The SF 36 questionnaire for quality of life was used.
Results: 25 patients were included, 17 common variable immunodeficiency, 4 X-linked agammaglobulinemia, 3 non-severe combined immunodeficiency, 1 GOOD syndrome. The main adverse effects reported correspond to local effects; induration (100%), pain after application (92%), edema, erythema. 24% presented mild/moderate systemic manifestations such as fatigue, headache, or pruritus. The preferred site of administration was abdominal, followed by the vastus lateralis of the quadriceps femoris and brachii muscles. Outpatient management, comfort, and better perception of symptoms were the main reasons for preference for ICSg (84%). In the quality of life evaluation, improvement was observed in physical functioning (92.8%), emotional role (81.5%) and decrease in limitation or pain (82%). 2 patients discontinued the subcutaneous application due to intolerable systemic effects (headache, severe and disabling pain, urticaria, and nausea).
Conclusions: The administration of the SCIg is safe and it is a reliable method. In our study, systemic adverse effects were observed in 24% (mild/moderate), with no reported severe reactions, in contrast to the reported rate of 44% with intravenous immunoglobulin. It was possible to maintain stable levels of IgG, as well as improvement in the perception of symptoms, independence, and quality of life.

Keywords: Replacement therapy, Subcutaneous immunoglobulin, Humoral immunodeficiencies

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(11)

Successful treatment of immune-mediated sensorineural hearing loss with oral calcineurin inhibitors and intravenous immunoglobulin

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Introduction: Autoimmune inner ear disease (AIED) typically presents as bilateral, fluctuating sensorineural hearing loss (SNHL) that rapidly progresses over the course of weeks; an autoimmune etiology may also underlie certain cases of unilateral SNHL. To prevent permanent hearing loss in cases refractory to first-line corticosteroids, alternative immunomodulators have been trialed but there is currently little consensus on second-line treatments. Herein, we present a series of 3 patients with fluctuating SNHL who were successfully treated or are undergoing treatment with calcineurin inhibitors (cases 1, 2) and intravenous immunoglobulin (IVIG) (case 3), all initiated within 1 or 2 months of symptom onset.
Case 1: 63 y.o. female with onset of bilateral, asymmetric SNHL. Despite minimal response to oral (8 mg/d) and intratympanic dexamethasone, she had significant improvement with cyclosporine (maximum dose 125 mg/d).
Case 2: 40 y.o. female with onset of right SNHL in March 2023. Despite excellent response to prednisone (60 mg/d), tacrolimus was initiated due to her inability to wean off corticosteroids. When tacrolimus levels approached the target range of 7 to 20 ng/mL, she went from having near-daily fluctuations to stretches of normal hearing for as long as 2 to 3 weeks. Fluctuations, if any, were self-limited and prednisone, thus far, has been tapered to 10 mg/d.
Case 3: 41 y.o. female with functional natural killer cell deficiency, mannose binding lectin deficiency, and specific antibody deficiency who developed right SNHL. After minimal response to prednisone (60 mg/d), she received intravenous methylprednisolone 1000 mg and IVIG 1,067 mg/kg (day 1) and an additional infusion of IVIG 1,067 mg/kg (day 2) with complete return of normal hearing to her right ear.
Discussion: To our knowledge, we are the first to report on treating fluctuating SNHL of suspected autoimmune etiology with tacrolimus, which may have an improved toxicity profile over cyclosporine, as well as with high-dose corticosteroids and IVIG in a patient with primary immunodeficiency syndrome. AIED has long been associated with systemic autoimmune diseases but its association with primary immunodeficiencies warrants further investigation. Finally, our findings suggest that physicians should increasingly consider immune-related etiologies (and treatments) in cases of SNHL.

Keywords: Immune-mediated hearing loss, Autoimmune inner ear disease, Primary immunodeficiency, Cyclosporine, Tacrolimus, IVIG.

Disclosures: Antoine Azar: I have relevant financial relationships with proprietary interests: ADMA (Consulting Fees (e.g., advisory boards)); Grifols (Consulting Fees (e.g., advisory boards), Grants/Research Support Recipient); Optinose (Consulting Fees (e.g., advisory boards)); Takeda (Consulting Fees (e.g., advisory boards)); X4 (Clinical Trial Investigator). The other authors have no financial relationships or conflicts of interest to report.

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(12)

Infection risk in a cohort of patients with Autoimmune Cytopenias and Primary Immuno-Regulatory Disorders treated with mycophenolate mofetil and sirolimus

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Introduction: Autoimmune cytopenias are a group of disorders characterized by immune-mediated destruction of blood cells. In children they are often secondary to immune-dysregulation which may require long-lasting immunosuppression. Mycophenolate mofetil and sirolimus represent two well-known second-line options to treat these disorders, also used for steroid-dependent patients. However, no data are available on the infection risk for patients undergoing long-lasting treatments.
Methods: A retrospective data review of patients suffering from Primary Immuno-Regulatory Disorders, mainly ALPS/ALPS-like syndromes, and immune thrombocytopenia treated with Mycophenolate and Sirolimus at Haematology Units of the G. Gaslini Children's Hospital and of the Policlinico of Catania have been performed on patients' clinical charts. Moreover, an exhaustive search was performed on the main scientific libraries.
Results: Between January 2015–May 2023, 112 patients underwent treatment with mycophenolate mofetil and/or sirolimus over a median of 27 (range (3–144) and 42 (range 3–168) months, respectively. Thirteen out of 112 (11%) developed 16 episodes of severe infections requiring hospitalization (Table 1). No patients died. Infections involved 11/69 (15%) and 2/91 (2%) patients treated with sirolimus and mycophenolate, respectively. The infection rate under sirolimus therapy was significantly higher in patients with ALPS-like syndromes (9, 13%) than in patients with ALPS and immune thrombocytopenia (2%) ($p = 0.007$); moreover, infection rate was higher in patients who sequentially received both therapies (8, 61%) ($p = 0.03$) and was significantly correlated with therapy duration ($p = 0.04$) (Figure 1). Infectious events-free survival was 98%, over 12 months, 95% over 36 months, 93% over 60 months and 90% over 72 months.

Table 1. (abstract: 12)
Patients with severe infectious events (A) and patients with and without severe infectious events (B).

A

Pt	Diagnosis	Genetic mutations	SIE n	MMF months	SR months	Type of infection	Previous therapy	Drugs during SIE
1	ALPS-like	-	2	53	31	Pyelonephritis Sepsis from E. coli	MTX, HCQ, azathioprine, CPM, tacrolimus, thalidomide, bortezomib, eculizumab, belimumab	MMF and SR
2	ALPS	-	1	144	0	Pneumonia	/	MMF
3	ALPS	-	1	0	22	Gastroenteritis	/	SR
4	ITP	-	1	4	46	Pneumonia	/	SR
5	ALPS-like	-	2	0	6	Pneumonia and sepsis	Steroid	SR
6	ALPS-like	NEMO deficiency	1	0	72	Pneumonia	Steroid	SR
7	ALPS-like	LRBA deficiency	1	24	100	Pneumonia	Steroid, Abatacept	SR
8	ALPS-like	IPEX	1	15	73	Pneumonia	/	SR
9	ALPS-like	-	1	6	52	Sars-Cov2 Pneumonia	Steroid, IVIG	SR, steroid, thalidomide
10	ALPS-like	RMRP	2	0	98	Abdominal infection and meningitis (Cryptococcus)	IVIG	SR
11	ALPS-like	STAT3 GOF	1	11	40	Pneumonia	Steroid, IVIG, Rituximab	SR
12	ALPS-like		1	0	35	Pneumonia	Steroid	SR
13	ALPS-like	TNFSR13B	1	1	4	Viral pneumonia	/	SR

B

	Patients with at least 1 SIE (n = 13)	No SIEs (n = 99)	p
Sex (n, %)			**0.035**
Female	3, 24%	57, 58%	
Male	10, 76%	42, 42%	
Diagnosis (n, %)			**0.007**
ALPS-like	10, 77%	45, 46%	
No ALPS-like (ALPS or ITP)	3, 23%	54, 55%	
Therapy (n, %)			**0.033**
Only mycophenolate	1, 8%	42, 42%	
Only sirolimus	4, 31%	19, 19%	
Both	8 (7 during SR, 1 during MMF) 61%	38, 39%	
Therapy duration (months - median, IQR)			
Total	54, 71	36, 69.5	0.043
Mycophenolate	18, 37	30, 60	0.764
Sirolimus	44.5, 46.8	23, 42.5	0.102

CPM: cyclophosphamide, ES: Evans syndrome, HCQ: hydroxychloroquine, IBD: inflammatory bowel disease, IPEX: immune dys-regulation, polyendocrinopathy, enteropathy, X-linked, ITP: immune thrombocytopenia, IVIG LRBA: lipopolysaccharide-responsive and beige-like anchor protein, MMF: mycophenolate mofetil, MTX: methotrexate, NEMO: NF-kb essential modulator, RMRP: RNA component of the mitochondrial RNA-processing endoribonuclease, SIE: severe infectious event, SR: sirolimus.

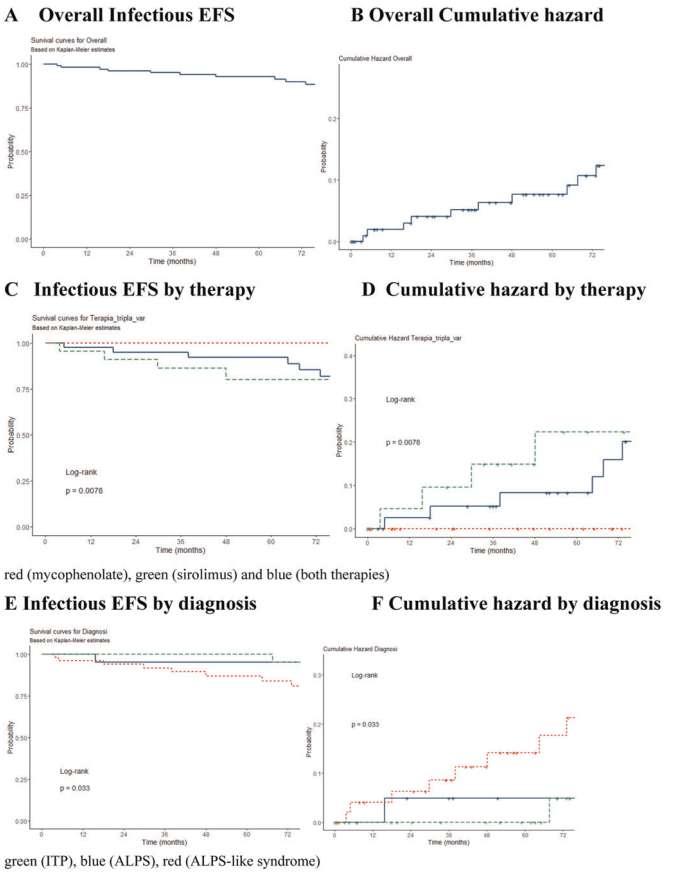

Figure 1. Infectious EFS and cumulative hazard: overall (A, B), by therapy (C, D), and by disease (E, F).

Conclusions: To the best of our knowledge, this is the first study describing the infectious risk related to mycophenolate and sirolimus treatments in patients with autoimmune cytopenias and immune-dysregulation. It highlights that the infections rate is rather low and mainly related to the underlying condition predisposing per se to these events.

Keywords: Mycophenolate, Sirolimus, Immune-dysregulation, PIRDs, Autoimmune cytopenias, Infections

Disclosures: Maurizio Miano: I have relevant financial relationships with proprietary interests: X4 Pharmaceutics (Advisory Board). Francesca Fioredda: I have relevant financial relationships with proprietary interests: X4 Pharmaceutics (Advisory Board). The other authors have no financial relationships or conflicts of interest to report.

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(13)

Long-Term Medical Management of Patients with Chronic Granulomatous Disease, Wiskott-Aldrich Syndrome, and Primary Immune Regulatory Disorders: A Primary Immune Deficiency Treatment Consortium Survey

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[10]*Professor/UCSF*
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[15]*Physician/University of Utah*
[16]*Emeritus Professor/University of California, San Francisco*
[17]*Senior Investigator/National Cancer Institute*
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Introduction: Chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome (WAS), and primary immune regulatory disorders (PIRD) are inborn errors of immunity that require long-term medical evaluation and management. Variability in management is likely impacted by lack of standard of care guidelines, and restricted access to diagnostic tests, imaging, and treatments.

Methods: A PIDTC developed survey containing 45 questions regarding recommended long term medical management of non-transplanted patients with CGD, WAS, and PIRD. The survey was distributed to PIDTC centers (n = 44) between March-June 2023. Data manipulation was performed using dplyr and graphs designed using ggplot. All code was implemented in R version 4.3.1.

Results: Sixty-eight physicians from 41 (93.1%) PIDTC centers responded. Laboratory testing was recommended for all patients: >77% (n ≥ 51 of 68) of respondents recommend CBC every 6 months. For WAS and PIRD >50% (n > 40 of 68) recommend measuring immunoglobulin quantities and lymphocyte enumeration at least annually, whereas ~25% recommend advanced T and B cell phenotyping (Figure 1). Periodic screening of disease specific functional or protein expression was recommended in all patients by 46–57% (Figure 2).

Over 70% (n ≥ 40 of 56) recommend immunoglobulin replacement for WAS and PIRD if IgG ≤ 300 mg/dL with >50% (n ≥ 33 of 56) aiming for a goal IgG 700–1000 mg/dl (Figure 3).

Prior to administration of non-live and live vaccines, >50% (n ≥ 27 of 53) of respondents recommend measuring IgG and T/B cell quantities; prior to administration of live vaccines respondents also recommend measurement of T cell function (72%) and response to non-live vaccines (88%).

Respondents (>60%; n ≥ 34 of 54) recommend Ig therapy and immunosuppression be discontinued prior to vaccination.

Discussion: Over 99% of respondents recommended lifelong follow up of CGD, WAS and PIRD with specialists. More than 50% of respondents recommend CBC, immunoglobulin quantities and lymphocyte subsets be obtained at least annually. However, variability in recommendations regarding frequency of screening laboratory studies remain. Respondents report difficulty obtaining insurance approval for laboratory testing (>50%) and treatment (80%). Multi-specialty collaborative efforts are urgently needed to develop consensus recommendations to guide management and justify insurance approval for testing and treatment of these medically complex patients.

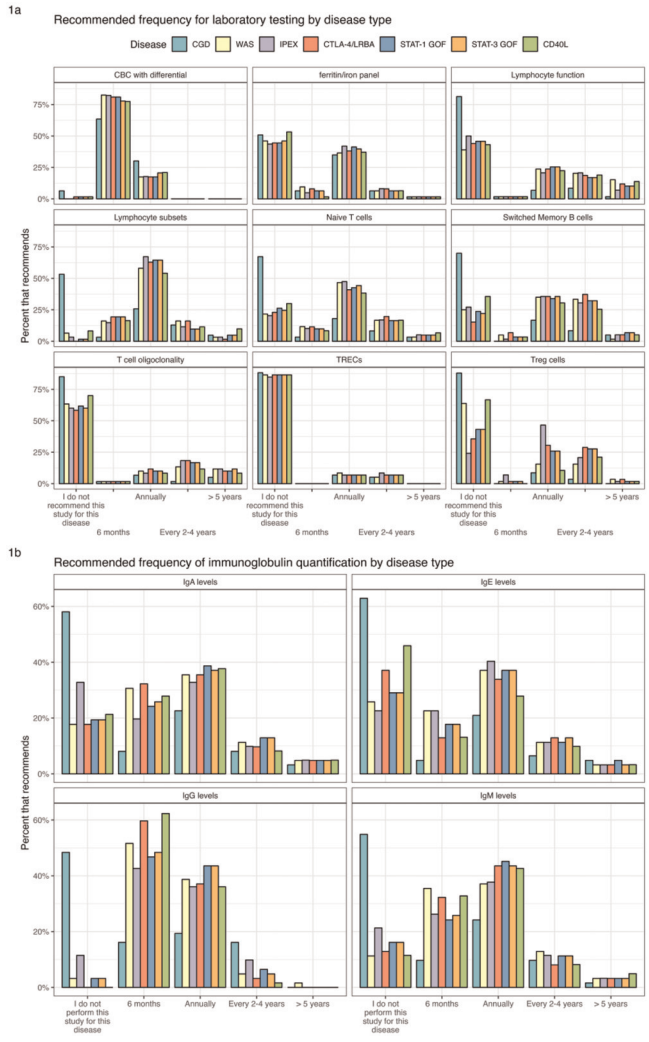

Figure 1. Recommended laboratory testing frequency by disease type.

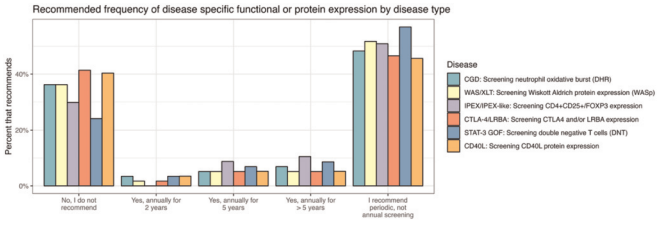

Figure 2. Recommended frequency of disease specific functional or protein expression by disease type.

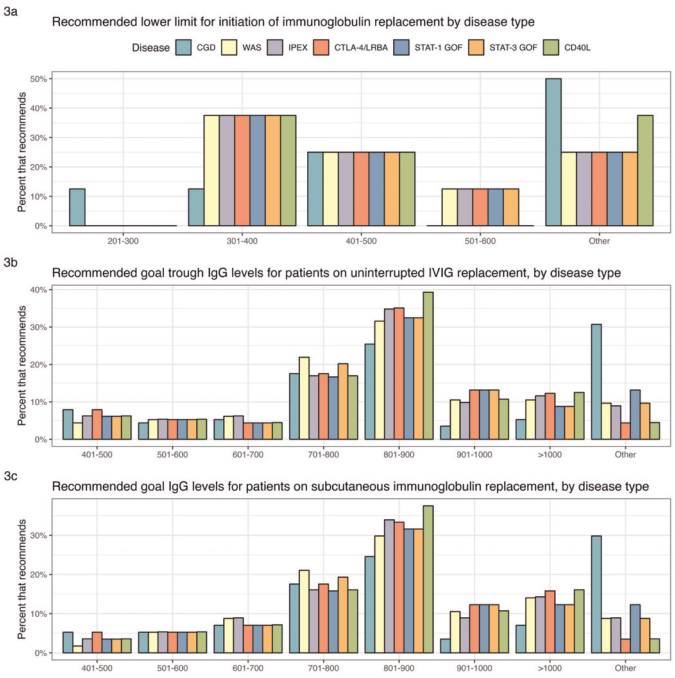

Figure 3. (3a) Recommended lower limit for initiation of immunoglobulin replacement by disease type; **(3b)** Recommended goal trough IgG levels for patients on uninterrupted IVIG replacement, by disease type; **(3c)** Recommended goal IgG levels for patients on subcutaneous immunoglobulin, by disease type.

Keywords: Chronic Granulomatous Disease (CGD), Wiskott-Aldrich syndrome (WAS), Primary Immune Regulatory Disorders (PIRD), Long-term management, Non-transplanted, Primary Immune Deficiency Treatment Consortium (PIDTC)

Disclosures: Kristin Shimano: I have relevant financial relationships with proprietary interests: Daiichi Sankyo (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Novartis (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Pfizer (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Sanofi (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Sobi (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)). Christopher Dvorak: I have relevant financial relationships with proprietary interests: Alexion Inc (Advisory Board); Jazz Pharma (Advisory Board). Elie Haddad: I have relevant financial relationships with proprietary interests: Jasper Therapeutics (Advisory Board); Octapharma (Advisory Board); Rocket Pharma (Advisory Board); Takeda (Advisory Board). Donald B. Kohn: I have relevant financial relationships with proprietary interests: Canadian Institutes of health Research, California Institue for Regenerative Medicine (Grants/Research Support Recipient, Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)). Michael Pulsipher: I have relevant financial relationships with proprietary interests: Adaptive (Grants/Research Support Recipient); Bluebird (Advisory Board); Cargo (Advisory Board); Gentibio (Advisory Board); Miltenyi (Grants/Research Support Recipient); Novartis (Advisory Board); Pfizer (Advisory Board). Morton Cowan: I have relevant financial relationships with proprietary interests: bluebird bio (Advisory Board, Consulting Fees (e.g., advisory boards)); Chiesi (Advisory Board, Consulting Fees (e.g., advisory boards)); Homology Medicine (Consulting Fees (e.g., advisory boards), Scientific Advisory Board);

Rocket Pharma (Advisory Board, Consulting Fees (e.g., advisory boards)); UpToDate (Royalties). Jennifer Puck: I have relevant financial relationships with proprietary interests: Invitae (spouse is employee, spouse is employee). Jennifer Heimall: I have relevant financial relationships with proprietary interests: CIRM (Scientific Advisory Board); CSL Behring (Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Health Economics & Outcomes Research Ltd (Consultant); Jobs Research Foundation (Scientific Advisory Board); Regeneron (Clinical Trial Investigator); Sumitomo (Consultant, Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); UpToDate (Royalties). Jennifer Leiding: I have relevant financial relationships with proprietary interests: bluebird bio (Employee, Stocks); Grifols (Advisory Board, Consultant); Horizon Therapeutics (Advisory Board, Consultant); Prime Medicine (Consultant, Scientific Advisory Board); Rocket Pharma (Consultant); Sobi (Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); White and Williams, LLC (Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). The other authors have no conflicts of interest to report.

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(14)

Unmasking the Mimic: Cytomegalovirus Pneumonia masquerading as CVID unravels as GATA2 Deficiency with Two Unique Pathological Mutations

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Background: GATA2 deficiency, a germline disorder resulting from heterozygous mutations in a critical transcription factor for hematopoiesis and angiogenesis, exhibits considerable variability in presentation, often characterized by susceptibility to viral and fungal infections. Profound monocytopenia, B-cell, and NK-cell lymphopenias are common features. This case study explores a patient with GATA2 deficiency who developed cytomegalovirus-induced pneumonia alongside gastrointestinal manifestations.
Case Presentation: A 45-year-old male patient presented with a persistent cough lasting four months, accompanied by fever and significant weight loss. Chest CT revealed cryptogenic pneumonia, and subsequent investigations identified a positive CMV viral load in bronchoalveolar lavage. A transbronchial biopsy confirmed intranuclear basophilic inclusions indicative of CMV infection. Additionally, blood tests returned positive results for CMV. Immunoglobulin levels revealed IgA < 0.13, IgG < 3, IgM < 0.25. An absolute T cell count (CD3+) of 3424cells/uL, CD4 T cells 1115cells/uL (31.9% of T cells) with a CD4/CD8 ratio 0.48 During hospitalization, the patient experienced multiple episodes of diarrhea. Colonoscopy revealed colonic ulcers, and biopsies excluded CMV in chronic colitis.
A PET-CT scan showed no lymphadenopathy or hepatosplenomegaly. Bone marrow biopsy indicated 80% hypercellularity without morphological alterations. Flow cytometry on the bone marrow revealed asynchronism in the expression of CD13 and CD10 antigens in Granulocytes/Neutrophils, B lymphocytes were identified in 0.35% (extremely low) with absence of mature B cells. Whole exome sequencing identified two heterozygous pathogenic GATA2 mutations (c.938A>G [p.His313Arg] and c.937C>T [p. His313Tyr]). Immunoglobulin replacement therapy was initiated.
Discussion: The hypogammaglobulinemia observed in our patient is often associated with the atypical plasma cell morphology identified in individuals harboring various mutations in GATA2. This correlation highlights the critical role of GATA2 in sustaining a robust and healthy plasma cell population. Our findings underscore the imperative for molecular testing in adult patients, aiming to exclude uncommon etiologies such as GATA2 deficiency, particularly when there are discernible abnormalities in lymphocyte subsets and monocyte counts. This report underscores the importance of expanding diagnostic considerations and leveraging molecular insights to guide targeted interventions in cases of hypogammaglobulinemia, even in the adult population.

Keywords: GATA2 deficiency, Hypogammaglobulinemia, Immunodeficiency, CMV, Adults

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(15)

Interferon Signalization in children with Juvenile Scleroderma

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Juvenile scleroderma (JSc) is a heterogeneous group of diseases associated with sclerotic skin lesions, grouped as systemic sclerosis (SSc) and localized scleroderma (JLS). This study aims to measure the cytokine and chemokine levels involved in interferon signaling in patients with JSc and determine their correlation with disease severity.
Method: Twenty-nine JLS, five SSc, and nine healthy controls were included in the study. Patients with morphea were scored according to the LoSCAT (activity index), LoSDI (damage index), and PGA-A (physician global assessment) indices. Cytokines and chemokines involved in interferon gene signaling (IFN-α, IFN-β, IFN-γ, TNF-α, IL-1, IL-6 IL-8, IP-10, MCP1 and CXCL-10) and interferon-stimulated genes (ISGs) including IFI27, IFI44, ISIG15, IFIT1, OAS1, RSAD2 were measured by ELISA and RT-PCR method respectively.
Results: A significant increase in IFN-α, IFN-β, IFN-γ, TNF-α, IL-1, IL-6 IL-8, IP-10, and MCP1 levels was observed in patients with SSc compared with the healthy control group. Furthermore, IFN-α and IP-10 were elevated in both JLS and SSc compared to the healthy control group. IFN-γ and IFN-α positively correlated with LoSAI and LoSDI levels, respectively. According to PGA-A analysis, IFN-β, IFN-γ, TNF-α, IL-8, IP10, MCP1, and CXCL11 were significantly higher in active disease than in the inactive state.
Conclusion: The results suggest that interferon signaling may be impaired in patients with JSc. Significant changes were observed in cytokines and genes related to IFN signaling, which may have a crucial role in monitoring disease activity. In addition, we have gained important insights into the possibility of using IFN-α and IFN-γ as biomarkers for monitoring JLS activity and damage.

Keywords: Interferon, Scleroderma, Juvenile, Autoimmunity

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(16)

Bone marrow damage in patients with Adenosine Deaminase 2 Deficiency

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Introduction: Deficiency of adenosine deaminase 2 (DADA2) is a heterogeneous congenital disorder, caused by mutations of ADA2 gene and characterised by both inflammatory/immunological and hematological symptoms. ADA2 deficiency is thought to create a lack of growth factor-like effect on bone marrow (BM) progenitor cells, a proinflammatory M1-macrophages polarisation, and neutrophils' activation.
Aims: To characterise the mechanisms of BM damage in DADA2 patients.
Materials and methods: All BM samples of patients with DADA2 available at both IRCCS Istituto Giannina Gaslini and IRCCS San Raffaele Scientific Institute and healthy donors were analysed. Fresh BM mononuclear cells (1 × 10–4) were cultured and colony forming unit (CFU) erythroid/myeloid assay were performed in presence of 10 ug/ml Anti-TNFα, 1 ug/ml or 10 ug/ml human recombinant ADA2, 1 ug/ml or 3 ug/ml Eltrombopag. Cytokine levels were measured in the BM plasma by flow cytometry bead array.
Results: Fourteen DADA2 patients (9 females, 5 males- median age 17 years) with a mixed hematological/inflammatory phenotype (4) or exclusively inflammatory symptoms (10) were studied. Eight/14 (57%) showed reduced erythroid (CFU-E 0.5, normal range 27–81/2 × 10–4) and myeloid (CFU-GM 3.5, normal range 33–100/2 × 104) progenitor cell growth. The addition of ADA2 had a stimulatory effect on myeloid progenitors, although not statistically significant (Fig 1A). The addition of anti-TNFα and eltrombopag 1 ug/ml had a significant stimulatory effect on the growth of myeloid progenitors (p = 0.01 and p = 0.05, respectively) (Fig 1B). Figure 2 shows the effect of anti-TNFa and ADA2 on the group of patients who showed a reduced growth of myeloid/erithroid progenitors in standard conditions and in a patient with severe Pure Red Cell Aplasia. TNFα marrow plasma levels were higher in 4/9 patients (44%) compared to 1/6 (17%) of controls (p = 0.002). No differences were noted in BM plasma IFNγ levels (Figure 1C).
Discussion: Our study shows that the BM of DADA2 patients is characterized by an inflammatory milieu and reduced growth of BM progenitor cells, partially rescued in vitro by anti-TNFα and Eltrombopag. Further studies are necessary to understand the mechanisms of BM damage and develop new therapies especially in patients with BM failure.

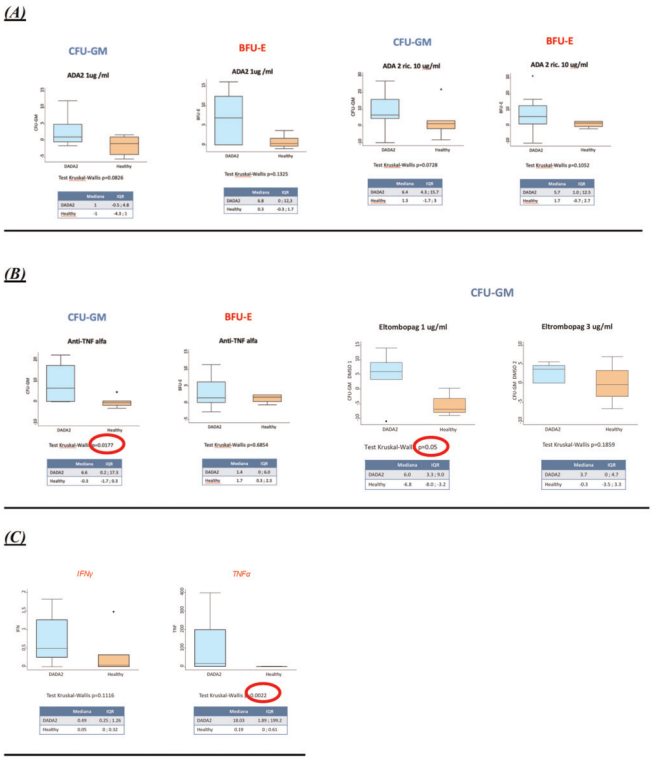

Figure 1 (A) *Effect of ADA2 (1 ug/ml and 10 ug/ml) on myeloid and erithroid progenitors;* ***(B)*** *Effect of anti-TNFα and eltrombopag 1 ug/ml on the growth of myeloid progenitors;* ***(C)*** *Expression of pro-inflammatory cytokines in BM plasma: plasma marrow TNFα levels were higher in the DADA2 patients compared to healthy controls (p=0.002). CFU-GM, colony-forming unit-granulocyte-macrophage; BFU-E, burst-forming unit–erythroid*

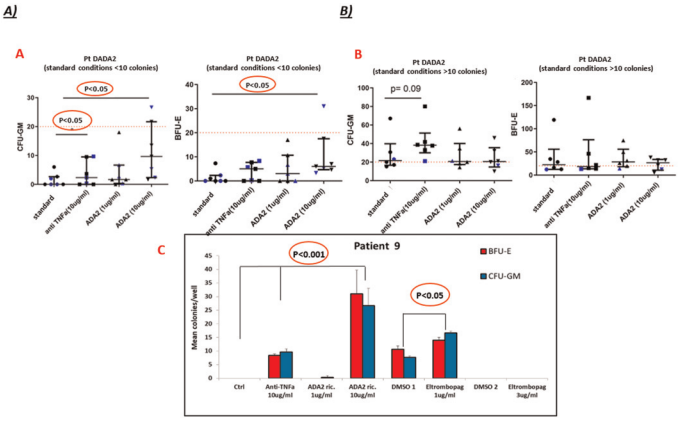

Figure 2. Effect of anti-TNFa 10ug/ml and recombinant ADA2 on patients with severely (A) and slightly (B) reduced growth of myeloid and erithroid progenitors in standard conditions and in a patient with severe Pure Red Cell Aplasia (C).

Keywords: DADA2, Bone marrow failure, Immune-dysregulation, Inflammation

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(17)

Severe Cardiac Tamponade in an Unusual Case of CTLA-4 Haploinsufficiency

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Introduction: Inhibitory receptors, such as cytotoxic T lymphocyte antigen 4 (CTLA-4), play a crucial role in immune regulation and peripheral immunological tolerance by modulating the function of T cells. One subset are the regulatory T cells, which are responsible for suppressing T cell proliferation and differentiation. CTLA-4 acts as a brake on T cell activation by competing with the costimulatory CD28 signal for binding to their shared co-stimulatory ligands, CD80 and CD86. This helps remove CD80 and CD86 from antigen-presenting cells. Heterozygous germline mutations in CTLA-4 can lead to haploinsufficiency, resulting in autosomal dominant immune dysregulation and immunodeficiency. CTLA4-haploinsufficiency usually presents with recurrent respiratory tract infections, lymphoproliferation, and enteropathy. These patients often meet diagnostic criteria for common variable immunodeficiency (CVID) due to a significant decrease in switched memory B cells and hypogammaglobulinemia.
Case: A 26-year-old male with a history of recurrent pneumonia, otitis media, and CVID (not on immunoglobulin therapy) presents to the emergency department with complaints of chest pain and cough for 1 week. Workup revealed pericardial tamponade on echocardiogram, leading to an emergent pericardiocentesis with pericardial fluid growing Streptococcus pneumoniae. He also had a parapneumonic pleural effusion requiring chest tube and lytic therapy. Further evaluation of his immune system reveals undetectable levels of IgM < 5 mg/dL (22–240), IgA < 5 mg/dL (65–421), IgG < 109 mg/dL (540–1822), CD19+ B cells at 0 cells/μL (110–660), NK cell (CD16+/56+) at 27 μL (70–760). Genetic testing confirms a pathogenic variant in the CTLA4 gene (p.Gly146Arg). The patient started on immunoglobulin replacement therapy and broad-spectrum antibiotics resulting in clinical improvement.
Discussion: CTLA-4 haploinsufficiency diagnosis is usually not made due to its variability of phenotypes. Patients are often labeled as CVID, and this may lead to limited conceptions of the diagnosis and create a false sense of security in terms of management. CTLA-4 haploinsufficiency typically presents with autoimmune dysregulation, a picture that this patient does not present now but should be monitored closely. Understanding CTLA-4 genotypical diagnosis can help open doors and guide treatment such as the addition abatacept, a CTLA4-immunoglobulin that binds CD80/86 on antigen presenting cells.

Keywords: CTLA-4, Abatacept, CVID, Cardiac tamponade, Hypogammaglobulinemia, Streptococcus pneumoniae, CD80/ CD86, Immunodeficiency, Regulatory T cells, Immunoglobulin

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(18)

Tracking Uncertainty in Germline Genetic Testing for Inborn Errors of Immunity: Sources, Attributes, and Resolution of Variants of Uncertain Significance in Over 44,000 Individuals

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Variant(s) of uncertain significance (VUS) are a challenge to the entire medical community. Additionally, individuals from underrepresented race, ethnicity, and ancestry (REA) groups are disproportionately impacted. Here, we present the prevalence of VUS in patients referred for germline genetic testing for inborn errors of immunity (IEIs) and the results of reclassification.
Patients were referred for diagnostic multigene panel testing for IEIs between September 2014 and September 2022. Variants were classified using Sherloc, a validated system based on American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines. Both the number of unique VUS (uVUS) and the number of times they were observed in individuals (oVUS) were counted. All-time uVUS were separated as being reclassified and non-reclassified, and the relative impact of evidence types was analyzed.
A total of 44,711 unrelated individuals were tested for IEIs with a mean of 232 genes tested per individual. Results showed a mean of 2.8 oVUS per individual; all 30,801 individuals without a molecular diagnosis (68.9%) had at least 1 oVUS. The rate of oVUS normalized to the number of genes tested was highest in Pacific Islander, Black, and Asian and lowest in Ashkenazi Jewish individuals, as the mean number of genes sequenced to observe one VUS was 48.6, 56.7, 58.4, and 118, respectively. White individuals had a lower VUS rate than other underrepresented REA groups. During this 8-year period, 1,706 (3.2%) of 54,032 uVUS were reclassified, affecting 4,981 individuals (11.1%); 1,481 (86.8%) of the reclassified uVUS were downgraded to benign/likely benign, and 225 (13.2%) were upgraded to pathogenic/likely pathogenic. Experimental studies and clinical evidence were enriched 17.2-fold and 10.4-fold, respectively, in downgraded uVUS and 18.9-fold and 15.1-fold, respectively, in upgraded uVUS when compared with non-reclassified uVUS.
Experimental studies and clinical evidence were the most impactful types of evidence for reclassifications. This highlights the partnership among researchers, clinicians, and laboratories to resolve VUS. Lastly, further research is needed to address the disparities in VUS rates among REA groups.

Keywords: Variant of uncertain significance, Reclassification, Germline genetic testing, Inborn errors of immunity

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(19)

POLD3 deficiency is associated with syndromic severe combined immunodeficiency including neurodevelopmental delay and hearing impairment

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Combined immunodeficiency diseases (CID) represent the most severe forms of inborn errors of immunity. Defective T cell development and/or function, leading to an impairment in adaptive immunity are responsible for these diseases. Genome duplication and maintenance, regulated by the DNA polymerase δ complex has been recently shown to contribute to CID. Biallelic mutations in POLD1, encoding the catalytic subunit of this complex or in POLD2, encoding an accessory subunit of the DNA polymerase δ have been recently linked to a syndromic CID with or without intellectual deficiency and sensorineural hearing loss. Here we report a homozygous POLD3 variant (NM_006591.3; p.Ile10Thr) in a Lebanese patient, the product of a consanguineous family, presenting with a syndromic severe combined immune deficiency (SCID) with neurodevelopmental delay and hearing loss. POLD3 is the accessory subunit 3 of the DNA polymerase δ that stabilizes the complex. The homozygous p.Ile10Thr variant in the POLD3 gene abolishes POLD3 as well as POLD1 and POLD2 expression. Our findings implicate POLD3 deficiency as a novel cause of syndromic SCID.

Keywords: POLD3, DNA Polymerase Delta, Severe combined immunodeficiency, Whole exome sequencing, Hearing loss, Neurodevelopmental delay

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(20)

Multi-Year Registry Study of Elapegademase-lvlr Treatment in Patients with Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID) Requiring Enzyme Replacement Therapy (ERT)

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Background: Deficiency of ADA causes a toxic elevation in deoxyadenosine nucleotides (dAXP) in lymphocytes, resulting in SCID. If hematopoietic stem cell transplant is unavailable or unsuccessful, patients may receive ERT. Beginning in 1990, the ERT available for the treatment of ADA-SCID was Adagen®, a PEGylated bovine ADA. However, due to concerns with the safety and stability, Adagen® was replaced in 2018 by Revcovi® (elapegademase-lvlr), a PEGylated recombinant ADA. Revcovi® was approved in the U.S based on two Phase III single-arm clinical trials with a small number of

patients. This Registry study was conducted as a post-marketing requirement to bolster the safety and effectiveness data on elapegademase-lvlr in a larger number of patients and to collect data on patients starting on ERT de novo.

Methods: Elapegademase-lvlr was prescribed and patients were managed as per standard of care and treating physician's judgement from September 2019–January 2023. Effectiveness measures included reaching pre-defined thresholds for plasma ADA activity and reduction in erythrocyte dAXP, as well as lymphocyte counts and rates of infections and hospitalizations. Patients were grouped as newborns/ very young children starting on ERT de novo, older children/ adults who had been taking Adagen® prior to elapegademase-lvlr, and adults who had taken part in the earlier trial.

Results: Thirty-two patients, (about 50% of those receiving ERT in North America) were enrolled. Most (75%) attained or maintained ADA and dAXP values that met or exceeded the defined thresholds, with the most significant results seen in the youngest Adagen®-naïve subjects, underscoring the value of early treatment. Lymphocyte counts remained low in older children/adults, as expected, but higher counts were achieved in the youngest patients. Rates of infections and hospitalizations remained stable, indicating that the older patients were maintaining similar immune function to that experienced with Adagen®. Patients who had been on elapegademase-lvlr the longest continued to maintain satisfactory ADA and dAXP levels as well as stability in rates of infections and hospitalizations, indicating long-term efficacy. There were no new safety findings of concern.

Conclusion: In this registry study, effectiveness of elapegademase-lvlr was maintained for up to 4 years of use.

Keywords: ADA-SCID, Enzyme replacement therapy, Adenosine deaminase severe combined immunodeficiency, HSCT, Registry, Immunodeficiency

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Susan Laubach: I have relevant financial relationships with proprietary interests: Chiesi (Grants/Research Support Recipient). Leo Lin: I have relevant financial relationships with proprietary interests: Chiesi (Employee). Talal Mousallem: I have relevant financial relationships with proprietary interests: Chiesi (Grants/Research Support Recipient); Horizon (Advisory Board). Jolan Walter: I have relevant financial relationships with proprietary interests: Chiesi (Grants/Research Support Recipient).

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(21)

A Patient with a Complete STAT1 Deletion with Lymphopenia and Elevated Double Negative T Cells

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Introduction: STAT1 is an important cytoplasmic transcription factor for interferon and IL-27 signaling in immune defense and regulation. There are four distinct STAT1 immunodeficiency diseases: autosomal recessive (AR) complete STAT1 deficiency, AR partial STAT1 deficiency, autosomal dominant (AD) STAT1 deficiency (due to loss-of-function or haploinsufficiency), and AD STAT1 gain of function disease. AD STAT1 haploinsufficiency was previously thought not to be disease-causing, but herein, we describe the first case, to our knowledge, of a patient with an entire heterozygous deletion of STAT1 gene and evidence of immunodeficiency.

Case description: A 6-year-old male presented with developmental delay, behavioral issues, subclinical hypothyroidism, abnormal EEG findings, and dysmorphic features including a broad forehead, hypertelorism, upslanted palpebral fissure, and thin upper lip. Chromosomal Microarray analysis revealed a 12.8 Mb loss in 2q32.1q33. This region encompassed 69 genes including the following AD genes: COL3A1, associated with vascular Ehlers Danlos syndrome, HECW2, associated with speech delay, and STAT1. Sequencing analysis confirmed an heterozygous STAT1 deletion. The patient's immunological history included two lifetime episodes of otitis media with no other significant infections and tolerance of BCG vaccine. On laboratory testing, he demonstrated persistent T cell lymphopenia with decreased CD3 (867 cells/mcL), CD4 (419 cells/mcL), and CD8 (275 cells/mcL) though normal CD19 and CD16/56. He displayed normal mitogen induced lymphocyte proliferation with normal T and B cell naïve/memory phenotyping. He had an increased proportion of CD3+CD4-/CD8- T cells at 14%. Cytokine profile revealed normal IL1β, IL2, IL4, IL5, IL6, IL8, IL10, IFNγ, TNFα, GMCSF, and CXCL9. Immunoglobulin levels were within normal range with low pneumococcal titers but adequate response to tetanus and diphtheria.

Discussion: We presume that this patient's immunodeficiency and dysregulation are due to the STAT1 haploinsufficiency, though functional studies will be needed to confirm it. It is also possible that there is another deleted gene influencing the immune system that has not yet been described. Although the patient is clinically well, without significant infections including BCG vaccine tolerance, unlike other patients with AR/AD STAT1 deficiency, the patient's immune abnormalities of lymphopenia and increased double negative T cells.

Keywords: STAT1 deletion, Double negative T cells, Vascular Ehlers Danlos syndrome, AR/AD STAT1 deficiency, COL3A1, Haploinsufficiency, Lymphopenia

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(22)

Abatacept in the treatment of common variable immunodeficiency with cytotoxic T lymphocyte antigen-4 haploinsufficiency in patient with comorbid systemic lupus erythematosus

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Cytotoxic T lymphocyte antigen-4 (CTLA-4) is a receptor on immune cells that inhibits T cell proliferation. CTLA-4 haploinsufficiency is a type of common variable immunodeficiency (CVID) that causes immune dysregulation leading to hypogammaglobulinemia, autoimmune conditions, and lymphocytic infiltration in multiple organs. Treatment has traditionally focused on addressing associated autoimmune complications and lymphocytic infiltration, as well as providing immunoglobulin replacement therapy (IgRT) for hypogammaglobulinemia. Therapies aimed at treating the underlying disease, such as abatacept, which downregulates CD28+ T cells, have shown some success, but formal treatment recommendations are lacking.

SN is a 52-year-old female with past medical history significant for systemic lupus erythematosus (SLE) and CVID with CTLA-4 haploinsufficiency. Her SLE has been long-standing with manifestations including biopsy-proven cutaneous lupus, pancytopenia, inflammatory arthritis, fatigue, cognitive changes, and fever. Her immunosuppressive treatment has been limited by pancytopenia and infections and has included hydroxychloroquine, quinacrine, methotrexate, azathioprine, mycophenolate mofetil, belimumab, and corticosteroids. She was initially noted to have hypogammaglobulinemia in 2016, as well as weak antibody response to pneumococcal vaccination. She reported many sinus infections, as well as a history of recurrent pneumonia and bronchitis. Additional comorbid conditions include hyperparathyroidism, hypothyroidism, prediabetes with positive GAD 65 antibody, and cytopenia attributed to her SLE. She was started on IgRT in 2016, which initially decreased the frequency of her infections; however, she developed increasing infections in 2021 with sinus infections occurring every three months. In 2022, mycophenolate mofetil and belimumab were stopped because of infections, and she started anifrolumab infusions. She subsequently underwent genetic testing, revealing CTLA-4 haploinsufficiency and an increased risk allele in NOD2. Given these findings, in November 2022 she was started on abatacept infusions, and anifrolumab was discontinued. Since that time, SN reports significant benefit, including increased energy, less pain, and decreased frequency of infections. She had been taking prednisone 10 milligrams daily for at least 10 years with SLE flares with prior tapers, but now she has been able to decrease to 5 milligrams daily. Recent blood work shows no evidence of active SLE.

This case provides support for the use of abatacept as a targeted therapy for CTLA-4 haploinsufficiency.

Keywords: Immunodeficiency, CTLA-4 haploinsufficiency, Abatacept

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(23)

A Role for Immunoglobulin Replacement Therapy in Cystic Fibrosis: A Case Report

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Cystic fibrosis (CF), a progressive and genetic multi-system disorder can manifest in the pediatric population with persistent or transient low immunoglobulin G (IgG) levels. Several reports have shown that high dose intravenous immunoglobulin (IVIG) therapy improves pulmonary function in patients with severe CF through its anti-inflammatory effects. However, there is currently no indication for immunoglobulin replacement therapy (IGRT) although listed in official guidelines as potentially providing benefit in patients with low IgG (evidence category III, strength of recommendation C). This case highlights the improvement in frequency and severity of pulmonary CF exacerbations after treatment with IGRT in a patient with hypogammaglobulinemia.

In this case, we present a 16 month male with cystic fibrosis (dF508 and R1162X), 3 prior pulmonary exacerbations requiring IV antibiotics (positive respiratory cultures for pseudomonas, acinetobacter, methicillin-resistant staph aureus, enterobacter, and haemophilus), recurrent fevers and notable hypogammaglobulinemia (IgG 160 mg/dL, reference 211–741 mg/dL; IgA < 7 mg/dL, reference 10–50 mg/dL) presenting with multiple office visits for pulmonary exacerbations. Given his severe presentation and otherwise negative infectious, rheumatologic, and lymphoproliferative workup, our diagnosis was concerning for hypogammaglobulinemia in the setting of cystic fibrosis and/or transient hypogammaglobulinemia of childhood given the patient's age. With documented recurrent infections despite antibiotic prophylaxis, the patient was initiated on IGRT. Subsequently, the patient normalized his IgG level up to 585 mg/dL. By 40 months of age, he only had one pulmonary exacerbation secondary to a viral illness with a two-day hospital stay.

Overall, our patient had severe exacerbations of his cystic fibrosis associated with hypogammaglobulinemia requiring hospitalization and IV antibiotics within the first year of life that significantly improved in frequency and severity following consistent IGRT treatment. IGRT (400–600 mg/kg), which has been less studied in cystic fibrosis replaces antibodies in an antibody deficiency, but is not known to have the same anti-inflammatory

effects as high dose IVIG (1–2 g/kg) therapy. This case emphasizes a role for judicious use of IGRT in the population of patients with CF who present with lower IgG, whether as an adjunct to current therapies or treatment for severe exacerbations.

Keywords: Immunoglobulin replacement therapy, Cystic fibrosis, Hypogammaglobulinemia

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(24)

Overcoming medical and socioeconomic barriers for gene therapy-assisted HSCT following prompt recognition of an Artemis-SCID infant

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Severe combined immunodeficiencies (SCID) are a group of rare (~1 in 50,000 live births), monogenic disorders that are universally fatal if not promptly identified and treated. Here we highlight an infant with SCID, initially detected by newborn screening (NBS). Immunophenotyping confirmed an absence of T and B cells. However, confirmatory genetic testing revealed a homozygous pathogenic mutation in the DCLRE1C gene encoding Artemis, a DNA repair protein. Artemis accounts for only 3% SCID cases, making it an exceedingly rare cause of an already rare disease. Because Artemis is an essential component of DNA repair machinery, Artemis-SCID is known as a radiosensitive form of SCID.

The primary treatment of SCID remains allogeneic hematopoietic stem cell transplant (HSCT). However, in patients with Artemis-SCID, successful immune reconstitution is less likely following HSCT. Moreover, pre-transplant conditioning regimens can induce irreparable cellular damage associated with short stature and shortened lifespan. The prompt recognition of Artemis-SCID, diagnosed just seven weeks after the patient's birth, fundamentally altered the treatment strategy for this patient. Instead of allogeneic HSCT, she became eligible for a novel autologous HSCT using lentiviral-mediated gene therapy.

The infant's family faced significant health disparities that nearly excluded them from the life-saving autologous HSCT. The family was uninsured, unfamiliar with the medical system, and exclusively Spanish-speaking. After extensive education, discussions of risks, and shared decision making, the family ultimately chose to pursue the life-saving therapy. The treatment was specific for Artemis-SCID and available at only one institution in the United States.

Through a clinical and scientific collaboration with the other institution's immunology and transplant teams, we obtained approval for the curative therapy, transferred the patient to another state, and acquired coverage to relocate the entire family for six months. We discuss our experience navigating medical, insurance, and governmental systems at humanitarian levels to reach a successful outcome.

In under-resourced areas, timely diagnoses of SCID are delayed or missed entirely. NBS and genetic testing have dramatically expanded the detection of SCID in the United States. However, we must also ensure that SCID patients have equitable understanding of and access to optimal treatment modalities.

Keywords: SCID, Artemis, Health disparities, Health inequities, Lentiviral gene therapy, Autologous HSCT

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(25)

Unveiling a Hiccup's Mishap: A Rare Case of Neuromyelitis Optica

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune condition affecting the central nervous system, marked by extensive demyelination and inflammation in the spinal segments and optic nerve. This leads to a constellation of symptoms such as visual loss (optic neuritis), extremity weakness and sensory loss (transverse myelitis), intractable vomiting and hiccups (area postrema syndrome). Here we present a case of NMOSD presenting with hiccups.

Case presentation: This is a 27-year-old Chinese woman with a medical history that includes systemic lupus erythematosus (SLE), lupus nephritis, Sjögren's disease and asthma who presented with persistent hiccups of 1 week. Despite initial treatment with baclofen, metoclopramide, and gabapentin, her symptoms persisted and worsened with blurring of vision (BOV) and tingling sensation in her upper extremities. Lumbar puncture with CSF analysis, Immunoglobulins, and Biofire panel were performed and revealed negative findings for xanthochromia, albumino-cytologic dissociation, oligoclonal bands, and IgG, IgM, MOG-igG4 antibody. Brain MRI, however, identified a focal non enhancing signal abnormality indicative of demyelination, redirecting to the diagnosis of NMOSD. Serum testing for anti-aquaporin 4 antibodies yielded a positive result, aligning with NMOSD. However, standard treatment, including a five-day course of methylprednisolone, failed to alleviate the symptoms significantly as the hiccups, BOV, and tingling sensation of upper extremities were still present. Subsequently, plasmapheresis, involving five exchanges, led to significant improvement without complications. The patient was discharged with prednisone and scheduled for outpatient neurology follow up.

Discussion: NMOSD primarily affects East Asians, with prevalence of 0.5–4 for every 100,000 population, with a notable female predominance. It involves autoantibodies that targets the aquaporin-4 (AQP4) channels in perivascular and peripheral astrocytes leading to perivascular lymphocytic infiltration, axonal loss, and astrocyte death exhibited in both gray and white matter, which differentiates it from multiple sclerosis. The International panel for NMO diagnosis (IPND) has published guidelines for its diagnosis. Treatment remains centered on intravenous steroids and plasmapheresis with maintenance therapy using immunosuppressive drugs such as prednisone or azathioprine, mycophenolate mofetil and rituximab. This case is unique as it failed to respond to high dose steroids and required plasmapheresis to relieve its symptoms.

Keywords: Autoimmune disease, Neuromyelitis optica, Demyelination

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(26)

Survival and Clinical Outcomes of XLA Patients 55 years or older

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Background: X-linked Agammaglobulinemia (XLA) is caused by mutations in the Bruton tyrosine kinase (BTK) gene, resulting in the absence of B cells and agammaglobulinemia. The introduction of antibiotics and replacement immunoglobulin G has improved life expectancy, but long-term comorbidities persist and remain poorly understood.
Objective: The study aims to characterize the demographic, clinical, functional, and molecular profiles of XLA patients who have survived beyond 55 years.
Methods: A survey conducted among twelve immunologists identified XLA patients aged 55 or older. Data on demographics, clinical history, genetic diagnosis, treatment, and comorbidities were collected.
Results: The survey identified 23 patients with XLA who lived beyond 55 years (range 55 to 74 years, median 65 years). Three patients died at an average age of 58.3 years and 21 out of 23 patients were white/Caucasian. Gene mutations were confirmed in 18 patients; of these, 6 had undetectable BTK levels while 8 had reduced or normal BTK expression. A family history of XLA was reported in 18 patients. Diagnosis was established at a median age of 6.5 years, and at 5 years in patients with known family history of XLA. Patients began receiving immunoglobulin therapy at a median age of 7.5 years, continuing for an average duration of 50.6 years. Common infections included upper respiratory infections (69.6%), pneumonia (60.9%), and sepsis (17.4%). The most frequent chronic comorbidities were bronchiectasis (60.9%), cardiovascular disease (43.5%), and malignancy (21.7%). Among the 20 living patients, eight were either fully or partially working. Most living patients (17/20) maintained a good quality of life defined as an ability to complete most independent activities of daily living (Kanofsky performance score >80). The immunologists caring for these patients attributed the long-term survival primarily to consistent immunoglobulin replacement (56%) and secondarily to hypomorphic mutations (27.3%).
Conclusion: This study is the first to report clinical, immunologic, and genetic characteristics of older patients with XLA. Compared to earlier studies, these patients experienced similar rates of respiratory infections and bronchiectasis but higher rates of malignancy. Despite significant comorbidities, most patients experienced quality of life consistent with independent living, primarily attributed to consistent immunoglobulin therapy.

Keywords: X-linked agammaglobulinemia (XLA), Immunoglobulin therapy, Comorbidities, Quality of life, Bruton tyrosine kinase (BTK), Long-term survival

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(27)

Cytokine panel testing in patients with Granulomatous-lymphocytic Interstitial Lung Disease (GLILD) associated with Common Variable Immunodeficiency (CVID)

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Introduction: CVID-related GLILD correlates with early mortality with no validated tools for diagnosis or monitoring of progression. The pathogenesis is poorly understood. A proposed mechanism describes activation of CD4+ T lymphocytes by antigen presenting cells leading to cytokine secretions, macrophage activation, TNF-α production, and immune cell agglomerates with granuloma formation in various organs. This study aims to identify potential biomarkers for diagnostic and therapeutic evaluation of GLILD.
Methods: We performed a retrospective review of electronic medical records of 27 patients diagnosed with GLILD and CVID with cytokine panels collected at Mayo Clinic, Rochester, MN and Scottsdale, AZ from October 2021 to present. 7 of the 27 patients had more than 1 panel collected over time. Data analysis was conducted on serum biomarkers including TNF-α, IL-6, IFN-β, IL-10, MCP-1, IL-1β, IFN-γ, MIP-1α, GM-CSF, IL-2 receptor α soluble (sIL-2R), IFN-α, and IL-18. Additional data collected include immunoglobulin profile, lymphocyte subsets, demographics, disease status, and treatments.
Results: Majority of patients have elevated levels of TNF-α (85%, n = 23), sIL-2R (77%, n = 21), IL-18 (70%, n = 19), and IL-6 (59%, n = 16) at baseline. TNF-α, sIL-2R, and IL-18 levels reduced after initiation of treatment in 2 different patients, one with abatacept and one with prolonged course of steroid. TNF-α, IL-6, IL-1β, and MIP-1α levels trended down with rituximab in 1 patient. A decrease in sIL-2R was observed in another patient on chronic steroids for cryptogenic organizing pneumonia. In 3 patients with no treatment, there was an increase in sIL-2R and IL-18 levels in 2 patients who had a progressive disease. TNF-α and sIL-2R levels was reduced in 1 patient with a stable disease.
Conclusion: Elevated levels of TNF-α, sIL-2R, IL-18, and IL-6 are seen in patients with GLILD, with treatment related reductions in these cytokines. Multiple parameters have been studied as potential predictors including

TNF-α, IL-8, IL-6, and IL-1β in hyper-inflammatory response in covid-19 infection and sIL-2R and IL-12 in CVID-related GLILD. However, other cytokines may have implicated roles as biomarkers for disease stratification, diagnostics, and surveillance of progression and response in patients with CVID-associated GLILD. Further studies on correlation with clinical manifestations and disease stage is warranted.

Keywords: Immunodeficiency, CVID, GLILD, Cytokine, Monitoring, Surveillance

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(28)

Genome sequencing identifies unexpected diagnosis for a toddler with persistent infection

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Genome sequencing (GS) can uncover unexpected diagnostic possibilities. Hunter syndrome (HS), caused by pathogenic/likely pathogenic variants in the IDS gene, is a progressive multisystem lysosomal storage disorder. Delayed diagnoses are common due to disease rarity and non-specific early findings. Molecular testing is recommended for confirmation. This case highlights GS' ability to provide an unexpected but definitive molecular diagnosis in a complex case with non-specific clinical manifestations.
We report a 28-month-old male who presented with malnourishment, fever, and respiratory failure, hospitalized at nine months old. Infectious disease evaluations were positive for disseminated tuberculosis, cytomegalovirus (CMV) and candida. His CMV affected his retina, bladder, liver, and lung and his candida infection evolved to probable sepsis. Invitae Primary Immunodeficiency (PID) Panel genetic testing was non-diagnostic for 429 genes implicated in PID.
Due to persistent immunological symptoms, we performed GS to identify potential molecular diagnoses. We initially detected and interpreted a novel hemizygous c.796C>T (p.Pro266Ser) missense variant in IDS in the proband as a variant of uncertain significance, due to absence of phenotypic overlap between the proband and a typical HS presentation, as well as the absence of prior reported HS cases with the variant. However, published reports of individuals with HS with IDS variants impacting this proline and the correlation with frequent upper respiratory infections as an initial indicator of the disease raised concerns. Subsequent fluorometric analysis confirmed the absence of IDS enzyme activity in the proband. The proband was clinically diagnosed with HS and clinical enzyme testing allowed for the reinterpretation of the IDS variant as likely pathogenic. Additional unidentified factors may also be contributing to his multiple disseminated infections. The child is currently undergoing treatment.
This case highlights the utility of GS after non-diagnostic genetic panel testing. GS led to an unexpected diagnosis of HS before the onset of neurological symptoms. For non-diagnostic panel results, GS provides a broader understanding of possible diseases and diagnoses. Clinicians should consider broad genetic testing, such as GS or exome sequencing, when panels are negative in immunodeficiency evaluations.

Keywords: Clinical utility, Genome sequencing, Hunter syndrome, Panel testing, Unexpected diagnosis

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(29)

Safety and feasibility of the use of dual cardiac-thymus transplant in a child with cardiac failure requiring heart transplant

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Cultured thymus tissue implantation (CTTI) can successfully restore T-cell immunity in infants with congenital athymia. There is evidence that infants receiving CTTI may develop immune tolerance to donor thymus HLA, but CTTI has not been applied to solid organ transplantation.
A full-term male infant with double-outlet right ventricle, malposed great arteries, and transverse aortic arch hypoplasia, underwent cardiac repair during the first week of life and required a subtotal thymectomy. He developed severe tricuspid insufficiency and was listed for cardiac transplant. Prior to transplant his lymphocyte enumeration showed decreased CD4+ T-cells at 34.2% (485 cells/ul) with 41.4% of CD4+ T-cells being naïve CD4+CD45RA+CD62L T-cells (126 cells/ul). B-cells and NK-cells were normal.
Heart and thymus tissues were harvested from the same living donor, with immediate heart transplant. The thymus cultured for 14 days and implanted into the left thigh. Immunosuppression consisted of anti-thymocyte globulin, tacrolimus and mycophenolate mofetil. Post-CTTI lymphocyte enumeration at 24-months showed 50.2% CD3+ T-cells (1153 cells/ul), 29.3% CD4+ T-cells (673 cells/ul), 12.3% CD8+ T-cells (282 cells/ul), with 46.7% of CD4+ T-cells being CD45RA+CD62L+ naïve T cells (314 cells/ul). B-cell and NK-cell levels were normal. Cardiac biopsy performed 12-months post-transplant showed focal mild cellular rejection, but resolved at the time of repeat biopsy at 24-months post-transplant. Donor specific antibodies (DSA), initially negative, became positive at 21-months post-transplant to MHC-class II. Mixed lymphocyte reaction at 11-months post-

transplant showed recipient Stimulation Index (SI) of 66 (SI to pooled PBMC of 107). Repeat study at 18-months showed SI to donor of 49 (SI to pooled PBMC of 63).

This is the first infant to receive heart/thymus from the same donor. Although tolerance to the allograft was not evident, T-cell reconstitution was similar to infants receiving CTTI for the treatment of congenital athymia. Ongoing allograft reactivity may be due to incomplete T cell ablation prior to CTTI, requiring the recipient continue on immunosuppression. This case study shows the safety and feasibility of using heart transplant and CTTI from the same donor in young infants requiring heart transplantation. CTTI as a strategy to induce donor tolerance will require approaches ablating autologous thymic function.

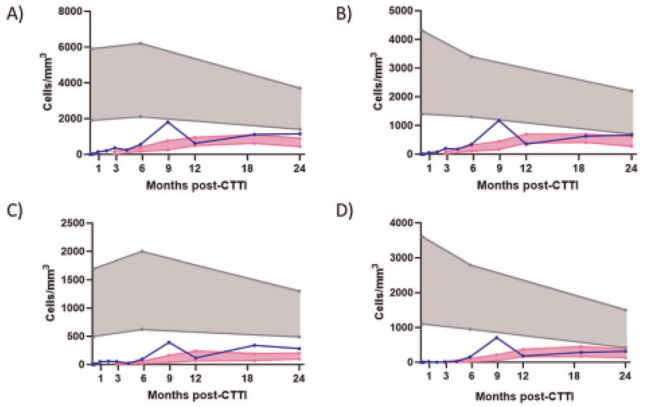

Figure 1. T-cell reconstitution following cultured thymic tissue implantation (CTTI) as measured by flow cytometric analysis. A) Total CD3+ cells, B) Total CD4+ cells, C) Total CD8+ cells, D) Total RA+CD62+CD4+ cells. Blue line denotes the dual heart-thymic recipients' T-cell numbers. Pink shaded region represents the interquartile range of T-cell numbers for children with congenital athymia with a 'typical' phenotype, post-CTTI (n = 49). The gray shaded region represents the range of T-cell numbers for healthy, age-adjusted children.

Keywords: Congenital athymia, Heart transplant, Tolerance, Immune reconstitution, Rejection, Thymus implantation

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(30)

Single-cell DNA sequencing for transgene copy number in gene therapy for Artemis-deficient severe combined immunodeficiency

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Gene therapy for autologous hematopoietic cell transplant has been developed for several inborn errors of immunity, including Wiskott-Aldrich disease, and leukocyte adhesion disorder 1, and severe combined immunodeficiency (X-SCID, ADA, Artemis). However, viral integration during gene therapy is not site directed and carries the risk of insertional mutagenesis, and for some genes, overexpression toxicity. Currently, vector copy number (VCN) is assessed in bulk DNA from sorted cell populations, which provides an average VCN, but not the single-cell distribution. Hematopoietic stem and precursor cells (HSPC) can be grown in single cell colonies after viral transduction, but the process is tedious, does not identify long-term hematopoietic stem cells (LT-HSC), and is subject to cell survival bias. There is a need for a single cell DNA assay to measure VCN in LT-HSC, and after engraftment, in specific mature blood cell types. Here, we present ongoing development of single-cell DNA sequencing for VCN in an investigational lentiviral gene therapy for Artemis-deficient SCID.

We utilized the Tapestri platform, which enables lipid encapsulation of single cells with multiplex barcoded PCR primers. Amplification and next-generation sequencing allow DNA markers to be resolved in single cells by a proprietary informatic pipeline. We designed a 108 amplicon panel, of which 9 amplicons recognize lentiviral elements or exon-exon junctions within the Artemis cDNA, and 99 amplicons recognize SNPs, allowing discrimination of chimerism in patients previously treated with allogeneic transplant prior to gene therapy. We generated two clonal B-cell lines from distinct patients: one from a patient with ART-SCID with a VCN of 6; and a control without vector. We generated cell mixtures with vector-positive cells ranging from 0.1%-50% and successfully identified vector-positive cells in all mixtures with a sensitivity of 100% and specificity of 99.6%. Bulk VCN was verified with ddPCR, although ddPCR was insufficiently sensitive below 1%. Ongoing work includes modeling the VCN per transduced cell and applying barcoded antibodies for cell surface phenotyping. Long-term goals include prospectively measuring VCN distribution in LT-HSCs in the cell product prior to transplant and in peripheral blood populations post-transplant, and developing this technique for gene therapies beyond ART-SCID.

Keywords: Gene therapy, SCID, Vector copy number, Single-cell, Transgene

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proprietary interests: Algen Biotechnologies (Advisory Board); AppleTree Partners (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Biogen (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Caribou Biosciences (Advisory Board, Owner/Co-Owner Founder/Co-Founder); Editas Medicine (Owner/Co-Owner Founder/Co-Founder); eFFECTOR Therapeutics (Advisory Board); Felix Biosciences (Advisory Board); Inari (Advisory Board); Intellia Therapeutics (Advisory Board, Owner/Co-Owner Founder/Co-Founder); Johnson & Johnson (Director); Mammoth Biosciences (Advisory Board, Owner/Co-Owner Founder/Co-Founder); Pfizer (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Roche (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Scribe Therapeutics (Advisory Board, Owner/Co-Owner Founder/Co-Founder); Synthego (Advisory Board). Jennifer Puck: I have relevant financial relationships with proprietary interests: Invitae (spouse is employee, spouse is employee). The other authors have no financial relationships or conflicts of interest to report.

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(31)

Immunizing Impaired Immunity: Viral Vaccination Rates in CVID

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Background: Patients with common variable immunodeficiency (CVID) are at increased infectious risk and may benefit from viral vaccination despite ongoing treatment with IgG replacement therapy (IgG-RT) due to low antibody concentrations and antigenic drifts/shifts in circulating viral strains. Non-live vaccines recommended in immunocompromised individuals include influenza, COVID-19, recombinant zoster vaccine (RZV), and human papillomavirus (HPV).
Objective: To measure rates of vaccination and infection to influenza, COVID-19, (varicella zoster virus) VZV, and HPV in a CVID cohort.
Methods: Living patients seen at any Mayo Clinic site 1/1/2022–1/1/2023 with an ICD-10 code D83.*, CVID, were identified by SlicerDicer. Those with a chart diagnosis consistent with CVID based on physician review were included in the study. Immunization records were drawn from electronic health record documentation. Only laboratory-confirmed infections were recorded.
Results: 245 living patients were identified with median age of 59 years (range 12–94). Patients were predominately female (64.9%) and White (98.4%), with 97.6% receiving continuous IgG-RT. 82.4% had at least 1 documented influenza vaccine administration from any year, but only 49.4% received an influenza vaccination during the 2021–2022 season. 81.6% received at least 1 COVID-19 vaccination, 33.9% received at least 1 dose of any VZV vaccine (52.3% in ages ≥ 50), and 9% received at least 1 dose of HPV vaccine (50.0% in ages 18–26 and 23.1% in ages 9–45). Rates of laboratory-confirmed infections for COVID-19, influenza, shingles, and HPV were 31.8%, 2%, 0.4%, and 1.6% respectively. An additional 15.5% reported clinical shingles infection.

Table.
Vaccination and infection rates.

	n (%)
Demographics	
CVID Patients	245 (100)
Female	159/245 (64.9)
White	241/245 (98.4)
Receiving Continuous IgG-RT	239/245 (97.6)
Vaccinations	
Influenza ≥ 1 Dose	202/245 (82.4)
Influenza 2021–2022 Season	121/245 (49.4)
COVID-19 ≥ 1 Dose	200/245 (81.6)
VZV ≥ 1 Dose	83/245 (33.9)
VZV ≥ 1 Dose (Ages ≥ 50)	79/151 (52.3)
HPV ≥ 1 Dose (Ages 18–26)	7/14 (50.0)
HPV ≥ 1 Dose (Ages 9–45)	18/78 (23.1)
Infections	
COVID-19	78/245 (31.8)
Influenza	5/245 (2.0)
Shingles	1/245 (0.4) lab-confirmed, 38/245 (15.5) reported
HPV	4/245 (1.6)

Conclusion: Vaccination rates against seasonal influenza, COVID, RZV and HPV in our cohort were broadly comparable to published CDC vaccination rates. Higher COVID-19 vaccination rates may reflect heightened infection concern and mandatory vaccination programs during the pandemic. While our study likely underestimates vaccination and infection rates from external sources, these findings highlight the need for new strategies to increase awareness of vaccine safety and efficacy towards improving vaccination rates in CVID.

Keywords: Vaccines, Common variable immunodeficiency (CVID), Influenza, COVID-19, Varicella zoster virus (VZV), Human papillomavirus (HPV), Recombinant zoster vaccine (RZV), IgG replacement therapy (IgG-RT), IVIG

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(32)

Clinical and Genetic Findings of >5,300 Individuals Tested via the navigateAPDS Sponsored Genetic Testing Program

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Introduction: Activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) is caused by disease-associated variants in the PIK3CD and PIK3R1 genes that lead to hyperactivity of the PI3K delta pathway and progressive immune deficiency and/or dysregulation. navigateAPDS, a no-charge, sponsored, genetic testing program, was established in the US and

Canada to help reduce barriers to testing. This study aims to review clinical and genetic findings from the navigateAPDS program.
Methods: Consented individuals who have ≥2 APDS-related clinical, laboratory, and/or family history criteria were eligible for comprehensive immunodeficiency genetic testing at Invitae®.
Results: 5372 patients from 1119 providers in 49 states were tested between March 2021 and October 2023. The median age at testing was 31 years, 36.7% were < 18 years, and 61.6% were female. A total of 403 patients (8%) received a positive molecular diagnosis (MolDx). PIK3CD or PIK3R1 variants were identified in 110 individuals (2.0%), including 22 individuals from 15 families who received an APDS MolDx (e.g., likely pathogenic or pathogenic PIK3CD or PIK3R1 variant) and 88 individuals who received a variant of uncertain significance (VUS).
Conclusions: The navigateAPDS program has identified multiple individuals with a positive APDS MolDx, demonstrating the ability of the program to assist clinicians in accurately diagnosing their patients. Additional clinical, functional, and family segregation studies will aid in VUS resolution and offer additional insights into the genetic underpinnings of APDS and its clinical manifestations.

Keywords: Activated phosphoinositide 3-kinase (PI3K) delta syndrome, Genetic testing, PIK3CD, PIK3R1, Next generation sequencing

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(33)

Adult-onset Severe Combined Immune Deficiency in a Patient with Cartilage-Hair Hypoplasia

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The ribonuclease mitochondrial RNA-processing (RMRP) gene encodes the non-coding RNA molecule of the RMRP endoribonuclease. It has been shown to play a role in cell cycling and telomere maintenance.
Bi-allelic variants in RMRP are associated with autosomal recessive cartilage-hair hypoplasia and auxetic dysplasia (CHH-AD) spectrum disorders. The phenotypic spectrum of RMRP-related conditions is highly variable; symptoms include metaphyseal chondrodysplasia, hypotrichosis, ectodermal dysplasia, pure red cell anemia, and Hirschsprung disease with varying degrees of immune dysfunction leading to severe immune deficiency and risk of lymphoma.
Immune dysfunction is progressive and a major component of prognosis. CHH-AD patients with severe immune deficiency require curative stem cell transplantation for survival.
Recent publications on the availability of genetic studies on newborn screening revealed patients with severe immunodeficiency with mild or no skeletal anomalies.
Here, we report the diagnosis of CHH in a Chinese woman who presented with recurrent sinopulmonary infections and oral ulcers, enlarged postauricular lymph nodes, chronic diarrhea, and a diffuse maculopapular rash over her entire body, with anemia and severe combined immune deficiency. There were no skeletal findings. Genetic testing revealed a pathogenic, non-coding duplication insertion on one allele and a novel variant of uncertain significance (48T>C) on the other allele, not present in population databases.

Keywords: Cartilage hair dysplasia, RMRP, Lymphopenia, Hypogammaglobulinemia

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(34)

An Unusual Case of X-linked Agammaglobulinemia Masquerading as CVID

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A 13-year-old male with history of atopic dermatitis, seasonal allergies, and recurrent upper respiratory infections (URIs) presented to the emergency room (ER) with fever and abdominal pain which started a few hours prior to presentation. In the ER he was febrile to 102.9 degrees Fahrenheit, tachycardic, and hypotensive. Physical exam was notable for a tired-appearing teenage male. Cardiopulmonary and abdominal exams were unremarkable. Laboratory results were notable for leukocytosis to 24,000 with neutrophilic predominance. Chest radiograph was unremarkable. Abdominal imaging including computed tomography (CT) and ultrasound were unrevealing. Blood cultures grew S. pneumoniae. Infectious Disease was consulted for occult pneumococcal bacteremia. An immune workup revealed B cell lymphopenia (CD19 count of 4 cells/microliter) with hypogammaglobulinemia. Immunoglobulin (Ig) G was low at 216 mg/dL, IgM was low at < 5 mg/dL. IgA and IgE were normal at 204 mg/dL and 17 mg/dL, respectively. Vaccine responses to tetanus, diphtheria, Haemophilus influenza B, poliovirus, measles/mumps/rubella (MMR), and varicella were absent. A preliminary diagnosis of common variable immunodeficiency (CVID) was made. The patient was treated with intravenous immunoglobulin (IVIG) and antibiotics. He recovered uneventfully and presented to the immunology clinic for follow up one month after discharge. Lymphocyte enumeration was repeated and showed persistent B cell lymphopenia with absolute CD19 count of 3 cells/microliter. This raised suspicion for X-linked agammaglobulinemia (XLA). The Invitae Primary Immunodeficiency panel was sent and revealed a pathogenic variant,

c.1567-12_1567-9del, in intron 15 of the BTK gene. This sequence change does not directly change the encoded amino acid sequence of the BTK protein, however RNA analysis indicates that this variant induces altered splicing and likely results in a shortened protein product.
Our case highlights an uncommon presentation of X-linked agammaglobulinemia (XLA) masquerading as CVID in a 13 year old with normal IgA and IgE. Previous case reports have described hypomorphic BTK mutations presenting without agammaglobulinemia, as in this patient. This case highlights the challenge of diagnosing "leaky XLA" versus CVID with associated B cell lymphopenia. The patient has since started subcutaneous immunoglobulin replacement therapy and has improved. BTK testing for his sister will be pursued to investigate carrier status.

Keywords: XLA, Immunoglobulin replacement, CVID

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(36)

A Novel Variant in TNFAIP3 Causes A20 Haploinsufficiency

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A 44-year-old woman previously diagnosed with specific antibody deficiency presented to the University of Wisconsin Adult Immunodeficiency Clinic for a second opinion concerning her immunologic diagnosis. In 2013, she had been diagnosed with specific antibody deficiency, and had been on subcutaneous immunoglobulin replacement since then with minimal further infectious complications. However, she now had new concerns of noninfectious symptoms, particularly painful oral ulcers, sicca symptoms, and undifferentiated rashes. Her family history was significant for two children who had been diagnosed with common variable immunodeficiency with a heterozygous variant in TACI (p.Ala181Glu). Of note, her oldest daughter had significant GI symptoms that had previously been attributed to small intestinal bowel overgrowth versus lymphoid nodular hyperplasia.
Given her new symptoms possibly consistent with autoinflammation and significant family history, we did not feel that her family's overall picture was suggestive of a mild humoral immunodeficiency. As such, we ordered a primary immunodeficiency genetic panel to further evaluate for both immunodeficiency and monogenetic autoinflammatory disease. This panel was significant for a variant of unknown significance in TNFAIP3 (c.1748G>A, p.Gly583Glu). Further family testing revealed that this variant was present in her daughter, but not her son (whose clinical picture was more consistent with mild humoral deficiency).
For further characterization of this variant, we reached out to researchers and clinicians at the National Human Genome Research Institute and the University of Pittsburgh Medical Center. Subsequent research assays showed decreased expression of TNFAIP3, likely consistent with A20 haploinsufficiency. We started colchicine at 0.6 mg twice daily which has led to significant benefit with her overall symptoms. Her daughter has started canakinumab, which has led to a significant reduction in her GI symptoms.
This case illustrates the importance of having clinicians who can both recognize monogenetic autoinflammatory disease and are willing to order and interpret genetic testing. In addition, this case sprovides an excellent example of collaboration between clinical and research immunologists/geneticists in discovering novel disease-causing variants in genes associated with inborn errors of immunity.

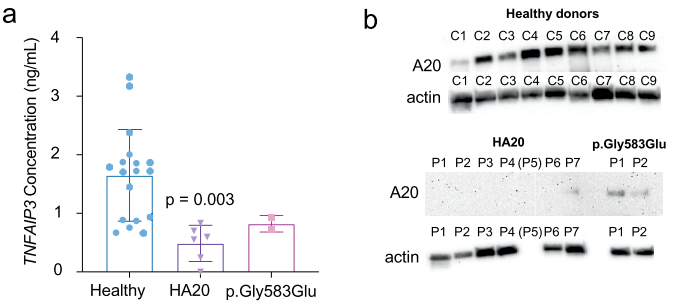

Figure. Two research based assays performed at the University of Pittsburgh Medical Center revealed decreased expression of TNFAIP3.

Keywords: Autoinflammation, A20 haplosinsufficiency, Genetic testing

Disclosures: Daniel Rosenberg: No financial relationships or conflicts of interest.

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(37)

A 2-year-old male with humoral deficiency and BACH2 variant

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Introduction: Pathogenic BACH2 gene variants are associated with common variable immunodeficiency (CVID). BACH2 has an important role in the adaptive immune system regulation particularly B cell class switch recombination and regulatory T cell differentiation. We present a 2-year-old male patient with a BACH2 variant who has recurrent sinopulmonary infections, abnormal B cell phenotyping, and specific antibody deficiency.
Case Presentation: A 2-year-old male patient presented for recurrent infections. Since birth, he has suffered from over 8 episodes of otitis media, 2 episodes of pneumonia, 2 episodes of gastroenteritis and many viral upper respiratory infections. He underwent adenoidectomy and myringotomy tube placement, pneumococcal vaccine boosters, and was started on inhaled corticosteroids for persistent bacterial sinopulmonary infections. Comprehensive functional immunological evaluation demonstrated normal immunoglobulins, normal complete blood cell counts with differential, normal lymphocyte subsets, negative aeroallergen IgE testing, normal NK studies (perforin/granzyme, CD107a mobilization, chromium release, NK phenotyping), and normal complement. His B cell phenotyping showed decreased percentage of total memory CD27+ B cells. He had 0/23 strep pneumoniae titers greater than 0.5 mcg/mL after primary pneumococcal conjugate vaccine (13 serotypes). After 3 doses of pneumococcal polysaccharide vaccine (23 serotypes), he had only 5/23 titers greater than 1.3 mcg/mL. He was immune to hepatitis B, measles, mumps, rubella, and tetanus but not varicella and diphtheria after primary series. He was started on azithromycin prophylaxis 5 mg/kg/dose three times weekly; However, after 3 months, he was diagnosed with pneumonia. The family is considering immunoglobulin replacement. Invitae 574 gene panel

for inborn errors of immunity and cytopenia produced negative results for known pathogenic variants. However, it did detect a heterozygous variant of uncertain significance in BACH2 at c.2402C>T (p.Pro801Leu).
Discussion: Autosomal dominant BACH2 haploinsufficiency has only been described in two families to date and can cause CVID-like disease similar to our patient's phenotype (PMID 28530713). Functional studies are needed to confirm the pathogenicity of the BACH2 variant but this case and the high population prevalence (0.03%) of this variant suggest that BACH2 variants might be a risk modifier for CVID-like disease similar to TACI variants and this warrants further research.

Keywords: Common variable immunodeficiency, CVID, Humoral deficiency, BACH2 variant

Disclosures: Melissa Gans: I have relevant financial relationships with proprietary interests: DBV (Clinical Trial Investigator); Elsevier (Royalties); Novartis (Clinical Trial Investigator); Opinion Leader Group (Consulting Fees (e.g., advisory boards)). The other authors have no financial relationships or conflicts of interest to report.

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(38)

Young Children With Recurrent Infection and Allergic Background Have Inadequate Baseline Pneumococcal Antibodies

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Introduction: Our previous report demonstrated that among 313 patients over 6 years of age with recurrent respiratory infections, 80% had lower pneumococcal antibodies (PA) and 20% had specific antibody deficiency (SAD). The study also showed that the patients with an allergic background had lower baseline pneumococcal antibodies (PA) than those without allergic background.
Methods: We extended our study to a group of 38 younger children aged 2 to 5 years with recurrent infections. We studied the pneumococcal antibody (PA) levels among patients with an allergic background (positive skin test or presence of sIgE to allergens), asthma, and atopic dermatitis. We compared the PA levels among the patients with these clinical conditions and those without them for the 23 serotypes contained in unconjugated pneumococcal polysaccharide vaccine (PPV23), the 13 serotypes in pneumococcal conjugated vaccine (PCV13), and the 10 serotypes not covered by the Prevnar 13 (non-PCV).
Result: The adequate PA level for this age group was defined as ≥50% of tested serotype antibodies being in the protective range (≥1.3 ug/mL), in distinction to ≥70% in the older age group. As a group, our children had an inadequate average percentage of PA serotypes /tested serotype (< 50%). PA levels were inadequate in 71% of children with regards to PPV23 serotypes, 63% to PCV13 serotypes, and 68% to non-PCV serotypes. SAD was present in 5% of children. As in older patients, presence of allergy, asthma, and atopic dermatitis did not affect the PA levels to the serotypes contained in different vaccines. However, patients with an allergic background demonstrated significantly lower PA levels to non-PCV serotypes.

Table.
Average number and percentage of adequate serotypes on different clinical conditions.

	Allergy		Asthma		Atopic Dermatitis	
	Yes	No	Yes	No	Yes	No
Patient Number	23	15	14	24	6	32
Average number of adequate PPV23 serotypes(No./23 as %)	8.1 (35%)	12.2 (53%)	11.1 (48%)	8.9 (39%)	10.2 (43%)	9.6 (42%)
P value	0.13		0.43		0.83	
Average number of adequate PCV13 serotypes (No./13 as %)	5.5 (42%)	7.1 (55%)	6.6 (51%)	5.9 (45%)	6.5 (50%)	6.1 (47%)
P value	0.13		0.65		0.83	
Average number of adequate Non-PCV serotypes (No./10 as %)	2.6 (26%)	5.1 (51%)	4.4 (44%)	3.0 (30%)	3.7 (37%)	3.5 (35%)
P value	**0.04**		0.25		0.90	

*Positive allergy prick test or selective IgE.

Conclusion: Approximately 60–70% of younger children with recurrent infection had lower baseline levels to the serotypes included in PPV23, PCV13, and non-PCV, like adults. Children with an allergic background had significantly depressed PAs to non-PCV serotypes suggesting that they may have difficulty dealing with natural infections. The lower SAD rate indicates that younger children respond to additional PPV more readily than older individuals.

Keywords: Recurrent respiratory infection, Pneumococcal antibodies, Specific antibody deficiency, Allergy, Asthma

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(39)

An educational outreach to identify racial and ethnic disparity awareness in immunodeficiency patient care

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Despite immunodeficiency disorders being primarily described in patients of White, Northern European descent, data from unbiased newborn screening show equal incidence across racial and ethnic groups. These data suggest a potential misconception among healthcare providers that immunodeficiency disproportionately impacts specific racial/ethnic groups more than others. Moreover, our group recently identified a disproportionate risk for early death (age < 65 years) among immunodeficiency patients who self-identify as Black compared to White. These data highlight an unmet need to identify and systemically remove barriers to immunodeficiency care, particularly within historically marginalized racial/ethnic groups.

An educational outreach was conducted, including primary care physicians/staff (n = 16) and subspecialty care physicians/staff (n = 24), which encompassed care providers within allergy/immunology (n = 18) and pulmonology (n = 6). Provider demographics were collected. Pre/post education surveys were used to assess immunodeficiency knowledge base and racial/ethnic awareness.
Respondents (n = 40) self-identified as White (68%), Asian (23%), and Black or African American (9%). Self-identified ethnicity was non-Hispanic (94%), Hispanic (3%), or undisclosed (3%). Most respondents were physicians (86%) or advanced practice providers (14%), with a bimodal distribution for years of independent care, <5 years (41%) and >20 years (23%). Pre-survey questionnaires identified a high rate of provider uncertainty as to the role of race/ethnicity in immunodeficiency care. Specifically, most providers (57%) responded 'yes' or 'unsure' when asked whether immunodeficiency affects specific races and ethnicities more than others. This was more prominent for primary care providers (67% 'yes'/'unsure') than allergy/immunology subspecialty providers (42% 'yes'/'unsure'). While providers demonstrated a proficient knowledge base in clinical immunodeficiency (83% correct response by multiple choice questionnaire), analysis of case stems randomized by race (n = 15 cases), suggested a potential referral bias (86% of White patients versus 50% of Black patients referred for subspecialty immune evaluation).
Discrepancy between general knowledge and racial/ethnic awareness in clinical immunology underscores confusion surrounding the role of race and ethnicity in immunodeficiency patient care. Emerging data from randomized case stems suggest a potential referral bias, which may disproportionately and negatively impact racial minority patients with immunodeficiency. Future work will expand to more providers and assess the impact of a dedicated educational intervention on referral bias directly.

Keywords: Educational outreach, Inborn errors of immunity, Racial/Ethnic awareness

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(40)

A case report description of a patient with CVID and Granulomatous Interstitial Nephritis

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Common Variable Immunodeficiency (CVID) can present with complex, multisystemic manifestations, including the rare complication of granulomatous interstitial nephritis. Our case of a 13-year-old Caucasian male with newly diagnosed CVID highlights the diagnostic challenge of distinguishing CVID-associated granulomatous disease from sarcoidosis, particularly in pediatric patients.
He presented initially with rash, pancytopenia, hypercalcemia, elevated vitamin D, hyperuricemia and acute kidney injury (AKI). Despite a broad infectious workup, no significant findings emerged. His rash improved with empiric doxycycline. Hypercalcemia and hyperuricemia were managed with fluid resuscitation, calcitonin, and zoledronic acid. Malignancy evaluation including Positron Emission Tomography (PET) scan, revealed multiple mediastinal hypermetabolic lymph nodes and pulmonary ground glass opacities, with small pulmonary nodules identified by Computer Tomography (CT). He was also noted to have splenomegaly. Peripheral smear, bone marrow biopsy, and genetic testing were non-revealing.
Elevated Angiotensin-Converting Enzyme (ACE) levels (359 U/L) initially suggested sarcoidosis. Renal biopsy, performed due to Stage 2 AKI, revealed non-caseating granulomatous interstitial nephritis. Prednisone treatment for presumed sarcoidosis led to steroid-induced hypertension and mood changes, with minimal improvement both clinically and radiographically.
Pneumocystis jirovecii pneumonia prophylaxis was initiated due to T-cell cytopenia. A lung biopsy, performed due to persistent pulmonary abnormalities, confirmed non-caseating granulomas indicative of Granulomatous Lymphocytic Interstitial Lung Disease (GLILD). Subsequently, the patient developed fever, elevated liver enzymes, and imaging findings suggestive of hepatitis and portal hypertension. Liver biopsy revealed epithelioid non-caseating granulomas with Human Herpes Virus 6 (HHV6) detected by PCR.
Treatment with rituximab, Granulocyte-Colony Stimulating Factor (G-CSF), and mycophenolate mofetil led to the resolution of granulomatous lesions and cytopenias.
This case underscores the critical importance of a thorough differential diagnosis in pediatric CVID patients presenting with granulomatous disease. It highlights the necessity to distinguish between CVID-associated granulomatous complications and sarcoidosis, as this impacts both prognosis and treatment strategies. The rarity of granulomatous interstitial nephritis in pediatric CVID further emphasizes the unique and educational nature of this case, contributing valuable insights to the limited literature on pediatric CVID presentations and management.

Keywords: CVID, Granulomatous Interstitial Nephritis, Pediatric CVID, Sarcoidosis

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(41)

Specifications of ACMG/AMP Variant Curation Guidelines for the Analysis of FOXN1 Sequence Variants: Recommendations by ClinGen's Severe Combined Immunodeficiency Disease Variant Curation Expert Panel

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The Clinical Genome Resource (ClinGen) is dedicated to building an authoritative resource that defines the clinical relevance of genes and variants for use in precision medicine and research. The ClinGen Severe Combined Immunodeficiency Disease (SCID) Variant Curation Expert Panel (VCEP), has undertaken the development of specifications to the 2015 ACMG/AMP Sequence Variant Interpretation Guidelines to increase the accuracy and consistency of variant classification in SCID-related genes. With support from Enzyvant/Sumitomo Pharma, the SCID VCEP generated gene-/disease-informed guideline specifications for variants in the FOXN1 gene. FOXN1 variants can cause a spectrum of diseases ranging from isolated nail dystrophy or T cell lymphopenia, which may improve with age, to congenital athymia with alopecia universalis. Disease severity is influenced by the particular variant and the patient's zygosity; heterozygous individuals typically, but not always, have a less severe presentation than homozygous or compound heterozygous individuals, highlighting the importance of accurate variant classification. To this end, guideline specifications included optimized population frequency, segregation data, computational prediction thresholds, identification of critical protein domains, application of functional assays, and key phenotypic information. Concurrent with guideline specification, a comprehensive literature review, aided by the Hypothes.is web-based annotation tool, identified 51 unique variants, reported in 102 patients of varying severity. Using published variants, internal laboratory data, and ClinVar submissions, the criteria were validated with 30 variants. In comparison to previously reported classifications, these specified guidelines resulted in reduced numbers of variants of uncertain significance through the integration of published data with that of participating diagnostic and research laboratories. Compared to ClinVar classifications, there was clinical concordance of 73% of variants, while eight classifications were clarified using the specified guidelines; three variants with conflicting ClinVar interpretations and five variants of uncertain significance in ClinVar were reclassified to pathogenic/likely pathogenic or likely benign/benign categories. The optimized FOXN1 guidelines and patient repository provide increased specificity and time efficiency, while enabling both publication of 3-star ClinVar classifications from the VCEP as well as independent use by investigators, clinicians, and clinical laboratories, ultimately enhancing clinical decision-making to improve patient outcomes.

Keywords: SCID, Variant classification, ClinGen

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(42)

Severe Combined Immunodeficiency Due To A Monoallelic ITPR3 Variant Presenting With Lymphohistiocytosis And Bone Marrow Failure Treated With Myeloablative Hematopoietic Cell Transplantation

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A 2y-old male with an abnormal TREC screen for NBS SCID presented with acute otitis media (AOM), pan-cytopenia, conical teeth, diffuse lymphadenopathy and hepatosplenomegaly. He had bilateral chronic otomastoiditis, tympanosclerosis and Bell's palsy. Bone marrow (BM) biopsy revealed hypercellularity with erythroid predominance, myeloid left shift, increased B cells with no malignancy and lymphohistiocytic infiltration of the marrow leading to BM failure. Detailed T and B cell immunophenotyping revealed total T and B cell lymphopenia, normal immunoglobulins, absence of naïve CD4+ T cells, expansion of memory CD4+ and CD8+ T cells, increased CD8+ TEMRA, switched memory B cells, which were mostly IgG+, and CD21- B cells, and severely decreased transitional (CD24++38++) and marginal zone B cells. Also, most of his circulating neutrophils were immature and CD10-. Exome sequencing revealed a heterozygous variant in ITPR3 (c.7570C>T, p.Arg2524Cys) encoding IP3PR3 (inositol 1, 4, 5 triphosphate receptor 3), a second messenger that mediates the release of intracellular calcium, essential for T and B cell activation. T cell proliferation to anti-CD3/anti-CD28 stimulation was significantly reduced. Assessment of calcium flux in T cells either after TCR activation (αCD3+αCD28) or with thapsigargin revealed decreased Ca2+ flux consistent with aberrant store-operated calcium entry (SOCE). A few other patients have been described with ITPR3, Arg2524Cys variants indicating it is a mutational hotspot. However, this patient is unique in the presence of lymphohistiocytic infiltration, not consistent clinically with HLH, partially responding to systemic steroids. He underwent a TCR $\alpha\beta$-depleted haploidentical peripheral blood stem cell transplantation (allo-HCT) with a myeloablative conditioning regimen of treosulphan, fludarabine, thiotepa, rATG and rituximab with tacrolimus for GVHD prophylaxis. He developed idiopathic pneumonia syndrome (IPS) post-HCT along with CMV viremia. He is receiving ruxolitinib for the IPS. At D+100, he had evidence of incomplete T cell reconstitution post-HCT with the presence of CD8+ TEMRA and chimerism showed 98% donor cells in CD3 and CD33 fractions. In summary, a pathogenic variant in ITPR3 is associated with SCID, conical teeth and bone marrow failure due to lymphohistiocytic infiltration of BM. Allogeneic HCT with a myeloablative conditioning regimen can potentially correct the underlying immunological defect and BM failure.

Keywords: ITPR3, Severe combined immunodeficiency (SCID), Calcium flux, Lymphohistiocytosis, Hematopoietic cell transplantation, Calcium signaling defect

Disclosures: Rajinder Bajwa: I have relevant financial relationships with proprietary interests: Jazz pharmaceuticals (Advisory Board). Roshini Abraham: I have relevant financial relationships with proprietary interests: Horizon Pharma (Amgen) (Scientific Advisory Board); Sobi (Scientific Advisory Board). The other authors have no financial relationships or conflicts of interest to report.

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(43)
Heterozygous loss-of-function variant in IKBKB presenting with Streptococcus pneumoniae meningitis and bacteremia

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Homozygous loss-of-function (LOF) variants in IKBKB encoding IKK2 have been reported with a SCID-like phenotype. A 9-month-old, fully-vaccinated, former 36-week gestational age female presented with fever, emesis, loose stools, and seizures. She went into cardiac arrest shortly after arrival to the hospital. Following return of spontaneous circulation, she was admitted to the intensive care unit. CT scans demonstrated diffuse paranasal sinus, mastoid and middle ear opacification and diffuse bilateral pulmonary opacities. Blood and cerebral spinal fluid cultures were positive for Streptococcus pneumoniae. She was treated with IV ampicillin. Her course was complicated by acute respiratory distress syndrome, hearing loss and obstructive hydrocephalus. She developed Salmonella enteritis and Escherichia coli urinary tract infection 3 months after initial presentation. Infection history before hospitalization was notable for one upper respiratory infection and wheezing at 6 months old. Family history was unremarkable. She had inadequate (2/23 = 9%) protective Streptococcus pneumoniae titers and inadequate response (5/23 = 22%) following pneumococcal polysaccharide vaccination, though this may be related to young age; low IgA; normal IgG and IgM; elevated CD3+, CD4+, and NK cells; 52.8% CD45RA and 29.3% CD45RO T cells; normal CD19+ B cells; normal CH50. A targeted 429-gene panel for inborn errors of immunity identified a variant of uncertain significance in IKBKB c.554C>A (p.Thr185Asn). Parental genetic testing was negative. Functional assessment of the IkBα degradation after PMA stimulation by flow cytometry showed reduced stimulation/basal median fluorescence intensity (MFI) ratio at 10, 30 and 60 minutes in the patient compared to the experimental control. Stimulation of patient PBMCs with LPS (canonical NFkB pathway) or LPS+ATP (inflammasome activation) revealed relatively decreased IL-6, IL-1B and IL-18 at 2 h and/or 24 h post-stimulation, suggesting impaired activation of these pathways. Given the severe pneumococcal infection with poor antibody response to pneumococcal vaccination, immunoglobulin replacement was initiated. Despite appropriate replacement, recurrent infections continued, including a fungal skin infection. Heterozygous gain-of-function variants in this gene have been reported with a combined immunodeficiency. Hematopoietic cell transplantation (HCT) has been used to treat the homozygous defects, but it may also be necessary in this patient with a heterozygous LOF variant due to severe and recurrent infections.

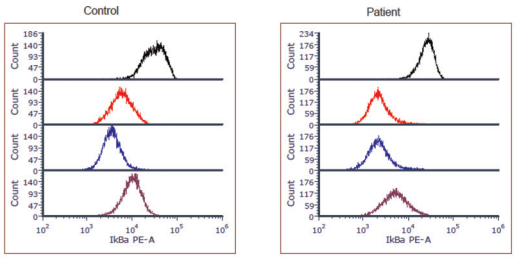

Figure 1A. IκBα Degradation in Patient (P) and Healthy Control (HC)
Black: Unstimulated (basal); Red: 10 minutes post-PMA stimulation; Blue: 30 minutes post-PMA; Purple: 60 minutes post-PMA

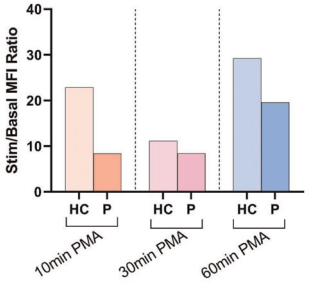

Figure 1B. IκBα Stimulated/Basal Median Fluorescence Intensity (MFI) ratio

Keywords: IKBKB, IKBa, Immunoglobulin replacement

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(44)
Optimization of care for a patient with Schimke Immuno-Osseous Dysplasia (SIOD)

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A 4-year-old male with unknown prior medical history presented to the ED with abdominal distension and facial swelling. He was noted to be small for his age and dysmorphic, although difficult to ascertain given facial swelling. He was diagnosed with nephrotic syndrome and treated with steroids. He had additional episodes of nephrotic syndrome, which led to complications including spontaneous bacterial peritonitis, renal failure, seizures, and cardiac arrest. During an admission, the patient was noted to have a wide-based gait and was diagnosed with hip dysplasia following an orthopedics evaluation. After years of dialysis, he received a renal transplant in 2018.

That same year, the patient underwent genetic testing, which revealed with a homozygous variant c.1933C>T (p. Arg645Cys) in the SMARCAL1 gene, leading to a diagnosis of Shimke Immuno-osseous dysplasia. He was subsequently referred to the immunology team—workup showed lymphopenia (absolute CD3-69 CU MM, CD 4- 36CU MM, CD8-16 CU MM, B-53 CU MM, and NK-24 CU MM. His IgG and IgA were within normal limits, and IgM was low at 16 mg/dL. He was responsive to 6/13 pneumococcal titers. He was started on pneumocystis jiroveci prophylaxis and immunoglobulin replacement therapy.

SIOD is a multisystemic disorder characterized by spondyloepiphyseal dysplasia leading to growth failure, dysmorphia, renal dysfunction, and immunodeficiency, especially T-cell lymphopenia. Inherited in an autosomal recessive pattern, SIOD results from mutations in the SMARCAL1 gene, which is involved in gene transcription. Phenotypic presentation begins in infancy and childhood with death occurring around 10-11 years of life, most frequently due to infection. Due to the multisystemic nature of this disease, management of SIOD requires careful coordination of care amongst various subspecialty teams, including nephrology, hematology/oncology, GI/nutrition, orthopedics, and immunology.

Keywords: Schimke Immuno-osseous dysplasia, Immunodeficiency, SMARCAL1, Lymphopenia, Pediatric immunodeficiency

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(45)

Assessment of TREC-based NBS SCID reporting practices for harmonization of results and interpretation: a global survey

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Introduction: Newborn screening (NBS) for severe combined immunodeficiency (SCID) using T cell receptor excision circles (TREC) has been implemented in all 50 states of the US and many international jurisdictions. SCID is a disorder that requires immediate medical intervention. Accurate interpretation of an abnormal TREC result is crucial. The CIS and APHL (Assoc. of Public Health Labs) jointly formed a working group (SCID Harmonization Initiative) to facilitate comparison of results, enhance quality monitoring, communication and global collaboration between programs for improvement of patient care. The group designed a survey to assess reporting of TREC results and ascertain interest in potential harmonization efforts.

Methods: The survey was sent to all known SCID programs. Only one response was analyzed per region.

Results: 80 responses were received (Figure 1). Of the 39 non-US countries, 15 (38%) reported national universal screening and 24 (62%) regional, pilot or other screening. Twenty-three (31%) reported results as TREC copy

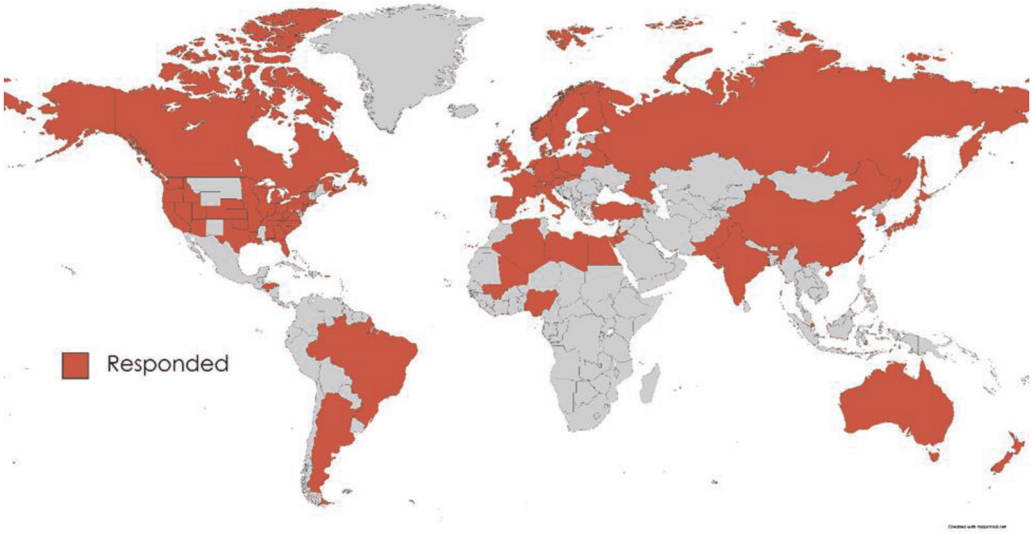

Figure 1. (abstract: 45) Map of responding SCID programs.

numbers/μL blood, 5 (7%) TREC copy numbers/μg DNA, 19 (25%) Ct/Cq, 6 (8%) Multiple of Median (MoM), and 22 (29%) other. Numerical/quantitative results were reported by default by 26 programs (35%), while 33 (44%) provided values on request or only descriptive terms. For full-term babies, 55 (71%) programs reported having an urgent screen-positive designation, while 38 (51%) had an urgent screen-positive designation for premature/low birth weight patients (Figure 2). Forty-three (64%) programs reported as being likely to adopt recommendations to standardize reporting terminology for SCID, while 16 (24%) were somewhat likely and 8 (12%) were not likely. The most common reported barriers to adopting these recommendations were IT requirements (31, 39%), specialist/healthcare provider buy-in (28, 35%) and staff acceptance (20, 25%).

Discussion: The survey confirmed SCID screening is reported quantitatively and qualitatively (with and without interpretative terms e.g. urgent, substantiating the need for harmonized reporting. This variability is directly linked to differences in analytical methods. A majority of programs reported being likely or somewhat likely to adopt harmonization of data reporting and interpretation, however, pragmatic and programmatic barriers exist. This committee is developing harmonization recommendations, which will be tested in the contributing centers who participated in this survey.

Keywords: Newborn Screening, SCID, TREC, T cell lymphopenia, Harmonization, NBS SCID, TREC reporting

Disclosures: Amy Gaviglio: I have relevant financial relationships with proprietary interests: Orchard Therapeutics (Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Spark Therapeutics (Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Takeda (Consultant). Monica Lawrence: I have relevant financial relationships with proprietary interests: Pharmacosmos (Advisory Board); Regeneron (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Takeda (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)). Jennifer Heimall: I have relevant financial relationships with proprietary interests: ADMA (Grants/Research Support Recipient); CSL Behring (Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Regeneron (Grants/Research Support Recipient); Sumitomo (Consulting Fees (e.g., advisory boards)), Grants/Research Support Recipient); UpToDate (Royalties). Jennifer Puck: I have relevant financial relationships with proprietary interests: Invitae (spouse is employee, spouse is employee). Roshini Abraham: I have relevant financial relationships with proprietary interests: Horizon Pharma (Amgen) (Scientific Advisory Board); Sobi (Scientific Advisory Board). The other authors have no financial relationships or conflicts of interest to report.

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(46)

APDS patients with immune complex vasculitis and resolution with leniolisib

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Table 1. (abstract: 46)
Case series summary.

	Case 1	Case 2	Case 3
Current age, Sex	19 y, M	24 y, F	7 y, F
Variant	p.E81 K *PIK3CD*	p.E81 K *PIK3CD*	p.E525 K *PIK3CD*
Clinical Phenotype	• Respiratory infections • EBV Lymphadenitis • Marginal zone B cell lymphoma	• Marginal zone B cell lymphoma	• Recurrent respiratory infections • Bronchiectasis • Lymphadenopathy • Recurrent Staphylococcal skin infections
Immune phenotype (*prior to leniolisib*)	• T cell-penia: CD3 545/μL, CD4 288/μL • Low proportion memory B cells (CD19+27+) 5.2% *(ref. 6.3–52.8%)* • High proportion CD21^{low} B cells 38% *(ref 0.2–8.6%)*	• T- and B-cell penia: CD3 529/ μL, CD4 222/ μL, CD19 108/ μL • Low proportion naïve CD4 16%, *(ref. 22–53%)* • High proportion CD21^{low} B cells 39% *(ref. 0.2–8.6%)*	• B- and NK-penia: CD19 170/μL, CD15/56 50/μL • Low proportion naive CD4 19% *(ref. 42–74%)*, low proportion naive CD8 7% *(ref. 39–73%)*
IgA vasculitis clinical manifestations	Skin-kidney: Purpura/edema Nephrotic syndrome (steroid resistant)	Skin: Purpura/edema	Skin-joint: Purpura/edema Lower extremity arthralgia
IgA vasculitis treatment	Pulse steroids, plasmapheresis, rituximab	Ibuprofen	Chronic systemic steroids (12+ months due to frequent flares), Colchicine
Current treatment	Leniolisib Subcutaneous IgG replacement therapy s/p rituximab	Leniolisib	Leniolisib Subcutaneous IgG replacement therapy

Activated phosphoinositide 3-kinase delta syndrome (APDS) is an autosomal dominant inborn error of immunity due to gain-of-function variants in PIK3CD or loss-of-function variants in the inhibitor subunit PIK3R1. There is heterogeneity in the clinical manifestations of immune dysregulation, including recurrent sinopulmonary infections, bronchiectasis, chronic herpesvirus infections, autoimmunity, lymphoproliferation, and malignancy. IgA vasculitis (also called Henoch-Schönlein purpura) is a form of immune complex-mediated vasculitis that activates complement and attracts neutrophils, macrophages and eosinophils to cause local tissue injury. Immune complex-mediated vasculitides have not yet been described in APDS patients.

We describe a series of three patients with APDS with refractory IgA vasculitis as part of their immune dysregulation phenotype. The severity of IgA vasculitis varied among the three patients and despite different treatment strategies, there was no improvement in their cutaneous disease until treatment with leniolisib. Leniolisib is an inhibitor of PI3K p110δ and an FDA-approved treatment for APDS.

Both ANCA and IgA vasculitis affect small blood vessels in the skin and the glomeruli, though they differ in that IgA vasculitis entails deposition of immune complexes while ANCA vasculitis does not. Patients with ANCA vasculitis in the context of APDS have been described in literature, while to our knowledge neither IgA vasculitis nor any other immune complex vasculitis (e.g., cryoglobulinemic vasculitis, post-strep glomerulonephritis, or hypocomplementemic urticarial vasculitis) has been reported in conjunction with APDS.

PI3K p110δ is broadly expressed across all hematopoietic cells, and while the clinical and immunological phenotypes of APDS have largely focused on T and B cells, it is unclear whether there are also neutrophil or macrophage derangements in APDS. Given that myeloid cells are thought to mediate the damage in immune-complex vasculitides like IgA vasculitis, it is thus surprising that existing immune-complex vasculitis would improve on leniolisib. These cases thus suggest a broader phenotype of APDS beyond the dysregulation of lymphocytes.

Keywords: APDS (Activated phosphoinositide 3-kinase delta syndrome), Leniolisib, IgA Vasculitis, PID, IEI (Inborn error of immunity)

Disclosures: Manish Butte: I have relevant financial relationships with proprietary interests: ADMA (Scientific Advisory Board); Chiesi (Grants/Research Support Recipient); Grifols (Advisory Board, Consulting Fees (e.g., advisory boards)), Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Pharming (Clinical Trial Investigator, Consultant). The other authors have no financial relationships or conflicts of interest to report.

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(47)

Pharmacokinetics, efficacy, and safety of weekly/biweekly dosing of Xembify® in treatment-experienced patients, and loading/maintenance dosing in treatment-naïve patients with primary immunodeficiency

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[5]*Chief Executive Officer/Optimed Research LTD*
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[7]*Allergy and Immunology/Institute for Asthma and Allergy*
[8]*Bioscience Research Group/Grifols*

Background: Subcutaneous immunoglobulin (IGSC) is equally effective as intravenous administration in prevention of infections in primary immunodeficiency (PID). IGSC allows a greater ease-of-use, patient independence, and quality-of-life. Current FDA-approved Xembify® (IGSC-20%) labeling allows flexible dosing frequencies from daily to weekly.

Methods: Multi-center, open-label study comparing IGSC-20% biweekly versus weekly dosing over 32 weeks in PID. Two patient cohorts were enrolled: A) treatment-experienced (n = 27) who were already maintained on IgG replacement therapy for at least 3 months received IGSC-20% at weekly and biweekly dosing intervals for two 16-week consecutive periods; B) treatment-naïve (n = 6) received a loading dose of 5 daily doses of 150 mg/kg IGSC-20% followed by weekly infusions (adjusted to achieve IgG trough value ≥700 mg/dL).

Results: In treatment-experienced patients, the 90% confidence interval (CI) of the geometric least-squares mean ratio for steady-state AUC0-7 days was 1.0030–1.0685 (lower boundary >0.8), indicating that biweekly was non-inferior to weekly administration. Mean-Cmax, median-Tmax, and steady-state mean trough values for IgG were similar after weekly and biweekly dosing. No serious bacterial infections (SBIs) were reported. Annual rate of any infections (per person-year) for biweekly and weekly dosing were similar. Treatment-emergent adverse events (TEAEs) ranged 48.0% (biweekly-dosing) to 59.3% (weekly-dosing) of patients, mostly mild or moderate. There were 3 and 5 severe TEAEs during weekly and biweekly dosing periods, respectively, and 1 severe TEAE in the treatment-naïve cohort; all unrelated to treatment. Suspected adverse drug reactions occurred in 5 (18.5%) and 1 (4.0%) treatment-experienced patients, during weekly-dosing and biweekly-dosing, respectively, and 2 (33.3%) treatment-naïve patients. None were severe. Treatment-emergent serious adverse events (SAEs) were reported in 12.1% of patients and one treatment-experienced patient had 2 hospitalizations for 3 infections. All non-infectious SAEs were unrelated to treatment. Quality of life evaluation (LQI, TQSM-9, and SF-12 from baseline) demonstrated better physical and mental health function associated with IGSC-20%.

Conclusion: Pharmacokinetics of biweekly IGSC-20% administration was noninferior to weekly administration in treatment-experienced PID patients. Biweekly IGSC-20% was as efficacious in preventing SBIs, infections, and hospitalizations for infections compared to weekly, and both produced increased treatment satisfaction. Loading/maintenance dosing in naïve patients was shown to be safe and effective.

Keywords: Subcutaneous immunoglobulin, Primary immunodeficiency, Clinical trial, Pharmacokinetics, Xembify, GC1906

Disclosures: William Lumry: I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Michael Palumbo:

I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Connie Hsu: I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Iftikhar Hussain: I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Donald McNeil: I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Tracy Bridges: I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Mark Scarupa: I have relevant financial relationships with proprietary interests: Grifols (Clinical Trial Investigator). Elsa Mondou: I have relevant financial relationships with proprietary interests: Grifols (Employee). Nisha Nanaware-Kharade: I have relevant financial relationships with proprietary interests: Grifols (Employee). Kim Hanna: I have relevant financial relationships with proprietary interests: Grifols (Employee). Jin Liang: I have relevant financial relationships with proprietary interests: Grifols (Employee). Jennifer Williamson: I have relevant financial relationships with proprietary interests: Grifols (Employee). Montserrat Querolt-Coll: I have relevant financial relationships with proprietary interests: Grifols (Employee). Juan Oliveras: I have relevant financial relationships with proprietary interests: Grifols (Employee).

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(48)

Next-generation sequencing with comprehensive bioinformatics analysis simplifies diagnosis of patients with hereditary angioedema

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Introduction: Hereditary angioedema (HAE) is an autosomal dominant genetic disorder that usually associated with C1-inhibitor deficiency, caused by the presence of pathogenetic allelic variants in the SERPING1 gene. The search for a causal disorder typically involves two separate methods: sequencing to detect the point or small indel disorders and multiplex ligation-dependent probe amplification to detect gross alterations. We propose to use only one method – next-generation sequence (NGS) with comprehensive bioinformatics analysis, which allows us to identify the entire range of variants in the SERPING1 gene.
Materials and Methods: The study included 102 DNA samples of Belarusian patients with HAE, who were diagnosed between 2010 and 2023. We performed NGS of SERPING1 gene in its full length (all exons, introns, promoter, 5′-,3′-UTRs) using Nextera XT (Illumina). Data processing included the stages of pre quality assessment (fastqc), filtering/cleaning reads library (trimmomtic), genome-wide alignment (bwa), variant calling and annotation (gatk, annovar). To detect gross alterations we compared the intensity of exon reads among all DNA samples included in the study with due regard for the depth of reads among samples in one run (bcftools).
Results: A pathogenetic disorder was detected in each DNA sample in the SERPING1 gene. We identified 31 unique variants: 22.6% of them were defects in splice sites (c.550+2 T→C, c.551-1 G→A, c.551-1 G→C, c.51 + 3 A→G, c.890 - 2 A→G, c.551-2 A→C, c.685+1 G→A); 41.9% – missense (c.1478 G→A, c.1202 T→C, c.1493 C→T, c.1037 A→C, c.1001 A→C, c.1058 T→C, c.5 C→T, c.1396 C→T, c.1397 G→A, c.512 C→G, c.728 T→C, c.550 G→A, c.1180 A→C); 22.6% – small deletions (c.520–524 del ATCGC, c.1293 del A, c.1106 del A, c.744–745 del CA, c.249 del T, c.387–388 del CT, c.1191_1192delAC_1193_1194insA); 3.2% – large deletion (4 exon); 9.7% – nonsense (c.289 C→T, c.301 C→T, c.896 G→A).
Conclusion: Our pipeline consists only tools that everyone can download without any fee and our study shoved its effectiveness in extensive analysis of variants in the SERPING1 gene. An adequate combination of bioinformatics tools can simplify the diagnosis, which will be instrumental in prescription of adequate therapy and save the lives of patients with HAE.

Keywords: Hereditary angioedema, C1 inhibitor deficiency, Gene SERPING1, Next-generation sequencing

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(49)

Early-Onset Common Variable Immunodeficiency in a Patient with Heterozygous Variants in Interferon Response-Associated Genes TRAF3 and IRF4

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Background: Common variable immunodeficiency (CVID) is the most common clinically relevant inborn error of immunity. Causes of CVID are poorly understood and the genetic cause remains unidentified in around 85% of the cases. Disturbed interferon response is known to occur in CVID. In this study, we describe a patient with early-onset CVID that displayed

abnormal B cell differentiation, hypogammaglobulinemia, recurrent infections, autoimmune/lymphatic colitis, and lymphoid hyperplasia.
Objectives: This study aims to characterize a novel phenotype associated with heterozygous variants in two interferon response-associated genes, TRAF3 and IRF4.
Methods: Genetic causes of the patient's symptoms were examined with WES. NanoString gene expression analysis was used to study the expression of 50 immune signaling-associated genes. The variants and the characteristics and function of the patient's immune cells were studied with RT-PCR, western blot, flow cytometry, and ELISA.
Results: WES analysis identified one rare missense and one novel protein-truncating variant in cis in TRAF3: NC_000014.8:g.[103336572G>A;103369748C>T], NM_145725:r.[34G>A;1116_1135del], p.[Ala12Thr;Gln373Profs*10]. Additionally, an ultra-rare missense variant was found in IRF4:NC_000006.11:g.398863C>A, NM_002460:r.(673C>A), p.(Pro225Thr). NanoString analysis demonstrated overexpression in type I interferon-stimulated genes in PBMCs. In concordance, stimulating fibroblasts with poly(I:C) revealed pronounced IFN-β excretion in the patient's cells. The immunophenotyping of the patient's lymphocytes revealed abnormal frequencies of B and T cell populations. The patient had normal total amounts of peripheral B cells with an increased proportion of naïve cells, indicating defective B cell function and differentiation. Although in vitro class-switch recombination assay showed that the patient's naïve B cells switch to IgG-producing plasma blasts to a greater extent than controls', IgG ELISA on the culture supernatants indicated nearly absent IgG secretion from the patient's B cells. Further analysis is underway to confirm the role of these variants in disease.
Conclusion: Our results suggest that the possible combined effect of TRAF3 and IRF4 variants disrupts interferon signaling and B cell differentiation. Further studies are required to elucidate how the variants in interferon response-associated genes contribute to CVID.

Keywords: Inborn errors of immunity, CVID, Interferons

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(50)

Utilizing an Ethical Lens to Assess a Series of Patients With X-Linked CGD Who Did Not Undergo Hematopoietic Stem Cell Transplant

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Patients with X-linked Chronic Granulomatous Disease (X-CGD) may be medically managed or receive definitive therapy with hematopoietic stem cell transplant (HSCT). We present three African American males with X-CGD evaluated for HSCT, but ultimately did not receive transplant.
Case 1: 23-month-old presented with right ankle osteomyelitis and large liver abscess. Although HSCT was discussed, no available HLA matched donors were identified in the National Marrow Donor Program. His father was considered for haploidentical transplant. Due to difficulty attending office visits and family meetings, there was apprehension regarding adherence as a transplant candidate. Family decided not to pursue HSCT; he remains on prophylaxis.
Case 2: 19-month-old presented with Serratia marcescens finger osteomyelitis. Sister was not a match so an unrelated donor was pursued. Medical mistrust factored into a lapse of care and delayed HSCT. At 32 months, he was hospitalized for lethargy and CT scans demonstrated hepatic and splenic lesions, mediastinal mass and multiple intracranial abscesses presumed due to Aspergillus fumigatus. These improved over a 3-month hospitalization with treatment, but did not resolve. Due to persistent lesions, he has not received HSCT and remains on antifungal therapy.
Case 3: 3-month-old with tuberculous meningitis, disseminated candidiasis and basal ganglia infarcts. He was deemed not to be a transplant candidate due to poor neurologic prognosis as harms would outweigh benefits. He died at 31 months old.
HSCT may not be the most appropriate management strategy for all patients with X-CGD. There are multiple factors influencing HSCT candidacy, including access, costs, health literacy, adherence, and trust. While developing the patient-physician relationship, physicians should assess factors that may indicate if patients are HSCT candidates. If possible, amelioration of identified barriers should be attempted. This series also demonstrates health inequity manifested by the inability to find an HLA matched donor based on racial and ethnic background. An ethical management strategy is one that seeks to benefit the patient and reduce harms. Prognosis and conditioning toxicity should be considered in the transplant discussion. The decision to undergo HSCT should be made through shared decision-making between patient, family and physician while considering patient safety and quality of life.

Keywords: Ethics, X-linked chronic granulomatous disease, Hematopoietic stem cell transplant, Shared decision-making, Adherence, Healthy equity, Trust

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(51)

Polymicrobial necrotizing pneumonia in a 3-year-old child with near-absent pneumococcal antibody and mitogen interferon-γ responses

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A 3-year-old boy presented with complaints of fever, rhinitis, and cough for 1 week with tachypnea and difficulty breathing for 1 day and was found to have tachypnoea with retractions and left sided reduced breath sounds with bronchial breathing, associated with hepato-splenomegaly and minor cervico-inguinal lymphadenopathy. He had two prior episodes of pneumonia, at 5 weeks old with rhinovirus and Abiotrophia defectiva bacteremia, and at 2 years with rhinovirus and adenovirus. His parents are first cousins. His family is from Kenya, but he was born in the US.

An evolving cavity in his right lung, seen on a chest Xray, prompted a CT scan of the chest, revealing a necrotizing pneumonia occupying almost the entire left lower lobe, with an expansile multiloculated cavitary mass. A chest tube was inserted, draining pus, which grew Kluyvera ascorbata, Enterobacter cloacae and Cronobacter sakazakii group. He was pan-seropositive for Epstein-Barr virus, but not viremic, and his urine was positive for Streptococcus pneumoniae antigen.

Owing to his atypical presentation, an immunodeficiency workup was initiated. He had normal immunoglobulin G/A/M, normal lymphocyte subsets on flow cytometry, and normal dihydrorhodamine-123 testing. Repeated QuantiFERON tests were indeterminate due to absent mitogen interferon-γ responses. Pneumococcal antibody testing revealed poor antibody response to 22 of 23 serotypes, despite receiving 4 doses of PCV 13. Total complement was deficient, but on re-testing was normal. Targeted panel gene sequencing revealed a pathogenic heterozygous variant in the gene encoding complement component C6 (c. 1138del), with 6 other hetero/hemizygous variants of unknown significance in CLPB, G6PD, IL17RC, NLRP1, RELA and RNF31.

Despite having a complex presentation, he responded well to treatment with β-lactam-β- lactamase inhibitors and 3rd generation cephalosporins and was discharged on amoxicillin/clavulanate which he has been tolerating well. He is being worked up for primary immunodeficiency.

With the history of consanguinity, a significant presentation and atypical organisms responding relatively quickly, an immunodeficiency diagnosis is being explored. While many of the variants found were in genes related to inflammation and immune dysregulation, his genetic analysis did not result in a clear genetic diagnosis.

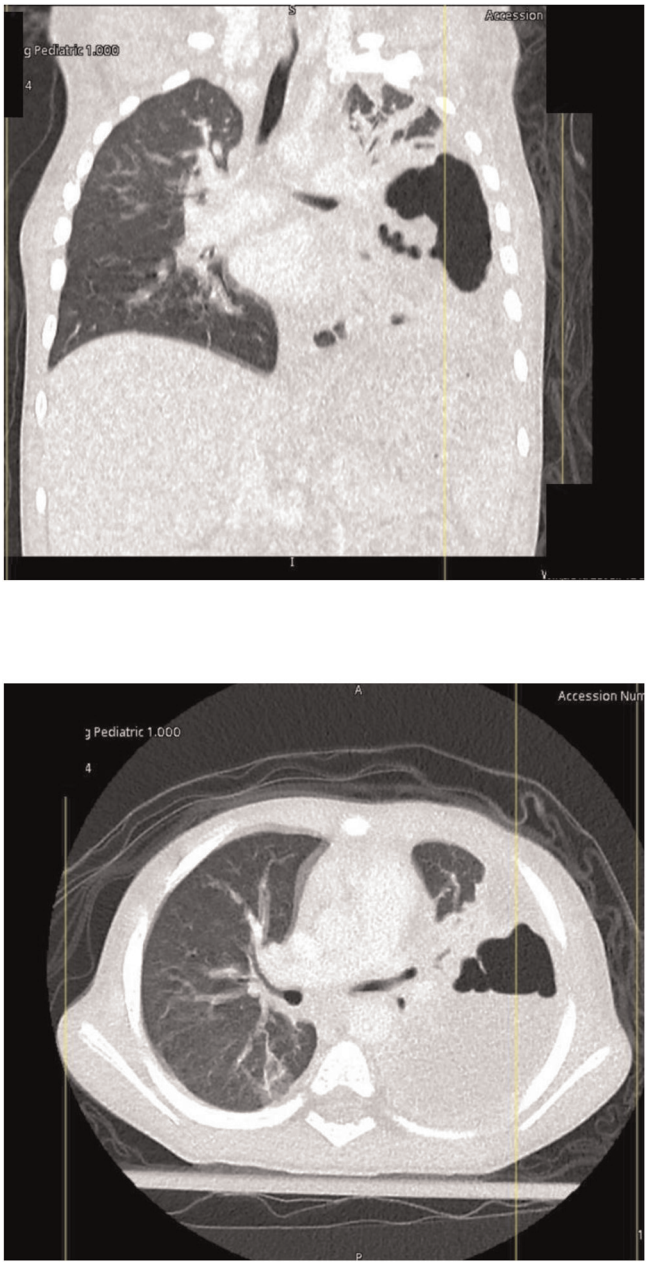

Figure. CT chest with contrast Necrotizing pneumonia occupying almost the entire left lower lobe with an expansile multiloculated cavitary mass.

Keywords: Polymicrobial, Necrotising pneumonia, Pediatric, Immune dysregulation

Disclosures: Heather Lehman: I have relevant financial relationships with proprietary interests: Chiesi (Clinical Trial Investigator); Novartis (Clinical Trial Investigator). The other authors have no financial relationships or conflicts of interest to report.

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(52)

Creation of a multi-institutional, prospective cohort of individuals with inborn errors of immunity

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Introduction: Much of our knowledge about inborn errors of immunity (IEI) is drawn from large patient registries. These cohorts mainly consist of convenience samples, are retrospective or cross-sectional, and have more limited individual-level information.
Objective: We sought to create a robust multi-institutional prospective cohort of individuals with IEI.
Methods: The New England Immune Deficiency Consortium (NEIDC) represents a collaboration between the clinical immunology programs at Massachusetts General Brigham (MGB), Beth Israel Lahey Health (BILH), and Boston Medical Center (BMC). Patients from NEIDC sites were prospectively recruited directly from immunology clinics. We used a shared REDCap database platform to facilitate inter-institutional data alignment. All IEI diagnoses were validated by a clinical immunologist, excluding secondary causes. The database captures detailed data on patients' demographics, immunophenotype (e.g. antibody levels, vaccine responses, lymphocyte counts and subsets, evaluation for monoclonality), genotypes, comorbidities, vaccination status, IEI complications (e.g. infections), and treatments (including antibody replacement therapy, and immunomodulatory therapy).
Results: As of December 2023, the NEIDC cohort consists of 578 unique patients with IEI. Most individuals were aged 18–64 (65%), were female (66%), and self-identified as White (92%). Pediatric patients represented 8% of the cohort. The majority of IEI patients in the NEIDC (97%) were diagnosed with predominantly antibody deficiency (PAD), approximately 66% with common variable immunodeficiency. 6% of individuals had additional features of combined immunodeficiency. Approximately 37% had gene panel or whole exome sequencing performed. In total, a monogenetic etiology was identified in 20% of patients, with the four most common etiologies being TACI deficiency, CTLA4 haploinsufficiency, NFKB1 deficiency, and activated PI3K-delta syndrome (APDS). Assessment of other detailed outcomes is ongoing.
Conclusion: We have created a prospective, multi-institutional cohort of IEI patients that is enriched for adult patients with PAD, providing a rich data resource for IEI research. Recruitment of additional consortium sites and patients is ongoing and will further expand the cohort and range of IEIs captured by the database.

Keywords: Multi-institutional cohort, Predominantly antibody deficiency, Immunophenotype, Genotype

Disclosures: Daniel DiGiacomo: I have relevant financial relationships with proprietary interests: BASF (Consultant); Pfizer (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)). Mei-Sing Ong: I have relevant financial relationships with proprietary interests: Pfizer (Grants/Research Support Recipient). Paul Maglione: I have relevant financial relationships with proprietary interests: Pharming (Advisory Board); Takeda (Grants/Research Support Recipient). Jocelyn R. Farmer: I have relevant financial relationships with proprietary interests: Bristol Myers Squibb (Consulting Fees (e.g., advisory boards)), Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); CSL Behring (Consulting Fees (e.g., advisory boards)); Pfizer (Grants/Research Support Recipient); Pharming (Consulting Fees (e.g., advisory boards)), Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received). The other authors have no financial relationships or conflicts of interest to report.

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(53)

Multidisciplinary Patient Centered Approach to Holistic Care for Adult Immunodeficiencies in Alberta

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Introduction: Global practice analysis has shown adults with Primary and Secondary Immune Deficiency (PID, SID) often receive fragmented service due to the absence of comprehensive, multidisciplinary care. Within Canada, there is a paucity of immunology specialists with expertise to care for adult PID/SID patients.
Aim: In Calgary, Canada, the Collaborative Immunology Program (CIP) was developed to provide comprehensive, multidisciplinary, and holistic care to patients with PID/SID. Our aim is to improve access to immunology expertise, support transition of pediatric immunology patients to adult medicine and disseminate knowledge about PID/SID to other providers.
Method: The CIP consists of (1) The Collaborative Immunohematology Clinic (CIC) and (2) the Subcutaneous Immunoglobulin Home Infusion Program (SCIg-HIP). The CIC provides holistic care for complex PID/SID patients. Patients are seen by a physician and/or nurse practitioner for assessment, diagnosis, and intervention; by a pharmacist to manage and improve access to pharmaceutical therapies; and by a social worker to address effects of chronic illness on mental health. The SCIg-HIP provides support for PID/SID and other patients receiving SCIg therapy at home through infusion training and case management. An administrative clerk supports the CIP by coordinating patient appointments and communications, and a data analyst facilitates research.
Results: This multidisciplinary model results in:

- More comprehensive care addressing physical and mental consequences of patient illness.
- Reduced wait time to access specialty care.
- Increased access to medications previously unavailable in Canada.
- Improved the transition process from pediatric to adult medicine, better continuity of care and family experience.
- Opportunities to improve understanding of immunodeficiencies and patient needs in Canada, including collaboration with the Alberta Children's Hospital immunology team to create a national survey and database.

Conclusion: The CIP is a multidisciplinary, patient-centred, and holistic care program improving access to immunology expertise, the transition

from pediatric to adult medicine, coordinating access to SCIg therapy, and providing awareness of PID/SID. The CIP model is better suited to address the complex needs of PID and SID patients.

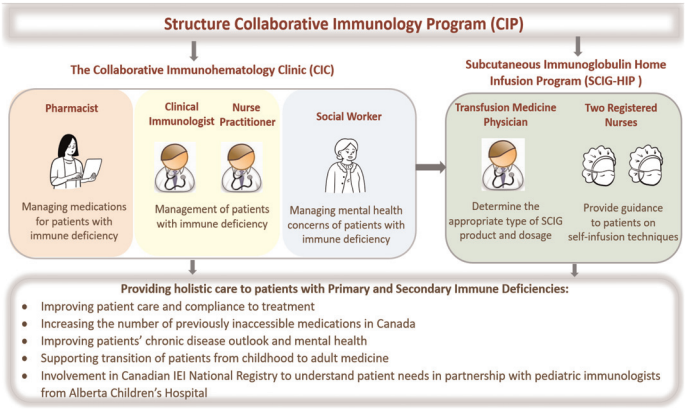

Figure 1. This shows the individuals involved in the CIP and how the CIC and SCIg-HIP work together.

Keywords: Immunodeficiency, Immune deficiency, Primary immune deficiency, Secondary immune deficiency, Collaborative, Multidisciplinary, Pediatric transition, Subcutaneous immunoglobulin

Disclosures: Rebecca Rock: I have relevant financial relationships with proprietary interests: Takeda Canada (Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). The other authors have no financial relationships or conflicts of interest to report.

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(54)

Real-World Evaluation of Healthcare Utilization in Patients with a Positive Molecular Diagnosis for Inborn Errors of Immunity

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Inborn errors of immunity (IEIs) lead to recurrent and often debilitating infections, autoimmunity, autoinflammation, lymphoproliferation and other life-threatening complications. Previous studies have shown that an early diagnosis leads to improved outcomes, decreased costs, and improved quality of life for patients and families. Here, we examined healthcare utilization changes pre- and post-positive molecular genetic testing for germline IEIs.

Komodo Healthcare Map™ insurance claims data were linked to targeted next-generation sequencing panel genetic testing results from Invitae® using a de-identified process. Claims were separated into all-cause (related to any condition) and IEI-related (based on ICD-10 codes for an IEI diagnosis). Patients were tested for up to 574 IEI-related genes. A positive molecular diagnosis (MolDx) was defined as a single pathogenic/likely pathogenic (P/LP) variant in an autosomal dominant or X-linked (XL) gene in males, or two P/LP variants confirmed in trans (homozygous or compound heterozygous) in an autosomal recessive or XL gene in females. McNemar's Test was used to compare pre- and post-testing utilization with $p < 0.05$ considered as significant.

A total of 4,516 patients had genetic testing for IEI with 12 months continuous enrollment both pre- and post-genetic testing report release (index) date. A subset of 320 patients had a positive MolDx. For those, the mean ± SD age of testing was 18.8 ± 17.5, 47.2% were female, with 53.8% commercial payor, 43.7% Medicaid, and 2.5% Medicare. In the pre-to-post genetic testing period, the number of patients with all-cause and IEI-related inpatient hospitalizations significantly decreased (n = 142 to 116, p = 0.008 and n = 78 to 57, p = 0.016, respectively). The number of patients with all-cause office outpatient visits (OOV) decreased pre-to-post from n = 312 to 308, p = 0.34, while IEI-related OOVs significantly increased from n = 167 to 185, p = 0.048.

This IEI-focused study in patients with a positive MolDx showed a decrease in hospitalizations after genetic testing, which may reflect improved medical and pharmacological management via disease-specific care. Future research should examine the broader economic impact following genetic testing in this patient population.

Keywords: Inborn errors of immunity, Healthcare utilization, Molecular genetic testing, Claims data, Hospitalizations, Real-world

Disclosures: Nicholas Rider: I have relevant financial relationships with proprietary interests: Jeffrey Modell Foundation (Grants/Research Support Recipient); NIH/NIAID (Grants/Research Support Recipient); Pharming Healthcare (Advisory Board); Takeda (Advisory Board, Grants/Research Support Recipient); UpToDate (Royalties). Craig Platt: I have relevant financial relationships with proprietary interests: Qiagen (Advisory Board); Sobi (Advisory Board). Yi-Lee Ting: I have relevant financial relationships with proprietary interests: Invitae Corporation (Employee). Michael Khayat: I have relevant financial relationships with proprietary interests: Invitae Corporation (Employee). Chad Moretz: I have relevant financial relationships with proprietary interests: Invitae (Employee). Flavia Facio: I have relevant financial relationships with proprietary interests: Invitae Corporation (Employee). Roshini Abraham: I have relevant financial relationships with proprietary interests: Horizon Pharma (Amgen) (Scientific Advisory Board); Sobi (Scientific Advisory Board). Britt Johnson: I have relevant financial relationships with proprietary interests: Invitae Corporation (Employee).

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(55)

Diagnostic utility of the whole blood transcriptome and mucosal microbiome alterations in patients with primary immunodeficiency

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Early diagnosis of primary immunodeficiency (PID) is critical as diagnostic delay is associated with increased morbidity and mortality. This study examined concomitant features of the whole blood transcriptome and mucosal microbiome of PID patients with the aim to develop a novel diagnostic test for primary antibody deficiency. Whole blood for RNA, and buccal swabs for microbial DNA, were collected from patients diagnosed with predominantly antibody deficiency (n = 62, age 2–67, 32 Female) and age-matched healthy donors (n = 70). The blood transcriptome of each participant was characterised with RNA-seq and >500 genes were identified as significantly differentially expressed between PID patients and healthy controls (p-value < 0.01). Transcriptome information was used to train a predictive model to differentiate patients with PID from the healthy population. In a blinded analysis, 500 representative genes predicted PID with an AUC > 0.85 using a training:testing validation approach. 16S rRNA sequence profiling of the microbiome revealed differences in the microbiome of PID patients, including higher relative abundance of several opportunistic pathogens including Lautropia.
Conclusion; a predictive algorithm using transcriptomic signatures, which we refer to as PrimDx, identified patients with PID with high accuracy. PrimDx may facilitate early diagnosis of PID, allowing timely initiation of treatment and better patient outcomes. Future studies will expand the PID transcriptome reference database to improve the power of this diagnostic approach, incorporating measuring immune modulation of the microbiome, and expanding the application to patients with other immunodeficiency conditions.

Keywords: Transcriptomics, Immunodeficiency, Microbiome, Prediction, Diagnostic, Antibody deficiency

Disclosures: Vanessa Bryant: I have relevant financial relationships with proprietary interests: CSL (Clinical Trial Investigator, Grants/Research Support Recipient, Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)). Mimi Tang: I have relevant financial relationships with proprietary interests: Pfizer (Advisory Board); Prota Therapeutics (Advisory Board, Grants/Research Support Recipient). Jo Douglass: I have relevant financial relationships with proprietary interests: Astra-Zeneca (Advisory Board, Consulting Fees (e.g., advisory boards)); BioCryst (Grants/Research Support Recipient); CSL (Advisory Board, Grants/Research Support Recipient); Equilum (Grants/Research Support Recipient); Grifols (Grants/Research Support Recipient); GSK (Advisory Board, Grants/Research Support Recipient); Immunosis (Grants/Research Support Recipient); Novartis (Advisory Board, Grants/Research Support Recipient); Sanofi-Aventis (Advisory Board, Grants/Research Support Recipient). The other authors have no financial relationships or conflicts of interest to report.

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(56)

Hyper IgE Cases with novel genotypes and phenotypes: How Different Do They Present?

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Hyper IgE Syndrome is a genetic immunodeficiency disorder, caused by either autosomal recessive homozygous or autosomal dominant heterozygous inheritance pattern. STAT3 mutation is mostly presented with eczema, recurrent staphylococcal skin abscesses, and pneumonia leading to pneumatocele formation. Four of our hyper IgE patients with an autosomal recessive novel phenotype or genotype are presented.
A 12-year-old boy from consanguineous parents, presented with ichthyosis, Eczema, sparse, brittle, easily broken hair, failure to thrive (FTT), and upper respiratory tract infections since infancy was referred to our clinic at the age of 5 months. He had received all the vaccines until then, including BCG at birth. He developed axillary and cervical lymphadenitis with fistula formation, hepatosplenomegaly, and high alkaline phosphatase at the age of three years. Lymph node and liver biopsies indicated caseating granulomatous lesions and the culture of the lymph node fistula discharge was positive for BCG. He received anti-mycobacterial for 18 months. Genetic results confirmed Netherton syndrome caused by a homozygous nonsense mutation in the SPINK5 gene (N755Mfs*27), disseminated BCG infection, suggesting a novel phenotype in a known mutated variant.
A ten-year-old girl from consanguineous parents presented with intractable atopy, ichthyosis, recurrent diarrhea, FTT, and mild learning disability. She suffered from vision impairment due to Stargardt's disease, which her mother and other family members had diagnosed. Reported as a complex phenotype with homozygous mutation in exon 5 of the SPINK5 gene, c. 410 +1G>A.
A 30-year-old male from consanguine parents with severe bronchiectasis due to recurrent bacterial and fungal pneumonia, which even led to left pneumonectomy at the age of six. No eczema or atopy or history of abscesses. Had slightly high IgE, low IgM, and functional antibody levels. Reported as a novel genetic homozygous missense mutation in ZNF341 (c.1033T>C). He has been referred to evaluate for the possibility of bone marrow and lung transplantation.
A 5-year-old girl with severe eczematous skin lesions and atopy, retractable staphylococcal occipital skin abscess, High IgE level, hypereosinophilia, and low levels of serum IgM and pneumococcal antibodies. Reported Novel homozygous mutation, as a deletion in exons 1, 2, and 3 of the Dock8 gene.

Keywords: Hyper IgE Syndrome, Phenotype, Genotype, Novel

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(57)

Development and Implementation of the TRIO Health Activated Phosphoinositide 3-kinase Delta Syndrome Characterization and Clinical Outcomes Immunologic Registry (APDS-CHOIR)

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Background: Activated phosphoinositide 3-kinase delta syndrome (APDS) is a rare disorder with autosomal dominant inheritance pattern that leads to immune deficiency and dysregulation. As APDS was first characterized in 2013, there are gaps in knowledge related to the demographic and clinical characteristics of patients affected by APDS. We have developed a patient registry in 2023 to collect clinical and laboratory data for qualifying participants to better understand population characteristics, natural disease history, and clinical outcomes in the US clinical setting.
Methods: Participants qualifying for the study are required to have a genetically confirmed pathogenic variant in PIK3CD or PIK3R1. Participants are followed for up to 3 years after enrollment into the registry. Demographic data including family history of APDS are collected. Prevalent comorbidities and infection history are captured at the enrollment visit, with incident diagnoses during care recorded during follow-up. Data related to APDS-related medications prescribed and discontinued during the follow-up period are collected, including reasons for discontinuation. To generate a clinical profile of the US APDS population, lab results within 1 year prior to enrollment through follow-up period are captured, including immunoglobin results, lymphocyte enumeration (CD4, CD8, and B-cell), serum PCR for EBV and CMV, and general complete blood cell and metabolic panels. Vaccines administered both prior to enrollment and administered during follow-up are collected, including details on whether vaccines were administered as part of vaccine challenge and physician assessment of results. Diagnostic and screening procedures ordered by treating physician are collected to understand healthcare resource utilization of this population.

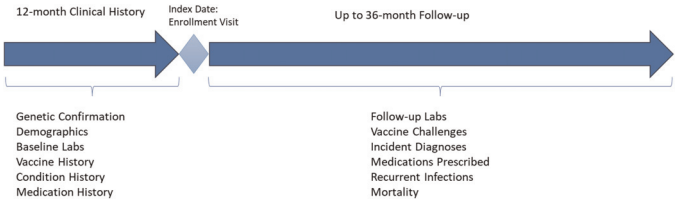

Figure. Study schematic for the APDS-CHOIR Registry.

Results: Currently, 16 participants have been enrolled from large immunology referral centers. Median age at enrollment is 20 years (range 4–61) with 75% female. Participants were diagnosed with APDS a median of 2 years prior to enrollment date, with 38% diagnosed within 1 year prior to index date. The most common clinical manifestations of disease reported are infections (81%), splenomegaly (63%), and allergic disorders (63%).
Conclusion: As the first and only patient registry dedicated to APDS, APDS-CHOIR was developed to better characterize laboratory and clinical characteristics, outcomes, and mortality rates in this rare disease.

Keywords: APDS, Patient registry, Immunodeficiency, Real world evidence, PIK3CD, PIK3R1

Disclosures: Nicholas Hartog: I have relevant financial relationships with proprietary interests: Chiesi USA (Consultant); Horizon Pharma (Scientific Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Pharming Healthcare, Inc. (Consultant, Scientific Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Takeda Pharmaceuticals (Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). Andrew Frick: I have relevant financial relationships with proprietary interests: Trio Health (Employee). Valeria Duran: I have relevant financial relationships with proprietary interests: Merck (Employee); Trio Health (Employee). Kelli Williams: I have relevant financial relationships with proprietary interests: ADMA Biologics (Clinical Trial Investigator); Amgen (Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Cogent Biosciences (Clinical Trial Investigator); Enzyvant (Advisory Board); GSK (Clinical Trial Investigator); Pfizer (Advisory Board); Pharming (Consulting Fees (e.g., advisory boards)), Scientific Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). Brian Hartline: I have relevant financial relationships with proprietary interests: Pharming Healthcare (Employee).

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(58)

Expanding the Phenotype of BCL11B Variants: A Novel Canadian Case Series

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B-cell lymphoma/leukemia 11B (BCL11B) is a gene encoding a zinc finger transcription factor. Variants in BCL11B have been associated with neurodevelopmental disorders, craniofacial abnormalities, immune dysfunction, and more recently significant atopy reported in a single patient. We describe the first case series of three Canadian patients with BCL11B heterozygous variants, all with atopy and varying degrees of immune dysfunction.
P1, a nine-year-old male with environmental and food allergies, eczema, eosinophilic esophagitis, and recurrent infections. He had dysmorphic features including up-slanted palpebral fissures, epicanthal folds, small teeth, and left-sided plagiocephaly.
P2, a 65-year-old male with eczema, rhinosinusitis with nasal polyposis, neutrophilic asthma, recurrent infections, and Large T-cell granular leukemia with no neurological abnormalities.
P3, a seven-year-old male with eczema, features of combined immunodeficiency, alopecia areata, global developmental delay, microcephaly, and cleft palate.
All patients underwent basic immune evaluation including complete blood count, quantitative immunoglobulins, vaccine titres, and flow cytometry. All patients underwent genetic valuation via a Clinical Inborn Errors of Immunity genetic panel, finding variants in BCL11B. P1 was heterozygous for c.2175dupC, p.Phe726LeufsX159. P2 was heterozygous for c.2644C>A, p.Leu882Met. P3 was heterozygous for c.2513A>C, p.Lys838Thr. P1 and P2 had additional variants.
We herein report three novel heterozygous variants in BCL11B involving the C-terminal zinc finger domains, resulting in a phenotype of atopy and varying degrees of immune dysfunction. Our clinical findings broaden the genetic and phenotypic spectrum of patients with variants in the BCL11B gene and strengthen the previously reported association with atopic disease. Variants in BCL11B involving C-terminal zinc finger domains may

lead to a predisposition to allergic disease through not-yet-identified pathways. The variants for P2 and P3 are located within ZnF6 and ZnF5 respectively. Missense variations in ZnF domains have been associated with both impaired canonical DNA binding as well as binding to novel sites. The frameshift mutation for P3 likely affects ZnF4, ZnF5, and ZnF6 resulting in a truncated protein with loss of these domains. We speculate that these variants may be associated with atopy and less severe findings of immune dysfunction potentially relating to the role of BCL11B gene in development of ILC2s and exacerbated TH2 response.

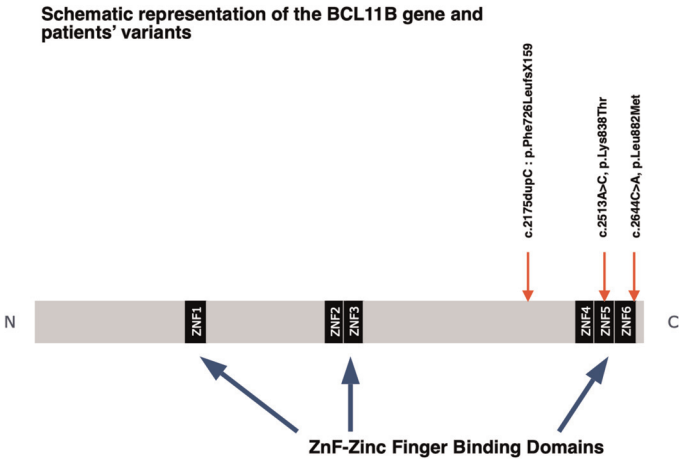

Figure. Schematic protein structure of BCL11B. The position of the variants in this case series are marked with red vertical arrows with respect to the location of the Zinc-Finger C2H2 Domains. Schema generated using Python using Uniprot entry Q9C0K0.

Keywords: BCL11B, Eczema, Atopy, Inborn errors of immunity, Immunodeficiency

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(59)

Comparison of quality improvement programs relevant in next-generation sequence data analysis

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Introduction: Since the advent of next-generation sequence technologies (NGS) the amount of data from various types of research has been constantly growing. Applying NGS platforms in clinical diagnostic allows to determine various kinds of mutations (SNP, INDEL, CNV, etc.), however, the presence of a high error rate (~0.1–15%) determines the requirement for preliminary estimate of obtained libraries. One of the most important step for any research is the qualitative assessment of sequencing libraries and subsequent processing. This stage gives a lot of useful information about overall quality of reads, the presence of adapter sequences, duplicates, etc. In this paper will be presented and tested the most commonly used software solutions: fastp, AfterQC, PRINSEQ++ and SolexaQA++.
Materials and methods: During the work, has been created software environment with all researched modules: AfterQC (v0.9.7), fastp (v0.23.2), PRINSEQ++ (v1.2.4), and SolexaQA++ (v3.1.7.2). Results of each run were written to a log file for later comparison. Automation of the testing process was performed by using additional tools: FastQC (v0.11.9), MultiQC (v1.12) and custom Python (v3.8) script. Testing dataset consisted of 50+ whole exome sequencing libraries.
Results: Wide functionality customization, multithreading support, allows fastp to process NGS data much more faster and with better quality results. The study was carried out on testing dataset with the following time costs: fastp – 12 sec (± 5 sec.), SolexaQA++ – 1 min. 26 sec. (±9 sec.), PRINSEQ++ – 1 min. 39 sec. (±9 sec.), AfterQC – 6 min. 28 sec (±25 sec). Manual quality control of the resulting libraries also confirmed the efficiency of fastp module.
Conclusion: Fastp is the most convenient tool for quality assessment and filtering of NGS data. The fastp-processed libraries had better quality indicators, along with a higher speed of their processing.

Keywords: Next-generation sequence, Whole exome sequencing, NGS data

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(60)

Assessing hyaluronidase-facilitated subcutaneous immunoglobulin 20% (fSCIG 20%) pharmacokinetics, safety and tolerability in primary immunodeficiency diseases: phase 2/3 study design

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Hyaluronidase-facilitated subcutaneous immunoglobulin 20% (fSCIG 20%) is an infusion of human immunoglobulin G (IgG) 20% and recombinant human hyaluronidase (rHuPH20) under development to treat primary immunodeficiency diseases (PIDDs), to achieve a facilitated subcutaneous immunoglobulin treatment with potentially halved infusion volumes versus current therapies. Following a phase 1 tolerability/safety study in healthy adults receiving fSCIG 20%, this phase 2/3, multicenter, open-label, randomized, two-arm crossover PK comparability registrational study (NCT05755035) will assess pharmacokinetic (PK) comparability between fSCIG 20% and fSCIG 10% (HYQVIA) in patients with PIDDs, as well as infection rates, safety, tolerability, immunogenicity and infusion parameters.
Part 1 will include patients aged ≥16 years with documented PIDD diagnoses requiring IgG replacement (Figure 1; patients aged 2–< 16 years will participate in single-arm Part 2). Patients will have received IgG (intravenous immunoglobulin [IVIG] or fSCIG 10%) every 3–4 weeks at a minimum dose of 0.3 g/kg/4 weeks for ≥12 weeks before screening, and have serum IgG trough levels of >5 g/L at screening. Patients receiving IVIG prior to the study will enter a 3-week ramp-up period starting 3–4 weeks after the last pre-study IVIG dose, depending on prior dosing interval. During ramp-up, doses will be increased in a stepwise manner, with patients receiving 33% (3-week dosing) or 25% (4-week dosing) of their maintenance dose in Step 1, followed by 66% and 50% of doses, respectively, in Step 2. All patients will then receive fSCIG 20% or 10% every 3–4 weeks based on their previous IgG treatment interval. The primary endpoint is area under the curve during the dosing interval at steady state (AUC0-τ,ss) based on total IgG levels. Key secondary endpoints include steady state PK parameters, including maximum concentration, time to maximum concentration and half-life, annualized rate of all infections, acute serious bacterial infections and episodes of fever, and healthcare resource utilization. Treatment-emergent adverse events, infusion tolerability, binding and neutralizing anti-rHuPH20 antibody development and infusion parameters will be evaluated.
Overall, 38 patients will be randomized and treated in Part 1.

Study/writing support funder: Takeda Development Center Americas, Inc./ Takeda Pharmaceuticals International AG.

Keywords: Hyaluronidase-facilitated subcutaneous immunoglobulin 20%, Inborn errors of immunity, Randomized clinical trial, Immunoglobulin replacement therapy, Immunodeficiency treatment

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(61)

Time To Diagnosis Matters: Patients With IEI Display Improved Health Status When Diagnosed Early

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Patients with inborn errors of immunity (IEI) have lifelong distinct health complications including severe infections and physical impairments. Studies show that perceived health status is an important predictor of health outcomes. We hypothesize that diagnostic delay adversely impacts patient reported health status. The purpose of this study is twofold: first, we investigated the relationship between age at the time of diagnosis and the reported health status. Secondly, we studied the impact of time to diagnosis upon reported health status.
We accessed the Immunodeficiency Foundation's (IDF) 2017 National Patient Survey dataset and stratified subjects by age at the time of diagnosis: 0–12, 13–30, 31–45, 46–55, 56–65, >65 years of age. The survey coded the health status of the patients on a 5-point scale, 1 for excellent and health and 5 for poor health. For the first analysis, we split patients into 6 groups based on their age at the time of diagnosis: 0–12, 13–45, 46–55,

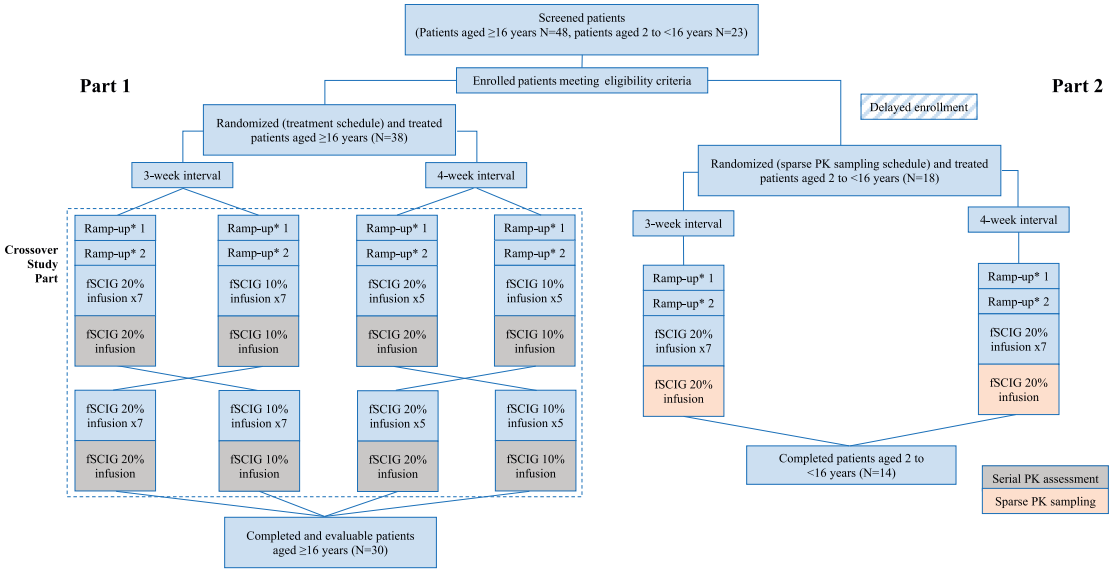

Figure 1. (abstract: 60) Study design schematic. *The ramp-up period will only be utilized for patients pre-treated with IVIG. fSCIG, hyaluronidase-facilitated subcutaneous immunoglobulin; IVIG, intravenous immunoglobulin; PK, pharmacokinetic.

56–65, >65 years of age. For the second analysis, we categorized the patients in 5 groups based on the duration of time to diagnosis: <1, 1–10, 11–25, 26–40, < 40 years elapsed. A single factor ANOVA and Tukey-Kramer post-hoc test was used to compare groups, where $p < 0.05$ was considered significant.

Average health status score across age at diagnosis groups was significantly different (mean 3.26 ± 0.95; $p < 0.0001$). where those diagnosed youngest (0–12 years) differed most from others. Similarly, we found a significant difference (mean 3.25 ± 0.95; $p = 0.0009$.) in the average health status of the patients with the shortest time to diagnosis (<1 yr) and the second group (1–10 yrs), as well as first and fifth group (>40 yr).

This analysis quantitatively validates the widely accepted notion that better health status is associated with an earlier age at diagnosis and shorter diagnostic odyssey among patients with IEI.

Keywords: Primary immune disorder, Inborn error of immunity, Epidemiology, Health outcomes, Patient reported health

Disclosures: Nicholas Rider: I have relevant financial relationships with proprietary interests: JMF/CDC (Grants/Research Support Recipient); NIH/NIAID (Grants/Research Support Recipient, Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)); Pharming (Advisory Board); Takeda (Advisory Board, Grants/Research Support Recipient); UpToDate (Royalties). The other authors have no financial relationships or conflicts of interest to report.

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(62)

Receiving a Diagnosis Improves Patient Reported Health Among Children with Inborn Errors of Immunity

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Patients with inborn errors of immunity (IEI) undergo a unique individual journey to diagnosis and often have symptoms of disease well-before receiving a formal diagnosis. Importantly, patients have a perspective on their health status which can be quantified and tied to clinical outcomes. We sought to understand how perceived health status changed between diagnosed and un-diagnosed IEI patients.

We accessed the Immunodeficiency Foundation's (IDF) 2017 National Patient Survey dataset and stratified subjects by age at 5-year intervals, from 0–90. We then calculated the proportion of subjects in each age bracket with serious infections and determined temporal association between health status measurement and timing of their IEI diagnosis. Reported health scores (RHS; coded on a 5-point scale; 1 = excellent; 5 = poor) were compared among those suffering infections with and without a formal diagnosis. From this, we focused our analysis on the 0–5 yr ($n = 564$) age group, which had the largest number of diagnosed patients. Secondarily, we investigated burden of care by comparing RHS between subjects who had seen ≥ 5 physicians to those who saw fewer before diagnosis. A two-tailed t test was used to determine significant differences in mean RHS across groups with $p < 0.05$ considered significant.

Of 564 patients with infections in the 0–5 age range,166 (29%) had received an IEI diagnosis. We found a significant difference in reported health scores when comparing diagnosed (dx) to undiagnosed (udx) patients, with infections, in this age group (dx = 2.8 ± 0.94 vs udx = 3.5 ± 0.92; $p < 0.0001$). We also found a significant difference between patients who < 5 physicians ($n = 886$) compared to those who saw ≥ 5 ($n = 252$) prior to diagnosis (3.18 ± 0.91) vs. 3.52 ± 0.81 $p < 0.0001$).

Patients with a diagnosis who saw fewer physicians leading up to diagnosis had significantly better RHS. Our work validates the assumption that a

compressed diagnostic odyssey resulting in diagnosis leads to improved reported health and potentially better outcomes.

Keywords: Primary immune disorder, Inborn error of immunity, Patient reported health

Disclosures: Nicholas Rider: I have relevant financial relationships with proprietary interests: JMF/CDC (Grants/Research Support Recipient); NIH/NIAID (Grants/Research Support Recipient); Pharming Healthcare (Advisory Board); Takeda (Advisory Board, Grants/Research Support Recipient); UpToDate (Royalties). The other authors have no financial relationships or conflicts of interest to report.

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(64)

Clinical and functional assessment of a novel PIK3R1 variant in a patient with immunodeficiency

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Inborn errors of Immunity have been identified in more than 500 genes as cause of Immune deficiencies. Activated Phosphoinositide 3 Kinase Delta (PI3Kδ Syndrome (APDS) is one of such rare conditions, first characterized in 2013. PI3Kδ is primarily expressed in Immune cells and is composed of a catalytic subunit p110δ and a regulatory subunit p85α. Causative gain of function (GOF) mutations in PI3KCD, the gene encoding for p110δ, and loss of functions (LOF) mutations in PI3KR1, the gene encoding for p85α have been associated with a common clinical phenotype of primary immune deficiency (PID) with increased susceptibility to infections, bronchiectasis, autoimmune features, cytopenias, elevated serum IgM and a lymphoproliferative clinical picture. GOF mutations in p110δ are known as APDS1, and LOF mutations in p85α are known as APDS2. To date, most causative known mutations in p85α are affecting the splice site of exon 11, leading to skipping of exone 11, and two other known mutations in the inter-SH2 (iSH2) domain interfering with the catalytic subunit p110δ inhibition. We describe here a patient with mixed Cellular and Humoral Immunodeficiency, who has been on replacement Immunoglobulin therapy for several years. Additional Clinical findings associate extensive pulmonary lymphoproliferative disease bilaterally and splenomegaly. Laboratory data indicated reduced number of Naïve T-cells, and B-cells, CD4+ Lymphocytopenia with a reversed ratio of CD4/CD8. A clinical screening using an APDS score card (previously described) met the threshold for concern (score of 12 out of 30). Genetic sequencing identified a novel mutation in PIK3R1, Exon 3, c.399C>G Ile133Met, classified as “Variant of Unknown significance”.
The mutation was identified in a highly conserved RhoGap Domain of p85α. Point mutation in the RhoGap domain may lead to loss of function in other proteins. Iin PIK3R1, the RhoGap domain binds Phosphatase and Tensin Homolog (PTEN), a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase, preferentially dephosphorylating PIP3 to PIP2, decreasing the signal production by activated PI3K.
Functional AKT assays are being pursued to validate the causative nature of the identified mutation. Patient was initiated on Leniolisib (recently FDA approved for APDS). 4 weeks following leniolisib treatment we have noted increase in memory T-cells, and in total B-cells.

Keywords: APDS, Primary immunodeficiency, Lymphoproliferation

Disclosures: Frank Lichtenberger: I have relevant financial relationships with proprietary interests: Pharming (Consulting Fees (e.g., advisory boards), Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). Daniel Suez: No financial relationships or conflicts of interest.

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(65)

High Proportion of Vitamin C Deficiency “Scurvy”, in Immunodeficiency Population

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Common Variable Immunodeficiency (CVID) is a complex and heterogeneous clinical condition defined by dysfunction of the humoral Immune System. Necessary features of this condition include history of recurrent infections, low Immunoglobulins, and Failure to mount a specific Immunoglobulin response to provocation with vaccine. However there is lack of predictability regarding autoimmune or autoinflammatory conditions, which are estimated to occur in at least half of patients with CVID. Gastrointestinal pathology is very common, but comprehensive studies of micronutrient status is lacking.
Vitamin C is a necessary cofactor for a diverse number of clinical functions, including but not exclusive to wound repair. Additionally this co-factor is directly involved and consumed in a multitude of host defense mechanisms. Deficiency can lead to increased infections through disruption of the skin barriers. Furthermore, frequent infections can increase vitamin C deficiency due to increased metabolism, creating further difficulty.
Here we describe a retrospective review of single center, with patients recviewed for recurrent infections or Immune dysfunction. When there was noted concern for barrier or mucosal delays to healing, patients were tested for Vitamin C levels. We retrospectively examined all patients that were checked for Vitamin C deficiency. Of the 87 patients cases reviewed, 27 had CVID or Combined Immunodeficiency, and 60 IgA deficiency, or did not have Primary Immunodeficiency. Comparing the two groups, the patients with CVID/CID had statistically lower levels of Vitamin C 0.72 ± 0.20 mg/dl versus 1.08 ± 0.15 mg/dl, $p = 0.004$. The incidence of Vitamin C deficiency was 37% in the group with CVID/CID, and 5% in the group without CVID/CID. Vitamin B12, folate, and Vitamin E, levels were checked frequently, but no pattern of deficiencies were noted.
While the true mechanism is unresolved, there appears to be significantly higher rate of Vitamin C deficiency specific to the CVID/CID population. Given the importance to host defense and wound repair, this finding clearly requires further review and evaluation.

Keywords: CVID, Combined immunodeficiency, Scurvy, Micronutrient deficiency

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(66)

Abnormal TRECs and transient lymphopenia associated with Twin anemia polycythemia sequence

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Introduction: Newborn screening identifies neonates at risk of severe combined immunodeficiency by measuring T-cell receptor excision circles (TRECs) that are by-products generated during the maturation process of T-cells. Abnormal TRECs may also have many other underlying etiologies including maternal immunosuppression or preterm birth. Twin anemia polycythemia sequence (TAPS) is a form of twin-to-twin transfusion syndrome (TTTS) that can complicate monochorionic twin pregnancies, characterized by equivalent amniotic fluid volumes for both fetuses and multiple small arteriovenous, placental anastomoses. Here we describe a case of TAPS resulting in abnormal TRECs and in one male twin while sparing his recipient brother.

Case description: A pair of monochorionic diamniotic male twins were born at 31 weeks' gestation, and twin B was referred to our Primary Immunodeficiency center after initial newborn screening revealed average TRECs of 0. Of note, twin A had normal TRECs on his newborn screen. The pregnancy was complicated by TAPS, and twin B was the donor twin. Although the TRECs normalized to an average of 554 after a repeat newborn screening sample was sent 48 hours later, post-natal bloodwork revealed anemia, and full T cell subsets obtained on the baby were noted to have CD3 low at 1377 cells/μL (2500–5500 cells/μL), CD4 low at 1293 cells/μL (1600–4000 cells/μL), and CD8 low at 88 cells/μL (560–1700 cells/μL). Lymphocyte mitogen stimulation assay was within normal limits on twin B. While Twin A was discharged from the NICU after 2 weeks, Twin B was hospitalized for almost two months, requiring extended oxygen support, several blood transfusions and antibiotics for pneumatosis intestinalis. Moreover, he was readmitted to the hospital due to difficulty breathing and required nasal IMV for bronchiolitis. The patient followed-up in our immunology clinic and was found to have persistent low T cell lymphopenia, which continues to improve on subsequent measurements.

Discussion: Donor twins in TAPS and TTTS may be at increased risk of lymphopenia compared to their recipient twins, and this should be considered in the context of abnormal TRECs on newborn screening.

Keywords: TRECs, Lymphopenia, TAPS, Twin anemia polycythemia syndrome, Newborn screening

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(67)

A Case of Lamotrigine-Induced Lymphadenopathy

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Lamotrigine is used to treat seizure disorders and psychiatric conditions. The mechanism of lamotrigine-induced lymphadenopathy, or pseudolymphoma, is unknown. We describe lymphadenopathy with unique features in a 61-year-old woman on lamotrigine, which resolved upon medication cessation.

A 61-year-old woman with depression and schizoaffective disorder had been on lamotrigine for over 10 years. She had fever, night sweats, and 50-pound weight loss starting two years prior to presentation. A right upper lobe mass with mediastinal and axillary lymphadenopathy was discovered with transbronchial biopsies suggesting organizing pneumonia. Although the lung imaging resolved with antibiotics, she felt poorly with chronic fatigue and bone pain. Waxing and waning axillary, retroperitoneal, and iliac lymphadenopathy persisted. Axillary lymph node fine needle aspiration and retroperitoneal and iliac excisional biopsies all showed follicular hyperplasia (Figure 1). White blood cell counts were normal aside from mild neutropenia. IgM was mildly low (30 mg/dL), with normal IgG and IgA. Total CD 19+ B cell counts were elevated at 1312 cells/μL, with normal CD8+ and CD4+ T cell counts. Unswitched memory B cells were mildly low at 1.5% (ref 3.8–52.7%) with normal switched memory, transitional, and immature Cd38lo/CD21lo B cells and plasmablasts. There was an unusual population of B lymphocytes that were slightly larger, CD20 bright and IgD positive (Figure 2). Bone marrow biopsy was unremarkable. Quantitative EBV PCR was undetectable. Rheumatologic evaluation was unremarkable outside of intermittently positive ANA, positive HLA-B27 antigen, and mildly elevated CPK (Table 1). Normal double negative T cell counts and CD40L expression were found. Heterozygous variants of undetermined significance in AP3D1, PRKDC, RNASEH2B and one increased risk allele in NOD2 were found. At 3-months off of lamotrigine, her lymphadenopathy significantly improved upon repeat PET-CT scan. Three months later, the patient had reduced pain, weight gain, and improved energy.

There are many possible mechanisms for lamotrigine-induced lymphadenopathy. For example, lamotrigine induces B-cell lymphoma-2 (Bcl-2) promoter activity. Evaluation of Bcl-2 levels, functional analysis of the unusual B cell population, assessment of PRKDC and RNASEH2B expression, and in-vitro examination of lamotrigine's effect on B cells could help to explain and possibly predict this rare side effect.

Figure 1: Para-aortic and inguinal excisional biopsies in a case of lamotrigine-induced lymphadenopathy

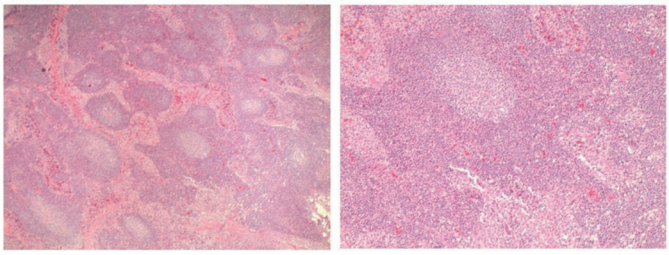

Figure 1: Para-aortic and inguinal excisional biopsies showing reactive lymph nodes with follicular hyperplasia with no germinal centers.

Figure 2: B cell populations in a patient with lamotrigine-induced lymphadenopathy

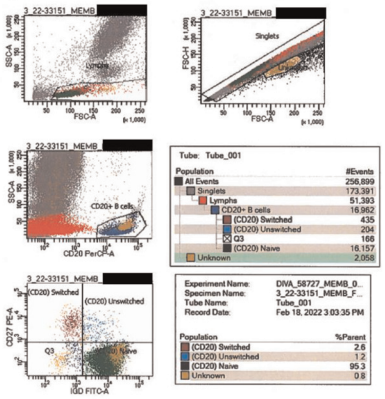

Figure 2: B cell flow cytometry showing a population of lymphocytes that are slightly larger, CD20 bright, and IgD+.

Table 1.
Laboratory data in a case of lamotrigine-induced lymphadenopathy.

Laboratory test	Result	Reference
White blood cell count	4.7 K/μL	3.5–11.5 K/μL
Hemoglobin	14.0 g/dL	12–16 g/dL
Platelets	300 K/μL	150–400 K/μL
Absolute neutrophil count	2200 cells/μL	2300–6700 cells/μL
Absolute lymphocyte count	1900 cells/μL	800–3200 cells/μL
Absolute eosinophil count	0–450 cells/μL	0–400 cells/μL
Creatinine	1.2 mg/dL	0.5–1.3 mg/dL
AST	12 U/L	10–40 U/L
ALT	15 U/L	10–40 U/L
HIV Antigen/antibody screen	Nonreactive	Nonreactive
Quantiferon-TB Gold Plus	Negative	Negative
Hepatitis C antibody	Nonreactive	Nonreactive
Hepatitis B surface antigen	Nonreactive	Nonreactive
Anti-nuclear antibody	1:80 speckled-> **1:640, speckled**	<1:80
Extractable nuclear antigens	7.12	<20
Anti double-stranded DNA antibody	1:10	<1:20
CPK	**167 U/L**	26–140 U/L
HLA-B27 antigen	**Positive**	Negative
Myositis autoantibody panel	Negative	Negative
Rheumatoid factor	<10.0 IU/mL	0–13.9 IU/mL
Anti-CCP IgG/IGA	4.45	<20
Beta 2 GPI IgA/IgG/IgM	9	<20
Anti-SCL 70 antibody	9.6	<20
Cryoglobulin screen	0%	0.0–0.1%
Lupus anticoagulant	Negative	Negative
Lactate dehydrogenase	169 U/L	91–180 U/L
Beta-2-macroglobulin, serum	**2.54->3.21 mg/L**	<2.51 mg/L
HS CRP	0.10 mg/dL	0.0–0.4 mg/dL
ESR	8 mm/hr	0–30 mm/hr
Vitamin D	50.3 ng/mL	20–100 ng/L
Ferritin	**2.7 ng/mL**	11.0–306.8 ng/mL
Iron	**27 μg/dL**	28–170 μg/dL
Total iron binding capacity	**527 ug/dL**	261–478 μg/dL
Fibrinogen	338 μg/dL	150–430 μg/dL
Urinalysis	No abnormalities	—
IgM	**28->36 mg/dL**	44–266 mg/dL
IgG	**587**->814 mg/dL	700–1620 mg/dL
IgA	170 mg/dL	50–462 mg/dL
IgE	23.4 kU/L	0–100 kU/L
Diphtheria antitoxoid	0.21 IU/mL	>0.10 IU/mL
Streptococcus pneumoniae antibody	**12/23 >1.3 μg/mL (borderline protective)**	16–23/23 >1.3 μg/dL
Tetanus antitoxoid	1.53 IU/mL	>0.10 IU/mL
Absolute CD3+ T cell count	1742 cells/μL	678–2504 cells/μL
Absolute CD4+ T cell count	1134 cells/μL	414–1679 cells/μL
Absolute CD8+ T cell count	496 cells/μL	162–1038 cells/μL
Absolute CD19+ B cell count	**1312 cells/μL**	96–515 cells/μL
Absolute CD16+/CD56+ NK cell count	235 cells/μL	45–523 cells/μL
Lymphocyte stimulation to mitogen	Normal	Normal
Lymphocyte stimulation to antigen	Normal response to candida **Low response to tetanus**	Normal response to candida and tetanus
Th1 (IFNγ+) cells	26.3%	>5.3%
Th17 (IL-17+) cells	0.7%	>0.3%
Double negative T cell count	2.4%	<2.5%
CD40L assay	Normal expression of CD40L on activated T cells	Normal expression of CD40L on activated T cells
CD38hi/IgMhi (transitional B cells)	1.2%	0.3–9.2%
CD38hi/IgMlo (plasmablasts)	0.1%	0.1–4.7%
CD38lo/CD21lo (immature B cells)	2.3%,	0.5–8.0%
CD27/IgD+ (unswitched memory B cells)	**1.5%**	**3.8–52.7%**
CD27+/IgD- (switched memory B cells)	2.3%	1.9–30.4%^
CD27-/IgD+ (Naïve B cells)	**95.3%**	24.4–90.6%
IL-12	**34.69 pg/mL**	0–8.4 pg/mL
TNFα	**107.17 pg/mL**	0–22.3 pg/mL
IL-2	**51.78 pg/mL**	0–60.8 pg/mL
IFNγ	**392.62 pg/mL**	0–24.1 pg/mL
IL-10	**138.12 pg/mL**	0–19 pg/mL
C3	120 mg/dL	66–162 mg/dL
C4	27.3 mg/dL	19–52 mg/dL
Uric acid	3.8 mg/dL	2.6–7.2 mg/dL
EBV VCA Ab IgM	<36.00 U/mL	<36.00 U/mL
EBV VCA Ab IgG	**>750.00 U/mL**	<18.00 U/mL
EBV EBVA AB IgG	**300.00 U/mL**	<18.00 U/mL
EBV PCR Quantitative	<390 copy/mL	<390 copy/mL
High resolution protein electrophoresis	Total protein 6/5 g/dL Albumin 4.4 g/dL Borderline hypogammaglobulinemia No M spike	No M spike
Serum immunofixation	No monoclonal proteins identified	No monoclonal proteins identified
Leukemia/lymphoma phenotyping by flow cytometry	No abnormal myeloid, B cell, T cell, or NK cell population identified	No abnormal myeloid, B cell, T cell, or NK cell population identified
CT thorax	No evidence of right lung mass. Residual scarring in the right lung. Mild small airways disease in the lower lung suggestive of asthma or aspiration. Large hiatal hernia.	
Bone marrow biopsy	Normocellular marrow for age (approximately 50%) showing trilineage hematopoiesis to maturation. Negative for involvement by a hematopoietic neoplasm	
Primary immune disease genetic panel	*NOD2* c.3019dup (p.Leu1007Profs*2) heterozygous, increased risk allele *AP3D1* c.2648C>G (p.Pro883Arg), heterozygous, uncertain significance *PRKDC* c.1968A>C (p.Gln656His), heterozygous, uncertain significance *RNASE* c.787A>G (p.Thr263Ala), heterozygous, uncertain significance	

(continued)

Table 1. (Continued)

Laboratory test	Result	Reference
PET CT whole body #1 (during lamotrigine)	Waxing and waning size and metabolic activity of multiple lymph nodes including increased size and metabolic activity of multiple bilateral axillary, abdominal, and pelvic nodes with decreasing size and metabolic activity of the paratracheal right hilar lymph nodes.	
PET CT whole body #2 (3 months post lamotrigine cessation)	Previously appreciated hypermetabolic activity in both axilla has completely resolved. There is minimal residual activity within a single enlarged right external iliac node.	

Keywords: Lymphadenopathy, Lamotrigine, Adverse drug reaction, Follicular hyperplasia

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(68)

LRBA dysfunction: a new diagnostic entity caused by biallelic LRBA missense variants results in reduced CTLA-4 expression and autoimmunity

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LRBA (lipopolysaccharide-responsive and beige-like anchor) interacts with CTLA-4 and promotes its surface expression as opposed to lysosomal degradation. CTLA-4 is constitutively expressed in regulatory T cells (Tregs) and can be induced in conventional T cells. CTLA-4 stimulates a suppressive function in Tregs by competing with CD28 to bind the costimulatory receptors CD80 or CD86 on antigen presenting cells. LRBA deficiency is a monogenic disorder caused by biallelic loss of function variants in LRBA resulting in lymphoproliferation and multi-system immune dysregulation. CTLA-4 haploinsufficiency is another disorder with a similar pathogenic mechanism and phenotype. Both can be treated with abatacept, a CTLA-4-Ig fusion protein.

We have identified 5 patients from the CIS listserv with biallelic missense variants in the LRBA gene, who have an attenuated LRBA deficiency phenotype, presenting with thrombocytopenia, hemolytic anemia and colitis. These patients all have normal expression of the LRBA protein on clinical flow cytometry testing. Several of the missense variants are shared between unrelated patients in the cohort indicating a mutational hotspot or founder effect for those with shared ancestry. We have developed a new flow cytometry assay to measure CTLA-4 surface and intracellular expression, which were both reduced in our cohort, indicating that the LRBA missense variants downregulated CTLA-4 expression. Our data suggests a previously undescribed diagnostic possibility, LRBA dysfunction, where an abnormal LRBA protein is causing degradation of CTLA-4 and resulting in autoimmunity. Possible explanations would include increased turnover of CTLA-4, the LRBA protein not co-localizing properly or reduced LRBA protein stability.

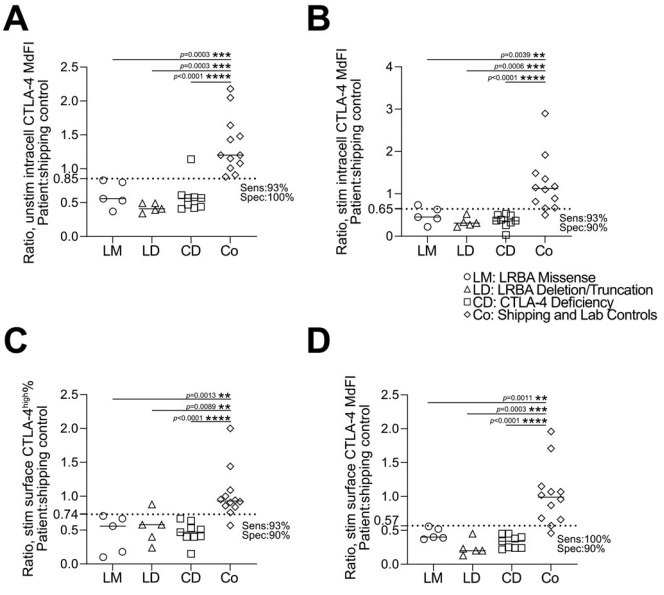

Figure 1. Reduced Treg CTLA-4 levels after TCR stimulation or mock stimulation for 5 patients in LRBA missense cohort (LM) compared with LRBA deficiency positive controls (LD), CTLA-4 haploinsufficiency positive controls (CD) and shipping negative controls (Co). LM: LRBA missense cohort of 5 unrelated individuals (each patient had biallelic missense *LRBA* variants in varying combinations of c.2582T>C, p.(Leu861Pro); c.3499A>G, p.(Thr1167Ala); c.2209G>A, p.(Val737Ile); c.392T>C, p.(Val131Ala); c.5941C>T, p.(Arg1981Cys); c.4927A>G, p.(Thr1643Ala), c.3095G>A, p.(Gly1032Asp); c.1859C>T, p.(Thr620Met). LD: LRBA deficiency with biallelic loss of function *LRBA* pathogenic variants. CD: CTLA-4 deficiency with heterozygous

pathogenic *CTLA4* pathogenic variants. Co: controls, where shipping controls were not sent, a lab control bled on the same day as the patient was used. (A) Intracellular CTLA-4 MdFI (median fluorescence intensity) in mock stimulated Tregs. (B) Intracellular CTLA-4 MdFI in stimulated Tregs. (C) Percentage of stimulated Tregs expressing CTLA-4^{high} (D) Surface CTLA-4 MdFI levels on stimulated Tregs. Values presented as a ratio of patient:shipping control sent together. Dotted lines display cutoff values corresponding to the highest predictive accuracy with sensitivity and specificity values noted. P values calculated using unpaired Mann-Whitney t-test. Lines represents median.

Keywords: LRBA, Immune dysregulation, CTLA4, IEI, Autoimmuinity

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(69)

Expanding the phenotypic spectrum of POP1 mutations: Identifying a child with immunodeficiency and hypereosinophilia

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Background: The POP1 gene encodes a protein subunit present in RNase MRP, an endoribonuclease functioning in mitochondrial RNA processing, and RNase P (RMRP), a ribonuclease that processes precursor tRNA. Defects in POP1 have been associated with anauxetic dysplasia, hallmarked by short stature, skeletal abnormalities, and intellectual disability. There have been scant reports on the immunological effects of POP1 variants, unlike the well documented effects of the pathogenic variants in RMRP that cause Cartilage-Hair Hypoplasia (CHH). Here, we report a patient with POP1 biallelic variants presenting with skeletal dysplasia, immunodeficiency, severe eczema, and hypereosinophilia.
Case Presentation: A 3-year-old male born preterm (36wk+5d) presented with a history of skeletal dysplasia, metopic craniosynostosis, Hirschsprung's disease, laryngomalacia, and severe eczema. His infectious disease history was significant for recurrent staphylococcal skin infections and RSV pneumonia at 10 months, which required a prolonged PICU admission. Immunologic evaluation was notable for hypereosinophilia (2.17 × 103/μl), low IgG (380 mg/dL) and elevated IgA (365 mg/dL), IgM (191 mg/dL), and IgE (75.3 mg/dL). Vaccine titers were protective to 3/22 pneumococcus serotypes and absent to tetanus and diphtheria. Lymphocyte analysis showed normal T/B/NK cell counts, and decreased percentages of CD27+IgM-IgD- switched memory B cells (0.8%), CD19+CD38+IgM- plasmablasts (2.5%), and naïve CD4+ T cells (58.8%). Mitogen stimulation initially demonstrated decreased CD3+ T cell proliferation to phytohemagglutinin that later normalized. Whole exome sequencing showed a homozygous variant of unknown significance in POP1, c.449G>T(p.Arg150Leu), CADD:31, located in a domain that had been reported in a milder form of anauxetic dysplasia, homozygosity was not detected in general population. Immunodeficiency was managed with immunoglobulin replacement therapy (IGRT) and prophylactic Trimethoprim/sulfamethoxazole. Additionally, he was referred for evaluation for bone marrow transplant. Since initiation of IGRT and Trimethoprim/sulfamethoxazole prophylaxis, the patient had no further infections.
Conclusion: Although the association of POP1 variants with skeletal abnormalities is well-established, there have been limited studies on their immunological consequences. In this case, we observed features of immune dysregulation, such as severe eczema and hypereosinophilia in a patient with POP1 variants. These findings, in conjunction with impaired humoral and cellular functions, suggest that POP1 may have overarching immunologic roles that intersect with CHH.

Keywords: POP1, Anauxetic dysplasia, Cartilage hair hypoplasia, Immune dysregulation, Immunodeficiency

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(70)

The Development of a Cost-Effective and Accurate Screening Method for Diagnosing CD3δ Severe Combined Immune Deficiency

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Introduction: CD3δ severe combined immune deficiency (SCID) in the Mexican Mennonite population is the result of a homozygous founder pathogenic variant (c.202C>T) within the CD3D gene, resulting in the complete absence of the CD3δ protein and absence of T cells. Patients are susceptible to lethal infections, leading to infant mortality if not treated by allogeneic hematopoietic cell transplantation. Timely diagnosis is crucial for early therapeutic intervention to mitigate disease consequences. Current testing methodologies are costly, time-consuming, and require outsourcing of sample preparation, processing, and analysis to genomic companies.
We aimed to develop a screening test tailored for regions with constrained medical resources. To achieve this, we developed One-pot Dinucleotide signaTurE CapTure (One-pot DTECT) a cost-effective, rapid, PCR screening methodology capable of identifying the c.202C>T mutation. Methodology has previously been validated for sickle cell disease.

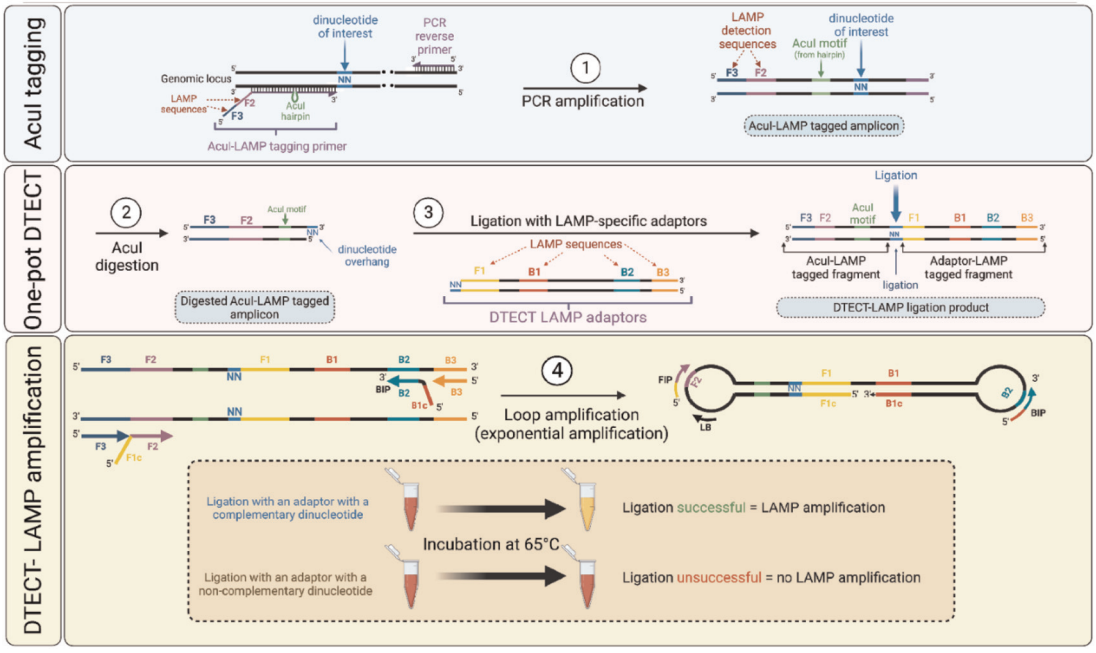

Figure 1. (abstract: 70) The clinical diagnostic platform using One-pot Dinucleotide signaTurE CapTure (DTECT).

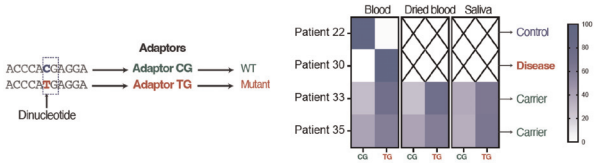

Figure 2a. Detection of CD3δ Severe Combined Immunodeficiency c.202C>T mutation with One-pot DTECT.

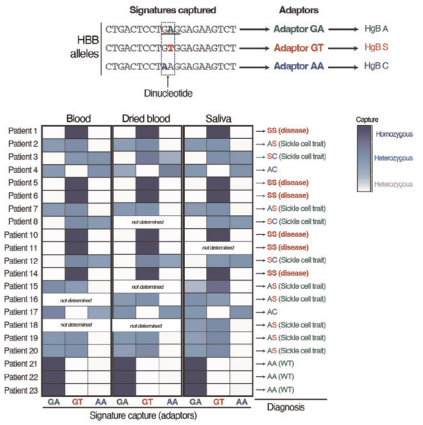

Figure 2b. Detection of Hemoglobin A, S and C with One-pot DTECT.

Methods: Blood, saliva, and dried blood spot samples were collected from patients with CD3δ SCID, carriers and healthy participants. Experimenters were blinded to participant genotype. One-pot DTECT is a platform that expedites the detection of genetic signatures, requiring a short incubation (10–60 min) of a PCR product at room temperature in an optimized, homemade one-pot mixture assembled from off-the-shelf reagents with various detection modalities, including qualitative, quantitative, and real-time visual detection (Fig 1).

Results and Conclusions: Our streamlined protocol unambiguously distinguished affected individuals from carriers and controls with 100% accuracy and 0% false positives/negatives. One-pot DTECT rapidly, precisely and inexpensively identifies specific pathogenic variants, such as CD3δ SCID, hemoglobin S and hemoglobin C (Fig. 2). It has significant potential for resource limited regions where the technology could be developed in-house or dried blood spots could be mailed to a reference lab, abrogating difficulties shipping blood or saliva. Validation on dried blood spots has potential for second tier testing on samples collected for newborn screening. Future directions include piloting use on dried blood spots in Chihuahua, Mexico, where access to genetic testing is challenging, and validating the assay for other pathogenic variants, such as founder mutations for ZAP70 or adenosine deaminase SCID.

Keywords: CD3δ severe combined immune deficiency, PCR, Screening test

Disclosures: Luis Murguia-Favela: I have relevant financial relationships with proprietary interests: ENCODED Therapeutics (Data Safety Monitoring Committee Member). The other authors have no financial relationships or conflicts of interest to report.

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(71)

Two allelic variants in the SERPING1 gene associated with hereditary angioedema detected in one adult patient without clinical manifestation of the disease. Case report

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Introduction. Hereditary angioedema (HAE) is a rare autosomal dominant genetic disease that usual results from a decreased level of C1-inhibitor and complement C4. Allelic variants in SERPING1, the gene that encodes C1-inhibitor, are responsible for the majority of cases of HAE (about 99%). HAE manifests with recurrent episodes of edema of the skin, gastrointestinal tract or upper airway usually in the childhood or adolescents.
Materials and Methods: The study included DNA samples of patient (22 y.o. women) and her mother (44 y.o.). The patient had a medical check in the Center due to multiple viral infections of various degrees of severity in past medical history. We performed next-generation sequencing analysis of the primary immunodeficiency panel of 141 genes (AmpliSeq, Illumina).
Results: Sequence analysis and deletion/duplication testing of the 141 genes considering to genomic position, population frequency < 1% and in-silico predictors revealed two allelic variants with clinical significance. This two variants were detected in SERPING1 gene. In exon 8: heterozygote c.1286 G > A, p.Gly429Glu (COSM3449760); in exon 2: heterozygote c.5 C > T, p.Ala2Val (rs185342631). This variants in scientific published papers are associated with HAE. Patient didn't have any clinical symptoms of HAE yet, her relatives as well. Her complement C4 was normal – 0.24 g/l (range: 0.15–0.57 g/l), C1-inhibitor was lower the normal – 0.157 g/l (range: 0.21–0.39 g/l). Genetic testing didn't reveal this variants in the DNA sample of the patient's mother and her C4 and C1-inhibitor levels were in normal range. The patient's father lives in another country and in his words never have any swelling, including severe abdominal pain.
Conclusion. Among Belarusian HAE patients the median age of onset is 12 years (range: 1–60, n = 92) and 9.8% of patients had onset over the age of 22 years. Some drugs may increase complement C4 levels, as well as immune treatment. The follow-up of the patient was lost and we were unable to re-measure complement C4. We have not seen similar cases before, even in the literature, and hope we will have the opportunity to continue our research.

Keywords: Hereditary angioedema, C1-inhibitor, Gene SERPING1, Next-generation sequencing

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(72)

A Rare Clinical Entity: Pediatric Myelofibrosis Associated with Agammaglobulinemia and Vasculitis

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Myelofibrosis is a myeloproliferative disorder that results in cytopenias, extramedullary hematopoiesis and bone marrow fibrosis that is primarily seen in the adult population. It is seldom seen in children, with the largest case series totaling 19 patients. Transcription factor 3 (TCF3) is a gene that encodes two transcription isoforms that play a critical role in lymphopoiesis, specifically in early B cell development. Homozygous and heterozygous variants in TCF3 have been associated with agammaglobulinemia and leukemia but not with myelofibrosis. Herein, we describe a case of pediatric myelofibrosis, agammaglobulinemia, and vasculitis associated with a TCF3 gene variant. A 15-year-old male with history of autism and Klinefelter syndrome was evaluated for recurrent sinopulmonary bacterial infections. His initial workup was remarkable for anemia, neutropenia, and positive c-ANCA antibody. Further evaluation showed hypogammaglobulinemia, absent B cells, myelofibrosis, and evidence of vasculitis (Table 1). There was no family history of immunodeficiency, autoimmunity, or malignancy. Invitae Primary Immunodeficiency panel revealed a heterozygous variant of uncertain significance (VUS) in TCF3: c.904G>A; p.Gly302Ser. Due to the history of agammaglobulinemia, the TCF3 variant was considered to explain his immunologic phenotype. He receives IVIG monthly, twice weekly Neupogen injections, and antimicrobial prophylaxis with fluconazole, trimethoprim-sulfamethoxazole, and levofloxacin. Stem cell transplant is expected in 2024, preceded by treatment with ruxolitinib to reduce the risk of transplant rejection. Allogeneic stem cell transplant has been successful for TCF3 positive leukemia. This case illustrates a novel constellation of diseases associated with a rare genetic variant. In the future, it will be important to consider TCF3 variants in patients presenting with agammaglobulinemia and hematologic derangements.

Keywords: Agammaglobulinemia, Myelofibrosis, TCF3 variant, Vasculitis

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(73)

Reconstitution of norovirus-specific T cell responses following hematopoetic stem cell transplantation in patients with inborn errors of immunity and chronic norovirus infection

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Chronic norovirus infection causes significant morbidity in immunocompromised patients, including those with inborn errors of immunity (IEI). No effective strategy for prevention or treatment currently exists. Herein, we describe the clinical course and establishment of norovirus-specific T cell immunity in two patients with IEI undergoing hematopoietic stem cell transplantation (HSCT), one with X-linked severe combined immunodeficiency (X-SCID) and the other with Dedicator of Cytokinesis 8 (DOCK8) deficiency.

Each patient suffered from chronic norovirus in the peri-HSCT setting and failed to clear the virus despite therapies commonly attempted for norovirus (Figure 1). Patient 1 (X-SCID) had severe, symptomatic chronic norovirus infection without detectable norovirus specific T cells on HSCT day +33. Severe diarrhea correlated with norovirus-antigen-positive pathologic changes in endoscopy samples (Figure 2) and viral evolution in the setting of long-term shedding (not shown). On day +209, after norovirus clearance, he had developed broad-spectrum polyfunctional CD4+ and CD8+ T cells specific to multiple peptides from norovirus nonstructural (NS3, NS5, and NS6) and structural (VP1) proteins (Figure 3). Similarly, patient 2 (DOCK8 deficiency) had ineffective, isolated structural norovirus peptide responses prior to HSCT (day−147), whilst polyfunctional CD4+ T cells were detectable to NS6 and VP1 on day +87 after successful norovirus clearance (Figure 4). The norovirus-specific T cell response on day+87 was nearly identical to the specificity seen in his healthy matched-related-donor sister (not shown).

In each patient, at the time of norovirus clearance, B cells remained absent. Norovirus-specific IgG responses were similar in both children pre- and post-norovirus clearance. Viral-specific IgA responses were not detectable in the X-SCID patient, but were detectable and similar pre- and post-norovirus clearance in the DOCK8 patient (Figure 5). Taken together, these data argue against a requirement for virus-specific-antibody or B cells in the clearance of norovirus infection.

This is the first report to demonstrate a temporal correlation between reconstitution of norovirus-specific T cell immunity after HSCT and clearance of chronic norovirus infection. This finding indicates that functional cellular immunity is sufficient for clearance of norovirus infection and that norovirus specific T cells may provide an effective therapy for chronic norovirus infection in immunocompromised individuals.

Keywords: Chronic norovirus, Severe combined immunodeficiency, Viral specific T cells, DOCK8 deficiency, Hematopoietic stem cell transplantation

Disclosures: Catherine Bollard: I have relevant financial relationships with proprietary interests: Caballeta Bio (Board Member); Catamaran Bio

FIGURE 1
Clinical Course, Peripheral Blood Lymphocyte Counts, and Norovirus Viral Loads in Patients with Chronic Norovirus in the Peri-HSCT Setting

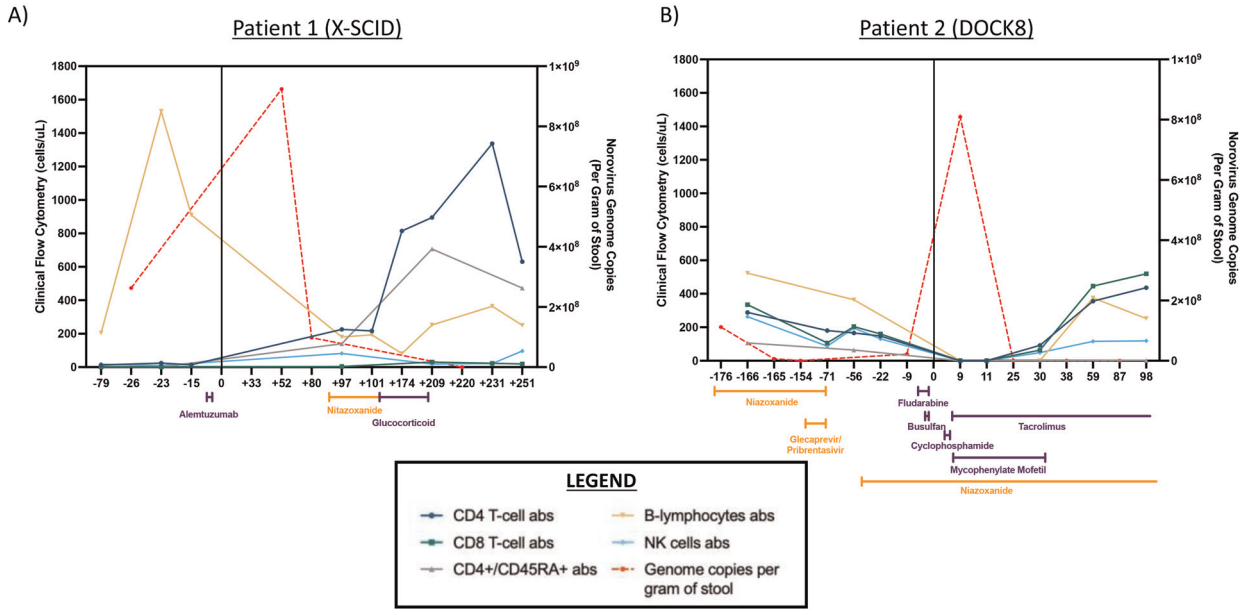
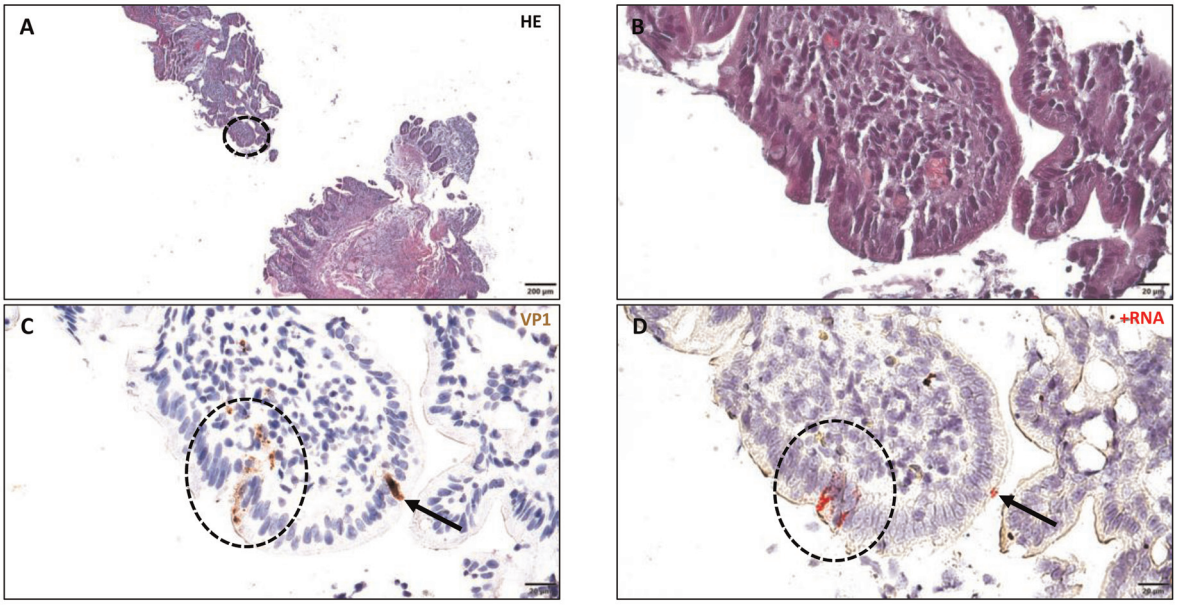


Figure 1 (abstract: 73)

FIGURE 2

Brightfield imaging of a duodenal pinch biopsy from a patient collected while shedding norovirus CNH153



The villus tip in the circled area (image A) appears essentially normal and consists of lamina propria lined by mucosal epithelial cells (enterocytes). HE. 4x, 40x. (C) Serial section shows rare epithelial cells randomly distributed in the mucosal epithelium exhibit cytoplasmic distribution of viral VP1 antigen (black circle, black arrow); also minimal granular viral antigen is observed in the lamina propria. mAb44 IHC, 40x. (D) Serial section using chromogenic in in situ hybridization (CISH) detects positive-sense RNA of norovirus GII.4 (red staining) in very rare epithelial cells (black circle, black arrow). CISH, positive sense, 40x. NOTE. To confirm adequate RNA integrity of the formalin fixed paraffin embedded samples, a medium-expressing housekeeping gene (peptidylprolyl isomerase B, PPIB) probe was applied to an unstained slide as a positive control. A probe targeting the dapB gene was used as a negative control.

Figure 2 (abstract: 73)

(Advisory Board, Owner/Co-Owner Founder/Co-Founder); Cellectis (Advisory Board); Mana Therapeutics (Advisory Board, Owner/Co-Owner Founder/Co-Founder). Michael Keller: I have relevant financial relationships with proprietary interests: Chiesi (Grants/Research Support Recipient). The other authors have no financial relationships or conflicts of interest to report.

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FIGURE 3

Norovirus Specific T-Cell Response in X-SCID Patient Before and After Norovirus Clearance

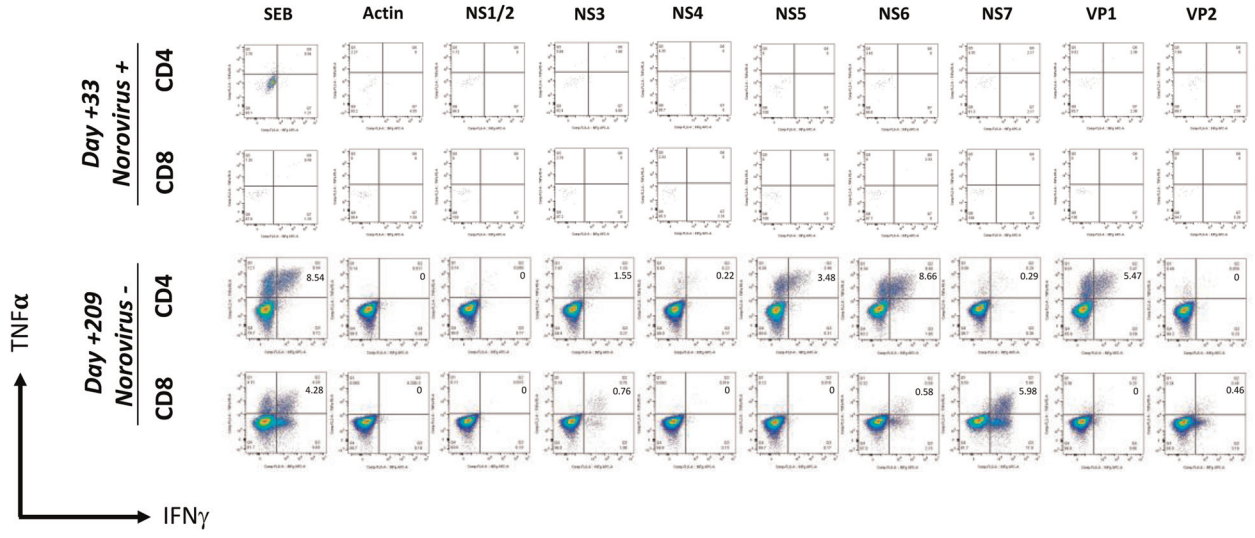

Figure 3 (abstract: 73)

FIGURE 4

Norovirus Specific T-Cell Response in DOCK8 Deficiency Patient Before and After Norovirus Clearance

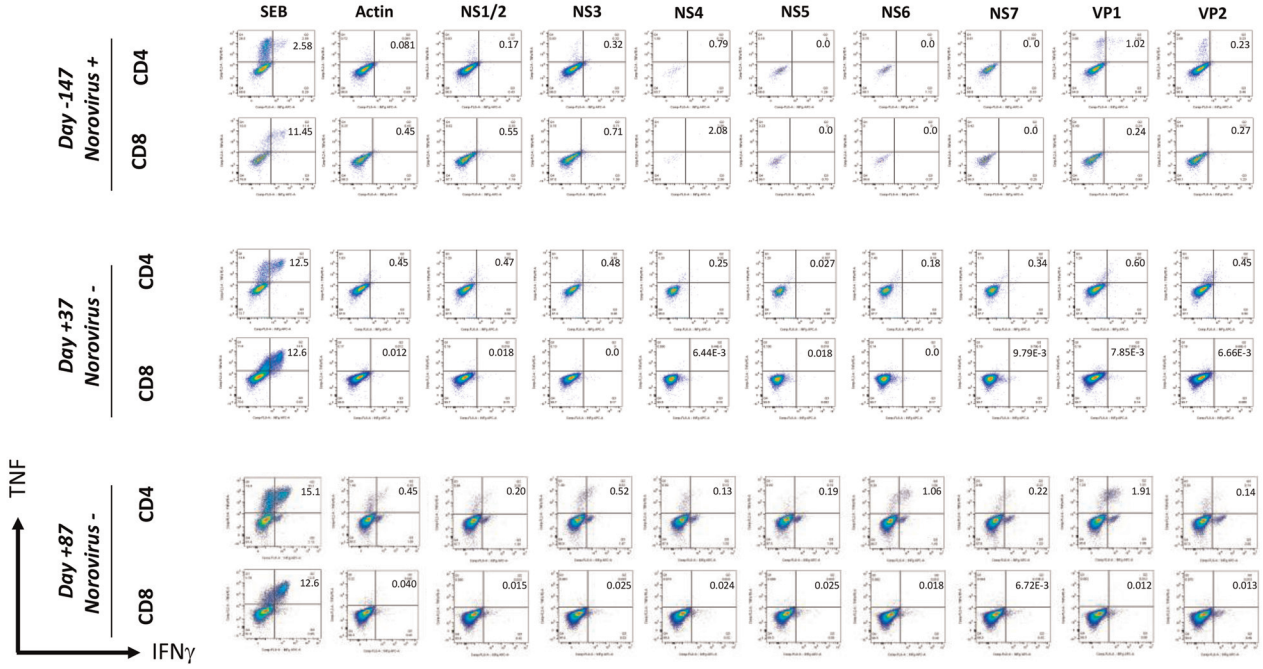

Figure 4 (abstract: 73)

FIGURE 5

Norovirus Specific IgG (A) and Norovirus Specific IgA (B) Before and After Norovirus Clearance in 2 Patients Undergoing HSCT for IEI

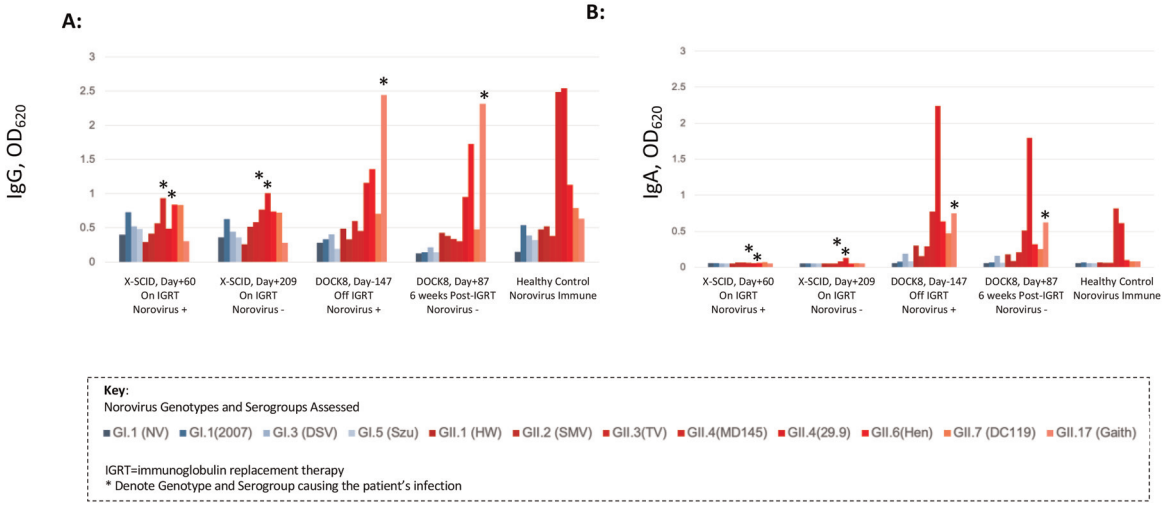

Figure 5 (abstract: 73)

(74)

Getting to the Heart of the Cause: Epidermodysplasia verruciformis in a Patient Born with Transposition of the Great Arteries and Mosaic Turner Syndrome

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A 34-year-old female with mosaic Turner syndrome (45, XO) was referred for immune evaluation due to biopsy-proven epidermodysplasia verruciformis (EV) affecting both hands. Her past medical history was significant for Dextro-Transposition of the Great Arteries (D-TGA), ventricular septal defect (VSD), and pulmonary stenosis for which she underwent modified right Blalock–Thomas–Taussig shunt in early infancy, followed by Rastelli operation, multiple additional cardiac surgeries, and a valve placement for severe pulmonary insufficiency at age 18. Her post-surgical course was complicated by cardiac cirrhosis. She later developed peripheral edema with hypoalbuminemia, low ceruloplasmin and alpha-1-anti-trypsin levels and was diagnosed with protein-losing enteropathy (PLE).
Regarding dermatologic history, the patient reported a 5-year history of hand warts, which prompted dermatologic evaluation. Skin biopsy revealed verrucous squamous lesions with features of epidermodysplasia verruciformis. Immune work-up revealed significant T-cell lymphopenia (CD4 of 70 cells/mL, CD8 of 23 cells/mL) and normal B and NK cells. HIV was non-reactive. She was found to have hypogammaglobulinemia with immunoglobulin (Ig) G of 314 mg/dL, and normal IgM, IgA levels, and titers. A review of her previous laboratories revealed persistent significant T-cell lymphopenia for the past 7 years.
Notably, the patient denied having recurrent sinopulmonary infections other than contracting SARS-CoV-2 twice. She denied having oral thrush, chronic diarrhea, or skin molluscum. She was up-to-date on all age-appropriate vaccinations and denied disease activation after live vaccines. There was no history of long-term immunosuppressive therapy. Her family history was unremarkable. There was no T-cell count before cardiac surgery. The patient's extensive cardiac history in combination with presumed reduced thymic tissue and/or age-related thymic involution and PLE, all contribute to T-cell lymphopenia and EV. However, thymic hypoplasia could not be ruled out.
PLE emerges as a significant consequence following cyanotic congenital heart surgeries. Elevated central venous pressures and thoracic duct damage contribute to mucosal lymphatic rupture, resulting in the drainage of lymph into the gastrointestinal tract. This process leads to the loss of T cells and proteins.
This case demonstrates a possible long-term consequence of T-cell lymphopenia in a patient with a history of complex cardiac surgery.

Keywords: Combined immunodeficiency, Congenital heart disease, Protein losing enteropathy, Lymphopenia, Epidermodysplasia verruciformis

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(75)

Fatal CMV infection in a 2-month-old Infant with STAT1 Loss of Function Mutation

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Background: STAT1 protein, a member of the STAT family, plays a crucial role in regulating various immune responses through the JAK-STAT pathway. Loss-of-function (LOF) mutations in STAT1 are associated with Mendelian susceptibility to mycobacterial disease, while gain-of-function (GOF) mutations are linked to chronic mucocutaneous candidiasis. Herein, we present a case of lethal CMV in an infant with autosomal recessive STAT 1 LOF mutation.
Case Presentation: A 2-month-old full-term female infant with a history of recent aseptic meningitis was admitted with a two-week fever, nasal congestion, reduced feeding, and yellow eye discharge. No additional symptoms, such as rash, vomiting, or diarrhea, were reported, and there were no known sick contacts or pets at home. Physical examination on admission showed fever, mild tachypnea, and reduced air entry bilaterally. There was no rash, organomegaly, or lymphadenopathy. Eye screening revealed no retinitis, and hearing assessment was normal. Initial complete blood count revealed leucocytosis (WBC 21.7 × 10 × 3/ul), anemia (HB 6.54 g/dl), and thrombocytopenia (61/8 × 10 × 3/ul.). She also had elevated transaminases (AST 378 IU/L, ALT 236.6 IU/L), abnormal renal profile (Cr 63.0 umol/L), and increased inflammatory markers (ESR 65 mm/Hr, CRP 25.8 mg/dl). TORCH panel testing revealed positive CMV IgG and IgM. The CMV PCR in peripheral blood was highly positive (18700000 UI/ml). Chest X-ray exhibited bilateral ground glass opacity and reticulonodular infiltration, which was supported by chest CT results. Despite the initiation of intravenous ganciclovir (15 mg/kg/day), the patient's respiratory distress worsened, necessitating transfer to the Intensive Care Unit (PICU) for ventilatory support. Valganciclovir (30 mg/kg/day) was administered, but unfortunately, her condition continued to deteriorate. She died due to acute respiratory distress syndrome despite High-Frequency Oscillatory Ventilation. Whole-exome sequencing (WES) revealed a homozygous, pathogenic variant of the STAT1 gene (c.1760_1761[p.Glu587AlafsTer18]). This mutation has been previously reported as a STAT1 LOF mutation.
This case highlights the critical role of STAT1 in regulating the immune response to viral infection, especially CMV infection. The lack of STAT1 expression eliminates the STAT1-dependent response to both type 1 and type 2 interferons and puts the host at risk of severe viral infection.

Keywords: STAT1 LOF, CMV infection, Lethal viral infection, Fever, Whole-exome sequencing

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(76)

Novel Hexokinase 1 Genetic Mutation Presenting with Recurrent Fever and Developmental Delay: Possible Insight on the Role of Glucose Metabolism Dysregulation and Autoinflammation

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Hexokinase 1 (HK1) is a key enzyme in the glycolytic pathway. Dysregulation of HK1 causes activation of NLRP3 inflammasome and subsequently overexpression of proinflammatory cytokines IL-1 B and IL-18. HK1 genetic mutation has been reported in cases of neurodevelopment abnormalities with visual impairment and nonspherocytic hemolytic anemia, but its role in recurrent fever and systemic inflammation has not been reported yet. This case report presents an early childhood boy with a history of developmental delay who experienced recurrent episodes of high-grade fevers at the age of 1 year. Each episode lasted 4–5 days and responded partially to antipyretics and oral antibiotics. The interval between fever attacks was irregular, sometimes only a few days apart. The patient was entirely well between the episodes of fevers. These fever attacks were associated with abdominal pain. He had no history of skin rash, joint pain, or symptoms suggestive of respiratory or urinary infections. Whole exome sequencing revealed a novel heterozygous variant in HK1 (c.2198C>T; p. Ser733Phe), which is predicted to have a potentially deleterious effect based on PolyPhen-2 and SIFT In silico analyses. HK1 is also expressed in white blood cells, particularly monocytes, and plays a significant role in glucose metabolism, which serves as a crucial source of energy for monocytes and neutrophils. Besides its involvement in energy utilization and the survival of mononuclear cells, HK1 also plays a vital role in cell signaling and protection against pathogens. HK1 functions as an innate immune sensor by binding to N-acetylglucosamine (NAG), a peptidoglycan subunit derived from a gram-positive bacterial cell wall. Dysregulation in HK1 enzyme activity affects these cells, leading to the activation of the NLRP3 inflammasome and the production of IL-1β. This case report highlights the possible new association of recurrent fever and HK1 mutation in addition to typical features such as neurodevelopmental delay and anemia. However, functional testing and experimental validation using animal models are needed to confirm the pathogenicity of this variant.

Keywords: Hexokinase 1, Autoinflammation, Recurrent fever, Developmental delay, Glucose metabolism

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(77)

Determining the Immunodeficiency in Patients with Down Syndrome at the University of Miami and Jackson Memorial Health Systems

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Introduction: Down Syndrome is known to be associated with immunodeficiency, leading to higher risks of cancers, infections, autoimmunity, and lymphoproliferation. These patients can have lymphopenia, humoral deficiency, impaired neutrophil function, and immune dysregulation. However, the prevalence of immune dysfunction in Down Syndrome is not well characterized.

Methods: A retrospective study of patients diagnosed with Down Syndrome who received evaluation by an immunologist between 2008 and 2023 at the University of Miami and Jackson Memorial Health Systems was conducted. Approval from local Institutional Review Board (Study #20230956) was obtained, allowing for the review of electronic medical records. Demographics, immunological history, and relevant laboratory data were analyzed.

Results: 17 charts were available for review; 7 females and 10 males; 13 individuals identified as White (2 Non-Hispanic/Latino, 11 Hispanic/Latino), and 4 identified as Black or African American. The average current age was 10 years (14 months to 23 years). Common infections included otitis media (5/17), pharyngitis (2/17), frequent upper respiratory infections (4/17), and lower respiratory infections (4/17). Isolated cases of genitourinary infections, skin abscesses, and fungal infections were noted. 9/17 (53%) of patients had total lymphopenia, 4/9 (44%) CD3 lymphopenia, 3/9 (33%) CD4 lymphopenia, and 4/9 (44%) CD8 lymphopenia. 4/7 (57%) patients had abnormalities in naïve and memory B cell phenotyping. 1/14 (7%) had low IgG, 3/14 (21%) low IgA, and 6/14 (43%) low IgM. Additionally, 8/11 (73%) patients had non-protective pneumococcal titers with less than 50% below 1.3 mcg/mL, with some patients not achieving protective levels even after receiving additional pneumococcal vaccines. Intravenous immunoglobulin was recommended to one patient.

Discussion: This study highlights the susceptibility of individuals with Down Syndrome to infections and immune deficiencies, which suggests compromised immune function. Tailored monitoring and interventions are crucial to address these vulnerabilities and improve care. Further research with larger samples is needed for a deeper understanding and better management of these challenges.

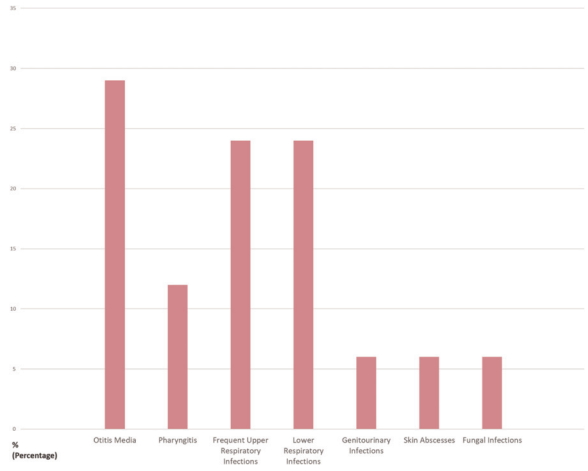

Figure 1. History of infections in Down syndrome patients.

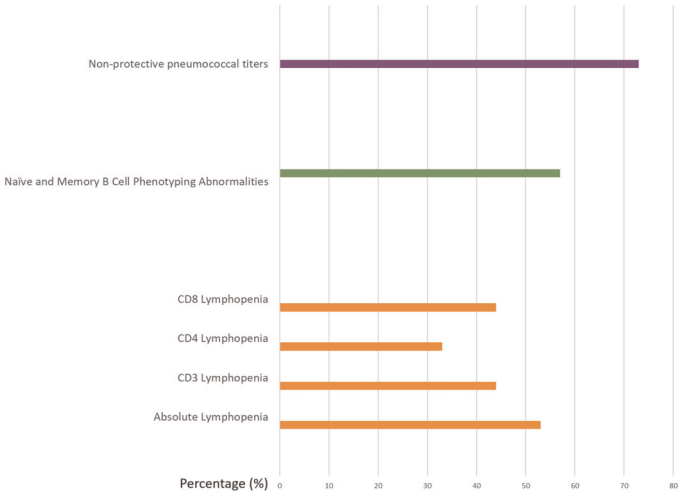

Figure 2. Immunological laboratory data in Down syndrome patients.

Keywords: Down syndrome, Trisomy 21, Immunodeficiency, Immunocompromised

Disclosures: Melissa Gans: I have relevant financial relationships with proprietary interests: DBV (Clinical Trial Investigator); Elsevier (Royalties); Novartis (Clinical Trial Investigator); Opinion Leader Group (Consulting Fees (e.g., advisory boards)). The other authors have no financial relationships or conflicts of interest to report.

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(78)

Misdiagnosis Of An Infant With Incontinentia Pigmenti And Importance Of Immunological Evaluation

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Introduction: Incontinentia pigmenti (IP) is a rare X-linked neurocutaneous disorder caused by pathogenic variants in the IKBKG/NEMO (NF-kappaB essential modulator) gene. Virtually all cases are seen in females because affected males usually do not survive till birth. Skin lesions are typically the first manifestation of IP leading to frequent misdiagnosis. We describe the case of an infant female who was misdiagnosed with impetigo prior to receiving a diagnosis of IP.
Results: The patient was born full term with an uneventful prenatal course and developed bullae lesions on both upper and right lower extremities within two hours of life. She was diagnosed with transient neonatal pustular melanosis due to the evolution of lesions into hyperpigmented macules which were treated with petroleum-based emollient. By three days of life, there was yellow crusting and mupirocin was recommended twice daily for five days. Although most lesions improved, there was never a complete resolution of cutaneous symptoms leading to repeat courses of topical mupirocin during the first two months of life. Eventually, the patient was diagnosed with IP clinically as there was the development of linear and whorled lesions consisting of dark brown linear patches, ruptured vesicles with collarettes of scale, and intact vesicles with yellow serous fluid in a linear arrangement along the lines of Blaschko. As part of a multidisciplinary workup, immunology evaluation was done revealing normal complete blood count with differential, lymphocyte subsets, lymphocyte proliferation to mitogen stimulation, immunoglobulin levels (except for physiological low IgG 256 mg/dL expected at this age), and protective tetanus and diphtheria titers. Further immunological evaluation such as toll-like receptor functional assay and IKBKG genetic sequencing are pending.
Discussion: IP can be easily misdiagnosed for conditions such as impetigo or herpes simplex virus. A proper diagnosis is essential as these patients should undergo immunological evaluation and genetic sequencing. The immunological manifestations of IP have not been well described apart from superimposed cutaneous infections and there is poor understanding whether these patients can have a milder immunodeficiency on the spectrum of NEMO mutations. More research is needed on the immune function in patients with IP.

Keywords: Incontinentia pigmenti, NEMO syndrome, IKBKG, Blaschko, Bullae lesions

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(79)

Pre-transplant decision-making among patients with cartilage-hair hypoplasia

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Cartilage-hair hypoplasia (CHH) is a syndrome arising from autosomal recessive variants in the RMRP gene, leading to cellular proliferation and differentiation defects. CHH is a multi-organ disease and may come to the attention of immunologists and hematologists for features of severe infections, autoimmunity, anemia, and malignancy with variable long-term outcomes without hematopoietic stem cell transplant (HSCT). In-depth immune phenotyping may reveal wide variability that may not correlate with clinical outcomes. There is no consensus on determining candidacy and ideal timing for HSCT. Multilayered shared decision-making often involves immunologists, hematologists, HSCT transplant teams, and families.

Table 1. (abstract: 79)
Patient characteristics, clinical and immune phenotype, transplant indications and outcomes.

	Age	Clinical Phenotype	Immune Phenotype	Transplant Age	Transplant Indication	Transplant Outcome
Patient 1	1.5	• Severe anemia • Atrial septal defect • Plagiocephaly	• T-cell lymphopenia • Low lymphocyte proliferation to mitogens	1	Severe anemia	4 months of survival
Patient 2	6.5	• Short stature • Sparse hair • Facial dysmorphism • Bone abnormalities	• T-cell lymphopenia • Normal lymphocyte proliferation to mitogens • Declining lymphocyte proliferation to anti-CD3/CD28 • Decreased percentage of naïve T-cells • Low lymphocyte viability	2	Declining lymphocyte proliferation to anti-CD3/CD28	4.5 years of survival
Patient 3	18	• Short stature • Bone abnormalities • Bronchiectasis • Chronic rhinovirus infections • Recurrent pneumonia • Evans syndrome	• T and B-cell lymphopenia • Low lymphocyte proliferation to mitogens and antigens • Decreased percentage of naïve T-cells • Hypogammaglobulinemia (s/p Rituximab)	12.5	Lymphopenia and recurrent immune-mediated cytopenia	5.5 years of survival
Patient 4	Died at 4 months of age	• Short stature • Relative macrocephaly • Respiratory depression at birth	• T and B-cell lymphopenia • Low lymphocyte proliferation to mitogens	2 months	Lymphopenia	Died post-transplant 2 months due to infections
Patient 5	22	• Short stature • CMV pneumonitis • H. influenzae sepsis and meningitis despite full vaccination	• T-cell lymphopenia • Low lymphocyte proliferation to mitogens	1	Severe/life-threatening infection	21 years of survival
Patient 6	Died at 7 months of age	• Short stature • Thoracic dysplasia • Bacterial pneumonia • CMV viremia	• T-cell lymphopenia • Low lymphocyte proliferation to mitogens • Decreased percentage of naïve T-cells • Low lymphocyte viability	5 months	T-cell lymphopenia	Died post-transplant 2 months due to infections
Patient 7	Died at 3 years of age	• Short stature • Sparse hair • Hirschsprung's disease • Bacterial pneumonia	• T-cell lymphopenia • Low lymphocyte proliferation to mitogens	2	Unclear from available medical history	Died post-transplant 11 months due to intractable autoimmune hemolytic anemia
Patient 8	10	• Short stature • Omenn syndrome (eosinophilia, elevated IgE, lymphadenopathy, hepatomegaly, rash) • Hirschsprung's disease • Pneumocystis jiroveci pneumonia • Respiratory viral infections	• Oligoclonal T cells • B and NK-cell lymphopenia • Decreased percentage of naïve T-cells • Low lymphocyte proliferation to mitogens • Hypogammaglobulinemia	1.5	Omenn syndrome	8.5 years of survival

Here, we report eight transplanted patients with CHH from three different centers (Table 1). Four (50%) patients were born after the introduction of newborn screening for severe combined immunodeficiency (NBS-SCID). Three screened positive by NBS-SCID, and one had borderline T-cell receptor excision circles. Seven (88%) patients had T-cell lymphopenia and decreased lymphocyte proliferation responses to mitogens. The decision-making for HSCT required repeated evaluation and continued conversation between clinicians and families, lasting from days to months or even years. Seven (88%) patients were transplanted before age three, including two patients within the first six months of life, whereas one was transplanted as a 12.5-year-old. The final indication for HSCT was primarily lymphopenia (n = 3, 38%), followed by declining lymphocyte proliferation studies (n = 1, 13%), Omenn syndrome (n = 1, 13%), severe infections (n = 1, 13%), and severe anemia (n = 1, 13%). Three (38%) patients died post-HSCT, with two (25%) succumbing to infections and one (13%) to intractable autoimmune hemolytic anemia. Five patients (63%) survived, with survival times of 4 months to 21 years.

Variable clinical and immunohematological findings and outcomes create a difficult conversation between clinicians and families regarding the indications and timing of HSCT. Besides infections and immunodeficiency, anemia could be an important indication for HSCT. Findings in our cohort differ from the Finnish experience, where patients were transplanted at an older age. Further studies are needed to understand the indication and

timing of HSCT. Clinical monitoring and close communication with families are essential in shared decision-making in this complex process.

Keywords: Cartilage-hair hypoplasia (CHH), Inborn errors of immunity, Immunodeficiency, Hematopoietic stem cell transplant (HSCT), Decision-making

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(80)

Recurrent parotitis as a presenting symptom of Common Variable Immunodeficiency (CVID): a case report

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Introduction: CVID is one of the most common immune deficiencies. While all patients with CVID have defects in humoral immunity, clinical presentations are very heterogeneous. Some patients present with recurrent upper respiratory and gastrointestinal infections, while others present with immune dysregulation such as autoimmunity. Parotitis has been described in patients with CVID but not as the isolated presenting symptom.

Case Presentation: Here we report a fully immunized 11-year-old who had treatment-resistant parotitis and was found to have hypogammaglobinemia. She had a history of chronic nasal congestion, distant history of recurrent ear infections, and a group A streptococcal peritonsillar abscess at age 2 years but was otherwise healthy with normal growth and development. She had no history of pneumonia or chronic diarrhea. At age 9, she developed recurrent left-sided parotitis which did not respond to an initial course of antibiotics. Treatment with systemic steroids and sialoendoscopy with insufflation of steroids resulted in improvement but not full resolution of her symptoms.

Laboratory evaluation revealed decreased IgG of 203 mg/dL (lower limit 586 mg/dL), low IgM of 45 mg/dL (lower limit 47 mg/dL), and absent IgA and IgE. CBC and total counts of T, B, and NK cells were normal. B cell phenotyping showed a decrease in total memory B cells (CD27+) at 1.5%, (normal 4.6% to 49.1%), switched memory B cells (CD27+IgD-IgM-) at 0.2% (normal 1.9% to 30.4%), and IgM-only memory B cells (CD27+IgD-IgM +) at 0.1%, (normal 0.3% to 13.1%). Pneumococcal vaccine responses were nearly absent. Evaluation for rheumatologic causes of parotitis including ANA, ANCA, complements C3 and C4 was normal. Genetic testing was unrevealing.

She was treated with IVIG and her parotid swelling resolved. Ongoing IgG replacement therapy was given subcutaneously, and she had no recurrence of parotitis for several months.

Discussion: To our knowledge, this is the first report of recurrent parotitis as the presenting symptom of CVID. Of note, she did not have a history of pneumonia, gastrointestinal infections, or other signs of CVID prior to diagnosis. Clinicians should consider CVID for patients with recurrent parotitis even in the absence of other history suggestive of CVID.

Keywords: Common variable immunodeficiency, CVID, Parotitis, Inborn errors of immunity, Primary immunodeficiency

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(81)

Liver Transplant as Definitive Therapy for Immune Defects Associated with Congenital Disorder of Glycosylation Type 1 B

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We present a unique case of immune correction following orthotopic liver transplantation (OLT) in an 18-year-old female with MPI-related congenital disorder of glycosylation (MPI-CDG) also known as type 1b. She had recurrent infections which improved following OLT as did her immune parameters suggesting a unique potential for OLT in treating immunodeficiency associated with this disorder.

MPI-CDG is a rare disorder caused by biallelic loss of function variants in the MPI gene which encodes the mannose phosphate isomerase enzyme which is important for protein mannosylation. Clinical manifestations include liver fibrosis, hypoglycemia, and coagulopathy. Hypogammaglobulinemia and leukopenia have been reported and immunoglobulin replacement has been used. However, liver transplantation has not previously been reported as a means of immune correction.

At age 6, our patient underwent evaluation for nose bleeds and easy bruising and was found to have thrombocytopenia, anemia, and splenomegaly. She was diagnosed with hyperinsulinism after a hypoglycemic seizure. Exome sequencing revealed compound heterozygous pathogenic variants in MPI. Complications included liver cirrhosis, portal hypertension, esophageal varices, and pulmonary arteriovenous malformations causing hypoxemia after general anesthesia events. She had recurrent sinusitis, otitis media, clostridium difficile, and salmonella colitis. She was not adherent to mannose therapy. Pre-transplant immune evaluation revealed low numbers of CD4 and CD8T cells and B cells. To address her liver cirrhosis, she underwent OLT and was successfully maintained on immunosuppressive therapy. Remarkably, despite immunosuppression with steroids and tacrolimus, her T cell and B cell counts improved dramatically, and she exhibited a reduced frequency of infections.

The underlying mechanism behind the immune correction observed in this case is not fully understood. However, we hypothesize that the new liver, with improved protein glycosylation likely resulted in increased antigen presentation and processing and along with increased lymphocyte counts resulted in decreased infections. This case is the first documented instance of immune correction following OLT in MPI-CDG. While this CDG may be treated with oral mannose, in cases where patients require liver transplant secondary to complications of their metabolic disorder, immune correction should be considered amongst the added benefits of OLT.

Table.

Lab value	Reference range (%)	Pre-transplant	Post-transplant
Absolute lymphocyte count	-/ uL	627	1920
CD3+ T cells	551–2,500/uL (62–89)	437 (69.6)	1,167 (60.8)
CD3+CD4+ T cells	246–1,811/uL (32–70)	216 (34.5)	444 (23.1)
CD3+CD8+ T cells	65–850/uL (7–35)	199 (31.8)	657 (34.2)
CD19+B cells	48–484/uL (6–20)	124 (19.8)	444 (23.1)
CD3-CD56CD16+ cells	45–406/uL (2–23)	16 (2.5)	92 (4.8)
Immunoglobulin M	40–180 mg/dl	16.6	18.2
Immunoglobulin G	641–1353 mg/dl	1340	789
Immunoglobulin A	66–295 mg/dl	22.5	11.9

Keywords: Congenital disorders of glycosylation, Lymphopenia, Orthotic liver transplant

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(82)

Newborn Screening for Severe Combined Immune Deficiency: The Canadian Landscape

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Introduction: Severe combined immune deficiency (SCID), a group of life-threatening inherited immune disorders characterized by abnormal production of T cells, is an excellent candidate for newborn screening (NBS) as early intervention significantly improves survival. Screening is performed by quantitating T-cell receptor excision circles (TREC), a biomarker of T cell maturation, however, there is no standardization of test methods, reporting or follow up. This study aims to analyze differences in NBS for SCID across Canada.

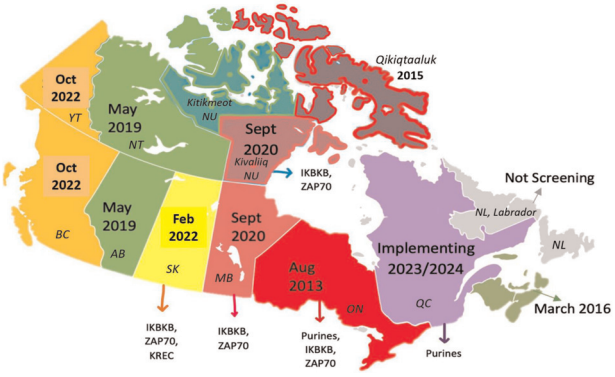
Methods: A comprehensive survey of SCID NBS procedures was developed with input from laboratory directors and clinical immunologists then disseminated to all NBS labs across Canada.

Results: Year of SCID NBS implementation varied across jurisdictions, with Ontario starting in 2013 and Newfoundland not screening. Some provinces also screen for additional inborn errors of immunity, such as IKBKB and ZAP70 (Fig 1).

Significant variability was noted in TREC assay methods, reporting measures and cut-off values for abnormal results (Table 1). Procedures to confirm abnormal results varied from using a second punch on the same card to collection of a new sample.

Terminology for reporting and the protocol for calling out abnormal results varied. In Ontario, dedicated NBS staff contact the primary care provider and families first, whereas in Alberta, this role is assigned to the immunologist. Turnaround times for TREC results ranged from days to over one week.

Definition of and approach to premature infants differed, with some provinces utilizing various gestational age (GA) definitions and others using GA and birth weight. Retesting procedures similarly differed (Table 1).



Territory	Perinatal travel/Birthing Unit	Screening Program
Qikiqtaaluk	Iqaluit, NU	Ottawa, ON
Kitikmeot	Stanton, Edmonton	Edmonton, AB
Kivalliq	Winnipeg, MB	Winnipeg, MB
Northwest Territories	Yellowknife, NT	Edmonton, AB
Yukon	Whitehorse, YT	Vancouver, BC

Figure 1. Month and year of implementation of newborn screening for SCID and additional inborn errors of immunity across Canadian jurisdictions.

Table 1.
TREC cut off values, reporting, prematurity definitions and retest protocols for Canadian provinces.

Province	TREC Cutoff	Reporting	Prematurity Definition	Prematurity repeat screening
British Columbia	>1.11 MoM	Quantitative for positive result	<37 weeks GA	If abnormal, repeat at 14 dol or at discharge Entire NBS panel repeated
Alberta	>1.12 MoM	Descriptive (quantitative only by request)	<32 weeks GA	Repeat at 21–28 dol Entire NBS panel repeated
Saskatchewan	<75 copies/ 3μL	Quantitative for positive result	<33 weeks GA <1500 g	Repeat at 21 dol Entire NBS panel repeated
Manitoba	< 33 Ct/μL	Descriptive and quantitative	<37 weeks GA <1500 g	Testing as per algorithm* Only TREC repeated
Ontario	<75 copies/ 3μL	Quantitative for positive result	<33 weeks GA <1500 g	If abnormal, repeat at 21 dol or at discharge Entire NBS panel repeated
Maritimes	<20 copies/ μL	Quantitative for positive result	<37 weeks GA <2000g	Repeat after 37 wk GA Only TREC repeated
Quebec	Implementing	Implementing	Implementing	Implementing
Newfoundland	Not Screening	Not Screening	Not Screening	Not Screening

dol: days of life; GA: gestational age; MoM: multiples of the median; NBS: newborn screen; TREC: T cell receptor excision circle.
*TREC 0–5 Ct/μL: proceed to confirmatory testing (ie lymphocyte subsets); >5–20 Ct/ μL: confirmatory testing if risk factors, eg high risk ethnic background, otherwise repeat TREC only at 10 dol; >20–33 Ct/ μL: repeat TREC only at 10 dol; if abnormal IKBKB or ZAP70, proceed to confirmatory molecular testing.

Conclusion: The Canadian provincialized health system has resulted in significant inconsistency in NBS programs, resulting in a 'postal code lottery' for whether a Canadian infant will be screened for SCID. Considerable heterogeneity exists in TREC methods and reporting, resulting in inability to compare data across jurisdictions. Canada has unique geographical and resource allocation barriers that should be further explored to assess screening turnaround times and access to resources in rural/remote communities. There is an urgent need for a national strategy for NBS in Canada for SCID and other conditions to establish standards and to work toward harmonization.

Keywords: Newborn screening, Severe combined immune deficiency, Canada, T cell receptor excision circles, Prematurity

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(83)

STAT3 Dominant Negative Disease: NIH Cohort

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Introduction: STAT3 dominant negative (DN) HIES is increasingly diagnosed, and patients are surviving further into adulthood. Through a natural history protocol, we have clinically and genetically characterized a relatively large STAT3 DN cohort, allowing insight into the clinical phenotype through late adult life.
Methods: We analyzed clinical and genetic data prospectively con our NIH IRB approved protocol. Charts were retrospectively reviewed for additional clinical information.
Results: Study population includes 164 patients with STAT3 DN HIES, with median age last seen or at death of 26 years (range 1–72); 91 (55%) were female. Pathologic variants were seen in STAT3 DNA binding domain (89), SH2 domain (66), and transactivation domain (9); majority were probands 120 (73%). Common clinical manifestations (>75) included: eczema (96%), boils (91%), recurrent pneumonias (87%), newborn rash (84%), retained primary teeth (84% greater than 8 years), and mucocutaneous candidiasis (82%). Bronchiectasis was seen in 67% and pneumatoceles in 47%. Less frequent but significant infectious manifestations included zoster in 37 (23%), bacteremia/sepsis in 35 (22%), osteomyelitis in 16 (10%), visceral abscess in 11 (7%), disseminated endemic fungi in 12 (7%), and necrotizing fasciitis in 8 (5%). Previously less recognized non-infectious manifestations included 10 gastro-intestinal perforations, 15 gastro-intestinal hemorrhages, 9 with vasculopathy and life-threatening event (i.e brain aneurysm bleed, myocardial infarction), 7 requiring joint replacement, and 8 with spine surgeries for degenerative disease. Of the 31 patients 45 years or older, 13 (42%) have needed surgery for DJD and/or intervention for aneurysm. Psychiatric diagnosis was seen in 55 (34%), most commonly with ADHD, autism spectrum disorder, depression and anxiety. The median age of survival was 55 years. Twenty-two patients died (age ranged 10–63 years), related to infection or pulmonary disease in 14. Six patients had a hematopoietic cell transplant (5/6 survived), one kidney transplant, and one lung transplant (deceased).
Conclusions: STAT3 DN HIES is a multi-system disorder with well-described manifestations of recurrent infections and eczematoid dermatitis. With improved therapies, patients are living longer and orthopedic, gastro-intestinal and vascular complications are being recognized. Description of the full phenotype will allow further understanding of STAT3's diverse roles and improve therapies.

Keywords: Hyper IgE syndrome, STAT3, Natural history

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(84)

Rituximab Responsive Immune Dysregulation in Pediatric Common Variable Immunodeficiency

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Introduction: Common variable immunodeficiency (CVID) is an inborn error of immunity associated with frequent infections, malignancy, and immune dysregulation. Granulomatous-lymphocytic interstitial lung disease (GLILD), a lymphocytic inflammation of the lung parenchyma, is a complication of CVID that primarily occurs in adulthood. The diagnosis of GLILD is often confirmed by histologic characteristics from lung biopsy, and treatment is primarily immunosuppression.

Case Report: A 9-year-old male with a history of chronic immune thrombocytopenia and recurrent sinopulmonary infections was diagnosed with CVID at 4 years of age. Genetic testing found two separate single nucleotide substitutions of ELF2 of uncertain significance. Other clinical findings included lymphadenopathy, splenomegaly and chronic transaminitis with liver biopsy showing lymphocytic infiltrates. He started immunoglobulin replacement therapy soon after diagnosis. Although asymptomatic, a screening chest X-ray at 8 years of age demonstrated bibasilar lung nodules. Follow up computed tomography showed innumerable bilateral lower lobe pulmonary nodules, bronchiectasis, and axillary and mediastinal lymphadenopathy (Figure 1A). Flow cytometry at that time revealed an elevated CD4:CD8T cell ratio, low CD19+B cell numbers, and low proportion of naïve T cells. Lung biopsy demonstrated reactive, T-cell lymphoid infiltrates with follicular hyperplasia, non-necrotizing granulomas, and organizing pneumonia consistent with GLILD. Treatment consisted of 4 weekly doses of rituximab (375 mg/m2) and mycophenolate, which replaced azathioprine due to intolerance. Within 8 months of treatment, there was radiographic improvement of his pulmonary nodules (Figure 1B), resolving lymphadenopathy, improved thrombocytopenia, and normal transaminases (Table 1). Flow cytometry 9 months post-rituximab showed normalization of his CD4:CD8 ratio, B cell reconstitution, and improvement in the numbers and percentage of naïve T cells.

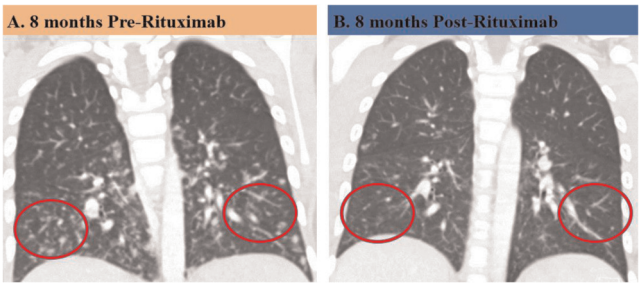

Figure 1. Panel A and B. Rituximab improves chest computed tomography.

Conclusions: GLILD is rare in children with CVID. This case highlights the need for routine radiographic screening including in asymptomatic pediatric patients with CVID. No consensus exists on GLILD screening modality and frequency; However, this case demonstrates the utility of a screening chest X-ray. Rituximab in combination with sustained immune suppression improved both pulmonary and other clinical/laboratory manifestations in this pediatric patient.

Table 1.
Select flow cytometric analysis and lab values before and after treatment for granulomatous-lymphocytic interstitial lung disease.

	10 months Pre Treatment Count (Percent)	10 months Post treatment Count (Percent)	Adult normal ranges
CD3	2452 (88.9%)	953 (87.7%)	67.9–81.0%
CD3+ CD4	2050 (74.3%)	617(57%)	39.2–50.8%
CD3+ CD8	4497 (64.2%)	268 (25%)	18.9–32.5%
NK	207 (7.5%)	54 (3.8%)	2.1–15.7%
B Cells	86 (3.1%)	71 (6.5%)	6.7–14.9%
Naïve T Cells	141 (6.9%)	188 (30.5%)	21.3–53.5%
Platelets	60	149	150–400 × 10^3/uL
AST	72	35	15–41 IU/L
ALT	83	28	8–40 IU/L

Keywords: Common variable immunodeficiency, Granulomatous-lymphocytic interstitial lung disease, Rituximab, Immune dysregulation

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(85)

Navigating the Gray Area: Borderline Hemophagocytic Lymphohistiocytosis Criteria and Dilemmas in Diagnosis and Treatment – A Case Report

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Hemophagocytic lymphohistiocytosis (HLH) poses a diagnostic challenge due to its variable presentation and overlapping features with other inflammatory conditions. This case report explores the complexities

surrounding diagnosis and treatment of a neonatal male presenting with borderline HLH criteria.

Despite the absence of definitive HLH criteria, our patient displayed signs of an HLH-like syndrome in the setting of a prolonged ICU course complicated by cardiac arrest, renal failure, liver failure, necrotizing enterocolitis, and bacteremia. This hyperinflammatory state persisted beyond treatment of his infectious processes, prompting treatment for suspected HLH. His resistance to high-dose corticosteroids and anakinra, plus a remarkable CXCL9 elevation, lead to the addition of emapalumab with swift improvement in his inflammatory markers. Etoposide was deferred due to end-stage renal disease. Emapalumab was later tapered to discontinuation and tacrolimus was simultaneously added given persistent elevation of sCD25. Later, he was weaned from corticosteroids and anakinra and was ultimately discharged home on tacrolimus after a 150-day admission, since remaining stable.

Concern for an HLH-like syndrome began with a ferritin of >10,000 ng/mL. Additional HLH criteria were met including hypofibrinogenemia, cytopenias, and elevated sCD25, in addition to developing fever. No other HLH criteria were met as workup was negative for splenomegaly, hemophagocytosis, and low/absent NKC cytotoxicity. Proceeding primary and secondary HLH workup was also largely negative including no attributable genetic mutation. Our patient did harbor a paternally-derived heterozygous variant of STXBP2 that can be associated with Familial Hemophagocytic Lymphohistiocytosis-5 (fHLH5), however only when homozygous; moreover, our patient did not express features unique to fHLH5.

This case navigates the diagnostic and treatment intricacies associated with borderline HLH presentations. Here, we use HLH criteria as a guide opposed to a strict diagnostic tool to ultimately treat an HLH-like syndrome in-part with biomarker-guided immunosuppression of hyperactive IFN-gamma and T-cell pathways. This yielded significant improvement in our patient's hyperinflammation per clinical status and inflammatory markers. We highlight the necessity for flexible and adaptive decision-making when faced with ambiguous presentations of life-threatening hyperinflammatory syndromes.

Keywords: Hemophagocytic lymphohistiocytosis, HLH, Hyperinflammation, STXBP2, Emapalumab

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(86)

Diagnostic Yield of Targeted Gene Panels in Evaluation of Suspected Immunodeficiency – The Mayo Clinic Experience

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Background: The availability and reduced cost of next generation sequencing has greatly enhanced identification of genetic defects implicated in inborn errors of immunity (IEI). Whole exome/genome sequencing (WES/WGS) has in some instances replaced targeted panels as a first line diagnostic approach. However, in clinical practice, targeted gene panels remain the most readily available, cost effective and time efficient genetic test. The reported diagnostic yield of targeted gene sequencing has varied widely, from 9%–70%.

Objectives: We evaluated the diagnostic yield of targeted gene sequencing in the evaluation of suspected IEI within the Mayo Clinic Enterprise.

Methods: A retrospective chart review was performed on all patients with suspected immunodeficiency who completed targeted gene panel sequencing (Invitae) at Mayo Clinic Rochester, Arizona and Florida, between January 1st, 2020 and December 31st, 2022.

Results: Targeted genetic sequencing of 151 patients from 3 Mayo Clinic sites was analyzed. The most common indication for testing was CVID (45 patients, 30%) followed by hypogammaglobulinemia (25 patients, 16.6%). Primary Immunodeficiency Panel led to a molecular diagnosis and changes in management in 10 patients (6.6%). Variants of uncertain significance (VUS) were identified in 143/151 (94.7%). Five patients had negative testing (3.3%). Expanded genetic testing (WES or WGS) was completed for 16/151 patients (10.6%). Additional variants were identified in 7 of these 16, none confirmed molecular diagnosis of IEI. An increased risk allele in NOD2 was detected in 29 patients (19.2%).

Conclusion: From a real-world clinical experience, our cohort demonstrated a lower-than-anticipated diagnostic yield from targeted gene sequencing as a first line molecular diagnostic test in the evaluation of suspected IEI. This may support a transition to upfront WES/WGS and potentially a multiomics approach to individualize care for IEI patients. Though no additional molecular diagnoses were made with expanded genetic testing, the small number tested (16/151) likely underrepresents the diagnostic yield. Barriers to WES/WGS including insurance coverage and cost often limited further evaluation. We observed a greater prevalence of mutations in NOD2 than expected in a healthy population. Further study is needed to understand whether NOD2 variants have a broader role in immune dysregulation, beyond that currently recognized.

Keywords: Genetics, Diagnostics, Immunodeficiency, WES, WGS, NOD2

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(87)

Phenotypic variability of Circulating Natural Killer Cells in healthy donors

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Natural Killer (NK) cells in humans exhibit a diverse range of surface and intracellular markers, indicating different stages of differentiation and levels of effector function. The more mature NK cell subsets are found in peripheral blood and their proportion may vary across individuals although understanding of intra-individual variation is limited. In this study, we investigated the distribution of specific NK cell subsets and functional markers over a 4-month period repeatedly in numerous healthy subjects. Peripheral blood mononuclear cells (PBMCs) were collected from 81 healthy participants on day 1 and from sub-sets of individuals available on the following time points: days 15, 29, 38, 57, 66, 99 and 134. Samples were stained using an NK cell-extracellular panel (CD3-/CD14-/CD19-CD45

+CD56+) and CD107a. Following fixation, permeabilization, and intracellular staining for perforin, flow cytometry was used to analyze the cells. These assessments were made by evaluating the samples following 2 hours of stimulation with phorbol myristate acetate/ionomycin (PMA/I) as well as the resting state of NK cells in the absence of stimulation.
The CD56bright and CD56dim NK cell subsets, perforin (MFI), and the percentage of CD107a positive cells were examined separately over time in selected individuals. We also assessed the impact of demographic variables such as age and gender on these markers.
This study contributes to understanding the intra-individual ranges of circulating NK cell subtypes and their degranulation abilities in an adult population.

Keywords: Natural Killer cells, CD56, Degranulation, Perforin, Healthy human donor, Variability

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(88)

Practical Considerations regarding the Immune Dysregulation and Immunodeficiency in Down Syndrome

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[13]*Professor/University of Colorado School of Medicine*

It is well known that patients with Down Syndrome have a high frequency, increased severity, and more prolonged infections. However, many do not reach immunology care due to premature death from infection which is the leading cause of premature mortality in this population. By identifying those patients with decreased immune function early and starting preventative treatments, we might be able to prolong some of these patients' lives. Chromosome 21 contains essential immune-related genes, including four of the six IFNR genes, B2 integrin, ICOSLG, UBASH3A, RUNX1, and AIRE genes. Among the immune defects that have been described include: T cell defects including mild to moderate lymphopenia; B cell abnormalities, particularly decreased naive B cells, variable hypogammaglobulinemia, and poor specific antibody responses; impaired neutrophil chemotaxis with variable neutropenia and lower number of granulocytes; and immune dysregulation with higher circulating levels of proinflammatory cytokines and chemokines than controls. Despite its high frequency in the population and its well described immune abnormalities, Down Syndrome is not included in "The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity." Moreover, there are no CIS or other society guidelines regarding routine immunologic screening or referral of these patients. In 2022, the American Academy of Pediatrics updated their guidelines entitled "Health Supervision for Children and Adolescents with Down Syndrome" with no recommendations regarding immunological practical considerations. We are developing a workgroup within the CIS Early Career Immunologist Committee in collaboration with the Down Syndrome Medical Interest Group to develop a report reviewing the literature describing the immune deficiency and dysregulation in Down Syndrome, and to provide practical considerations for routine screening of these patients for immune dysfunction with potential treatment options. We hope this report can be used by hospitalists, primary care physicians, and immunologists to prevent and treat the immune deficiency and dysregulation in this significantly vulnerable population.

Keywords: Down syndrome, Primary immune deficiency disease, Immune dysregulation

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(89)

Hypogammaglobulinemia, Lymphocytopenia and Recurrent Septicemia in Schimke Immuno-Osseous Dysplasia: a case report

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Background: Schimke Immuno-osseous Dysplasia (SIOD) is a rare autosomal recessive disorder caused by a mutation in the SMARCAL1 gene, which encodes an enzyme responsible for DNA repair and cellular division. The estimated incidence is 1 in 1–3 million births. SIOD can

present with multi-systemic manifestations, affecting the immune, hematological, renal, neurodevelopmental, endocrine, and musculoskeletal systems.

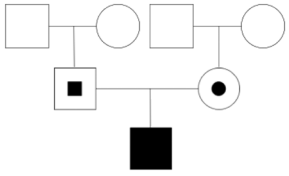
Case presentation: This is a 4-year-old boy, with a history of failure to thrive and prematurity, who presented with nephrotic syndrome secondary to focal segmental glomerulosclerosis. The patient had multiple admissions due to severe bacteremias (Streptococcus pneumoniae, Pseudomonas aeruginosa), encephalopathy, posterior reversible encephalopathy syndrome secondary to severe intractable hypertension, requiring dialysis initiation. Genetic evaluation identified two compound heterozygous pathogenic variants, in trans, in the SMARCAL1 gene (c.1191del and c.1860G>A), both of which caused protein truncation with absent or disrupted protein, leading to a severe phenotype of SIOD.

Lymphocyte subsets revealed low CD3+(851cells/uL), CD4+(193cells/uL), CD19+(250 cells/uL). IgG hypogammaglobulinemia (79 mg/dL) requiring IVIG and antibiotic prophylaxis with Trimethoprim-Sulfamethoxazole. Vaccines were up-to-date, but lymphocyte mitogen proliferation displayed an inadequate response, with suboptimal antibody titers to Streptococcus pneumoniae (1/23 serotypes), Diphtheria toxoid (0.08 mcg/mL), and Hemophilus influenzae B (0.17 mcg/mL).

Discussion: Approximately 100 SIOD cases have been reported in the literature. The average life expectancy varies based on symptom management, with infections accounting for nearly 25% of the mortality. T-cell lymphopenia is reported to be about 79%, while T-cell immunodeficiency, evidenced by infection susceptibility, is observed in 49% of cases. The mechanism of lymphopenia remains unclear, although theories include intrinsic T-cell receptor signaling deficits, or extrinsic factors such as impaired hematopoietic precursor proliferation. Furthermore, SIOD patients may present with severe hypogammaglobulinemia. We hypothesize that not only the impaired humoral immunity synthesis, but also the protein loss due to kidney disease might play a role. Thus, it is imperative to provide therapies and tailor management for the immunological dysfunction in accordance with each patient's genetic and immune profile.

Conclusion: This case reminds us to consider immune work-up in patients with SIOD. Early clinical diagnosis allows for timely multisystemic evaluation and targeted treatment in order to prevent complications that may be life-limiting.

(A)



(B)

Gene	Variant	Zygosity	Variant classification	Inheritance
SMARCAL1	variant c.1191del (p. Thr399Argfs*38)	heterozygous	pathogenic	Father
SMARCAL1	variant c.1860G>A (p. Trp620*)	heterozygous	pathogenic	Mother

(C)

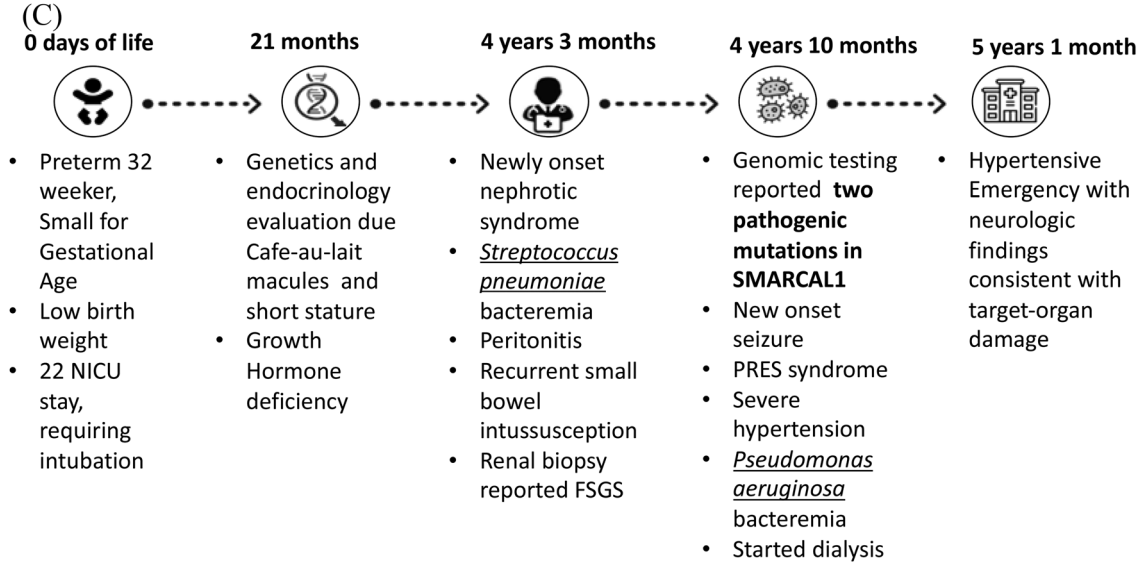


Figure 1. (abstract: 89) (A) Pedigree for studied individual. Circles and squares indicate females and males, respectively. (B) *SMARCAL1* variant details. (C) Timeline of the events in the case.

Table 1.
Immunological features of SIOD patients in literature.

Lymphocyte subset	Absolute count [cells/mm3]	Normal range [cells/mm3]
Mature T cells (CD3)	851	1,220-3000
Helper T cells (CD4)	193	670-1930
Cytotoxic T cells (CD8)	683	350-1160
Natural Killer (CD16, CD56)	192	60-540
B cells (CD19)	250	310-1120

Immunoglobulin level	Total count [mg/dl]	Normal range [mg/dl]
IgA	29.3	25-152
IgE	<25	70-300
IgG	79	444-1186
IgM	135.5	41-186

Vaccine titers	Patient's titers	Cut off for protection from invasive disease
Diphteria Toxoid IgG Ab	0.08 IU/mL	≥0.10 IU/mL
Haemophilus Influenzae B IgG Ab	0.17 mcg/mL	≥1.00 mcg/mL
Streptococcus Pneumoniae serotype 1	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 2	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 3	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 4	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 5	2.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 8	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 9N	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 12F	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 14	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 17F	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 19F	0.5 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 20	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 22F	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 23F	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 6B	0.7 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 10A	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 11A	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 7F	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 15B	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 18C	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 19A	0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 9V	<0.3 mcg/mL	≥0.3-0.50 mcg/mL
Streptococcus Pneumoniae serotype 33F	<0.3 mcg/mL	≥0.3-0.50 mcg/mL

Table 2.
Immunological features of SIOD patients in literature.

Case	No. of patients	Lymphopenia	Recurrent infections
Present case	1	1	1
Orozco et al	1	1	1
Marin et al	1	1	1
Castellano-Martinez et al.	2	0	0
Malhotra et al.	1	1	0
Hara-Isono et al.	2	1	1
Wang et al.	1	1	0
Ramdeny et al.	1	1	0
Bertulli et al.	2	2	2
Prato et al.	2	2	0
Xiong et al.	1	1	1
Ji n et al.	1	1	0
Haffner et al.	1	0	0
Arad and Pirzadeh	1	0	0
Power et al.	2	2	1
Lipska-Zietkiewicz et al.	34	25	17
Liu et al.	1	1	1
Barraza-Garcia et al.	1	1	1
Carroll et al.	1	1	1
Pedrosa et al.	1	0	1
Santangelo et al.	1	1	0
Baradaran -Heravi et al.	5	4	3
Yue et al.	1	1	1
Lev et al.	3	3	1
Lucke et al.	3	3	1
Basiratnia and Fallahzadeh	1	2	0
Clewing et al.	20	16	8
Petty et al.	1	1	1
Ehrich et al.	2	2	2
Spranger et al.	5	2	2
Schimke et al.	1	1	1
Total	101	79/101	49/101

Keywords: Schimke immuno-osseous dysplasia, Hypogammaglobulinemia, Lymphocytopenia, Recurrent Septicemia, SMARCAL1

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(90)

Silent Suspects: Drivers of Invasive Pneumococcal Diseases

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Background: Invasive pneumococcal disease (IPD) is a severe manifestation of infection such as pneumonia, bacteremia, and meningitis caused by Streptococcus pneumoniae. While the incidence has declined over the years with the use of the pneumococcal conjugate vaccination, risk factors such as extremes of age, and comorbidities that include primary immunodeficiencies, may predispose an individual to IPD. Specifically, deficiencies in complement, immunoglobulins, and splenic dysfunction have been associated with an increased risk of IPD.
Case Presentation: A previously healthy 17-year-old female with a history of anxiety, allergic rhinoconjunctivitis presented to urgent care with 3 days of productive cough, and 1 day of fevers, shortness of breath, and scant hemoptysis. Physical exam revealed diminished breath sounds and crackles on auscultation. Chest imaging revealed dense consolidations consistent with multilobar pneumonia. The patient was started on intravenous antibiotics, and was admitted to Mayo Clinic Hospital, St. Mary's Campus. Blood cultures grew Streptococcus pneumoniae. The patient rapidly improved with antibiotics and was discharged with a course of amoxicillin. She followed-up with immunology at Mayo Clinic, and subsequent evaluation was significant for an IgA of < 1 mg/dL with IgM and IgG normal/ elevated. Other studies including immunophenotyping and genetic testing (429 gene PID panel testing) were unrevealing, and she was diagnosed with selective IgA deficiency (SIgAD). Though the patient denied gastrointestinal symptoms, tissue transglutaminase IgG was > 100 mg/dL and a duodenal biopsy revealed histologic changes consistent with Celiac disease. The patient received the Pneumococcal 20-valent Conjugate Vaccine, which resulted in a positive serologic response.
Discussion: SIgAD is the most common primary immunodeficiency (PID), and while the majority of patients with SIgAD are asymptomatic, affected individuals can present with recurrent sinopulmonary and gastrointestinal infections. This case, however, represents an unusual presentation of SIgAD manifesting as IPD in a young, healthy patient without a history of recurrent infections. Additionally, her underlying Celiac disease and associated functional hyposplenism may have contributed to the severe presentation. Pneumococcal vaccination is important to prevent recurrent IPD for these individuals. This case illustrates the importance of maintaining a broad differential that includes PIDs in young, healthy patients presenting with IPD.

Keywords: Invasive pneumococcal disease (IPD), Primary Immunodeficiency (PID), Selective IgA deficiency (SIgAD), Celiac disease

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(91)

Beyond IgG Levels: Assessing Pneumococcal Vaccine Response with Multiplexed Opsonophagocytosis Assay

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Evaluating humoral immunity in patients with suspected immune defects often relies on measuring Pneumococcal IgG levels, which may not consistently correlate with clinical protection against infections. This study investigates the effectiveness of the Multiplexed Opsonophagocytosis Assay (MOPA) in measuring pneumococcal antibody function (PAF) and its role in determining specific antibody responses to PneumoVax.
We analyzed 24 patients with recurrent infections, comparing Streptococcus pneumoniae IgG levels and MOPA for 14 pneumococcal serotypes pre-vaccination. Protective thresholds were defined as >1.3 for IgG and >8 for MOPA.
Results showed a significantly higher average percentage of protective serotypes per patient with MOPA (27.1%) than IgG (13.7%) (paired T-test, $p < 0.0001$). Additionally, the likelihood of a serotype being considered protective was 4.5 times greater with MOPA than with IgG (McNemar's OR 4.5; $p < 0.0001$). Medical record review also indicated that patients displaying low IgG, but protective MOPA results did not exhibit increased sinopulmonary infections. Subsequent post-vaccination analysis in 9 patients for 9 pneumococcal serotypes showed strong concordance between IgG and MOPA in identifying protective antibodies for 8 of the 9 samples. Analysis of the remaining patients and serotypes is currently underway.
In summary, our study suggests that MOPA offers higher sensitivity in identifying protective pneumococcal immunity, both pre- and post-vaccination, compared to traditional IgG binding levels. These findings highlight the potential of MOPA as a more effective tool in assessing pneumococcal vaccine responses in clinical settings.

Keywords: Multiplexed opsonophagocytosis assay, Pneumococcal vaccine response, Pneumococcal antibody function, Streptococcus pneumoniae IgG levels

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Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Takeda (Research Grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received)). The other authors have no financial relationships or conflicts of interest to report.

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(92)

Selective IgA Deficiency in a Patient with Susac Syndrome

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Susac Syndrome (SS) is an autoimmune endotheliopathy characterized by a clinical triad of hearing loss, branch retinal artery occlusion (BRAO), and encephalopathy. A significant proportion of patients with primary immunodeficiencies are known to develop autoimmune diseases but there have been no prior reports of SS diagnosed with immunodeficiencies. We report a case of a young woman with SS diagnosed with concurrent selective IgA deficiency (IgAD).

A 37-year-old woman presents with a history of SS first diagnosed in 2017. At the time of diagnosis, she presented with encephalopathy, multiple subcortical strokes, hearing loss, and BRAO. She further developed significant lower extremity spasticity as a result of SS and had a progressive decline in ambulation over the course of several years. After a complete neurological workup, her neurologist decided to start long-term immunosuppressive therapy, Rituximab, to prevent further progression of her disease.

On workup prior to initiating Rituximab, it was noted that she had a low IgA of 3 mg/dL. IgG and IgM were within normal limits (1,067 mg/dL and 105 mg/dL, respectively). Diphtheria and tetanus titers were in the normal range. Cell counts and lymphocyte proliferation assay were normal. Her titers to the 23 pneumococcal serotypes were only 8 out of 23. However, this was deemed to be related to timing from her last Pneumovax as a child. With regards to infections, she complained of 1 to 2 sinus infections a year and perhaps 1 ear infection a year. She denied any prior episodes of pneumonia, skin infections, admissions to a hospital for an infection or requiring intravenous antibiotics, personal history of other autoimmune diseases, or a family history of immunodeficiencies. With this workup, she was diagnosed with selective IgA deficiency with clinically normal immune function. She was given the 23-valent polysaccharide vaccine and obtained her COVID vaccine series at that time. She was subsequently started on Rituximab.

To the authors' knowledge, this is the first published report of a patient with SS and IgAD. This case illustrates the need to investigate the presence of primary immunodeficiencies in neurological diseases, particularly autoimmune.

Keywords: Susac syndrome, Immunodeficiency, Autoimmune diseases, Selective IgA deficiency

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(93)

Infusion reactions to adeno-associated virus (AAV)-based gene therapy: Mechanisms, diagnostics, treatment and review of the literature

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The use of adeno-associated virus (AAV) vectors in gene therapy has demonstrated great potential in treating genetic disorders. However, infusion-associated reactions (IARs) pose a significant challenge to the safety and efficacy of AAV-based gene therapy. This review provides a comprehensive summary of the current understanding of IARs to AAV therapy, including their underlying mechanisms, clinical presentation, and treatment options. Toll-like receptor activation and subsequent production of pro-inflammatory cytokines are associated with IARs, stimulating neutralizing antibodies and T-cell responses that interfere with gene therapy. Risk factors for IARs include high titers of pre-existing neutralizing antibodies, previous exposure to AAV, and specific comorbidities. Clinical presentation ranges from mild flu-like symptoms to severe anaphylaxis and can occur during or after AAV administration. There are no established guidelines for pre- and post-administration tests for AAV therapies, and routine laboratory requests are not standardized. Treatment options include corticosteroids, plasmapheresis, and supportive medications such as antihistamines and acetaminophen, but there is no consensus on the route of administration, dosage, and duration. This review highlights the inadequacy of current treatment regimens for IARs and the need for further research to improve the safety and efficacy of AAV-based gene therapy.

Keywords: Infusion-associated reactions, Gene therapy, Adenovirus, Immune responses, Clinical trials, Innate immunity, Adaptive immunity, Safety, Efficacy

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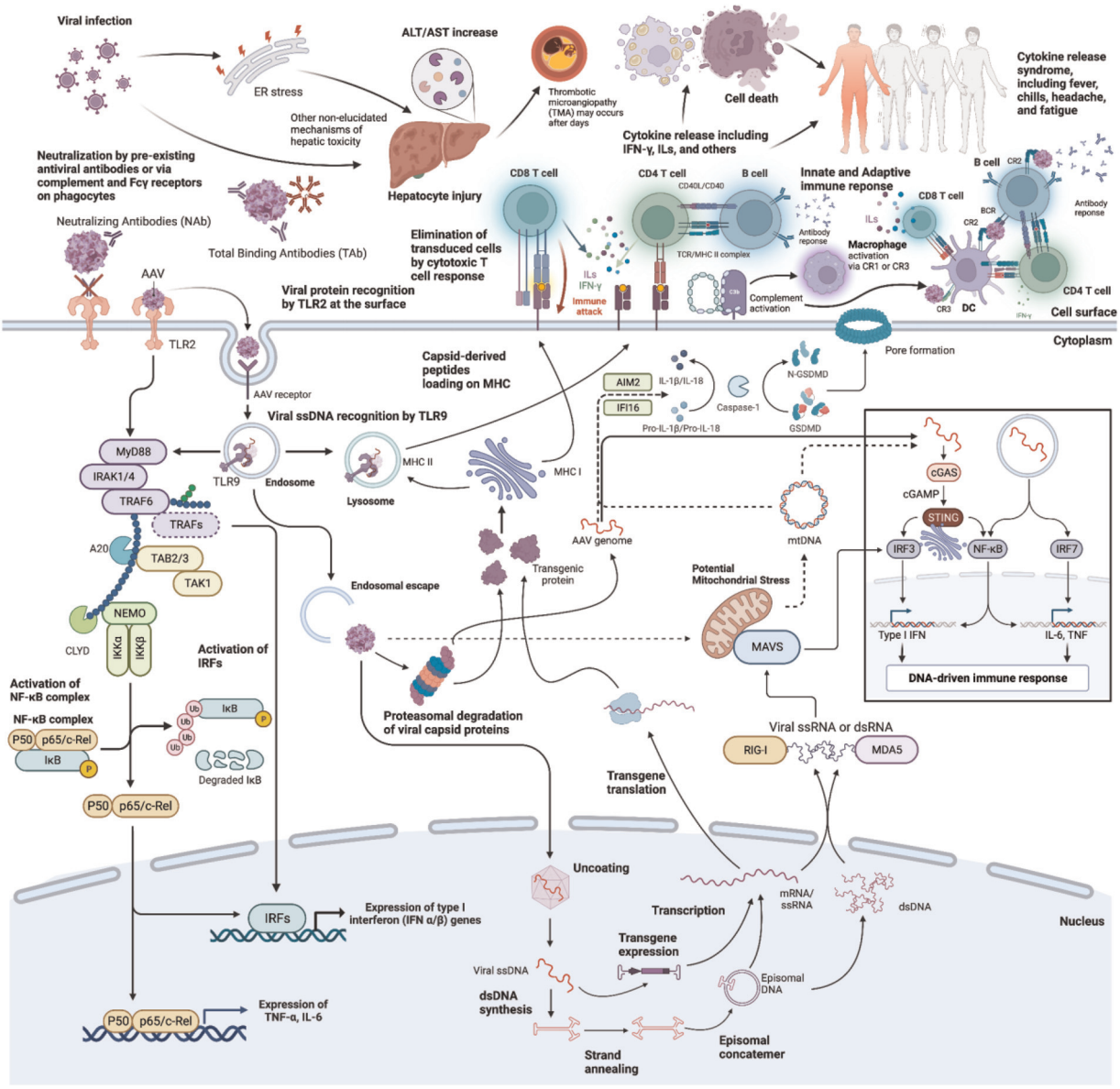

Figure 1. (abstract: 93) Mechanisms of immune-mediated adverse responses following AAV infusion therapy. The initial response to AAV involves neutralization through pre-existing neutralizing antibodies (NAbs) and/or total binding antibodies (TAbs) via complement and Fcγ receptors on phagocytes. AAV capsids have the capability to engage toll-like receptor 2 (TLR2) at the cell surface. Inside the endosome or lysosome, AAV capsids may rupture, exposing their viral genome to TLR9. Once TLR2 or TLR9 has been activated, it initiates the MyD88/IRAK pathway, triggering the production of proinflammatory cytokines such as TNF-α, IL-6, and interferons (IFNs). Additionally, AAV-mediated stress can release mitochondrial DNA (mtDNA). Both mtDNA and the viral DNA exposed within the cytosol activate cytosolic DNA sensors through cyclic GMP-AMP synthase (cGAS), which stimulates cGAMP synthesis, activating the STING/IRF3 pathway and resulting in the upregulation of type I IFNs. DNA binding also activates the assembly of inflammasomes mediated by AIM2 and IFI16, which promotes the maturation of IL-1β and IL-18 and pore formation with gasdermin D (GSDMD). Nuclear-localized AAV genomes may also induce mtDNA release through mitochondrial antiviral signaling (MAVS) via DNA binding with RIG-I or MDA5, and the activation of cGAS with downstream responses. The production of transgenic viral proteins leads to the presentation of antigens and further adaptive immune responses involving CD8+ T cells and B cells through CD4+ T cells. The innate immune response is also activated, leading to the activation of macrophages and dendritic cells. These immune responses can result in ER stress, hepatic toxicity, and thrombotic microangiopathy (TMA). The release of cytokines can lead to cell death and further cytokine release syndrome, including fever, chills, headache, and fatigue. Pathways supported by circumstantial evidence are indicated by dashed arrows.

(102)

An Observational Cohort Study to Evaluate the Efficacy and Safety of Allogeneic Processed Thymus Tissue-agdc Post-FDA Approval: The Congenital Athymia Patient Registry

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Allogeneic processed thymus tissue-agdc is approved for use as a cultured thymic tissue implantation for immune reconstitution in pediatric patients with congenital athymia, a rare form of severe T cell immunodeficiency. In May 2022, an observational cohort study (Congenital Athymia Patient Registry) was initiated to better understand immune reconstitution, long-term survival, and adverse events after administration of allogeneic processed thymus tissue-agdc. Enrollment criteria included a confirmed congenital athymia diagnosis, treatment with allogeneic processed thymus tissue-agdc, and written informed consent. All patients received tissue implantation at a single clinical site (Duke University). Primary endpoints are survival at 12 months post-treatment and extent of T cell immune reconstitution post-implantation. Secondary endpoints are incidence of serious adverse events (SAE), incidence of AEs of special interest (AESI) such as acute kidney injury (AKI) and autoimmunity. Survival beyond 24 months post-treatment will be evaluated as an exploratory objective. At the time of submission, 21 patients (7 females, 14 males) of the targeted 75 participants have been enrolled. Results are from medical record data abstraction at baseline (pre-implantation), every 3 months during the first year after implantation, every 6 months during year 2, and annually thereafter. Median (range) age was 14 (5–381) days at diagnosis and 1126 (235–2328) days at implantation (first 20 patients enrolled). The most frequent genetic etiologies were 22q11del (45%) and CHD7 mutations (20%). To date, 7 patients have reached 12 months post-treatment. Prior to implantation, 14/20 patients (70%) have been diagnosed with atypical phenotype (autologous graft-versus-host disease) based on rash, cytopenia, adenopathy, and other symptoms. One death occurred at 76 days post-implantation for causes unrelated to allogeneic processed thymus tissue-agdc. Preliminary results of extended lymphocyte enumeration over time indicate that 4 patients have achieved naive CD4+ cell counts ≥100 cells/mm^3 by the 12-month visit, with 3 patients meeting this threshold by 9 months. There were 17 participants who experienced ≥1 SAE or AESI; 11 experienced AKI. The data collected provide supplemental safety and efficacy results following clinical trials of allogeneic processed thymus tissue-agdc and evidence for future guidelines for patient care.

Keywords: 22q11.2 deletion, CHARGE syndrome, Congenital athymia, DiGeorge syndrome, Immune reconstitution, Naive T cells, Primary immunodeficiency, Registry, Study design, Thymus

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Oral Presentation Abstracts

(94)

Dominant negative IKKα and immunodeficiency with immune dysregulation

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IKKα is an essential serine/threonine kinase in the activation of the non-canonical NF-κB pathway encoded by the gene CHUK. IKKα is also the second kinase of the IKK complex in the canonical NF-κB pathway where its role is redundant with IKKβ. In human, bi-allelic null mutations of CHUK have been associated with fetal encasement syndrome and is lethal in utero while the mouse model is perinatally lethal. Recently, a single homozygous missense variant in the interaction domain of IKKα with its activator NIK has been characterized in a patient suffering from a combined immunodeficiency. In this work, we report the pathogenicity of a heterozygous missense variant of CHUK. The patient was suffering from early-onset hypogammaglobulinemia associated to recurrent lung infections with a syndromic clinical presentation reminiscent of a Hay-Wells syndrome. She died of a diffuse large B-cell lymphoma at 16 years old. The molecular characterization of the variant and the characterization of patient's cells showed a profound defect in the activation of the non-canonical pathway both in stromal cells and immune cells. This defect was linked to a dominant negative effect of the variant. Reconstitution of patient's cells with a wt allele by lentiviral transduction partially restored the phenotype. Interestingly, neutralizing autoantibodies against type I interferons were detected in the plasma of this patient, as recently described in other non-canonical NF-kB defects by Tom Le Voyer et al. Thus, we described a new mode of inheritance (negative dominance) in the very rare deficiency in IKKα and expanded the NF-kB defects in which autoantibodies against type I interferons arise.

Keywords: Immunodeficiency, CHUK, NF-kB.

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(95)

Patterns and presentations of mosaic variation in monogenic acquired errors of immunity

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Acquired genetic variants are a key driver of malignancy, and are also associated with non-malignant disorders, including monogenic immune disease. To better understand the relative prevalence and presentation of

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mosaic and germline variants in monogenic immune disease, we queried results from >4 million individuals referred for high-depth clinical genetic sequencing for a range of clinical indications, including suspected monogenic disease and hereditary cancer testing. From a set of 582 genes present on the 2022 IUIS Inborn Errors of Immunity list and/or Invitae® Inborn Errors of Immunity and Cytopenias Panel, we identified 68,302 pathogenic or likely pathogenic germline variants in 64,665 individuals, and 3,778 suspected mosaic variants in 3,585 individuals. The majority of mosaic variants were identified in individuals referred for hereditary cancer testing, and in genes associated with cancer risk. In a subset of 18 genes previously associated with acquired monogenic immune disease, mosaic or germline variants were reported in 14 genes: 323 germline variants across 12 genes, and 22 manually curated mosaic variants across a partially-overlapping set of 12 genes. At least 6 individuals with mosaic variants had a known or suspected history of leukemia or lymphoma at the time of testing. For 10 genes with both mosaic and germline variants, mean age at testing was older for mosaic variants (32.5 years old) than germline variants (20.3 years old). Missense variants at p.Met41 in UBA1 were the most prevalent mosaic variants (7/22, 31.8%) and were exclusively identified in males tested at 56 years of age or older (mean 73.9 years old), the majority of whom had clinical features consistent with VEXAS syndrome including anemia, thrombocytopenia, and relapsing polychondritis. These results improve our understanding of mosaic variants in monogenic acquired errors of immunity.

Keywords: Mosaic variation, Monogenic, Acquired errors of immunity

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(96)

Molecular and functional identification of unstable regulatory and autoreactive effector T cells that are expanded in patients with FOXP3 mutation

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Immune dysregulation polyendocrinopathy enteropathy X linked syndrome (IPEX) is a prototypical autoimmune disease caused by loss of regulatory T cell (Treg) function due to a mutation in the FOXP3 gene. Although much work has been done in the murine models of FOXP3 deficiency, there is very little evidence of Treg stability and no evidence about TCR autoreactivity in FOXP3-deficient patients. Here, we combined cytometric and epigenetic data, single-cell RNA/protein/TCR profiling, and bulk TCR sequencing to shed light on Treg plasticity and TCR autoreactivity in patients with IPEX (Borna S. et al, Sci Transl. Med. in press). We found that in patients with IPEX Treg are expanded, as also demonstrated by an increase in the frequency of TSDR demethylated cells, and the memory Treg separates into two populations. The first population consists of prototypical CD25highCD127low Treg. The second population of Treg is specific for patients with IPEX; these Treg are clonally related to the typical Treg population, but they have reduced/lost expression of Treg markers including CD25 and FOXP3. We named this atypical Treg population loss-of-identity Treg. We further show that they have an autoreactive TCR repertoire and a signature of TNF-α signaling indicating that they have been exposed to the autoimmune inflammatory environment. Consistent with the immune dysregulation observed in these patients, our functional tests revealed that FOXP3-deficient Treg gained Th2 Teff-like phenotype. In addition, we observed increased TCR autoreactivity in the effector T cell (Teff) compartment, which, together with the expansion of autoreactive unstable Treg, indicates a dual source of autoreactive T cells as a consequence of FOXP3 deficiency. These findings provide new mechanistic insights into the disease pathophysiology, which could be used for diagnostic and prognostic purposes, as well as for monitoring the effects of immunomodulatory treatments.

Keywords: FOXP3, IPEX, Autoimmunity, Regulatory T cells, Immune dysregulation, TCR, TSDR

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(97)

C1q Deficiency is an interferonopathy often refractory to Fresh Frozen Plasma

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C1q deficiency caused by biallelic pathogenic variants in C1QA, C1QB or C1QC genes leads to increased susceptibility to encapsulated bacterial infections and predisposition to systemic lupus erythematosus (SLE)-like symptoms. Severe lupus-like features often require immunosuppressive treatments including corticosteroids, antimetabolite or biologic therapies increasing risk of serious bacterial infections. Alternatively, fresh frozen plasma (FFP) infusions can restore C1q activity, although the complement activity rapidly drops off within hours and frequent treatments are often necessary. Herein we present a cohort of pediatric C1q deficiency patients (n = 6) with severe autoimmune features who experienced challenges with FFP infusions. The clinical and laboratory features, treatment course, FFP infusion frequency and reactions as well as the molecular defects for each subject were obtained. The FFP treatments were limited in efficacy, logistically challenging and infusion reactions were common. Additionally, we present a novel flow cytometric assay for quantifying Type I and Type II interferon (IFN) signatures using CD169 (SIGLEC-1) and CD274 (PD-L1) on CD14 bright monocytes respectively as stable surrogate markers. Fresh EDTA blood samples shipped overnight or frozen PBMC samples from C1Q deficiency subjects demonstrated uniquely elevated Type I IFN [%CD169+ 97–99%; CD169 MFI 29847–55564; n = 4] compared to healthy controls [pediatric reference intervals (5th–95th): %CD169+ 0–2%); median fluorescence intensity (MFI): 1205–8343; n = 125)]. In contrast, the Type II IFN signature [%CD274+ 0–1%; CD274 MFI 1140–3834; n = 4] was comparable to control samples [pediatric reference intervals (5th–95th): % CD274+ 0–1); MFI 781–4585; n = 125)]. During the validation of this assay, several other subjects with type I and II IFN signatures also were identified and a subset of these were independently validated against a Nanostring assay. Further some of these patients were assessed after initiation of relevant therapy and the same assay was utilized to monitor treatment response including JAK inhibitor. In the C1q deficient subjects tested, all demonstrated a constitutive type I interferon expression demonstrating the diagnostic and monitoring utility of this rapid flow assay. Larger studies will be needed to determine the most effective therapy options for C1q deficiency given the broad immunoregulatory role of the C1q complex.

Keywords: C1q deficiency, Type I interferon, Systemic lupus erythematosus, Fresh frozen plasma, JAK inhibitor.

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(98)

Unique challenges and unique solutions in hematopoietic stem cell transplantation for rare inborn errors of immunity

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Introduction: We are increasingly recognizing a wider phenotype in children with inborn errors of immunity (IEI) who present with extra-immune manifestations, immune dysregulation and predisposition to malignancy in the era of whole exome sequencing. We present our experience on the unique challenges faced during hematopoietic stem cell transplantation in these children and cost-effective solutions offered.
Patients and methods: We conducted a retrospective analysis of the children with rare inborn errors of immunity over a ten-year period and defined "rare" IEI as patients with SCID like phenotype, very early onset inflammatory bowel disease and autoinflammatory conditions as per the 2019 IUIS classification. The study was approved by the hospital ethical committee.
Results: From January 2013 to January 2023, we performed HSCT for 198 children with inborn errors of immunity, of which fifty-eight children were rare IEI. We used a haploidentical donor in 25 children (41%), matched family donor in 22 children (36%) and a matched unrelated donor in 13 children (23%). We documented engraftment in 97% of the children and primary graft failure in 1 child (3%) and secondary graft failure in four children (11%). In children with very early onset inflammatory bowel disease (VEOIBD) the conditioning toxicity was higher requiring optimal management of mucositis. Uncontrolled CMV and adenoviral reactivation resulted in high mortality in our cohort with DOCK −8 deficiency. Children with Griscelli syndrome had a high propensity to hypertension and PRES and seizures. We documented ongoing inflammatory bowel disease (IBD) in children with XIAP after a successful HSCT. Graft rejection was high in children with IFNGR1− MSMD requiring pretransplant immunosuppression with fludarabine and dexamethasone and plasma exchange. Children with MHC Class 1 and XLP had poor immune reconstitution with no thymic recovery resulting in mortality. The overall survival in this cohort was 71%, with most of the mortality secondary to viral infections.

Table 1.
Underlying genetic mutations in the rare PID.

S.NO	Underlying mutation and phenotype	Numbers
1.	SCID like phenotype	3
	LRBA	2
	ORAI-1MHC Class II	3
	CD247	1
	IKZF1	1
	Cerununnos	1
	NHEJ1 mutation	1
	MHC Class I	2
2.	MSMD	
	IL-12	3
	IFN-GR1	4
3.	Hyper Ig	
	EDOCK 8	4
	STAT 3	1
4.	HLH	
	Griscelli	11
	Chediak Higashi	3
5.	Inflammatory bowel disease	
	IL-1O Ra	4
	XIAP	4
	IPEX	2
	LRBA	1
	X-LP	1
6.	CVID	2
7.	Autoimmune cytopenia	
	ADA2(CECR1) deficiency	1
	Immunodeficiency 26 with Thrombocytopenia	1
	MYSM1	1
8.	Stroke	
	Activated PI3 K deficiency	1

Conclusion: HSCT in rare IEI poses unique challenges and multicenter international collaboration is required to improve outcomes in these children. The treatment needs to be individualized for each of these rare conditions and long term follow-up is required to understand the impact of our interventions.

Keywords: Inborn error of immunity, HSCT, GVHD, Infections, SCID variant, MSMD, Hyper IgE, HLH, IBD

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(99)

C-terminal mutants in IRF8 associated with mild natural killer cell deficiency

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IRF8 is a transcription factor that is important for B cell, NK cell, and myeloid cell function. IRF8 deficiency leads to susceptibility to mycobacterial disease in a dominant inheritance pattern and recessive mutations can lead to monocyte and dendritic cell deficiency and/or NK cell deficiency (NKD). Conversely, an up-regulation of IRF8 expression has been reported for certain B cell lymphomas and IRF8 expression is regulated by IL-15 signaling in human NK cells. Most NKD are associated with severe, often fatal viral infections and malignancies, nevertheless some patients present with nonfatal but chronic and debilitating viral infections, mainly Epstein-Barr virus and herpesvirus. Here using next generation sequencing on our cohort of NKD patients we identify truncating variants at the C-terminal region of IRF8 in two female adults with chronic EBV infection, decreased NK cell frequencies, and impaired NK cell cytotoxic function. While truncation variants often suggest loss of function due to haploinsufficiency, we instead observed that IRF8 protein in both individuals' PBMC and EBV-BLCL was upregulated, suggesting that the C-terminal portion of the protein is important for its proteasomal degradation. Interestingly, the mutants didn't affect the DNA binding domain or the IRF association domain, which argue against loss of function as a mechanism of the disease. Association of C terminal-truncation variants are also observed in B cell lymphomas, suggesting a possible gain-of-function (GOF). How GOF leads to NKD remains to be elucidated, nevertheless our preliminary data using YTS cell lines suggest the defect associated to the C-terminal truncations in NK is not functional but rather a developmental defect. In conclusion, our data suggest that the C-terminal region of IRF8 is important to modulate the proteasomal degradation of IRF8 and that in its absence, the up-regulation of the protein is deleterious for the proper NK cell maturation.

Keywords: NKD, IRF8, B cell lymphoma

Disclosures: Lisa Satter: I have relevant financial relationships with proprietary interests: ab2bio (Clinical Trial Investigator); Grifols (Advisory Board, Consultant, Scientific Advisory Board, Speaker/ Honoraria (includes speakers bureau, symposia, and expert witness)); horizon (Advisory Board, Consultant); incyte (Clinical Trial Investigator, Scientific Advisory Board); Pharming (Clinical Trial Investigator, Scientific Advisory Board); Takeda (Consultant). The other authors have no financial relationships or conflicts of interest to report.

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(100)

Clinical Characteristics Associated With Mortality Among Patients With Congenital Athymia Treated With Allogeneic Processed Thymus Tissue-agdc

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Allogeneic processed thymus tissue-agdc implantation has FDA approval for immune reconstitution in pediatric patients with congenital athymia.

Patients were enrolled across 10 prospective, single-center, open-label clinical trials and pooled for analysis. In the clinical trials, patients receiving allogeneic processed thymus tissue-agdc implantation had an estimated 1-year survival rate of 77%(95% CI, 0.670, 0.841) and 2-year survival rate of 76%(0.658, 0.832). This post hoc analysis evaluated clinical characteristics of patients who died post-implantation as of the most recent data cutoff (April 2021). Overall, 95 patients were included in the efficacy analysis set. Of these, 26 patients died and 69 survived. Median (interquartile range) age at implantation was not statistically different in patients who died vs survived (184 [107–438] vs 266 [135–389] days, respectively; P = 0.383). Of 26 deaths, 22 (85%) occurred within the first year post-implantation (median [range] time to death post-implantation, 130 [0–339] days; Figure 1A). The most common cause of death was infection (n = 12), all occurring in year 1. Respiratory failure (n = 2) was the most common cause of death >1 year post-implantation. Patients who died of infection had <50 naive CD4+ T cells/mm^3 (Figure 1B). In the first year, the mean (SD) number of infections was statistically greater in those who died (7.1 [4.8]) vs survived (4.5 [3.5]; P = 0.009). There were no significant differences by infection type, including bacterial (72.7% vs 53.4%; P = 0.108), fungal (45.5% vs 28.8%; P = 0.143), and viral (40.9% vs 42.5%; P = 0.897) infection, or in rate of serious infection (80.8% vs 76.8%; P = 0.679) in those who died vs survived, respectively. Additionally, there were no significant differences in rates of immunosuppressant use at any time (died, 69.2%; survived 63.8%; P = 0.618), pre-implantation renal dysfunction (a risk factor per label; died, 23.1%; survived, 5.8%; P = 0.144), or CHD7 mutation (died, 3.8%; survived, 15.9%; P = 0.218) in the 2 groups. In conclusion, most deaths occurred within the first year post-implantation and were most commonly caused by infections while patients had <50 naive CD4+ T cells/mm^3, whereas late deaths were associated with respiratory failure. Further follow-up is needed to better understand the factors contributing to best outcomes of allogeneic processed thymus tissue-agdc implantation.

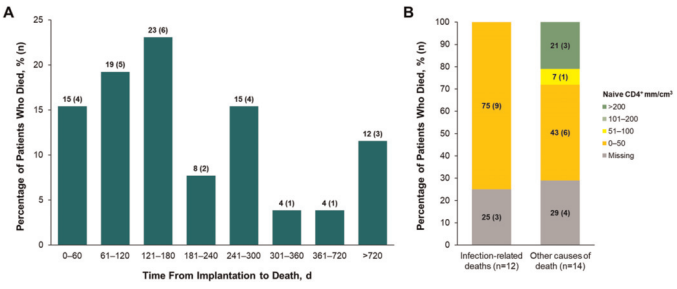

Figure 1A. Distribution of time post-treatment to death Figure 1B: Naive T cell counts in patients who died.

Keywords: Thymus, Cell therapy, Clinical outcome

Disclosures: Wu Eveline: I have relevant financial relationships with proprietary interests: Enzyvant Therapeutics, Inc. (Consulting Fees (e.g., advisory boards)); Pharming Healthcare, Inc (Consulting Fees (e.g., advisory boards), Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). Natalia Chaimowitz: I have relevant financial relationships with proprietary interests: Horizon (Scientific Advisory Board); Sumitomo Pharma America (Scientific Advisory Board, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)). Christine Steinhart: I have relevant financial relationships with proprietary interests: Sumitomo Pharma America (SMPA) (Employee). Priya Patel: I have relevant financial relationships with proprietary interests: Sumitomo Pharma America (Employee). Elizabeth McCarthy: I have relevant financial relationships with proprietary interests: Sumitomo PharmaAmerica, Inc (Grants/Research Support Recipient). Jennifer Heimall: I have relevant financial relationships with proprietary interests: CIRM (Scientific Advisory Board); CSL Behring (Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Health Economics & Outcomes Research Ltd (Consultant); Jobs Research Foundation (Scientific Advisory Board); Regeneron (Clinical Trial Investigator); Sumitomo (Consultant, Grants/Research Support Recipient, Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); UpToDate (Royalties).

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(101)

Predictive Model for Aiding in Early Common Variable Immunodeficiency Diagnosis

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Introduction: Common variable immunodeficiency (CVID) is a common primary immunodeficiency characterized by a failure in B-cell differentiation with defective immunoglobulin production putting patients at risk of recurrent sinopulmonary infections and autoimmune disease. Making a diagnosis is often challenging and delayed due to the heterogeneous nature of the presentation, especially in the pediatrics population given their propensity for recurrent infections early in life. CVID can present as early as 4 years of age although it's often diagnosed in adulthood. Adult literature has shown a 10-year lag in diagnosis. Early diagnosis of CVID is crucial for initiation of lifesaving therapies such as immunoglobulin replacement. We utilized a machine-learning approach to aid in early diagnosis of CVID in pediatric patients.
Cohort: Includes 151 CVID patients followed by immunology at Children's Hospital of Philadelphia. The cohort was manually validated by an immunologist confirming that patients met ESID CVID criteria. Cases were matched to controls (N: 429) without major comorbidities with a ratio of 1:3.
Methods: Random forest classifiers were trained on diagnosis terms from patient electronic medical records (EMR) in iteratively larger time-bins spanning from the date of their first encounter to the time (if applicable) of CVID diagnosis. We split our data into training and test sets at a ratio of 70:30, and evaluated our models based on how well they predicted an eventual CVID diagnosis. Top performing models were selected by assessing F1 scores (a metric that harmonizes precision and recall in a classifier model).
Results: Our top performing classifier predicted eventual CVID diagnosis with an F1 score of 0.954. In our test dataset, this represents 30 of 32 CVID diagnoses being classified correctly (false negative: 2), as well as 128 of 128 non-CVID patients correctly classified (false positive: 0). The top features of importance are displayed in Figure 1.

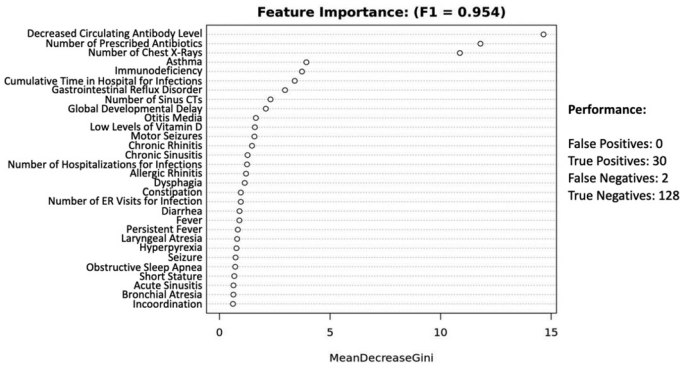

Figure 1. Top Model- Feature of Importance, clearly delineates that decreased circulating antibody levels, number of prescribed antibiotics and ordered chest x-rays are highest in our CVID cohort leading up to clinical diagnosis.

Discussion: Implementing machine learning predictive algorithms can assist in early pattern recognition and detection of patients with evolving CVID diagnosis, which undoubtedly will be a valuable tool for general pediatricians and immunologists.

Keywords: CVID, Predictive algorithm, Artificial intelligence, Machine learning

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(103)

Biallelic OSMR deficiency causes a novel primary atopic disorder

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Introduction: Primary atopic disorders (PADs) are a subset of monogenic inborn errors of immunity characterized by severe allergic disease. OSMR encodes Oncostatin M receptor beta (OSMRβ), a cell surface receptor that binds OSM and IL-31 and is a member of the gp130 family. The gp130 family is comprised of several signaling proteins, some of which have previously been linked to PADs, implicating OSMR as a candidate PAD gene.
Methods: Clinical assessments and sequencing were performed. OSMR variant-expressing constructs were generated using site-directed mutagenesis and expressed in HEK293 cells. Extracellular and intracellular flow cytometry and immunoblotting were performed on cells transfected with wild-type or variant OSMR. Patient skin biopsies were used to generate dermal fibroblasts to assess OSMRβ before and after correction by lentiviral transduction of WT-OSMR.
Results: We identified probands from four kindreds with biallelic, potentially damaging variants in OSMR (P1 – homozygous: c.1979_1980delAC, p.Tyr660fs*16; P2 and P3 – homozygous: c.1307T>A, p.V436D; P4 – compound heterozygous: c.1307T>A, p.V436D/c.1046C>A, p.A349D). Patients all had a similar core phenotype, including severe atopic dermatitis, peripheral eosinophilia, and elevated serum IgE levels. Functional studies using HEK293 cells revealed that all the patient OSMR variants prevented localization of OSMRβ to the cell surface, consistent with biallelic OSMR deficiency. This lack of cell surface OSMRβ expression was then validated in patient primary dermal fibroblasts. Furthermore, OSM- and IL-31-mediated activation of STAT1/3/5 was diminished in the fibroblasts and associated with distinct transcriptional changes, including a loss in interferon and inflammatory signature. These signaling defects were rescued upon lentiviral transduction of WT-OSMR.
Conclusion: In this study, we describe a novel PAD caused by germline biallelic variants in OSMR. These patient variants, located in the extracellular fibronectin III and transmembrane domains of OSMRβ, prevented normal cell surface expression and function of the OSMRβ protein, and were associated with severe early-onset allergic disease, particularly atopic dermatitis.
S.S. and M.S. are co-first authors. J.J.L. and S.E.T. are co-senior authors.

Keywords: Primary atopic disorders, Atopic dermatitis, OSMRβ, Severe allergic disease

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(104)

PD-1 Inhibition with Nivolumab Can Cure EBV-driven Lymphoproliferative Disorders, Avoiding Need for Toxic Allogeneic Bone Marrow Transplantation

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Background: EBV-associated NK and T-cell lymphoproliferative disorders (LPDs), collectively known as EBV HLH, are historically associated with poor prognosis and require allogeneic bone marrow transplant (BMT) for cure. Treatment with "HLH-directed" high dose steroids and chemotherapy regimens lead to short-lived remission of the secondary hyper-inflammatory process, but fail to treat the underlying chronic active EBV infection, and thus are followed by an inevitable relapsing/remitting disease. For reasons not yet well understood, the condition most commonly affects people of East Asian, Central and South American ethnicity; this can make it challenging to find a well matched unrelated BMT donor. Nivolumab is monoclonal antibody against the PD-1 receptor, which acts as a checkpoint inhibitor to increase host specific effector T-cell activity.
We report three heavily pre-treated pediatric patients with EBV LPDs successfully treated with nivolumab.
Results: Table 1 shows the patient and disease characteristics: two patients had EBV driven T-cell LPD, one had EBV-NK-LPD. They all presented with a

hyper-inflammatory syndrome, which initially improved with high dose steroids (± etoposide). Patients #1 and #2 demonstrated the classical relapsing-remitting clinical course, requiring multiple lines of therapy and accumulating significant treatment and disease related toxicities prior to being referred to our center. Patient #3 has started nivolumab in her first remission, at 2 months from initial diagnosis. All three patients had limited donor options for allogeneic BMT, making immunotherapy particularly attractive.

Nivolumab was administered intravenously and dosed at 3 mg/kg q3weeks. Treatment was well tolerated, with no adverse events. Patient #1 received 9 doses, and is in a remission at 3.5years, patient #2 received 7 doses and is in a remission at 10 months. Patient #3 continues on treatment, with no flares of the secondary hyper-inflammation to date. Figure 1 shows data for patient #2 demonstrating sustained control of EBV viremia and systemic inflammation with nivolumab.

Table 1. (abstract: 104)
Patient, disease and treatment characteristics.

	Patient 1	Patient 2	Patient 3
Demographics	18 y, white Caucasian male	8 y, Hispanic female	16 y, Hispanic female
Diagnosis	EBV driven T-cell LPD	EBV driven T-cell LPD	EBV driven NK-cell LPD
Clinical presentation	Fever, abdominal pain, jaundice, sore throat, headache, hepato-splenomegaly. Initial presentation complicated by respiratory failure (ARDS) requiring intubation/ ventilation	Fever, abdominal pain, jaundice, hepatosplenomegaly	Fever, abdominal pain, malaise, sore throat. Initial presentation complicated by ARDS requiring intubation/ ventilation, and vasoplegic shock requiring vasopressors
CBC	WBC 1.3, ANC 760, Hb 13.4, Plt 42k	WBC 4.0, ANC 1710, Hb 8.2, Plt 167k	WBC 1.83, ANC 980, Hb 10.5, Plt 34k
Ferritin	12,396 ng/mL	5,306 ng/mL	26,453 ng/mL
Hepatic profile	Bilirubin 7.7 mg/dL (total), 6.2 mg/dL (direct) ALT 137 U/L, AST 187 U/L	Bilirubin 8.06 mg/dL (total), 5.6 mg/dL (direct) ALT 1664 U/L, AST 1701 U/L	Bilirubin 0.6 mg/dL (total), ALT 93 U/L, AST 225 U/L
Coagulation studies	Fibrinogen 316 mg/dL PT 16.6 sec, INR 14.7 PTT 47 sec	Fibrinogen 112 mg/dL PT 15.7 sec, INR 1.2 PTT 30 sec	Fibrinogen 86 mg/dL PT 17.6 sec, INR 1.4
Triglycerides	ND	476 mg/dL	405 mg/dL
CRP	ND	4.57 mg/L, LDH 820U/L	3.9 mg/dL
sIL2R	8,852 U/mL	21,375 U/mL	51,959 pg/mL
EBV (Whole Blood)	2,153,720 copies/mL	907,000 copies/mL	274,000 copies/mL
EBV (Sorted Studies)	81,187 IU/mL (T-cells) 1089 IU/mL (NK cells) 331 IU/mL (B cells) <200 IU/mL (Myeloid) *(Once on treatment)*	103,111 IU/mL (T-cells) 923 IU/mL (NK cells) 6714 IU/mL (B cells) 0 (Myeloid) *(Once on treatment)*	84,251 IU/mL (NK cells) All other cells- 0
Bone Marrow Studies	Increased hemophagocytosis Flow cytometry: unusual T cell population	Florid histiocytic hyperplasia with hemophagocytosis. Interstitial T-cell lymphocytosis with frequent EBV-EBER positive cells	Increased hemophagocytosis. NK/T-cell lymphoproliferative disorder, with neoplastic lymphocytes staining EBV-EBER positive.
CSF studies	Negative	Negative at diagnosis EBV reactivations on initial treatment, incl. episode with EBV meningoencephalitis (CSF positive for EBV)	Negative
Genetic studies	Inherited HLH Disorders panel negative	pHLH and PID panels negative	pHLH panel negative
Previous treatments	High dose Dexamethasone Etoposide IVIG	High dose corticosteroids Etoposide Rituximab Emapalumab Ruxolitinib CHOP chemotherapy	High dose dexamethasone Etoposide Rituximab
Complications of upfront treatment	Pancreatitis Anaphylaxis to etoposide Steroid-induced hyperglycemia Recurrent infections- severe soft tissue infections requiring surgical intervention	Seizures, PRES Pneumatosis Duodenal hematoma Multiple severe infections (legionella, pseudomonas)	Steroid induced psychosis
Disease trajectory prior to nivolumab	Relapsing-remitting course prompting repeat courses of high dose steroids	Recurrent flares of EBV and hypercytokinemia, including severe flare with EBV reactivation involving CNS	Commenced nivolumab in first remission after high dose steroid (+etoposide)- 2 months from diagnosis
Nivolumab doses received	9	7	3 (Treatment ongoing)
Duration of follow up	3.5years	10months	Treatment ongoing
Clinical status at last follow up	Alive and well, studying and working full time.	Alive and well.	Alive and well. Full time schooling and competitive sporting activities

ARDS Acute Respiratory Distress Syndrome, WBC White Blood Cell Count, ANC Absolute Neutrophil Count, Hb Hemoglobin, Plt Platelet Count. ALT Alanine Transaminase, AST Aspartate Transaminase, PT Prothrombin Time, INR International Normalized Ratio, PTT Partial Thromboplastin Time, ND not done, pHLH primary Hemophagocytic Lymphohistiocytosis, PID primary immune deficiency.

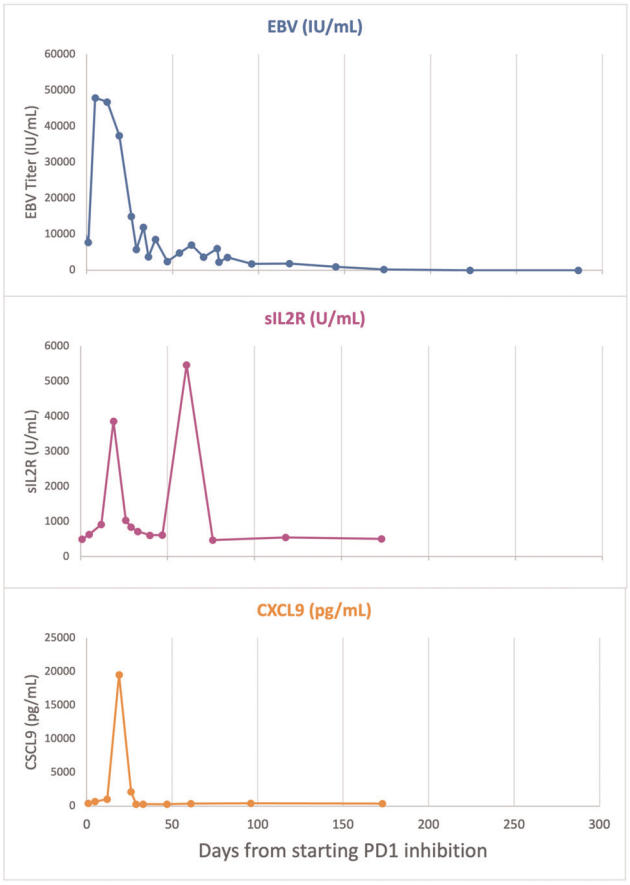

Figure 1. Graph representing EBV viral load, sIL2R and CXCL9 over time for patient #2, with day 0 being the first dose of nivolumab. Within a month, EBV whole blood titers had improved from the 20,000–50,000 range, though remained positive (2000–7000 IU/mL) for many months. EBV viremia cleared to 0 7 months after the start of therapy (and 3 months after discontinuation).

Conclusion: Nivolumab monotherapy led to sustained remission of EBV-T/NK-LPD in these patients, avoiding the need for potentially highly toxic BMT.

Keywords: EBV, Lymphoproliferative disorder, HLH, Nivolumab, BMT, Pediatric and young adult

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(105)

The Molecular and Phenotypic Spectrum of 125 patients with Griscelli Syndrome

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Griscelli syndrome is a rare, life-threatening immunodysregulatory disorder characterised by impaired cytotoxic activity leading to susceptibility to haemophagocytic lymphohistiocytosis (HLH) and hypopigmentation. We present a cohort of new and previously described cases, providing a comprehensive characterisation of 125 cases of Griscelli syndrome, of which 98 cases (78.4%) have confirmed pathogenic biallelic RAB27A variants.

Methods: We conducted molecular analysis of new unpublished and previously published cases, and completed a detailed literature review of phenotypic, management and mortality data. Survival curves according to Kaplan–Meier method were used to investigate outcome predictors in different subgroups of patients.

Results: A total of 125 Griscelli syndrome cases were described. We identified 3 founder mutations from different ethnicity groups with divergent phenotypic profiles (RAB27A R82C Qatari, Q172fs Eurasian, R184X European) (Figure 1). The main presentation was HLH (80%), with central nervous system involvement in 50%. 25 cases presented with no HLH symptoms (20%) and were picked up through positive family history. Silver-grey hair was present in 62% and hypopigmented skin in 31% of 125 cases. Founder mutation analysis reveals significant differences in systemic HLH rates: 87.5% in Q172fs Eurasian mutation compared to 21.4% in R82C Qatari mutation. On the contrary, hypopigmentation was found in almost all R184X European mutation while being present in 28.6% of R82C Qatari. More than 2/3 of cases (68%) had no functional immunology testing (natural killer cell activity, granule release assay, sCD25).

41 patients (32.8%) underwent haematopoetic stem cell transplantation (HSCT) at median age 2.25 (0.10–16) years. Mortality rates were 15% (6/41) among HSCT recipients versus 62.7% (37/59) of the un-transplanted group ($p < 0.0001$).

Conclusion: Hypopigmentation is often absent in Griscelli syndrome and should not exclude the diagnosis. Founder mutation analysis showed diverse phenotypic profiles. Survival of cases post-HLH who underwent transplantation is superior to un-transplanted group, suggesting adequate HLH control followed by early HSCT is needed. Asymptomatic cases picked up through family history/genetic screening may benefit from pre-emptive HSCT, but access to functional immunological testing is required. High mortality related to HLH remains concerning and emphasises the need for better molecular characterisation and clinical prognostic factors to guide management decisions.

Keywords: Griscelli syndrome, RAB27A, Phenotype, HSCT, Functional testing

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(106)

Outcomes Following Hematopoietic Cell Transplant for CD3δ Severe Combined Immune Deficiency: a PIDTC Natural History Study

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Introduction: Patients with CD3δ severe combined immune deficiency (SCID) present with absent to very low T cells and are susceptible to serious infections and infant mortality if not treated by allogenic hematopoietic cell transplantation (alloHCT). We analyzed long-term outcomes and immune reconstitution in the Primary Immune Deficiency Treatment Consortium (PIDTC) cohort.

Methods: Seventeen patients with CD3δ SCID treated at PIDTC centers from 1992–2023 and enrolled on PIDTC 6901/6902 SCID natural history studies were evaluated. Study variables were analyzed using descriptive statistics.

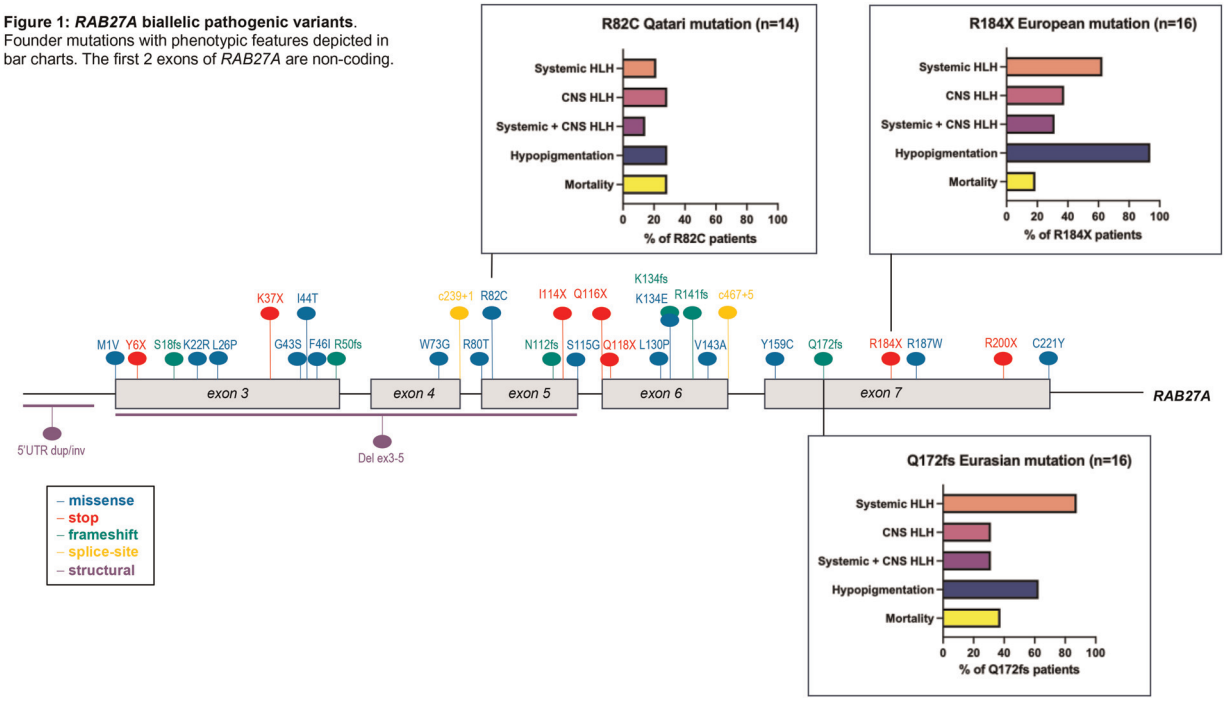

Figure 1: *RAB27A* biallelic pathogenic variants. Founder mutations with phenotypic features depicted in bar charts. The first 2 exons of *RAB27A* are non-coding.

Figure: (abstract: 105).

Results: Demographics and transplant characteristics are presented in Tables 1 and 2. Median follow up was 29 months (1–222 months). For patients transplanted after 2010, 2-year overall survival (OS) and 2-year event free survival (EFS) was 12/12 (100%) compared to 2-year OS of 3/5 (60%) and 2-year EFS of 2/5 (40%) for those transplanted prior to 2010. Before 2010, mismatched related donors (MMRD) with a variety of conditioning regimens/T cell depletion were used for 3/4 patients requiring subsequent alloHCT, boosts or donor lymphocyte infusions. The fourth patient requiring subsequent alloHCT received two matched sibling donor alloHCT, one unconditioned, one reduced intensity conditioning. Two deaths occurred in those with graft failure.

Table 1.
Baseline characteristics of CD3δ SCID patients.

		n (%)
Total number of CD3δ SCID patients		17
Treated at US center		10 (58)
Treated at Canadian center		7 (42)
Demographics		n (%)
Female		7 (42)
Male		10 (58)
		Median (range)
Age at diagnosis (days)		104 (1–495)
Age at alloHCT (days)		133 (25–534)
Pathogenic variant Genetic mutation		n (%)
Homozygous c.202C>T		12 (70)
Homozygous c.51_52del		2 (12)
Homozygous c.279C>A		1 (6)
Homozygous c.128G>A		1 (6)
Heterozygous c.202C>T; c.51_52del		1 (6)
Type of SCID*		n (%)
Typical		12 (71)
Leaky		5 (29)
Trigger for Diagnosis		n (%)
Newborn screening		5 (29)
Family History		4 (24)
Infection		8 (47)
Baseline Characteristics prior to alloHCT		n (%)
Infection at time of alloHCT	Active Infection	9 (53)
	Resolved infection	3 (18)
	No previous infection	5 (29)
Failure to thrive		6 (35)
Maternal Engraftment (n = 11, not done in 6)		n (%)
Present		1 (9)
Lymphocyte subsets at Diagnosis ($\times 10^6$/L)		Median (range)
Absolute Lymphocyte count		1455 (930–2880)
CD3+ T cells		13 (0–348)
CD3+CD4+ T cells		0 (0–236)
CD3+CD8+ T cells		0 (0–168)
B cells		1060 (368–1958)
NK cells		238 (26–740)

alloHCT – allogeneic hematopoietic cell transplant; SCID – severe combined immune deficiency.
*SCID definition as per PIDTC 2022 criteria: Dvorak *et al. J Allergy Clin Immunol* 2023;151:547–555.

Three of 17 patients developed grade II-IV acute graft-versus-host disease (GvHD) and 1 chronic GvHD. Post-alloHCT course was complicated by cytopenias in 2 patients, autoimmune events in 3, and 30 episodes of infection.

Absolute CD4+ T cell count was <500 × 106/L in 4/10 (40%) patients with data available at 1-year post-alloHCT; all patients with low T cell reconstitution received MMRD alloHCT with a variety of conditioning. Full T cell chimerism was apparent at 2–5 years post alloHCT in 6/6 patients with available data; 2/6 had <10% chimerism of other cell lines. Year of transplant was not associated with T cell reconstitution or chimerism.

Conclusion: Improved alloHCT after 2010 has resulted in excellent outcomes. Surviving patients still experience significant complications, and may have incomplete T cell immune reconstitution and poor chimerism in B, NK and myeloid cell lines. Further research is required to identify the optimal alloHCT approach to maximize engraftment of all cell lines and immune reconstitution.

Table 2.
Allogeneic hematopoietic cell transplantation characteristics and outcomes.

General characteristics	n = 17
Total Number of alloHCT	21*
Initial alloHCT before 2010, n = 17	5 (29)
Initial alloHCT after 2010, n = 17	12 (71)
2-year Overall Survival	15 (88)
2-year Event Free Survival**	13 (76)
Follow up post-alloHCT; median (range) (months)	29 (1–222)
alloHCT characteristics	n (%)
Donor type	
MSD	6 (29)
MORD	1 (5)
MMRD	10 (48)
URD	4 (19)
alloHCT Product Type	
PBSC	10 (48)
Bone marrow	10 (48)
Cord blood	1 (5)
Conditioning	
No Conditioning	4 (19)
IS	6 (28)
RIC	10 (48)
MAC	1 (5)
Serotherapy	7 (33)
ATG	4 (19)
Alemtuzumab	1 (5)
ATG + Alemtuzumab	9 (43)
No serotherapy	
GVHD Prophylaxis	6 (28.5)
T-cell depletion w/Soybean lectin	2 (9.5)
CD34+ selection	2 (9.5)
CsA and MMF	3 (14)
IS only	3 (14)
IS + ATG/alemtuzumab	5 (24)
Unknown	1 (5)
None	
Additional treatment	
Boost or DLI	4 (19)*
Post-alloHCT Characteristics	n (%); n = 21*
GvHD	
Acute GvHD, grade II-IV	3 (14)
Chronic GvHD	1 (5)
Infections	
Viral infections	13 (62)
Bacterial infections	11 (52)
Fungal infections	6 (29)
Complications	
Cytopenias	2 (10)
Autoimmune events	3 (14)
Chimerism	
Full chimerism (>90%)	5 (24)
Mixed chimerism (5–90%)	4 (19)
Graft rejection (<5%)	3 (14)
No data available	9 (43)

*1 patient received 1 boost, 2 DLI and a second alloHCT; 1 pt received 3 alloHCT; 1 pt received 2 alloHCT; 1 patient received 1 boost.
**Event free survival defined as number of patients alive without 2nd transplant or boost/DLI.
alloHCT – allogeneic hematopoietic cell transplant; ATG - Anti-thymocyte globulin; CsA -cyclosporine; DLI – donor lymphocyte infusion; GvHD -Graft-versus-host-disease; IS -Immunosuppression; MAC -myeloablative conditioning; MMF-Mycophenolate mofetil; MMRD – mismatched related donor; MORD -matched other related donor; MSD - matched sibling donor; PBMC - peripheral blood mononuclear cells; RIC – reduced-intensity conditioning; URD - unrelated donor

Keywords: CD3δ severe combined immune deficiency, Hematopoietic cell transplantation, Immune reconstitution, Primary Immune Deficiency Treatment Consortium

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(107)

A Novel mutation in proteasomal gene PSMD7 results in activation of NLRP3 inflammasome and potentially predisposes to Necrotizing Fasciitis

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Introduction: Necrotizing fasciitis (NF) is a severe infectious disease affecting soft tissues. Recent findings suggest that germ line mutations in genes regulating the innate immune responses may predispose to NF and lead to an autoinflammatory form of NF. Here, we describe a patient who presented with NF and carried heterozygous variant in TRIM23, a gene associated with autophagy, and in two genes, PSMD7 and PSMA5, which encode proteasomal proteins. PSMD7 is a proteasome non/ATPase 26S subunit that is critical for the degradation of ubiquitinated proteins in the proteasome. High PSMD7 expression has been associated with poor prognosis in cancer, but the impact of PSMD7 in immunological diseases is not well understood. The patient had persistent life-threatening inflammation and was therefore treated with IL-1β receptor antagonist anakinra with clear clinical response.
Methods and Results: Patient derived macrophages responded to NLRP3 inflammasome activation with an increased secretion of IL-1β, in addition, increased expression of CASP5 was observed following activation with lipopolysaccharides (LPS), suggesting dysregulation of non-canonical inflammasome as well. Further, high levels of sequestosome 1 suggested impairment of autophagic degradation. In order to characterize the role of PSMD7 in immune cells, we used CRISPR-Cas9 to create a THP-1 cell clone carrying heterozygous PSMD7 knockout (KO). Following NLRP3 inflammasome activation with LPS and ATP, PSMD7 KO cells produced significantly higher amounts of IL-1β compared to the mock (Fig. 1). The impact of PSMD7 KO on systems degrading ubiquitylated proteins, proteasome and autophagy, will be studied. Mutations in several other proteasome genes have been associated with interferonopathies but here we describe for the first time a mutation in PSMD7 leading to significant activation of the NLRP3 inflammasome.

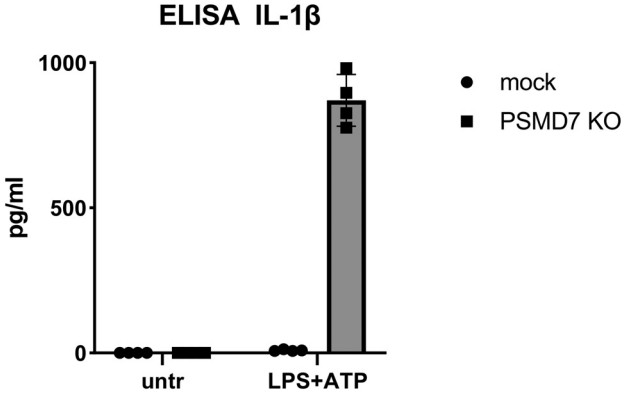

Figure 1. ELISA IL-1β of PSMD7 KO clone after LPS activation.

Keywords: Necrotizing fasciitis, Proteasome, Proteasomal degradation, PSMD7, NLRP3 inflammasome

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PU.1-associated inborn errors of immunity: new mutations, phenotypes, and inheritance patterns

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Background: Heterozygous loss-of-function mutations in SPI1, the gene encoding the transcription factor PU.1, were recently identified in six congenital agammaglobulinemia patients. Since originally identified mutations occurred de novo, questions about disease penetrance and the existence of extended phenotypes remain.
Objective: To address questions of penetrance, determine new patterns of inheritance and identify other SPI1-associated disease phenotypes, we functionally assessed ~141 rare, protein altering coding and non-coding SPI1 variants found in patients (n = 59) or listed in the Genome Aggregation Database (gnomAD; n = 78).
Methods: To assess stability of PU.1 mutants, we introduced variants into a SPI1 expression plasmid containing a constitutively transcribed SPI1 coding sequence connected to an infrared RFP (iRFP) gene or mCherry gene via a self-cleaving 2A peptide sequence. Mutant PU.1 proteins were over-expressed in HEK-293 cells, which lack native PU.1, and expression compared to wildtype PU.1 using immunoblots.
To determine if stable nPU.1 mutant proteins were transcriptionally active, we transfected mutated SPI1-iRFP expression plasmids into reporter lines containing an eGFP gene under transcriptional control of the PU.1 λB binding motif. Transcriptional activity was assessed by frequencies of reporter cells expressing both iRFP and eGFP.
To identify PU.1 mutants that potentially interfered with wild type PU.1, we co-transfected mutated SPI1-iRFP and/or wild type SPI1-mCherry expression plasmids into reporter lines. Interference was determined by comparing cells expressing both iRFP, mCherry and eGFP versus cells expressing only mCherry and eGFP.
Results: We identified 21 new loss-of-function (LOF) PU.1 mutations that conveyed effects through haploinsufficiency and one new dominant interfering variant. Among LOF SPI1 mutation carriers we identified 11 agammaglobulinemia patients, 14 common variable immunodeficiency patients and 8 unaffected carriers. We also identified six new gain-of-function variants, four were listed in gnoMAD and two associated with non-immunodeficiency phenotypes. Four of these new variants occurred de novo in single patients, eight new variants were inherited across one or more generations. Remaining variants could not be phased.
Conclusions: SPI1 mutations can convey a loss or gain of function and are associated with a spectrum of disorders. SPI1 mutations can be vertically transmitted and, in our cohort, have a clinical penetrance of 79.5%.

Keywords: SPI1, PU.1, Agammaglobulinemia, CVID, Transcription factor, B-cell

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(109)

CD8+ T Cells and Monocytes from Children with Secondary Hemophagocytic Lymphohistiocysis (HLH) During Rheumatic Disease Share Transcriptional Changes with Other Forms HLH and Inflammatory Diseases

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Macrophage activation syndrome (MAS) is a potentially fatal complication of rheumatic diseases and a form of secondary hemophagocytic lymphohistiocytosis (sHLH). sHLH/MAS is characterized by a dysfunctional hyperinflammatory response in which there is abnormal activation of lymphocytes and phagocytes. CD8+ T cells play a critical role during sHLH/MAS through the secretion of the cytokine, interferon gamma (IFNg), which

drives myeloid cell activation and excessive cytokine expression. Expansion of a subpopulation of CD8+ T cells has recently been described in individuals with active sHLH/MAS which are CD38+ HLA-DR+. Circulating monocytes are highly responsive to their surrounding environment but have not been well-studied in sHLH/MAS. In patients with rheumatic disease, sHLH/MAS is most commonly associated with systemic juvenile idiopathic arthritis (sJIA). We analyzed lymphocytes from subjects with MAS secondary to sJIA (n = 6) or matched healthy subjects (n = 2) by single cell RNA sequencing (scRNA-Seq). Lymphocytes from subjects with MAS revealed profound expansion of a CD8+ T cell subpopulation expressing markers of activation and exhaustion including LAG3, CTLA-4, and PD-1 as well as CD38 and HLA-DRA and were enriched for IFNg expression. We analyzed CD14+ monocytes from children with MAS (n = 6) compared to individuals with sJIA without MAS (n = 4) and matched healthy children (n = 8) by flow cytometry and RNA sequencing (RNA-Seq). We found significant upregulation of CD16 surface expression during MAS by flow cytometry ($p < 0.01$). Bulk RNA-Seq data showed specific transcriptional changes in CD14+ monocytes during active MAS, including upregulation of SLAMF7 which is induced by IFNg. We sorted monocytes from subjects with MAS secondary to sJIA (n = 8) or healthy subjects (n = 4) and deeply analyzed transcription using scRNA-Seq. Myeloid cells from subjects with active MAS revealed a strong IFN signature. Monocytes from pediatric subjects with lupus shared some transcriptional changes with MAS monocytes. These data identify expansion of a specific subpopulation of CD8+ T cells during MAS that are the primary source of IFNg and confirm an important role for cytokines, primarily IFNs, in driving gene expression in monocytes during MAS. Together, our data show that CD14+ monocytes and CD8+ T cells have specific transcriptional signatures during MAS that likely contribute to pathophysiology.

Keywords: Hemophagocytic lymphohistiocytosis, Cytokines, Monocytes, CD8 T cells

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Thursday Poster Abstracts

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(35)

Identification of a novel XIAP pathogenic variant associated with XIAP deficiency presenting as VEOIBD

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Inflammatory bowel disease (IBD) is a multifactorial disease and monogenic causes are considered in patients with severe or recalcitrant disease, or with very early onset disease (VEOIBD). Identification of monogenic etiologies is critical given opportunity for directed therapies. X-linked inhibitor of apoptosis (XIAP) deficiency is a rare inborn error of immunity associated with up to 4% of pediatric IBD. It has a highly variable phenotype from asymptomatic to hemophagocytic lymphohistiocytosis (HLH, 61%), splenomegaly (48%), IBD (23%), cytopenias (21%), hypogammaglobulinemia (14%), and rarely infection, uveitis, or arthritis. Treatment is manifestation focused including IL-18 suppressive therapy and immunosuppression. Curative treatment with hematopoietic stem cell transplant (HSCT) has variable outcomes and is reserved for recalcitrant IBD or significant HLH.

We report a 6-year-old male with chronic abdominal pain, diarrhea, emesis and growth failure, diagnosed with VEOIBD with Crohn's disease. Endoscopy revealed duodenal and ileocecal valve ulcers, with chronic duodenitis, gastritis, ileitis, colitis and diffuse granulomata. Neutrophil oxidative burst activity was normal. He was initiated on infliximab and required increasing doses of infliximab and additional Methotrexate to achieve clinical improvement and therapeutic drug levels. On follow up endoscopy, he had persistent inflammation. He underwent Invitae monogenic IBD panel testing, which revealed a variant of uncertain significance (VUS) in the XIAP gene (c.478 A > G, p.Met160Val) predicted to cause a missense mutation that disrupts protein function. His mother and brother (both asymptomatic) and maternal uncle (suspected XIAP deficiency) were found to have the same mutation. Testing revealed low XIAP expression, and low XIAP function confirming XIAP deficiency.

The patient subsequently developed recalcitrant severe IBD, with plan for IL-18 suppressive therapy, and referral for HSCT evaluation. This case demonstrates an XIAP VUS confirmed to be pathogenic, emphasizing the importance of critically evaluating VUS, and the importance of evaluating VEOIBD patients for monogenic etiologies to direct therapies.

Keywords: VEOIBD, XIAP, VUS, IBD, XIAP deficiency

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(63)

Clinical Roadmap for Implementing Results from Electronic Health Records Queries

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Objective: Clinical heterogeneity contributes to the 7-year median diagnostic delay that patients with activated PI3Kδ syndrome (APDS) suffer. One mechanism to surmount this obstacle is to query electronic health record (EHR) systems to aggregate these disparate symptoms into a risk score. We sought to understand how healthcare systems could care for patients identified through these methods.

Methods: We developed a structured query language (SQL) script using literature-validated APDS-associated ICD-10 codes to find patients. This SQL query calculates an "APDS Score" which stratifies risk for an individual subject. We tested our query in seven large, US-based medical centers. We used data from two centers (Table 1) to develop a 10-question survey about how to cull these records and implement appropriate next steps. We then disseminated the survey to the clinicians involved in the query; 7 clinicians in 6 sites responded.

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Table 1.
EHR query results from two centers.

Children's Hospital Number One		Children's Hospital Number Two	
Starting Population ~2.1 million		Starting Population ~1.2 million	
Query Outcomes, Score for 8 patients		Query Outcomes, Score for 8 patients	
APDS Score	Number of Features	APDS Score	Number of Features
23	8	16	5
22	7	15	5
15	4	11	4
11	6	10	5
11	5	8	2
10	5	8 (VUS)	3
9	3	6	2
5	4	3	2
Total records captured: **420,147**		Total records captured: **39,791**	
Total records based on lowest score of patient with APDS (score of 5): **17,729**		Total records based on lowest score of patient with APDS (score of 3): **3545**	
Score/records found:		Score/records found	
≥6: 12,184		≥6: **1092**	
≥7: **7741**		≥7: 433	
≥8: **6177**		≥8: 323	
≥9: **3340**		≥9: **130**	
≥10: **2172**		≥10: **86**	
≥11: **1262**		≥ 11: **60**	
For the 8 APDS subjects at this location		For the 8 APDS subjects at this location	
Maximum APDS Score: **24**		Maximum APDS Score: **16**	
Median APDS Score: **11**		Median APDS Score: **9**	

Results: In a multiple-choice question on curating the high number of records, 5 of 7 respondents suggested filters to remove secondary immunodeficiency patients, performing a sensitivity analysis using the highest scoring ~50 records, then re-running the script. Respondents also suggested setting an APDS score threshold, preferably one that selects for a manageable number of records. Five respondents noted this score threshold should be paired with a high number of clinical features. Once identified, absorbing the patients into care has limitations; one respondent noted an institutional capacity of only 192 new immunology patients per year, necessitating further triage strategies. The entire group concluded that verification through chart review would be needed by individuals familiar with inborn errors of immunity (IEIs). Additional staffing as well as legal and economic impacts were noted. (Figure 1)

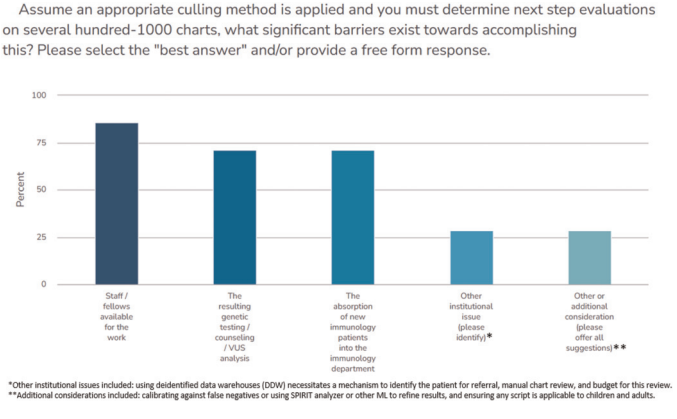

Figure 1.

Conclusion: EHR analytical approaches represent a strategy for reducing diagnostic delays among patients with APDS and other IEIs but further methods to refine the search, and means to expeditiously evaluate new referrals need to be devised. EHR methods are increasing in the literature. If institutions do not prepare to adopt modified workflows with existing care coordination teams or supply alternate workflows to immunology departments, patients with IEIs may be left languishing, despite having been identified.

Keywords: EHR, Artificial intelligence, AI, SQL, Clinical implementation, IEI, APDS, Diagnostic delay, Electronic health records, Machine learning

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(110)

Patient with Trisomy 21 and Congenital Chylothorax with Secondary Hypogammaglobulinemia

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Introduction: Trisomy 21 is the most common chromosomal abnormality among newborns and is associated with multi-system involvement, including immunodeficiency. Congenital pulmonary lymphangiectasia (CPL) is a rare birth disorder where infants have enlarged pulmonary lymphatic vessels. These vessels, part of the immune system, carry lymph, a fluid with proteins and white blood cells, CPL can lead to congenital chylothorax.

Case Description: A 6-month-old female with trisomy 21, pulmonary lymphangiectasia leading to chylothorax, and recurrent effusions was noted to have mild hypogammaglobulinemia due to lymphatic losses. She was initially evaluated at 3 months old with concerns of low immunoglobulins (Ig). She was started on immunoglobulin replacement therapy and

demonstrated an appropriate rise in IgG. Her PICU course was complicated by respiratory failure requiring prolonged intubation, Acetinobacter tracheitis, Rhinovirus infection, bilateral deep vein thrombosis on anti-coagulants, pleural effusion, and enterococcal respiratory culture growth. At that point, her IgM level normal, IgA undetectable, and IgG dropped to < 320 despite IVIG, she initially had appropriate elevation of IgG with 2 doses of IVIG but later had a drop along with lymphopenia to 1500.

At 5 months of age, she underwent surgical selective embolization of lymphatic collaterals, despite which her hypogammaglobulinemia per-sisted, which raised concerns about inborn errors of immunity. Trisomy 21 has been postulated to display increased propensity for immunodeficiency due to decreased activation of NFAT, a key transcription factor involved in T cell activation.

She continues on IVIG and live vaccines withheld until 8 months after her last IVIG dose, will decide to stop IVIG based on follow-up. However, in this patient with T cell lymphopenia (with normal CD4:CD8 ratios), we would be reluctant to recommend age-appropriate live vaccines without further assessing T cell function.

Discussion: Every individual case is unique which shows that some might require immunoglobulin replacement secondary to Ig loss, as in our case, to prevent infection and some cases might not require the replacement depending on clinical symptoms. Although IVIG has been used to treat Ig loss due to chylothorax, a small research involving eight children revealed that the drug's efficacy in preventing infectious complications was questionable.

Keywords: Trisomy 21, Chylothorax, IVIG

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(111)

Chronic Granulomatous Disease: a clinical or a molecular diagnosis?

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Introduction: Chronic Granulomatous Disease (CGD) is characterized by defects in NADPH oxidase complex which is responsible for oxidative burst, this defect leads to impaired neutrophil and monocyte intracellular bacterial and fungal killing. An Inflammatory Bowel Disease (IBD)-like phenotype can be seen in a proportion of CGD patients, and it has been described as the first manifestation in many cases. We present the case of a young man whose clinical presentation suggested CGD, but in whom the diagnosis was delayed due to unrevealing tests.

Case description: A 21-year-old fraternal twin male with a medical history of Crohn's disease, starting with manifestations from 6 months of age and Bipolar disorder was referred to our clinic for evaluation of recurrent pneumonia and skin abscesses. His IBD history was notable for multiple failed treatments including Ustekinumab, Adalimumab, Vedolizumab and Infliximab. Since being started on immunosuppression for his bowel disease, he developed pneumonia once or twice a year, requiring intravenous (IV) antibiotics, as well as increasingly difficult-to-treat skin abscesses. His family history is unremarkable; he has two unaffected brothers. His immune evaluation was reassuring, including normal immunoglobulins, lymphocyte subsets, mitogens, and vaccine titers. He had four neutrophil oxidative burst tests, of which two were reported as normal and two were abnormal, citing sample stability issues; graphs were not made available to the clinicians. He had a genetic Primary Immunodeficiency (PID) panel that revealed two heterozygous pathogenic variants in DUOX2, POLR3A, and multiple variants of unknown significance (VUS) in CYBB,DOCK 8, and STXBP2. Despite multiple normal neutrophil oxidative bursts, due to his clinical presentation and the VUS in CYBB gene, we had the assay repeated at a research lab, and it was consistent with a diagnosis of CGD. He was started on Bactrim and Itraconazole prophylaxis and is currently awaiting to start IFN-gamma.

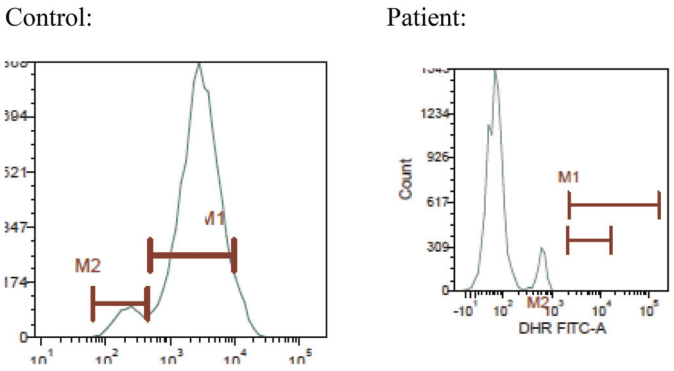

Figure. Neutrophil oxidative burst graph as seen with dihydrorhodamine flow cyto-metric test both in the control and in the patient.

Discussion: Clinical presentation should guide our diagnostic testing and degree of suspicion. This experience highlights the importance of the patient's phenotype and the persistence of the clinician when faced with results that do not seem to fit the clinical picture.

Keywords: Chronic granulomatous disease, Genetic mutation, Primary immunodeficiency

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A Pediatric Case of RAG1 Deficiency Caused by Novel Variants: From Diagnosis to Bone Marrow Transplant and Immune Reconstitution

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Introduction: RAG gene defects in humans are associated with a broad spectrum of clinical and immunological phenotypes, notably with altered T and B cell development. We describe a novel case of hypomorphic RAG1 deficiency.

Clinical Presentation: A 4-year-old African American boy was evaluated for recurrent otosinopulmonary infections since infancy, only temporarily alleviated with multiple courses of antibiotics. Immunophenotyping highlighted pan-hypogammaglobulinemia, decreased CD19 B cells,

elevated NK cells, normal T cells counts, critically low B cells, and non-protective strep pneumococcal titers. Total complement, neutrophil oxidative burst assay, lymphocyte mitogen and antigen proliferation were normal. Further testing showed normal BTK expression results, and Primary Immunodeficiency Panel identified two novel RAG1 variants (pGly393Val) and (pGly709Ala). Flow cytometric analysis revealed patient only had 0.5% T cells expressing Valpha 7.2 chain, resulting in aberrant T cell receptors, which is consistent with impaired capacity to rearrange distal Valpha genes and a strong indication of RAG deficiency. This patient had residual VDJ recombination. The patient was initiated on IVIG and the decision was made to proceed with reduced-intensity conditioning, haploidentical T-replete bone marrow transplant (BMT). He had successful donor cell engraftment across T, B, NK, and myeloid lineages. Post-BMT course was remarkable for CMV and BK viral reactivation and transient autoimmune hemolytic anemia. By six months post-transplant, he was off all immunosuppression, without any GVHD, and with evolving immune reconstitution, including naïve T cells within normal range and endogenous immunoglobulin production.

Discussion: This case elucidates the complexities involved in diagnosing and managing rare inborn errors of immunity, highlighting the pivotal role of collaborative efforts and multidisciplinary approaches in providing optimal patient care.

Keywords: RAG1, Severe combined immunodeficiency, Hypogammaglobulinemia, Bone marrow transplant

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(113)

Neutropenia and myelodysplasia without syndromic features in a 5-year-old boy with novel SAMD9 variant

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SAMD9 gain-of-function variants have been associated with MIRAGE syndrome, a multi-system disorder with myelodysplasia and extra-immune involvement. We report a child with recurrent sinopulmonary infections and severe neutropenia alone, found to have myelodysplasia and a rare variant in SAMD9.

A 5-year-old boy with short stature presented with mild neutropenia and thrombocytopenia, thought to be viral induced. He also had history of recurrent otitis media and two episodes of pneumonia. Immune phenotyping showed normal immunoglobulins, mild B and NK cell lymphopenia and mild naïve T-cell skewing. CD3+CD4−CD8− populations were not elevated. Pneumococcal vaccine titers were not protective. His neutropenia persisted (ANC nadir = 130 cells/uL) 6 months after initial evaluation, and panel genetic testing for inborn errors of immunity identified a heterozygous variant of uncertain significance in SAMD9 (c.2326C>A, p.Gln776Lys), which was not observed in parental testing. He subsequently underwent bone marrow biopsy that showed megakaryocyctic myelodysplasia with monosomy 7 consistent with myelodysplastic syndrome. Additional bone marrow failure workup for Fanconi anemia, Diamond Blackfan, and Dyskeratosis Congenita was negative. He is currently scheduled for a haploidentical bone marrow transplant.

SAMD9 protein facilitates endosome fusion to negatively regulate cell proliferation. Activating variants in SAMD9 have been associated with MIRAGE syndrome (myelodysplasia, infections, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy), which is a rare heterogenous disease which shares some phenotypic overlap with M7MLS2 (monosomy 7 myelodysplasia and leukemia syndrome-2), and typically presents with more severe infections and additional cytopenias early in life. The patient's SAMD9 variant was in the P-loop NTPASe domain in which several pathogenic variants have been identified. This variant was not present in Gnomad v.4.0.0. and has been reported in only 1 patient with MIRAGE syndrome.

Our patient exhibited profound neutropenia and myelodysplasia without additional features of MIRAGE syndrome, nor pancytopenia or other features of M7MLS2. SAMD9 related MDS should be considered as potential diagnosis in patients with persistent cytopenias and recurrent infections alone. This case also illustrates the value of genetic testing in clinically well patients with unexplained cytopenias for whom bone marrow evaluation might not otherwise be considered.

Keywords: Myelodysplasia, Neutropenia, SAMD9, MIRAGE syndrome

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(114)

Phenotypic Differences in Monochorionic Diamniotic Twins with Chronic Granulomatous Disease

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Chronic Granulomatous Disease (CGD) is an inborn error of immunity with defective NADPH oxidase activity leading to severe infections and hyperinflammation. We discuss different phenotypes in twin brothers with X-linked CGD.

Case presentation: 16-month-old monochorionic diamniotic male twins born in the Philippines were referred from Guam for management of genetically confirmed hemizygous pathogenic splice site mutations in CYBB (c.483+1G>A) and Bacillus Calmette-Guérin (BCG)-associated mycobacterial lymphadenitis. There was poor access to prophylactic therapy and anti-microbial treatment was interrupted due to a typhoon.

Twin A had a history of pneumonia, severe diaper dermatitis, and recurrent vomiting. Exam showed weight in the 10th percentile (%ile), length 0.1%ile, hepatosplenomegaly, inguinal lymphadenopathy and a non-healing inguinal wound. Laboratory evaluation revealed reduced activity (1%) on dihydrorhodamine (DHR) assay, persistent peripheral eosinophilia (600–5700 TH/uL) unresponsive to anti-parasitic treatment, elevated AST 45–768 U/L, ALT 31–1353 U/L and acute inflammatory markers. Imaging demonstrated diffuse mesenteric lymphadenopathy. During his hospitalization, he was noted to have bilateral glaucoma of unclear etiology.

Twin B had a history of meningitis, Serratia and Pseudomonas pneumonias, severe CMV and SARS-CoV-2 infections, presumed Nocardia pulmonary abscess, severe diaper dermatitis, and recurrent vomiting. He was smaller than his brother (weight 0.5%ile, length 0.1%ile) with cervical and inguinal lymphadenopathy and splenomegaly. Labs demonstrated reduced DHR activity (5%) and elevated acute inflammatory markers. Imaging

demonstrated diffuse mediastinal and retroperitoneal lymphadenopathy. During his hospitalization, he developed peripheral eosinophilia (500–3100 TH/uL) and elevated transaminases (AST 59–1564 U/L, ALT 48–1339 U/L) similar to that in his brother.
Esophagogastroduodenoscopy biopsies in both brothers revealed an eosinophilic abscess and mild duodenal eosinophilia without granulomas. Lymph node biopsies revealed numerous granulomas. Liver biopsies revealed chronic inflammation and fibrosis without granulomas.
Discussion: Differences in timing, severity, and tissue involvement in identical twins highlight non-genetic contributions to disease phenotype. Eosinophilia in the periphery, gastrointestinal and genitourinary tissue has been reported in CGD; the etiology is likely multifactorial. Tissue damage and difficulty eradicating infections were likely exacerbated by limited access to diagnostic and pharmacologic approaches. Efforts to improve health equity, including access to interferon therapy and antimicrobial prophylaxis, in under-resourced Guam are ongoing.

Keywords: Chronic granulomatous disease, Eosinophilia, Immune dysregulation

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(115)

Off-label treatment with the selective PI3Kδ inhibitor leniolisib in 2 pediatric patients with activated phosphoinositide 3-kinase delta syndrome 2 (APDS2)

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Background: Autosomal dominant loss-of-function mutations in PIK3R1 encoding for the regulatory subunit (p85a) of class IA phosphoinositide 3-

Table 1. (abstract: 115)
Summary of immunological findings of Patient 1 and Patient 2.

	Patient 1 male				Patient 2 female				Age-matched reference values	
	First visit (2 years)	At diagnosis (5 years)	Baseline leniolisib (11 years)	After 6 months of leniolisib (12 years)	First visit (2 years)	At diagnosis (5 years)	Baseline leniolisib (11 years)	After 6 months of leniolisib (12 years)		
Hemoglobin (g/l)	95	93	148	134	90	113	117	102	118–157	
Neutrophils (cells/mm^3)	6,600	6,550	5,700	7,850	7,100	3,100	3,870	1,830	1,400–5,500	
Lymphocytes (cells/mm^3)	3,900	3,470	4,140	5,300	5,900	3,400	2,220	3,490	3,000–13,500	
Monocytes (cells/mm^3)	1,800	1,160	1,220	1,790	1,200	400	770	810	100–1,200	
Eosinophils (cells/mm^3)	10	1,480	170	790	430	830	540	90	50–700	
Platelets (cells/mm^3)	314,000	462,000	405,000	462,000	578,000	376,000	470,000	438,000	130,000–450,000	
PBMCs										
CD3+ T cells (cells/mm^3)	2,488	2,023	3,581	2,990	4,440	2,672	1,591	2,502	850–4,300	
CD4+ T cells (cells/mm^3)	975	952	769	1,083	1,846	1,347	910	1,146	500–2,700	
CD8+ T cells (cells/mm^3)	1,979	922	1,461	1,726	1,938	1,208	479	1,022	200–1,800	
CD4/CD8 ratio	0.49	1.03	0.42	0.62	0.95	1.12	1.9	1.12	1.1–2.5	
CD19+ B cells (cells/mm^3)	229	180	183	166	327	349	158	160	390–1,400	
CD19+/CD27+ cells (%)	58.9	17.4	ND	90	48.2	62.5	ND	ND	8.1–33.3	
Memory B cells										
CD19+/IgD+/CD27− cells (%)	27.0	59.0	ND	11.5	38.9	31.4	ND	ND	59.7–88.4	
Naïve B cells										
CD19+/CD24++/CD38++ cells (%)	27.2	60.6	ND	5.2	21.6	9.9	ND	ND	2–70	
Immature transitional B cells										
CD16+/CD3− NK cells (cells/mm^3)	1,349	1,210	686	1,203	141	634	216	400	61–510	
Immunoglobulins (mg/dl)									2 years	4–5 years
IgG	75*	312	1285	753	71*	714	1105	1297	424–1,051	463–1,236
IgA	<10	<10	<10	<10	<10	<10	<10	<10	14–123	25-154
IgM	780	155	454	294	769	258	442	467	48–168	43–196
Viruses (copies/ml)										
CMV	Negative	223	58	Negative	ND	857	Negative	Negative	Negative	
EBV	Negative	Negative	Negative	Negative	ND	Negative	Negative	Negative	Negative	
Mutation	c.1425+2T>A					c.1425+1G>				

*Prior IVIG substitution; History data until baseline extracted from Olbrich P et al. doi: 10.1111/pai.12585
CMV, cytomegalovirus; EBV, Epstein-Barr virus; ND, not done; PBMCs, peripheral blood mononuclear cells.

Table 2. (abstract: 115)
Clinical symptoms.

Signs and symptoms present at start of leniolisib treatment	Patient 1, male		Patient 2, female	
	Present at baseline	After 6 months	Present at baseline	After 6 months
Lymphoproliferation	Present	Present	Present	Present
Lymphadenopathy				
Head and neck	Present (<1 cm)	Present (<1 cm)	Present(<1 cm)	Present (<1 cm)
Pulmonary	no	no	no	no
Gastrointestinal	no	no	no	no
Other				
Lymph nodular hyperplasia	No	No	No	No
Lymphoma	No	No	No	No
GI manifestations	No	No	No	No
Non-infectious pulmonary manifestations	No	No	No	No
Hepatomegaly	No	No	No	No
Splenomegaly	No	No	No	No
Cytopenias	No	No	No	No
Chronic fatigue/reduced activity (subjective)	Yes	No	Yes	No

kinase (PI3 K) results in activated PI3Kd syndrome (APDS) type 2, characterized by childhood-onset combined immunodeficiency, lymphoproliferation, and immune dysregulation. Here we describe 2 pediatric patients with APDS2 who switched from the mTOR inhibitor, sirolimus, to the specific PI3 K delta inhibitor, leniolisib. Clinical history including initial immunological parameters have been described elsewhere (Table 1). Following incomplete clinical success with different immunomodulatory treatments, patients switched from sirolimus to leniolisib, while maintaining monthly subcutaneous immunoglobulin therapy.

Methods: Observational 6-month study of real-life experience from the leniolisib early access program. Two clinically and immunological stable pediatric APDS2 patients < 45 kg switched from sirolimus to leniolisib (30 mg BID), while continuing immunoglobulin replacement therapy. Clinical and immunological follow-up was performed during the first 6 months of treatment. All previously available therapeutic data from these patients (antibiotics, IRT, MTOR, and steroids) were compared with new clinical and immunological outcomes after starting leniolisib.

Results: Clinical and immunological response to leniolisib treatment are summarized in Tables 1 and 2. During the 6-month treatment with leniolisib, both our patients showed excellent adherence, no infections, and no other severe adverse events, apart from transitional hair loss in patient 2. The children and parents reported subjective improved well-being (less tired, more active), suggesting a potentially favorable risk-benefit profile with no clinical, infectious, or immunological worsening after switching to leniolisib during this period.

Observation: Leniolisib has shown encouraging results in 2 pediatric patients within a compassionate use program. Further well-defined prospective studies are required to determine the long-term benefits of this potentially promising targeted therapy in APDS, particularly in young children.

Keywords: APDS2, Children, PI3Kδ inhibitor, Leniolisib

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(116)

Relative location of prime-boost immunization determines memory B cell fate

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An essential objective in HIV vaccine development is the induction of broadly neutralizing antibodies (bNAbs), a goal made difficult by the necessity of critical and improbable mutations. Current vaccine strategies focus on shepherding the precursor, unmutated B-cells that give rise to bNAbs to neutralization breadth by serial immunization. Thus, the optimization of boosting strategies aimed at promoting the re-recruitment of antigen-experienced B-cells into germinal centers (GCs) for additional rounds of somatic hypermutation is necessary. Prior studies have suggested the location of boost immunization as an important determinant of GC quality, but how this variable affects memory B-cell fate is unknown.

Here, we used fate-mapping of GC B cells (by a S1pr2-Cre × Rosa26 LSL-TdTomato allele) with mice harboring a knock-in allele of a bNab precursor BCR to study this question. Immunization with a vaccine targeted at the knock-in BCRs (CH848 10.17DT NP vaccine) followed by tamoxifen administration at day 6 post-immunization allowed for tracing of early GC responders through boost immunization.

Despite similar serologic responses, boost immunization at that same side of the primary immunization (ipsilateral) led to a ~2 fold increase in GC B cells compared to a contralateral boost. Within this group of GC B cells, ~30% were tdTomato+ with ipsilateral boosting compared to < 1% at the contralateral boost site, demonstrating a remarkable 15-fold increase in the total quantity of GC B cells re-engaged from the primary immunization. Less than 5% of GC B cells from the contralateral boost bound CH848DT; a higher percentage of both tdTomato+ (~80%) and tdTomato- (~20%) cells from the ipsilateral boost bound the immunogen. Among these binding cells, the mean avidity for CH848DT was ~100-fold higher in the ipsilateral group. BCR sequencing revealed the acquisition of critical, improbable mutations only within tdTomato+ compartment, highlighting the importance of post-GC memory B cell reentry into GCs to achieve optimal affinity.

Our results highlight the importance of locale in the optimization of vaccine regimens and demonstrate the power of lineage tracing in evaluating vaccine responses. We show stronger and higher quality GC responses with local compared to distal boosting.

Keywords: B-cell biology, Germinal center dynamics, Vaccinology

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(117)

Clinical and Immunologic Phenotype of Prolidase Deficiency

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Introduction: Prolidase deficiency (PD) is a rare autosomal recessive multisystemic disease caused by variants in the PEPD gene encoding Prolidase D. Common clinical features include recurrent infections, poor wound healing with skin ulcerations, and inflammatory complications with rare occurrence of hemophagocytic lymphohistiocytosis (HLH). Therefore, clinical immunologists are often involved in patient care.
Objective: To describe the clinical and immunologic phenotype of PD seen in this cohort to raise awareness of the disease.
Methods: A retrospective chart review of nine patients molecularly diagnosed with PD, followed at the NIH.
Results: Nine patients ranged in age from 6 to 38 years (median 12 years) at their last NIH visit. Four were female. Five had homozygous deleterious variants; four had compound heterozygous variants. The age of diagnosis ranged from 9 days to 24 years (median 17 years). Eight of 9 patients had chronic ulcers of the lower extremities, with a median age of onset of 2.75 years. Six patients had recurrent sinopulmonary infections, with 5 having chronic lung disease. Five patients had atopic dermatitis. Three patients had inflammatory autoimmune-like presentation, including two diagnosed with systemic lupus erythematosus (one having an HLH-like presentation) and another with oligoarticular juvenile idiopathic arthritis. Seven had liver disease including four with portal hypertension and esophageal varices. Six patients had digital clubbing and 6 had telangiectasias. Eight had splenomegaly, and eight had thrombocytopenia with four receiving splenectomies. Five had chronic anemia. There were two fatalities, a 7-year-old boy from progressive pulmonary disease and a 6-year-old girl from respiratory failure. Four had high serum IgE (range 60–3065 IU/mL), 6 had high IgG (417–2936 IU/mL) and 4 had high IgA (5–1276 IU/mL). Two patients had lymphopenia, one with B lymphopenia and one with low CD4/CD8; however, both were on immune suppression.
Conclusion: PD is a rare multisystemic disease with shortened lifespan and without any described curative therapies. Patients may present to clinical immunologists due to recurrent infections, skin ulcers, and inflammatory complications, thus familiarity with the disease is necessary to decrease the time to diagnosis. The pathophysiology of PD is poorly understood, and further study is required to improve patient outcomes.

Keywords: Prolidase deficiency, PEPD, Prolidase D

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(118)

Comprehensive analysis reveals a Neuroimmunological association Induced by oncogenic Hepatitis Viruses

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Hepatitis viruses (e.g., HCV) have been associated with neurological conditions (e.g., cerebrovascular events, encephalomyelitis, cognitive impairment, psychiatric disorders, and depression, such as anxiety and fatigue. However, the neuroimmune networks and underlying mechanisms induced by viral hepatitis infections remain uninvestigated. To gain insights, we performed an integrative analysis of the molecular networks caused by different hepatitis viruses (HBV, HCV, and HDV), which are oncogenic. We conducted differential expression analysis (Limma, DESeq2), with batch effect removal using the Combat package, followed by a meta-analysis using the MetaVolcano package of 1125 transcriptomes (microarray and bulk RNA sequencing) from infected patients (445 = Liver; 122 = PBMC) versus control transcriptomes (446 = Liver; 112 = PBMC). We found meta-significant up-regulated genes as follows: 645 (HBV/Liver), 201

(HCV/Liver), 1478 (HDV/Liver), 129 (HBV/PBMC), 123 (HCV/PBMC); and down-regulated: 223 (HBV/Liver), 43 (HCV/Liver), 1327 (HDV/Liver), 42 (HBV/PBMC) and 87 (HCV/PBMC). Enrichment analysis using these meta-DEGs above revealed shared biological processes by upregulated meta-DEGs mainly associated with the immune response such as Type-II interferon (e.g., CCL19, CCL20, HLA-DPA1), Inflammatory Response (e.g., CXL2, IL6, CD14, AGTR1), and cell cycle (e.g., TIMP1, OSMR, RAB25, AREG). Inversely, downregulated meta-DEGs enriched several BPs, such as neuroinflammatory response (e.g., IL6, IL1B, IFG1, except for the HCV group), dendritic cell migration (e.g., CXCR1, CXR2, CCR1), and positive regulation of ERK1 and ERK2 cascade (e.g., TEK, RAMP3, FGA). Network analysis revealed a robust topological interconnection between several neuroimmune pathways. Altogether, this work shows a previously uncharacterized neuroimmunological network underlying the development of oncogenic hepatitis, which requires further investigation for its association with disease severity.

Keywords: Viral hepatitis, Neuroimmune, Hepatic encephalopathy, Hepatocellular carcinoma, Integrative analysis

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(119)

Novel CD40 Genetic Variants in an Infant with Hyper-IgM Syndrome and Parental CD40 analysis

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A 7-month-old female presented with persistent fevers and hypoxia. Chest CT imaging showed diffuse ground glass opacities. Despite a week of intravenous ampicillin-sulbactam treatment, her symptoms persisted. A switch to empiric trimethoprim-sulfamethoxazole for presumed Pneumocystis jiroveci pneumonia resulted in clinical improvement. Immunology evaluation was notable for normal IgM with undetectable IgG and IgA levels. Further analysis showed significantly elevated naïve B cells and a scarcity of switched memory B cells. Genetic testing identified two novel variants in CD40: c.445G>A (affecting exon 4) and a large deletion spanning exons 7 to 9. Flow cytometry confirmed absent surface CD40 expression on B cells, diagnosing hyper-IgM type 3 syndrome.

Parental investigation revealed the variants to be pathogenic, each inherited from one parent. Both parents had reduced CD40 expression and a lower count of switched memory B cells compared to healthy controls.

Given her diagnosis, the patient started on immunoglobulin replacement therapy. She subsequently underwent a hematopoietic bone marrow transplant (HCT) using a 7/8 matched unrelated cord blood donor. The conditioning regimen included busulfan (cumulative AUC 75 mg*hr/L), fludarabine (35/m2 × 4), and Thymoglobulin (3 mg/kg × 3). GvHD prophylaxis was administered using tacrolimus and mycophenolate. Unfortunately, she experienced acute graft rejection, characterized by failure of lymphocyte and neutrophil engraftment. Current plans involve a salvage transplant with a paternal haploidentical donor, highlighting the challenges and complexities of HCT in primary immunodeficiencies.

This case not only sheds light on novel pathogenic variants of CD40 causing hyper-IgM syndrome but also illustrates the intricate decisions and outcomes associated with bone marrow transplantation in pediatric patients with primary immunodeficiencies. It underscores the importance of familial genetic testing and a tailored approach to transplantation in rare immunological disorders.

Keywords: Hyper-IgM syndrome, CD40, Pediatric immunodeficiency, Bone marrow transplantation, Primary immunodeficiency diseases, Combined immunodeficiency, Genetic analysis in immunodeficiency

Disclosures: Vincent Bonagura: I have relevant financial relationships with proprietary interests: CSL-Behring (Consultant); Takeda Pharmaceuticals (Consultant). The other authors have no financial relationships or conflicts of interest to report.

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(120)

Treatable Acute Neuroinflammatory Disease Associated with Complement Factor I Loss-of-function in the Plain Community

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Introduction/Aims: Complement factor I (CFI) regulates the alternative complement pathway by proteolyzing C3b bound to mammalian cells. Disruption of this regulatory effect is associated with a variety of phenotypes including recurrent atypical hemolytic uremic syndrome, age-related macular degeneration, recurrent invasive bacterial infections, and a range of neuroinflammatory presentations. We describe a cluster of patients with acute neuroinflammation associated with homozygous missense CFI variant p.Tyr459Ser in the Plain community, elucidate the molecular consequences of this variant, and propose a novel approach to treatment.

Cases: 17-year-old previously healthy Amish female presented with acute onset fever, vomiting, and altered mental status, which rapidly progressed to fulminant meningoencephalopathy necessitating emergent craniectomy. Work-up included CSF studies with significant neutrophilic pleocytosis, brain imaging with diffuse white matter enhancement, negative infectious studies, low serum C3 and C4, and AH50 0 units/mL. Whole exome sequencing revealed homozygous missense CFI variant c.1376 A > C, p.Tyr459Ser, evoking diagnosis of complement factor I deficiency. Patient cerebellar tissue stained positively for granular C3 on several vessels as compared to that of a patient with infectious encephalitis as control. After no initial response to high-dose steroids, she clinically improved over 2–3 weeks with intermittent plasmapheresis. Recrudescence of symptoms prompted treatment with eculizumab, a C5 inhibitor, after which her symptoms quickly resolved. She remains well with minimal neurologic deficit on penicillin prophylaxis and hypervaccination. The homozygous variant has since been identified in nine additional Amish patients, four of whom have also had neuroinflammatory presentations.

Molecular mechanism: Mutant protein CFI p.Tyr459Ser is stable when recombinantly expressed in HEK293 cells, arguing against pure

quantitative deficiency. Functional analysis of the recombinantly expressed mutant by C3b degradation test followed by inactivated C3b ELISA revealed significantly reduced C3b degradation activity compared to recombinant wildtype CFI and similar to known loss-of function variant Ile340Thr.

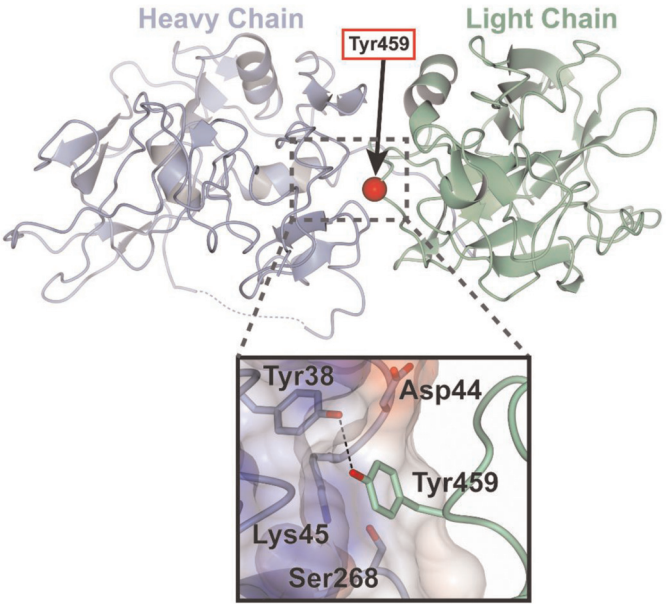

Figure 1. The three-dimensional structure of complement factor I (CFI) and the location of Tyr459. A) Ribbon diagram of CFI with the heavy chain colored blue and light chain colored green. The position of Tyr459 is indicated by a red sphere at its C-alpha position and is labeled. B) Zoom-in view of Tyr459 at the interface between the heavy and light chains. The surface electrostatic potential of the heavy chain is drawn as a semi-transparent surface. The sidechain of Tyr459 in the light chain, and of Tyr38, Asp44, Lys45 and Ser268 from the heavy chain are shown. The figure was generated in CCP4MG using the crystal structure of CFI chains D and I from PDB ID: 5o32.

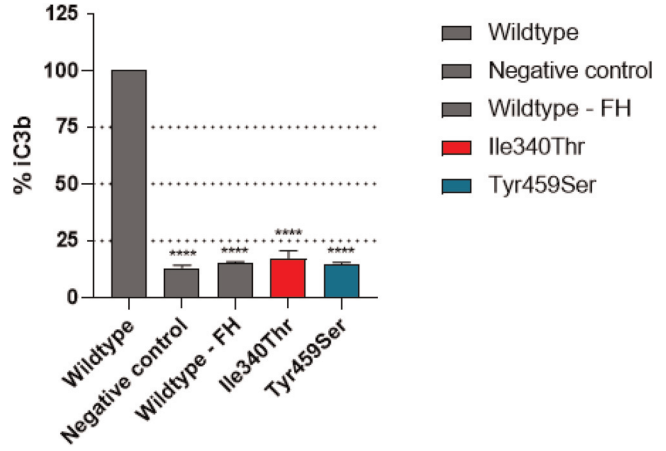

Figure 2. Functional analysis of recombinant complement factor I (CFI) proteins by C3b degradation assay. Formation of inactivated C3b (iC3b) as a product of C3b degradation by equal quantities of recombinant FI variants with factor H (FH) as cofactor. The % iC3b is normalized for the recombinant wildtype and compared to iC3b formation of the variants. Control samples are indicated in grey: wildtype FI, negative control (mock transfection; no CFI), wildtype CFI without cofactor FH. Known loss of function variant Ile340Thr is indicated in red. Samples were compared to the wildtype using one-way ANOVA followed by Dunnett's multiple comparison test. The symbol **** depicts statistically significant differences between wildtype FI and mutant FI at $p < 0.0001$. The C3b degradation assay and iC3b ELISA were executed three times ($n = 3$).

Conclusions: We describe a novel homozygous missense variant causing complete complement factor I loss-of-function with estimated incidence of 1 in 1100 in the Plain community. Further understanding and awareness of this condition as a rare cause of potentially life-threatening neuroinflammation is imperative to prompting expedited genetic testing and consideration of disease-specific therapy with eculizumab.

Keywords: Complement Factor I, Neuroinflammation, Eculizumab

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(121)

Ocrelizumab induced B-cell depletion in a newborn male

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Ocrelizumab is an IgG1 humanized monoclonal antibody directed against CD20 used in the treatment of multiple autoimmune diseases, including multiple sclerosis (MS). It depletes pre-B-cells, naïve and memory B-cells, but does not affect differentiated plasma cells.

A 15-day old male was referred to the immunology clinic due to finding of absent B-cells on lymphocyte panel. His history was notable for a vaginal birth at 38 weeks without complications, including pre- or post-natal infections. His pediatrician assessed lymphocyte counts due to maternal history of ocrelizumab use and parental concern for B-cell lymphopenia. Maternal history was notable for a diagnosis of MS necessitating ocrelizumab treatment at 2 weeks and 30 weeks pregnant. While on the medication, maternal immunoglobulin levels were not monitored and infection history was notable for one sinus infection. On initial evaluation of the newborn, repeat labs confirmed CD19+ and CD20+ cell absence, with normal T and NK cell enumeration. CBC was notable for normal hemoglobin, platelets and white blood cell counts. Quantitative immunoglobulins showed normal IgG with low IgM and IgA levels. Primary immunodeficiency panel did not reveal any pathogenic mutations associated with defects in B-cell development. Re-evaluation at 4 months old was notable for normal CD19+ and CD20+ counts, normal IgG, IgM and low IgA levels.

To date, this is the first report of ocrelizumab leading to B-cell depletion in a neonate. There are no longitudinal studies that have examined the effect of ocrelizumab administered during pregnancy in human neonates. Studies in monkeys have shown that administration during pregnancy can lead to renal toxicity, perinatal death due to infection, and decrease in circulating B-lymphocytes in the neonate. Retrospective studies have not shown major adverse outcomes in neonates; however, these studies have focused on ocrelizumab infusions during the first trimester of pregnancy when maternal IgG transfer does not occur. More studies are needed to evaluate the safety of this medication when administered after the first trimester particularly as other CD20 antibodies, such as rituximab, can lead to cytopenias and B-cell depletion with variable times to B-cell recovery in the neonate.

Keywords: B-cells, CD20, Secondary immunodeficiency

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(122)

A Quantitative Approach for Identifying Health Disparities Driving Diagnostic and Treatment Delays in VEO-IBD

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Background: Health disparities exist in both the diagnosis and management of patients with primary immune disorders (PI). Very-early onset inflammatory bowel disease (VEO-IBD) includes heterogenous immune disorders. We aimed to quantify drivers of disparate delays in VEO-IBD diagnosis and treatment as a prototype for other PIDs.
Methods: We identified 110 patients with VEO-IBD and mined their electronic health record (EHR) data from first encounter in Epic (2008) - February 1, 2022. Variables including demographics, prescriptions, laboratory studies, procedures, and PUCAI (Pediatric Ulcerative Colitis Activity Index) disease score, were extracted from the EHR. Descriptive statistics were performed to identify significant differences between variables clinically predictive to disease control.
Results: Among the 110 patient VEO-IBD cohort, the average age was 10 years (1–25 years). Self-reported gender included 53 female (48%). Self-reported data revealed White, Non-Hispanic patients comprised 51% (n = 56) of patients. Asian patients represented 12% (n = 13), Black, Non-Hispanic 11% (n = 12), and Native American/Alaskan Native 1% (n = 1) of patients. Data regarding race or ethnicity was unavailable for 3% (n = 4).
Albumin, calprotectin, C-reactive protein, and PUCAI were highly correlated to disease severity. Using two-tailed t-tests, statistical difference was noted in disease severity by PUCAI scores (< 20 controlled); underrepresented minority Black, Hispanic and Native American/Alaskan Native patients (mean 23.5; 95% CI ± 2.3) vs. White patients (mean 17; 95% CI ± 2.3) ($p < 0.05$; p value < 0.005). Statistically significant differences were observed in mean albumin ($p < 0.05$; p value < 0.005) in underrepresented patients (5.0 g/dL) vs. White patients (6.5 g/dL). No statistical difference ($p > 0.05$; p value 0.392) found in mean calprotectin for underrepresented patients (1057 μg/g) vs. White patients (962 μg/g), or mean C-reactive protein (both populations 5.9 mg/dL; $p > 0.05$; p value 0.998). Underrepresented patients comprised all patient deaths (n = 5).
Discussion: We report statistically significant differences in albumin and PUCAI score, and increased disease mortality among underrepresented patients, suggesting a disproportionate burden of disease morbidity and mortality. Similar to the state newborn screen, future work will be directed toward standardized, unbiased approaches to screening for VEO-IBD using EHR for timely disease recognition and management.

Keywords: Very early onset inflammatory bowel disease, Health disparities, Primary immunodeficiency disparities

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(123)

Helper T cell immunity in humans with inherited CD4 deficiency

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Human CD4+ T helper (Th) cells are critical for host defence against many infectious agents. Here, we report seven patients (aged 5–61 years) from five unrelated families of different ancestries with autosomal recessive CD4 deficiency. All patients are alive and suffered mostly from HPV-driven recalcitrant warts; one had Whipple's disease. All patients are homozygous for CD4 variants that are loss-of-function for the main isoform of CD4. However, most variants are isomorphic for a shorter alternative CD4 isoform that is expressed on the cell surface and retains the ability to interact with LCK, but not with HLA class II. Analysis of peripheral blood cells by conventional flow cytometry revealed that all patients completely lack CD4-expressing T cells and display high counts of TCRαβ+CD4-CD8– T cells. These CD4–CD8– αβ T cells phenotypically and transcriptionally resembled canonical Th cells typically found in healthy individuals, rather than pathogenic CD4–CD8– αβ T cells characteristic of autoimmune lymphoproliferative syndrome. Finally, responses of patients' CD8– αβ T cells to HLA class II-restricted antigen presentation in vitro is intact. Thus, compensatory development of Th cells by an alternative isoform of CD4 enables patients with inherited CD4 deficiency to acquire protective immunity against an unexpectedly large range of pathogens. However, the predominant isoform of CD4 is indispensable for protective immunity against at least HPVs and Trophyrema whipplei.

Keywords: Human CD4+ T cells, CD4 deficiency, Inborn errors of cellular immunity, HPV

Disclosures: Stuart Tangye: No financial relationships or conflicts of interest.

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(124)

Neutropenia in X-linked agammaglobulinemia patients, is possibly the most common presenting sign

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Background and Aims: X linked agammaglobulinemia (XLA) is the most common cause of primary agammaglobulinemia. Other rare mutations causing a similar clinical phenotype, include mutations in the TCF3 gene. XLA typically presents with hypogammaglobulinemia, and recurrent bacterial infections. Neutropenia, has been previously described occurring in 10–26% of XLA patients. However, in our experience neutropenia related infection were a more common feature. Our study was conducted to assess the prevalence and impact of neutropenia, and neutropenia related infections, as the initial presentation of XLA patients in our patient population.

Methods: We conducted a retrospective review of XLA patients treated between January 2003–December 2022, at 4 Medical centers in Israel, that reported having XLA patients presenting with significant neutropenia. A retrospective review of medical records and hospital clinic visits was performed with approval of the Institutional Review Boards.

Results: Out of about 40 XLA patients in Israel 23 (57%) had significant neutropenia at presentation. 18 (45%) had a significantly low ANC< 500, and 20 (50%) had neutropenia related infections. 4 patients received GCSF. 5 patients had bone marrow aspiration done as an investigation for their neutropenia reviling maturation arrest. 10/23 (43%) had more than 4 m delay between first neutropenic infection to the diagnosis of agammaglobulinemia. One patient succumbed to a fatal neutropenia related pseudomonas sepsis. After the initiation of IVIG replacement therapy, neutropenia resolved in all patients.

Table 1 – Clinical Characteristics of Patients

Patient	Age at diagnosis (months)	Age at first neutropenia (months)	Absolute Neutrophil count (cells/μl)	Affected relative
1	15	15	200	No
2	3	3.5	100	Yes
3	6	5	100	Yes
4	5	6	800	Yes
5	3	3	200	Yes
6	52	48	100	No
7	14	10	100	No
8	2	4	100	Yes
9	24	8	370	No
10	-	8	0	No
11	14	5	300	No
12	11	9	180	No
13	5	5	630	Yes
14	4	4	340	Yes
15	15	12	20	No
16	15	12	300	No
17	36	7	110	Yes
18	43	36	480	No
19	45	7	1300	Yes
20	30	26	1140	yes
21	18	2	110	No
22	10	10	60	Yes
23	42	17	400	No

Table 1. Showing the severity of neutropenia at presentation, and the delay between the onset of neutropenia and neutropenia related infections, to the diagnosis of agammaglobulinemia.

Conclusions: Neutropenia, and neutropenia related infections, as a presenting feature of XLA is common. Diagnosis at the first sign of disease can prevent further sever infections and related morbidity and mortality. It is likely that neutropenia to some degree occurs in most patients with XLA. Interestingly, we also present a patient with TCF3 mutation presenting with agammaglobulinemia and severe neutropenia resolving after IVIG replacement. Previous studies have failed to explain the mechanism of neutropenia in XLA patients. This case may suggest neutropenia may be related to the agammaglobulinemic state and not to the underlying genetic disorder. In Summary, infants and children with persistent or symptomatic neutropenia should have Ig levels checked.

Table 2 – Presentation and Treatment

Patient	Clinical Presentation	Pathogen	Treatment	Complications
1	sepsis & soft tissue infection	Pseudomonas Aeruginosa	IVIG	-♛
2	Fever	-	IVIG	-♛
3	Fever	-	IVIG	. ♛
4	Fever	-	IVIG	-♛
5	Fever	-	IVIG	-♛
6	Severe cellulitis, Pleuropneumonia	Haemophilus Influenza NTB	IVIG & GCSF	Chronic lung disease ♛
7	Cellulitis	-	IVIG	. ♛
8	Fever		IVIG & GCSF	-♛
9	Recurrent bacterial infections – pulmonary, soft tissue	-	IVIG	. ♛
10	Sepsis, fatal	Pseudomonas Aeruginosa	IVIG & GCSF?	Fatal infection ♛
11	Ulcerative lesions and bacteremia	Pseudomonas Aeruginosa	IVIG and Ab	. ♛
12	Multiple Abscess, leg	Pseudomonas Aeruginosa	IVIG AB	. ♛
13	Pneumonia	-	IVIG Ab	-♛
14	Positive family Hx	-	IVIG	-
15	Pneumonia	Adenovirus	IVIG, GCSF	-♛
16	Fever	-	IVIG	-♛
17	Rec Pneumonia	-	IVIG Ab	-♛
18	Pneumonia, septic arthritis ,diarrhea	Pneumococci, giardia	IVIG Ab	. ♛
19	Pneumonia	-	IVIG Ab	-
20	Pneumonia	-	IVIG Ab	-
21	Pneumonia, Bacteremia, Dysentery	Salmonella, Haemophilus NTB	IVIG Ab	. ♛
22	Pneumonia, Otitis, Perianal abscess	Pseudomonas Aeruginosa	IVIG Ab	. ♛
23	Pneumonia, Impetigo	-	IVIG Ab	. ♛

Table 2. Showing the data regarding the presenting infection, pathogen if isolated, treatment and outcome. The crowns represent all patients whose neutropenia was accompanied by a significant neutropenia related infection.

Keywords: Agammaglobulinemia, XLA, Neutropenia, Early diagnosis

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(125)

Recurrent Non-tuberculous Mycobacterial infection in unusual area in a combined immunodeficiency – single case report

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A 7-year-10 months old male child, first born to non-consanguineous parents had recurrent pneumonia with eczematous skin lesions from 6 months of age. He was evaluated elsewhere and diagnosed severe combined immunodeficiency and started on oral antibiotic prophylaxis. At 2 years of age, he developed persistent ear discharge. Otoscopic examination showed polyp in both ear, biopsy of the right-side polyp showed Acid fast stain bacilli (AFB) and culture grew Mycobacterium avium. He was initiated on anti-tuberculous treatment (ATT) for total 1 year (rifampicin, ethambutol, clarithromycin and Levofloxacin). While on treatment he developed pseudomonas aeruginosa meningitis and treated with intravenous anti-microbials. 7 months after stopping ATT again developed bilateral ear discharge, examination showed granulation tissue in the middle ear. Biopsy of the middle ear granulation tissue showed AFB stain positive and culture grew Mycobacterium avium. He was reinitiated ATT medications and given for total 2 years. Next generation sequencing showed pathogenic homozygous DOCK2. Currently child on monthly intravenous immunoglobulin prophylaxis and oral antibiotic prophylaxis (Azithromycin and levofloxacin). Parents were counselled for hematopoietic stem cell transplantation. While evaluating for stem cell transplant he developed measles infection and developed interstitial pneumonia, acute respiratory distress syndrome and succumbed to the illness.
Importance of this case.
DOCK2 combined immunodeficiency is very rare and recurrent non tuberculous infection in ear is very rare association.

Keywords: Non tuberculous mycobacteria, DOCK2 deficiency, Ear polyp, Measles

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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(126)

Use of ruxolitinib for patients with hyperinflammatory syndromes – a real-world experience pilot study

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Purpose: Recent case reports and single-arm clinical trials indicate that the use of the JAK inhibitor ruxolitinib is effective in dampening inflammation in patients with hemophagocytic lymphohistiocytosis (HLH). The purpose of this study was to examine how ruxolitinib is being used more broadly for the treatment of pediatric patients with HLH and other hyperinflammatory syndromes.
Methods: This retrospective case series included children and young adults treated at St. Jude Children's Research Hospital and Le Bonheur Children's Hospital since 2018. Patients treated with ruxolitinib for FDA-approved indications and those on clinical trials were excluded. Demographic, clinical, laboratory, and drug administration data were collected. IBM SPSS Statistics, Version 25.0, was used to calculate the descriptive statistics.
Results: Thirteen patients were included in this study. Four met HLH-2004 diagnostic criteria, all with secondary HLH (sHLH; 1 cancer-related, 1 multisystem inflammatory syndrome in children [MIS-C], and 2 transplant-related with EBV trigger). The remaining 9 did not meet the criteria but exhibited systemic hyperinflammation (3 cytokine release syndrome (CRS), 3 macrophage activation syndrome, 3 MIS-C). Mean age at diagnosis was 10.4 years (min 3, max 22). Median ferritin on the day of ruxolitinib initiation (n = 9) was 9,400 ng/mL (min 366, max 78,719) and >100,000 ng/mL (n = 2). Median initial ruxolitinib daily dose was 0.5 mg/kg/day (min 0.1, max 1.8). Median time on therapy was 11 days (min 3, max 103). Ruxolitinib was used as a combination therapy in all patients (1–5 additional agents; mode = 4, n = 4 [31%]). No patients discontinued ruxolitinib due to toxicity. Seven patients improved on therapy (54%), all with non-HLH hyperinflammatory syndromes (median number of additional agents = 3). Of the remaining 6 (46%) who did not improve on therapy (median number of additional agents = 4), three had progressive disease (all sHLH), one did not respond, and two died (1 transplant-related sHLH, 1 CRS).
Conclusion: Ruxolitinib was well tolerated over a wide range of doses, lengths of administration, and in a variety of hyperinflammatory conditions. Efforts are currently ongoing to expand this study as a multi-center registry to gather more robust data on real-world experience to inform future research.

Keywords: Ruxolitinib, JAK inhibition, Hyperinflammation

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(127)

Autoimmune Lymphoproliferative Syndrome or Autoimmune Lymphoproliferative Syndrome-Like? Why the Genetic Distinction Matters

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As monogenic inborn errors of immunity are increasingly discovered, a growing number of entities with marked immunodysregulation and autoimmunity that clinically and immunophenotypically resemble autoimmune lymphoproliferative syndrome (ALPS), but have identifiable mutations outside the FAS/FASL pathway, are being characterized. Given the non-specific diagnostic criteria and heterogeneous presentations of ALPS, it is important for clinicians to be able to recognize ALPS "mimickers." Here we describe a patient who met diagnostic criteria for ALPS but was ultimately diagnosed with autosomal dominant STAT1 gain of function (AD STAT1 GOF) disease and its implications for management and prognosis.
A 15-year-old male was seen by Immunology for recurrent oral ulcers, skin, fungal, and viral infections, as well as sinopulmonary bacterial infections. He had previously been seen by Pulmonology, Rheumatology, and GI with a negative workup for Behcet syndrome and IBD. Imaging showed hepatosplenomegaly, with no lymphadenopathy noted on physical exam or CT. Immune work-up was notable for elevated (7.4%) alpha beta double negative T (DNT) cells, IL-18 and sFAS-ligand, with additional flow cytometry meeting criteria for probable APLS. However, a genetic panel identified a likely pathogenic STAT1 variant (c.516C>G), leading to a diagnosis of AD STAT1 GOF disease. He was started on azithromycin and fluconazole prophylaxis, with additional JAK inhibitor suggested, but family opted for monitoring. He was also evaluated by Hematology/Oncology and Neurology. The patient has been clinically stable on the regimen above.
One study showed that 12% of patients with STAT1 GOF mutation died at a median age of 30 years with severe infection (38%), cancer (24%), and/or cerebral aneurysmal hemorrhage (15%). Paired with antimicrobial prophylaxis, ruxolitinib, which inhibits JAK-induced activation of STAT proteins, has shown promising results in controlling immunodysregulation and preventing infections in STAT1 GOF disease. This case highlights the need for continued revision of APLS diagnostic criteria and the potential utility of broader gene panels/advanced diagnostic tools such as next generation sequencing in evaluating patients with suspected ALPS. A specific molecular diagnosis can have important clinical implications, allowing for the use of targeted therapies that interfere with the cellular mechanism of disease.

Keywords: APLS, Autoimmune lymphoproliferative syndrome, STAT1

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Increased dosage of elapegademase-lvlr improved metabolic and immunologic function in a patient with late-onset adenosine deaminase deficiency and neutralizing anti-drug antibodies

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Adenosine deaminase (ADA) deficiency causes accumulation of lymphocytotoxic metabolites, resulting in severe combined immunodeficiency (SCID) diagnosable by screening at birth or combined immunodeficiency (CID) diagnosed later in life. Enzyme replacement therapy (ERT) with pegylated recombinant bovine ADA (PEG-ADA) elapegademase-lvlr is an FDA-approved treatment for ADA-SCID/CID. We report a 16-year-old female with late-onset ADA-CID in whom inadequate circulating levels of PEG-ADA were associated with antibodies to elapegademase-lvlr. Increasing the dose resulted in higher drug levels and improved metabolic detoxification and immunologic function.

ADA-CID was diagnosed at 11 years old. History included MRSA abscesses, warts, tinea capitus and short stature. B lymphocytes were absent, and IgE and TSH were elevated. Initial ERT was with PEGylated purified bovine PEG-ADA (Adagen); after 10 weeks ERT changed to elapegademase-lvlr at 0.2 mg/kg/week with subsequent adjustments for weight. By 20 weeks of ERT, plasma ADA activity had increased from < 0.5 to 25.5 umol/h/ml (threshold 15 umol/h/ml) and red cell %dAXP had decreased from 6.3% to 0.5% (normal < 0.2%).

Antibody to un-PEGylated bovine ADA was detected by ELISA at 137 weeks of ERT. Efficacy of ERT waned after 168 weeks while receiving 0.37 mg/kg/week divided twice weekly. At 173 weeks, plasma ADA activity was undetectable and RBC %dAXP rose to 8.2%. Kinetic studies showed increased clearance of elapegademase-lvlr. Neutralizing anti-ADA antibody was detected with peak level at 189 weeks. Based on the kinetic studies and worsening immunologic laboratory parameters, at 201 weeks ERT dose was increased to 0.55 mg/kg/week divided thrice weekly to maximize time in the therapeutic range. Since that change, plasma ADA activity has been maintained above the threshold of 30 μmol/h/mL and immunologic function has normalized. The elapegademase-lvlr dose has been decreased twice since week 201 with sustained plasma ADA levels. At 260 weeks, at a dose of 0.37 mg/kg/week divided thrice weekly, plasma ADA activity was 52.47 umol/h/ml and RBC %dAXP was 0.5%.

Anti-drug antibodies in patients treated with PEG-ADA are usually non-neutralizing; in this case neutralizing antibodies were identified as the efficacy of ERT diminished. Through significant increases in elapegademase-lvlr dose and frequency, therapeutic efficacy was restored without immunosuppressive agents.

Keywords: Late-onset ADA deficiency, Enzyme replacement therapy, Anti-drug antibody

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(129)

The neuroimmune signature induced by HTLV infections

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Accumulating evidence indicates an intricated neuroimmunological relationship that is critical in cancer development and patient outcomes. This relationship occurs through bidirectional systemic communications by neurotransmitters and immune-associated molecules (e.g., cytokines and chemokines). However, the neuroimmune signature in Adult T-cell Leukemia/Lymphoma (ATL), an aggressive malignancy caused by Human T-cell Leukemia Virus (HTLV) infections, remains unclear. Since some patients with HTLV infections can also develop HTLV-1-associated myelopathy (HAM/TSP), we hypothesize that, to some extent, those with ATL may also present neuroimmunological dysregulation. To address this issue, we conducted a meta-analysis (utilizing the Fisher method and batch effect correction) of publicly (GSE33615, GSE29312, GSE38537, GSE233437, and EGAD00001007014) available transcriptomic data (PBMC) from 137 ATL patients, 45 asymptomatic, and 18 patients with HAM/TSP, versus 62 controls. We found 2138 up-regulated and 5884 down-regulated meta-differentially expressed Genes (meta-DEGs; adj. p value < 0.05) when comparing ATL versus controls, while asymptomatic and HAM/TSP presented 2430 and 552 as well as 1000 and 675 up-and down-regulated meta-DEGs, respectively. Gene ontology enrichment analysis indicated the presence of significantly enriched neuroimmune biological processes (BPs) in ATL patients, including neuroinflammation, neuron death, and vesicle-

mediated transport in synapses. Network analysis revealed an intricately interconnected and correlated association between neuroimmune genes (e.g., TNF, SNCA, ADORA2A) and pathways, as shown by clusterprofiler and corrplot R packages. An intrinsic correlation between neuro and immune pathways could be observed in patients with ATL when using the q.value as a correlation score. Principal Component Analysis (PCA) indicated that this neuroimmune network stratifies ATL patients from healthy controls, and neuroimmune genes, such as TNF, IL1B, SNPH, and APP, are among the most significant vectors for the group stratification. This ongoing work suggests that PBMCs from ATL have a dysregulated network of neuroimmune genes and pathways, which we are currently investigating for its association with ATL severity.

Keywords: Systems immunology, HTLV, Neuroimmune response

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Biologic Use and Outcomes in CVID Enteropathy

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Background: Gastrointestinal diseases are a leading cause of morbidity and mortality in CVID. Data assessing biologic use and outcomes across therapeutic classes are limited.
Methods: We examined the clinical response (clinical remission: stool frequency, SF, ≤ 2.8/day; enhanced clinical response, ECR: ≥ 60% SF reduction; clinical response, CR: ≥ 30% SF reduction), treatment courses, and complications related to biologic use in CVID enteropathy patients at Mount Sinai Hospital from 2014–2023.
Results: A total of 34 unique biologic treatment courses were administered in 14 CVID enteropathy patients who previously failed conventional therapies (median age at first treatment: 40, range 14–77, years; female: 50%) during the study period. At baseline, median body mass index was 18.0 (range 14.1–22.0) kg/m^2, 13/14 (93%) exhibited malabsorption, with 7/14 (50%) required total parenteral nutrition. Overall clinical response rates were higher for anti-TNF-α agents (44%; remission 1/9, ECR 3/9), JAK-inhibitors (60%; ECR 1/5, CR 2/5), and CTLA4-Ig (40%; remission 1/5, CR 1/5). There were lower clinical response rates for α4β7 integrin blockers (20%, remission 1/10, ECR 1/10) and anti-IL12/23 agents (20%, CR 1/5, with subsequent intolerance), though they remain beneficial for selected patients. Concurrent therapies (topical steroid and/or cholestyramine) were utilized in 50% of responding courses. Median time to treatment response was 12 weeks (range 6–27). Eventual treatment failure after an initial response was observed in 33%, with duration of response ranging 5–43 months. Biologic selection based on genetics (LRBA, STAT3 GOF, NFKB1) led to therapeutic response in 3/3 cases (ECR 1/3, CR 1/3). Infectious complications during treatments included gastrointestinal infections (n = 4), lower respiratory infections (n = 2), and line-associated bacteremia (n = 3). Serious adverse events occurred in 1 patient, for drug-induced liver injury after vedolizumab.
Conclusion: Outcomes to available biologic classes in CVID enteropathy is mixed, and eventual treatment failures may occur for some. Genetic insights may aid in biologics selection when available. There remain significant unmet medical needs for novel therapies and predictive treatment biomarkers for inflammatory gastrointestinal diseases in CVID.

Keywords: CVID, Biologics, Inflammatory complications, Enteropathy, Outcome

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A Peculiar Presentation: STAT3 Loss of Function with Recurrent Osteomyelitis and Review of the Literature

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Introduction: Signal transducer and activator of transcription 3 loss-of-function Autosomal Dominant Hyper-IgE Syndrome (STAT3-LOF; AD-HIES) is characterized by immune (eczema, recurrent skin and lung infections, elevated serum IgE) and non-immune (vascular, connective tissue, and skeletal abnormalities including osteoporosis, scoliosis, and risk for fractures) features. Osteomyelitis is a rare infection in patients with Hyper-IgE syndromes, most often reported with MRSA.
Methods: A PubMed review with key terms "STAT3-LOF," "AD-HIES" and "osteomyelitis" was performed in addition to the chart review of our index case.
Results: An 18-year-old female with severe eczema, frequent episodes of pneumonia requiring IV antibiotics, multiple episodes of skin abscesses including MRSA positive infections, and Strep pyogenes bacteremia with associated septic and toxic shock prompted an immune evaluation that revealed a heterozygous STAT3 pathogenic variant (c.1144C>T, p.R382W); IgE level >10,000; normal TH17 studies, DHR flow, IgG/A/M and CH50 consistent with STAT3-LOF. Next generation sequencing failed to identify additional causes for an underlying inborn error of immunity. Interestingly, she has had multiple admissions due to osteomyelitis from Mycobacterium abscessus requiring surgeries and prolonged treatment courses. Initially she received IV amikacin and imipenem and oral azithromycin and linezolid. Sensitivity testing showed resistance to linezolid, intermediate susceptibility to imipenem, and inducible resistance to all macrolides. She was transitioned to omadacycline and clofazimine. Repeat MRI showed acute on chronic osteomyelitis with abscess and extension of phlegmon into deep soft tissues. Amikacin and cefoxitin were additionally started and omadacycline and clofazimine were continued. She completed two months of four drug therapy and continued omadacycline and clofazimine with additional instances of positive cultures with Mycobacterium abscessus necessitating prolonged therapy. The patient subsequently developed erosive osteomyelitis of her maxilla with cultures growing Streptococcus mitis group, Eikenella corrodens and few Staphylococcus epidermidis. She had improvement with ampicillin-sulbactam and now is on a prolonged treatment course of amoxicillin-clavulanate. Additional cases from the literature are detailed in Table 1.

Table 1.
Patients with Hyper IgE syndrome and osteomyelitis, a review of the literature.

Publication	# Patients	Organism	Infection Location	Genetic Mutation
Wong et al	1	MRSA	Vertebral	STAT3 mutation negative
Tan et al	1	NA	Paravertebral	unknown
Amaro et al	1	MRSA	Left Ankle	DOCK8, SPINK5, STAT3, TYK2 mutation negative
Milner et al	1	NA	NA	STAT 3 mutation p.A703T

Conclusion: While skin and lung infections are a common complication in patients with STAT3-LOF AD-HIES, clinicians must be vigilant for osteomyelitis including with uncommon microbes, e.g. Mycobacterium and Eikenella.

Keywords: STAT3 loss of function, Autosomal dominant Hyper-IgE syndrome, Osteomyelitis

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Expansion of Tbet+ T and B cells in the lung of hypomorphic Rag1 mice

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Introduction: Human hypomorphic RAG1/2 mutations with partially preserved RAG activity is often associated with organ-specific inflammatory autoimmune complications. Lung is one of the most affected tissue sites with obstructive phenotype or restrictive manifestations which significantly worsens the quality of life. It has been demonstrated that Tbet+ B cells are expanded in human hypomorphic RAG deficiency and granulomatous lung diseases but their exact role in the disease pathomechanism is not fully understood.
Objectives: To design an experimental system to study the role of Tbet+ B and T cells in the lungs of hypomorphic Rag1 mice.
Results: Using a mouse model of partial RAG deficiency (Rag1R972Q/R972Q), we detected an expansion of Tbet+ B and T cells in the spleen and in the perivascular area of the lung, especially after a 3-month treatment with R848, a TLR7 agonist. Flow cytometry analyses showed a marked decrease in naïve CD4+ and CD8+ T cells and an increase in effector memory T cells in the lung. CD8+Tbet+ T cells produced a significant amount of IFNγ, one of the most important cytokines driving the differentiation of Tbet+ B cells in mutant mice as compared to wild-type mice. Moreover, we found significantly elevated IL-21 production by CD4+Tbet+ T cells in the lung of R848-treated KI mice compared to untreated ones.
Conclusions: Overall, our results show an expansion of Tbet+ cells in the lungs of hypomorphic Rag1 mice after TLR7 agonist administration. We also demonstrate that lung-resident T cells secrete cytokines that potentially contribute to the generation of Tbet+ B cells.

Keywords: Partial RAG deficiency, Tbet+ B cells, Immune dysregulation, Interstitial lung disease

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(133)

Looking for ALPS: 10 years experience of a combined assessment of serum FASL levels and circulating double negative T cells at the CHU Sainte-Justine

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Autoimmune lymphoproliferative syndrome (ALPS) is a rare inborn error of immunity characterized by an impairment of lymphocyte homeostasis caused by defective apoptotic mechanisms. ALPS clinical presentation is characterized by lymphoproliferation (lymphadenopathy and/or organomegaly), autoimmunity (mainly autoimmune cytopenia), and an increased incidence of lymphoma which is associated with typical biomarkers such as increased TCRαβ+ CD4− CD8− "double negative" (DN) T cells, high levels of vitamin B12, IL-10 and soluble (s)FASL, and impaired FAS-mediated apoptosis. The clinical and biological features were combined to create the diagnosis criteria for ALPS in 1999 and revised in 2009 and 2019.
Between 1st January 2014 and 31st December 2023, our clinical laboratory performed 561 measures of sFASL and DN T cells on 427 single pediatric patients. We were able to retrieve clinical data on 386 patients. Among the 386 patients, the main reason for assessing DN T cells and sFASL was

cytopenia (76%), tumoral syndrome (12%) or a combination of both (4%). sFASL median level was 200 pg/mL (range 40–4380 pg/mL) while the median percentage of DN T cells on TCRαβ+ T cells was 1.7% (range 0.1–21%). There was a positive correlation between sFASL levels and the percentage of DN T cells (Pearson correlation coefficient $r = 0.35$, $p < 0.001$). and an even stronger positive correlation between sFASL and Vitamin B12 levels ($r = 0.66$, $p < 0.001$). Twenty-three patients (6%) met the 2009 NIH criteria for a probable diagnosis of ALPS, and 7 patients (2%) fulfilled the 2019 ESID criteria for probable ALPS. Sensitivity for ALPS-FAS patients were 100% and 66.7% for the 2009 NIH criteria and the 2019 ESID criteria respectively, while specificity was 95 and 98.7%. The positive predictive value for ALPS-FAS diagnosis was 13 and 28.6%, respectively. Our study offers 'real-life' feedback on the process of identifying ALPS patients in a pediatric population presenting with compatible phenotypes and emphasizes the need for reconsidering the place and thresholds of the biomarkers to improve their positive predictive value while maintaining their sensitivity.

Keywords: Autoimmune lymphoproliferative syndrome, FasL, TCRαβ+ CD4− CD8− T cells

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(134)

Exploring Molecular Landscapes and Immunological Dynamics in Glioblastoma: Insights from Oncolytic Virotherapy

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Gliomas, particularly glioblastoma (GBM), present tremendous challenges in treatment due to their aggressiveness and high recurrence rates. The frequent reappearance of GBM, characterized by increased resistance to chemotherapy, results in a poor prognosis for patients. In the quest for more effective treatments, experimental treatments for GBM using oncolytic viruses are in Phase 3 clinical trials testing in Japan. Although it is well-known that these viruses function through direct infection, lysis of tumor cells, and stimulation of the immune response within the tumor microenvironment, a comprehensive understanding of the molecular mechanisms and dynamics involved in this potential anti-tumor therapy remains uncharted territory. To address this issue, we conducted a differential expression analysis using the likelihood ratio test (LRT) on The Cancer Genome Atlas (TCGA), of 661 glioma samples ranging from grade 2 to GBM, using the Deseq2 package. This analysis revealed 3.827 downregulated and 4.044 upregulated genes, providing a comprehensive overview of the molecular landscape of gliomas. Gene Set Enrichment Analysis (GSEA) unveiled, among others, a significant interferon alpha and gamma response in glioblastoma samples as well as a complement activation signatures. Furthermore, the analysis pointed towards a prevalent mesenchymal phenotype in GBM (CD44, BMI1), in detriment to a pro-neural phenotype (OLIG2, SOX2, Nestin) providing crucial insights into the tumor's cellular and molecular signatures. The metanalysis to investigate the Zika's oncolytic impact on GBM, performing using the SVA package with 3 different datasets (GSE114907, GSE102924, GSE234128), revealed 375 downregulated and 1.256 upregulated genes in GBM, and induced a robust interferon alpha and beta response (e.g., through IFNB1, IFT1, OASL). This result indicates a potentialization of the intrinsic GBM molecular signatures triggered by Zika oncolytic treatment. We are currently investigating new oncolytic viruses as GBM treatment, such as VSV and HSV-1 platforms, which will provide valuable molecular information for the development of tailored oncolytic therapies.

Keywords: Glioblastoma, Oncolytic viruses, Glioma

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(135)

Integrative characterization of the neuroimmunological interactions of Major Depressive Disorder and its intersection with COVID-19

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Mental disorders are among the primary causes of the global health burden, affecting approximately 700 million people worldwide. Among them, depression is among the main contributors to this burden, and due to several factors, such as the 2019 coronavirus disease (COVID-19) pandemic,

mental health problems have been globally exacerbated. Noteworthy, depression increases the susceptibility to several immune-related diseases, such as cancer, autoimmunity, and infectious diseases, indicating neuroimmune relationships that are still poorly explored. To gain new insights in this regard, we performed an integrative analysis (meta-analysis using the Fisher method and batch effect correction) of 340 transcriptomes publicly available (GSE215865, PMID:30185774; both RNAseq data) of peripheral blood mononuclear cells (PBMC) from patients with Major Depressive Disorder (MDD; 70 controls and 69 MDD) and COVID-19 patients (65 controls, 85 COVID-19 non-depression, and 33 COVID-19 depression). This approach revealed 2.202 upregulated and 10.183 downregulated common differentially expressed genes (DEGs). Functional enrichment analysis identified upregulated DEGs involved in biological processes (BPs), such as those related to cell cycle (CDC20, CENPF, BUB1), immunoglobulin production (IGLV3-10, IGKV2D-29, IGLV6-57), B cell receptor signaling pathway (IGHG4, IGHM, IGHA2), and type I interferon (IFNAR1, OAS1, ISG15). In contrast, downregulated DEGs enriched mainly nervous system processes (CHL1, NCAM2, NTRK1), including synaptic signaling (GRIN2B, TNR, GABRG2), sensory perception (OR13A1, PJVK, PHF24), and behavior (NRXN1, UCN, SHANK2). Network analysis characterized an interconnected network between these aforementioned up- and downregulated DEGs. Therefore, this ongoing study expands the current understanding of the pathophysiological factors related to neuroimmune dysregulation in MDD and individuals with COVID-19, broadening perspectives on the intersection between psychiatric disorders and viral infections.

Keywords: Neuroimmune dysregulation, Mental disorders, Major depressive disorder, COVID-19, Transcriptome analysis

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(136)

Hematopoietic stem cell transplantation for very early onset inflammatory bowel disease caused by IL10RA deficiency – preparation is the key to success

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Background: Interleukin 10 and Interleukin 10 receptor deficiencies are monogenic inborn errors of immunity causing very early onset inflammatory bowel disease. We present the challenges during hematopoietic stem cell transplantation (HSCT) in a child with IL10RA deficiency.
Case Study: Ms. K is a 2-year-old girl child born of third-degree consanguineous marriage with a history of two sibling deaths. The child was asymptomatic till 15 days of life when she developed complaints of fever, multiple loose stools and passing pus through the anus. Examination revealed a rectovaginal fistula and she underwent a colostomy in 2018. A genetic analysis confirmed the diagnosis of IL10RB deficiency. Her bowel inflammation was controlled with steroids, diet modifications, was taken up for HSCT from a fully matched father in September 2020 with fludarabine, treosulfan and thiotepa conditioning with tacrolimus and short methotrexate for GVHD prophylaxis. The transplant course was uneventful. The donor chimerism remained at 100% for three months and then gradually started to drop. We stopped the immunosuppression and commenced graded Donor lymphocyte infusion. She received nine DLI but there was a progressive drop in the chimerism until total autologous reconstitution. She had symptoms of IBD requiring steroids.
We planned a second HSCT using the same donor but administered one cycle of pre-transplant immunosuppressant regimen with Fludarabine and dexamethasone. In February 2022, we admitted her for a second HSCT from the father using the same conditioning regimen with three amendments to prevent rejection. We used rabbit ATG at 1.5 mg/kg/day for 3 days, infused higher CD34 of 10*10 6 cells/kg and added post-transplant cyclophosphamide at 25 mg/kg/day on Day 3 and Day 4. The child engrafted by day+16 and had no major toxicity. Her immunosuppressive drugs were withdrawn in February 2023 and her colostomy was closed in August 2023. She is growing and active with no signs of inflammatory bowel disease and complete chimerism.
Conclusion: In low-and-middle-income countries, loose stools are attributed to cow milk protein allergy resulting in an inordinate delay in diagnosis. HSCT is a curative option and the main challenge in autoinflammatory disorders is graft rejection which was handled with adequate preparation.

Keywords: IL10RB, Inflammatory bowel disease, Pre transplant immunosuppression, Graft rejection

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(137)

Case of Mitochondrial Encephalomyopathy Secondary to COVID-19 in a Pediatric Case of SIFD Syndrome with a Novel TRNT1 Mutation

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Syndrome of Congenital Sideroblastic Anemia, B-cell Immunodeficiency, Periodic Fevers, and Developmental Delay (SIFD) is a rare autosomal recessive disease caused by mutations in the tRNA nucleotidyltransferase 1 (TRNT1) gene. We present the case of a 13-month-old boy with developmental delay, microcytic anemia, and recurrent febrile illnesses. The patient was found to have hypotonia, increased deep tendon reflexes, and basophilic stippling on the peripheral smear, which led to a diagnosis of sideroblastic anemia. Further immunological workup revealed B cell lymphopenia. Whole exome sequencing identified two novel heterozygous mutations in the TRNT1 gene (Thr49Fs and Ile122Thr), confirming the diagnosis of SIFD syndrome. Our patient had a milder phenotype compared to previously reported cases. He maintained his hemoglobin without frequent transfusions, and his immunoglobulin levels were normal. However, he developed left ventricular dilated cardiomyopathy at the age

of 2 years, which was treated with heart failure medication. At the age of 5 years, despite completing a full series of mRNA COVID-19 vaccines, COVID-19 infection resulted in mitochondrial encephalomyopathy and respiratory failure. A subsequent immunology evaluation revealed low IgG levels (412 mg/dL) and a poor response to tetanus antibody, prompting the initiation of immunoglobulin replacement therapy. This case highlights the importance of genetic testing in multisystem disorders and the variable clinical course in SIFD patients. Additionally, it emphasizes the unique susceptibility to COVID-19 due to immunodeficiency and mitochondrial defects. The evolving immunophenotype in these patients emphasizes the importance of periodic immunological assessments.

Keywords: SIFD, TRNT1, Sideroblastic anemia, B cell, Cardiomyopathy, Hypogammaglobulinemia, COVID-19, Encephalomyopathy, Developmental delay, Periodic fevers

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(138)

OTULIN-related conditions: Report of a new case and review of the literature using GenIA

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OTULIN encodes an eponymous linear deubiquitinase (DUB) essential for controlling inflammation as a negative regulator of the canonical NF-κB signaling pathway. Biallelic loss-of-function (LOF) mutations in OTULIN cause an autosomal recessive condition named Otulin-Related Autoinflammatory Syndrome (ORAS) or Otulipenia, also known as AutoInflammation, Panniculitis, and Dermatosis Syndrome (AIPDS). Monoallelic OTULIN LOF has been linked to an incompletely penetrant, dominantly inherited susceptibility to invasive Staphylococcal infections. At the same time, a recent novel ORAS-like inflammatory syndrome was described in association with a heterozygous missense mutation that appears to exert dominant negative effects. In this manuscript, we report the identification of a novel homozygous missense mutation, p.(Trp199Arg), in a Moroccan infant with an ORAS phenotype. We go on to systematically review the literature for all OTULIN-related human disease phenotypes. After identifying over ten relevant original research articles on OTULIN-related disease, we use the GenIA database to collect, extract and harmonize all clinical, laboratory and functional data for the patients and variants in these studies. We show how GenIA facilitates comprehensive synthesis across the genotypic, phenotypic and mechanistic data associated with the OTULIN-related conditions described thus far. This enables us to provide a more in-depth view of the diverse mechanisms and pathways by which the OTULIN mutations described thus far may lead to human immune disease, as well as raise additional questions for future investigation.

Keywords: Systematic review, OTULIN, ORAS, IMD107, Autoinflammation, Immunodeficiency, Ubiquitin, NF-kappaB, GenIA, Human genetics

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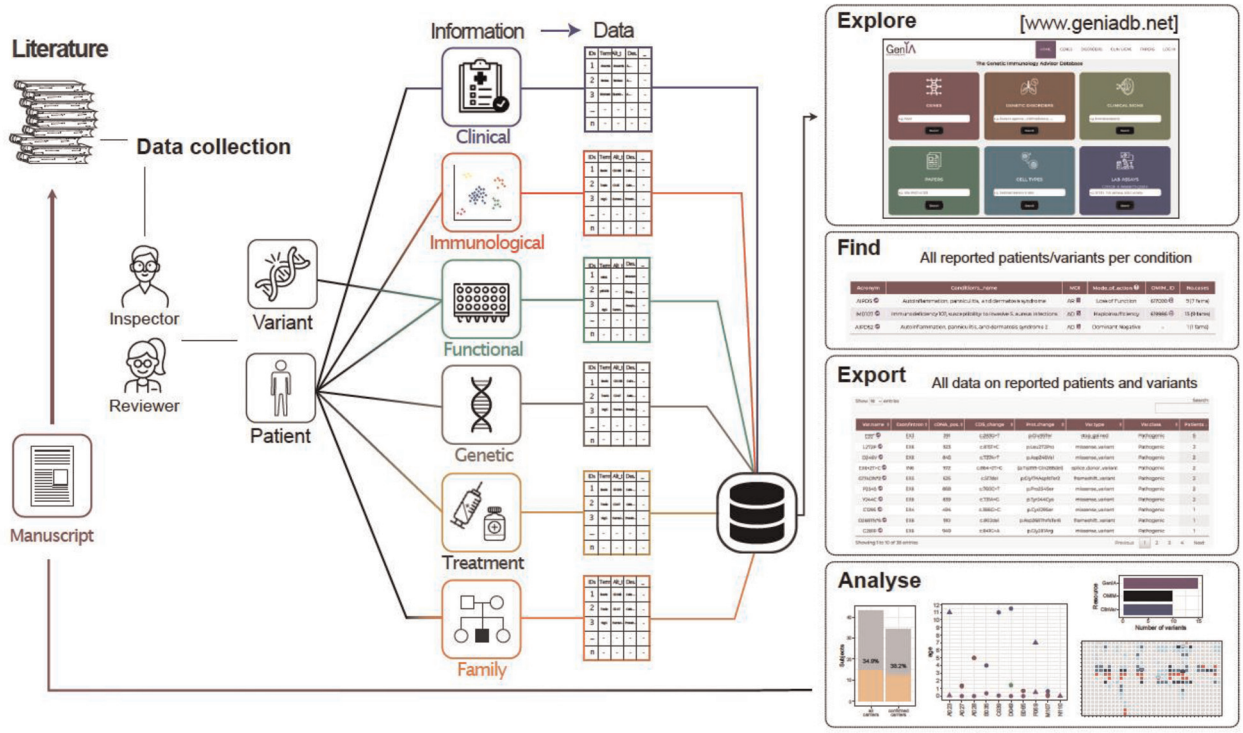
Algorithm for GenIA-based Data Collection, Extraction and Analysis



Known Disease-related OTULIN Variants and Phenotypic Features

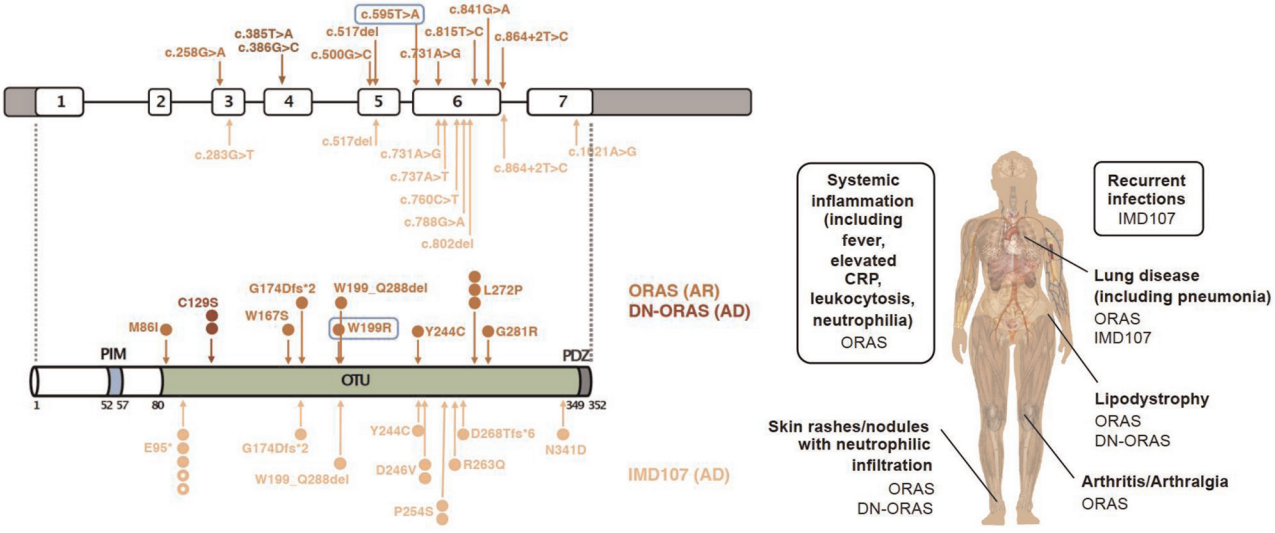


Figure. (abstract: 138)

(139)

Novel CARD14 Variant: A Case of Autoinflammatory Disorder in a 5-Year-Old with Therapeutic Insights

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Background: CARD14, a member of the CARMA protein family along with CARD11 and CARD9, plays an important role in initiating NF-κB and MAPK signaling pathways by forming the CBM complex with BCL10 and MALT1. CARD14 is highly expressed in the skin and mucosal tissues. Autosomal dominant gain-of-function mutations in CARD14 have been associated with psoriasis and pityriasis rubra pilaris. This case report presents a unique autoinflammatory disorder involving a novel CARD14 variant (c.1488del; p.Trp497fs).
Case Presentation: A 5-year-old boy presented to the rheumatology clinic with a history of recurrent fever and a skin rash that began at the age of 2 years. The fever was accompanied by fatigue, early morning stiffness, and occasional limping without a clear etiology. Over the last year, urticarial-like pruritic skin rashes with a generalized distribution occurred with each fever episode. While there was no family history of similar cases, joint disease was noted in elderly family members. On examination, the boy was slightly underweight, and minimal knee effusion with a normal range of motion was observed. CBC results were unremarkable, but both ESR (54–67 mm/hr) and CRP (6 mg/dL) were elevated. Liver enzymes, ferritin, and renal profile were normal. Whole exome sequencing identified a novel CARD14 variant (c.1488del; p.Trp497fs), predicted to result in absent or disrupted protein formation, though functional testing was not performed. Initial treatment involved IV Tocilizumab, resulting in the normalization of inflammatory markers and improved fever episodes, but the rash was persistent. Upon identifying the CARD14 variant, the patient was started on Adalimumab (TNF-inhibitor) at a dose of 20 mg SC every two weeks. Six months later, the patient responded well to the medication, with fever resolution, maintained normalized inflammatory markers (ESR 10 and CRP < 0.6), and a notable improvement in rash severity.
Conclusion: This case highlights a novel CARD14 variant associated with an autoinflammatory disorder, expanding our understanding of the spectrum of CARD14-related diseases. However functional testing is needed to confirm the pathogenicity of this. The use of a TNF-inhibitor, as suggested in prior studies with common CARD14 variants in psoriasis, proved beneficial in managing our patient symptoms

Keywords: CARD14, Autoinflammation, TNF-inhibitor, Recurrent fever

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(140)

Late Onset and Long Lasting Neutropenias: preliminary data on WES analysis

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Background: Late Onset and Long Lasting Neutropenia (LO/LL NP), shows a mild phenotype and a peculiar immunological pattern.
This form of neutropenia seems more to have a background of immune dysregulation because of development overtime of autoimmune markers/phenomena and also due to the presence in a proportion of patients of variants in immune dysregulation genes.
The application of wider genetic methods would be strongly advisable to support this idea.
Aim of the study: Provide stronger evidence, by using Whole Exome Sequencing that genetic variants related to immune dysregulation, may be in the background of LO/LL NP neutropenias.
Methods: Patients registered in the Italian Neutropenia Registry i) affected with chronic neutropenia both with and without antibodies against neutrophils, ii) diagnosed at age ≥3 yrs up to 25yrs with duration of neutropenia beyond 12 months or iii) diagnosed below 3 years of age but lasting longer than 3yrs were considered eligible for the present study. Whole Exome Sequencing (WES) was performed on DNA extracted from whole blood. The bioinformatic analysis was initially carried out with an in silico gene panel of 538 genes belonging to immune diseases and selected from the IUIS Committee for Inborn Errors of Immunity annual report and the Panel App database.
Results: Nine patients (6 females, 67%) affected with LO/LL (1/9; 11% without specific antibodies against neutrophils), diagnosed at a median age of 12 years (0–17.3yrs) and with a median duration of follow up of 6.9 yrs (3.5–16.2yrs), were studied with WES. The study of the PID/PIRD updated panel including 538 genes was negative in 5/9 (56%) negative cases while in the remaining 4/9 (44%) some variants were found (Table 1).

Table 1.
Characteristic of genetic variants found with WES.

#PT	GENE	ZYGOSITY	INHERITANCE	FRANKLIN CLASSIFICATION	TRANSMITTED BY
PT1	MALT1	het	AR	VUS/LP	*de novo*
PT2	TGFBR2	het	AD	VUS/LP	father
	RELA	het	AD	VUS/LP	mother
	TRNT1	het	AR	VUS/LP	mother
PT3	SLC7A7	het	AR	LP/P	mother
	BRCA1	het	AR/AD	LP	father
	MPO	het	AR/AD	P	father
PT4	SPINK5	het	AR	P	mother

Conclusions: These preliminary results seem to indicate the involvement of potentially damaging variants in genes commonly associated with

immune dysregulation. The transmission of these variants, even in genes with dominant inheritance, from an otherwise healthy parent seems to indicate the possibility of incomplete penetrance or complex, polygenic inheritance. Further clinical investigations will be performed on the parents who transmitted the pathogenic variants and the bioinformatic analysis will also be extended to the rest of the exome in the probands.

Keywords: Long lasting and late onset neutropenia, Whole exome sequencing, Immune dysregulation

Disclosures: Francesca Fioredda: I have relevant financial relationships with proprietary interests: X4 Pharmaceutics (Advisory Board). Maurizio Miano: I have relevant financial relationships with proprietary interests: X4 Pharmaceutics (Advisory Board). Helen Papadaki: I have relevant financial relationships with proprietary interests: X4 Pharmaceutics (Advisory Board). The other authors have no financial relationships or conflicts of interest to report.

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(141)

Comprehensive characterization of innate and adaptive immune profile of COVID-19 early convalescent children

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Objective: To address the immune profile of recovered pediatric patients three to eleven weeks after acute SARS-CoV-2 infection.
Methods: Patients previously healthy or with a preexistent chronic disease, up to 18 years-old, with a positive RT-PCR or serology for SARS-CoV-2 were enrolled (n = 23). The control group without COVID-19, was matched by age, sex, and underlying chronic diseases (n = 25). Blood samples were collected for immunophenotyping, hematological and inflammatory markers, and cytokine measurement.
Results: In our series, 17/23 (73.9%) of convalescent children had chronic conditions, while comorbidities were present in 20/25 (80%) of control children. Five children developed MIS-C (21.7%). Laboratory results of convalescent patients were equivalent to controls, except for higher lymphocyte numbers compared to controls. All the other hematological, inflammatory and cytokine markers were equivalent between groups. Convalescent patients presented equivalent numbers of neutrophils, classic and non-classic monocytes as the controls, but those populations presented increased TLR2 expression, indicating higher activation. Higher TCD4 counts were also observed, but not TCD8, resulting in higher CD4/CD8 ratio. Naive, TemRA and follicular CD4+T cells and TRECs were also increased in those patients, as well as activated CD4+T lymphocytes. Higher numbers of effector memory EM2 and EM3 in CD4 and EM2 in CD8 T cells in convalescent patients were also observed. All other major T cell subsets, i.e., central memory, EM1, Tregs and exhausted T cells were equivalent between groups. Memory B cells were also higher in convalescent patients. NK cell numbers were similar between the groups, but CD107a+ NK cells were higher in the convalescent group, which also indicate the persistence of greater activation of these cells.
Conclusion: Overall, in this short time after the acute infection, the activation profile of phagocytes, T cell subtypes and NK cells remains in those patients, and the higher production of TRECs and naive T cells compared to uninfected controls suggest a recovery of the adaptive immune system. An extended period of observation is currently being carried out to assess the long-term effects of the virus on the immune system of children and adolescents.
Supported by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo).

Keywords: COVID-19, Convalescent phase, Children and adolescents, Innate immunity, Adaptive immunity

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(142)

A non-consanguineous family with hepatic veno-occlusive disease and immunodeficiency

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Patient 1: Female, 15 years old, presented with hemophagocytic lymphohistiocytosis secondary to CMV at 7 months of age and disseminated mycobacterial infection at 8 months, progressing to chronic hepatopathy with cirrhosis-like features. Inborn errors of metabolism and hepatitis B and C serology tests were negative. At 3 years of age, diagnosed with non-Hodgkin lymphoma, and started chemotherapy including rituximab. Due to hypogammaglobulinemia, IGIV replacement was initiated. Fusarium was detected in bronchoalveolar lavage. At 9 years old, diagnosed with tuberculous lymphadenitis. Presents recurrent sinopulmonary infections with frequent antibiotic use, learning disabilities, and ADHD. Initial laboratory assessment: T CD3 lymphopenia (893/mm³, RR: 1200–2600), B lymphopenia (110/mm³, RR: 270–860), hypogammaglobulinemia (IgM 19.4, IgA < 5, IgG 499 mg/dL), and elevated ALT and AST. Liver biopsy was suggestive of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Chest CT revealing bronchiectasis. Genome sequencing identified compound heterozygous pathogenic trans variants in SP110 (exon 14 deletion and p.Arg373Serfs*22).
Patient 2: Female, 10 years old, patient's one sister, presents T CD8 lymphopenia (561/mm³, RR: 620–2000) and B lymphopenia (413/mm³, RR: 720–2600) since 6 months of age. Antimicrobial prophylaxis was initiated. Developed hypogammaglobulinemia requiring IGIV replacement and hepatosplenomegaly with elevated AST/ALT at 18 months. At 2 years, experienced diarrhea and acholic stools. Doppler ultrasound suggestive of hepatic cirrhosis. She also presented recurrent sinopulmonary infections. Genetic panel identified compound heterozygous pathogenic trans variants in SP110 (exon 14 deletion and p.Arg373Serfs*22).
Patient 3: Male, 2 years old, brother of patients 1 and 2, showed hepatomegaly at 5 months on physical examination. Laboratory evaluation

revealed hypogammaglobulinemia (IgM < 25, IgA 7.6, IgG 393 mg/dL) and elevated AST/ALT. Doppler ultrasound showed signs of chronic hepatopathy. Genetic panel identified compound heterozygous pathogenic trans variants in SP110 (exon 14 deletion and p.Arg373Serfs*22). Antimicrobial prophylaxis and IGIV replacement were started.

Discussion: This case series describes siblings from the same non-consanguineous family presenting mutations in SP110 with a severe phenotype of combined immunodeficiency and chronic hepatopathy. Parental segregation and mutation analysis were performed, confirming a compound heterozygous pattern consistent with autosomal recessive inheritance. Early recognition of hepatic veno-occlusive disease associated with immunodeficiency is crucial for effective management.

Keywords: Hepatic veno-occlusive disease, Combined immunodeficiency, Hypogammaglobulinemia

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(143)

Follow up of Cell-Immune Response using CovidCELL DTH skin test in Kidney Transplanted Patients

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Rationale: During the COVID emergency it was evident the lack of suitable methods to address the question of cellular immune response induced after infection/vaccination with SARS-CoV-2 that could be implemented in large-scale population studies. Our research group provided CovidCELL, a reliable, reproducible, cheap, and simple skin test based on the classical delayed-type hypersensitivity (DTH) immune reaction adapted to this virus as an elegant solution to know the cellular immune status of infected/vaccinated patients. Results of this in vivo method in a long-term follow up study on kidney transplanted patients and its correlation with humoral immune response is presented in this communication.

Methods: IgG anti-S/NCP SARS-CoV-2: commercial ELISAs were used to detect specific IgG against the S1 and N proteins of SARS-CoV-2 following manufacturer's instructions (SARS-CoV-2 IgG anti-S1 /anti-NCP immunoassay, Euroimmun). Results were expressed as OD ratio (OD ratio = >0.8 were considered positive).

CovidCELL: 25 μL (0.1 mg/mL) reconstituted lyophilized RBD (receptor binding domain) was administered as the intradermal test (IDT) puncture and performed according to usual clinical practice in the in vivo diagnostic techniques office. The patients were instructed to take a photograph after 12, 24, 48 h. DTH measurements were obtained based on the results of the photographs.

Results: Results of monitoring humoral (anti-S and anti-NCP IgG levels) and cellular (CovidCELL DTH test) immune results of 14 kidney transplanted patients is shown in the following table. Immune biography reflects the clinical history of vaccination/infection of these patients related to SARS-CoV-2.

Table.

	in vivo DTH		IgG anti-S		IgG anti-N		Immune Biography
TX-01	12	POS	6,6	POS	1,2	POS	💉💉💉💉 ☣
TX-03	0	NEG	5,9	POS	0,3	NEG	💉💉💉💉
TX-04	5	POS	8,1	POS	1,6	POS	💉💉💉💉
TX-05	7	POS	7,6	POS	0,9	POS	💉💉💉💉💉
TX-07	8	POS	7	POS	0,4	NEG	💉💉💉💉 ☣
TX-08	9	POS	8,4	POS	0,2	NEG	💉💉💉💉
TX-09	10	POS	6,4	POS	3,4	POS	💉💉💉💉 ☣
TX-11	7	POS	7	POS	3	POS	💉💉 ☣ 💉
TX-12	10	POS	7	POS	1,2	POS	💉💉💉💉
TX-14	13	POS	7,9	POS	4,7	POS	💉💉💉 ☣
TX-15	22	POS	5,1	POS	0,2	NEG	💉💉💉💉 ☣
TX-17	8	POS	6,7	POS	0,5	NEG	💉💉💉💉💉
TX-19	2	NEG	6,8	POS	1,9	POS	💉💉💉💉
TX-24	11	POS	5,5	POS	0,3	NEG	💉💉💉 ☣ 💉

DTH measurements are shown in mm.
IgG anti-S/anti-N results are expressed as OD ratios. Positive: OD Ratio>=0.8.
Immune biography:
- doses of Pfizer vaccine administered are represented as 💉
- infections confirmed with a positive SARS-CoV-2 test+symptoms are represented as ☣

Conclusions: All patients showed a positive humoral response to the RBD-Spike immunodominant antigen, 6/14 patients showed a humoral response against the natural NCP antigen of the virus, whereas 12/14 showed a positive cutaneous CovidCELL DTH test reflecting the variable degree of immunogenicity elicited by vaccination/infection. Using affordable and simple tests, individualized measurement of these immune parameters should be used to guide vaccination schemes and immunogen recommendations.

Keywords: DTH skin test, Cellular immune response, Immunogenicity SARS-CoV-2 vaccines

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(144)

Neutralizing Interferon Lambda 1 Autoantibodies in a Pediatric Patient with Chronic Granulomatous Disease and Colitis

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Rationale: Interferon lambda, a type III interferon, has been identified as a critical cytokine for viral immunity, primarily at epithelial surfaces like the respiratory and gastrointestinal tracts. Recent reports have also implicated interferon lambda-1 (IFNλ-1) in promoting colon mucosal healing, which may play a role in the endogenous control of inflammatory bowel diseases. Here, we report the presence of blocking anti-IFNλ-1 autoantibodies in a patient with chronic granulomatous disease (CGD) and granulomatous colitis, which was detected both prior to and after her development of gastrointestinal pathology.

Methods: Plasma samples collected from patients with CGD (n = 63) and healthy individuals (n = 4) were screened for the presence of various anti-

cytokine autoantibodies using a particle-based screening assay. The neutralizing capacity of the autoantibody in the patient's plasma was evaluated by flow cytometry using A549 cells.
Results: We detected high levels of anti-IFNλ-1 autoantibodies in a female, pediatric patient with phox47 CGD and colitis. In an assay using A549 cells, her plasma potently blocked IFNλ-1-induced STAT1 phosphorylation.
Conclusion: We have identified a patient with CGD colitis who has neutralizing interferon lambda 1 autoantibodies. This finding warrants further investigation of the relationship between IFNλ1 and gastrointestinal mucosal disease, as well as the presence of autoantibodies in patients with CGD.

Keywords: Chronic granulomatous disease, Autoantibodies, Interferon lambda 1

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(145)

Assessing MEFV variant pathogenicity by ASC- Specks Flow Detection

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Familial Mediterranean fever (FMF) is due to mutations in MEFV encoding the pyrin. This disease is characterized by repeated episodes of fever and serosal inflammation, associated with chronic inflammation and potential life-threatening long-term consequences such as amyloidosis). Although initially considered as a recessive disorder, ~30% of all clinically diagnosed cases display only one mutation. This implies that many patients identified as just carriers may suffer from an attenuated disease with potentially severe consequences. Thus, there is a critical need to assess the pathogenicity of a given MEFV variant in a simple and reliable way,
Apoptosis-associated speck-like protein (ASC) is a critical component of most inflammasomes, which are the main actors of the inflammatory responses. Upon activation of inflammasomes, ASC forms large protein aggregates called "specks". This filamentous structure creates multiple caspase-1 activation sites and serves as a signal amplification mechanism for inflammasome-mediated cytokine production.
We designed a flow cytometry-based assay to assess ASC speck formation in peripheral circulating monocytes of FMF patients, serving as a readout to identify cells undergoing inflammasome activation in response to various stimuli, mainly Lipopolysaccharides, NLRP3 agonist (nigericin) or pyrin activators (i.e., Clostridium Difficile Toxin A (TcdA), or the synthetic derivative of staurosporine UCN-01.
Through analysis of 25 FMF patients, we showed that our ASC-Speck Flow Assay correctly identified FMF patients with pathogenic variants in MEFV compared to healthy controls and patients with other autoinflammatory disorders. Interestingly, our assay could also pinpoint patients with monoallelic variants who display abnormal pyroptosome activation and could benefit from appropriate therapy.
Our study shows that accurate assessment of ASC specks by flow cytometry holds significant potential for guiding preventive or therapeutic strategies across a spectrum of inflammatory conditions where inflammasome involvement is critical.

Keywords: ASC, Flow cytometry, Autoinflammatory disease, Familial Mediterranean fever

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(146)

Transient severe T cell lymphopenia in a patient with Cornelia de Lange Syndrome captured by TREC screening

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Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder characterized by growth delay, upper limb malformations, characteristic craniofacial appearance, and intellectual disability. Infections have been described as a significant cause of morbidity and mortality in these patients. Though several gene mutations have been associated with CdLS, the most common mutations occur in the gene that encodes for cohesin loader Nipped-B-like (NIPBL). Mutations in this gene have also been associated with alterations of immunoglobulin gene diversification which could explain increased risk for infections. While B cell lymphopenia, decreased serum immunoglobulin levels and/or impaired T cell populations have been described, no previously published cases have been captured by T cell receptor excision circle (TREC) screening.
A 2-week-old female, born full term with multiple skeletal anomalies and coarse facies was evaluated for abnormal newborn TREC screen. The initial work up was significant for severe T cell lymphopenia (CD3+ = 255) with low but present CD4+ naïve T cells (CD4+CD45RA+ = 115, 64%). Additional studies revealed low immunoglobulin G (337 mg/dL) and A (< 5 mg/dL), negative maternal engraftment and normal lymphocyte proliferation to mitogens. The patient was initiated on immunoglobulin replacement therapy and prophylactic antimicrobials. Genetic testing revealed one pathogenic heterozygous mutation in PAX1 c.158C>A(p.Ser53). Mother carries this pathogenic mutation, and she is phenotypically normal. Whole genome sequencing revealed a mutation in NIPBL c.6705_6707del (p. Lys2235del), confirming the diagnosis of CdLS. The patient has been followed for two years with normalization of T cell counts and immunoglobulin levels. She has not had any severe infections despite the discontinuation of antimicrobial prophylaxis and immunoglobulin replacement.
Patients with Cornelia de Lange Syndrome (CdLS) have an increased susceptibility to infections that lead to significant morbidity and mortality. Though T cell impairment has been documented in CdLS, severe T lymphopenia captured by TREC screening has not previously been described to our knowledge. Our patient also has a heterozygous mutation in PAX1, which in homozygous individuals has been associated with thymic hypoplasia. It is plausible this mutation had a confounding effect. This case highlights the importance of considering and screening for immunodeficiencies in patients with CdLS.

Table.
T lymphocyte trend over the years.

Date	3/11/2021 (cells/μL)	4/6/2021 (cells/μL)	5/4/2021 (cells/μL)	8/12/2021 (cells/μL)	3/15/2022 (cells/μL)	4/11/ 2023 (cells/μL)
CD3+ absolute	255	280	250	580	1860	2983
CD4+ absolute	171	210	180	480	1440	2169
CD8+ absolute	66	50	40	90	340	749
CD45RA+	115 (64%)	150 (73%)	150 (80%)	370 (77%)	1210 (84%)	1752
CD45RO+	47 (26%)	60 (27%)	30 (18%)	100 (22%)	230 (16%)	
CD19+	389	600	1006	630	1180	2113

Keywords: Severe T cell lymphopenia, Cornelia de Lange syndrome, TREC screen, NIPBL mutation

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DiGeorge Syndrome with an atypical presentation: Lymphoproliferation and malignancy

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Introduction: DiGeorge syndrome (DGS) belongs to the spectrum of manifestations of chromosome 22q11.2 deletion syndrome, with emphasis on thymic and parathyroid aplasia and congenital heart disease.
Objective: To report an atypical clinical case of DGS in a child with chronic lymphoproliferation, autoimmunity and progression to parotid lymphoma.
Case Report: a 6-year-old girl, with history of congenital heart disease and autoimmunity, with mild facial dysmorphisms, without hypocalcemia, without lymphopenia. At 8 months of age, she started to present with febrile hepatosplenomegaly and disseminated progressive lymphadenopathy (thoracic, intraabdominal and cervical), which evolved by the age of 5 years to a lymphoma in the parotid gland. A genetic panel was performed for autoimmune lymphoproliferative syndromes (ALPS) and no pathogenic variants were found. Empirical treatment was performed for ALPS, with partial response to corticosteroid therapy. A genetic panel (Invitae, supported by Jeffrey Modell Foundation) for inborn errors of immunity was performed, with a TBX1 gene mutation being found, and a subsequent MLPA examination confirmed the presence of a pathogenic deletion in the regions associated with DGS.
Discussion: We describe the first case of DGS with manifestations of chronic lymphoproliferation and progression to parotid lymphoma. The TBX1 mutation found in this case is associated with lymphoproliferation and malignancy. Such as COMT, SMARCB1 and DGCR8 genes, the TBX1 gene mutation is associated with cardiac, craniofacial, thymic and parathyroid defects. The genetic basis for the high variability and penetrance of DGS manifestations remains unknown and influences the observed clinical variability.
Conclusion: Although common, the lack of recognition of the condition and access to genetic tests, in addition to the great variability of the clinical presentation of DGS postpones the diagnosis. Early diagnosis could positively influence the evolution of the cases.

Keywords: DiGeorge syndrome, Lymphoproliferation, Malignancy, TBX1 mutation

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Disseminated Histoplasmosis in an Adult with STAT1 Mutation

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Introduction: STAT1 defects vary in severity and clinical presentation. STAT1 gain of function (GOF) mutations have been described with a wide clinical spectrum, including nontuberculous mycobacteria, disseminated fungal, bacterial, and viral infections in addition to immune dysregulation. We present a 30-year-old female with disseminated histoplasmosis that was found to have one pathogenic variant in STAT1.
Methods: Retrospective chart review was conducted. Laboratory investigations included lymphocyte immunophenotyping by flow cytometry, lymphocyte proliferation to mitogens and antigens, quantitative immunoglobulins, genetic evaluation by next generation sequencing, and assays for further evaluation for MSMD and STAT GOF.
Results: A previously healthy 30-year-old Caucasian female presented with fevers, fatigue, malaise, profuse diarrhea, and abdominal pain of 5 days duration. She was found to have mild mediastinal and retroperitoneal lymphadenopathy on CT imaging. She was diagnosed with disseminated histoplasmosis with positive histoplasma antigen in serum and urine. She was treated with oral itraconazole continuously starting April 2022. Immunology was consulted by Infectious disease due to concern for underlying immunodeficiency due to the protracted course of persistently elevated histoplasma antigen in urine despite adequate treatment for more than a year. Infection history was unremarkable except for recurrent oral candidiasis. Patient is adopted, so family history is unknown. Next generation sequencing revealed a pathogenic variant in STAT1 (c.1310C>T; p. Thr437Ile). STAT GOF assay done at Medical College of Wisconsin showed enhanced phosphorylation of STAT1 at 15 and 30 minutes, and the total protein level was also high, which is consistent with STAT1 GOF.
Conclusion: STAT1 GOF mutations are highly penetrant with a median age of onset at 1-year. Chronic mucocutaneous candidiasis and invasive fungal infections have been reported with STAT1 GOF. A variety of clinical phenotypes, including fungal, viral, and bacterial infections, autoimmunity, malignancy, and aneurysms, have been described for STAT1 GOF variants, which has led to the expansion of the clinical spectrum associated with it. The presence of these complications accounts for poor outcomes.

Keywords: STAT1, Gain of function, Histoplasmosis

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Mycobacteria Chelonae Panniculitis presenting as Refractory Cellulitis in Patient with Hypogammaglobulinemia

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Introduction: Immunodeficiencies are commonly associated with increased susceptibility to infections and abnormal opportunistic pathogens. Mycobacterium chelonae (M. chelonae), classified among rapidly growing nontuberculous mycobacteria, often demonstrates multidrug resistance particularly following surgical procedures. In immunocompromised hosts, identification of M. chelonae is important to start appropriate therapy and to abort further dissemination. Here we present a case of M. chelonae panniculitis presenting as refractory cellulitis in a patient with hypogammaglobulinemia.
Case Presentation: A 47-year-old woman with a history of recurrent sinopulmonary infections, severe persistent asthma (on systemic steroids), chronic ulcerative laryngitis, and refractory cellulitis has been referred to Allergy/Immunology clinic for evaluation. The cellulitis started as a lower abdominal skin tear that was rapidly spreading despite receiving several antibiotics over a period of 7 months. Lesions evolved into erythematous to violaceous plaques situated along striae of the lower abdomen. Immune and infectious work up revealed significantly reduced serum IgG (374 mg/dL), serum IgA (42 mg/dL) and serum IgM (31 mg/dL) as well as unprotective pneumococcal antibody titers. Patient was started on IgG replacements intravenously and underwent skin biopsy and culture which identified M. chelonae organisms as etiology of the mycobacterial panniculitis. Susceptibility guided antimicrobial regimen of azithromycin, tigecycline, and linezolid showed clinical response. Concurrent to the panniculitis course, patient's laryngeal lesions were biopsied to evaluate her chronic ulcerative laryngitis not responding to conventional treatments. Unexpectedly, the biopsy revealed laryngeal rhabdomyosarcoma (RMS). Patient underwent surgical resection and is receiving chemotherapy and radiation.
Discussion: Patients with hypogammaglobulinemia are at increased risk of severe, recurrent and/or unusual infections. Our patient suffered from intractable skin lesions for several months with prolonged antimicrobial courses before a rigorous immune and infectious work up uncovered hypogammaglobulinemia and identified M. chelonae, a rare cause of chronic infections in immunocompromised hosts. Placement on targeted treatments cleared the infection and prevented further dissemination. Laryngeal RMS, reported in 22 adults in literature thus far, adds further complexity to the case. This case emphasizes the importance of maintaining a broad differential and obtaining a biopsy to properly identify rare organisms and/or malignancies when atypical presentations are encountered in patients with immunodeficiencies.

Keywords: Hypogammaglobulinemia, Immunodeficiency, Mycobacteria chelonae, Rhabdomyosarcoma, panniculitis, Immunocompromised

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(150)

From pancytopenia to hyperleukocytosis, an unexpected presentation of immune reconstitution inflammatory syndrome in an infant with methylmalonic acidemia

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Inborn errors of vitamin B12 metabolism, as methylmalonic acidemias (MMA), can be associated with immunodeficiency despite the absence of metabolic decompensation. We report the case of a 2.5-month-old infant with transcobalamin 2 (TCN2) deficiency (MMA subtype) who presented with an acute respiratory distress syndrome (ARDS) secondary to immune reconstitution inflammatory syndrome (IRIS) in the context of pulmonary infection with Cytomegalovirus (CMV) and Pneumocystis jirovecii (PJ).
This 2.5-month-old infant was admitted for severe pancytopenia without any other symptom (hemoglobin 46.0 g/L, platelets 8.0 × 10^9 /L, absolute neutrophil count 0.7×10^9/L and absolute lymphocyte count 3.2×10^9/L. Urine neonatal screening results revealed methylmalonic aciduria and further testing confirmed high methylmalonic acidemia (33.6 µmol/L; normal 0–0.5). Plasma ammonia, pH and anion gap were normal. Bone marrow aspiration revealed near-absence of erythroid precursors, myelodysplasia, megaloblastosis and 10% of myeloblasts suggestive of vitamin B12 error of metabolism. 48 hours after the initiation of intramuscular vitamin B12 treatment, the child developed acute respiratory failure simultaneously with hyperleukocytosis (52 × 109/L; neutrophilia: 28 × 109/L and lymphocytosis: 23 × 109/L). Severe interstitial lung disease was confirmed on imaging. Investigations for infection revealed CMV and PJ on bronchoalveolar fluid PCR. Complete immunological workup and a genetic panel did not reveal inborn error of immunity. Importantly, lymphocytes and CD4 T cell counts were normal. Despite ganciclovir and trimethoprim-sulfamethoxazole, respiratory status and hyperleukocytosis did not improve. IRIS induced by vitamin B12 supplementation in the context of an active infection was suspected. High dose intravenous corticosteroids

were initiated with rapid resolution of the respiratory distress and hyperleukocytosis.

- Intracellular vitamin B12 deficiency, such as in MMA, impacts T cell functions independently of lowered T cell numbers secondary to DNA repair defects. In children with interstitial pneumonia-related ARDS, especially in those with suspected metabolic diseases, normal lymphocyte counts and immunophenotyping should not eliminate the possibility of opportunistic infections.
- IRIS was described in children with human immunodeficiency virus initiating antiretroviral therapy or after stem cell transplant, but not in the context of metabolic diseases. IRIS may appear in highly treatment-responsive forms of pancytopenia such as in MMA and rapid treatment of dysregulated inflammation with high-dose corticosteroids should be initiated.

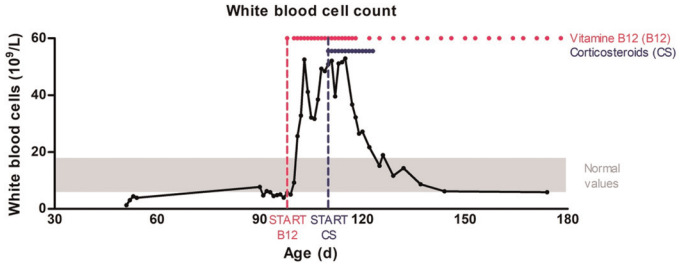

Figure 1. Evolution of white blood cells count before and after treatment.

Keywords: Immune reconstitution inflammatory syndrome, Inborn errors of metabolism, Immunodeficiency, Pancytopenia, Methylmalonic acidemia

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(151)

A Primary Neurological Presentation of CASP-8 Deficiency State

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Introduction: Inborn errors of immunity (IEI) are often thought to be synonymous with frequent infections, but many patients with IEI present with a primary immune dysregulatory phenotype. Autoimmune or demyelinating neurologic conditions, including chronic inflammatory demyelinating polyneuropathy (CIDP), have been rarely reported in IEI. In a 2020 USIDNET cohort, only 1.4% of patients with CVID were reported to have an autoimmune neurologic condition. Therefore primary neurologic complaints may go overlooked as a potential sign of underlying IEI. We present the case of a young patient with CIDP ultimately diagnosed with IEI.
Case: A 19-year-old male presented to Immunology clinic with a history of delayed motor milestones, regression and history of growth failure since 1 year of age, diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). He is wheelchair bound, but able to transfer independently. He denies history of recurrent infectious, persistent lymphadenopathy, or any history of autoimmune conditions, cytopenias or chronic diarrhea. CT Chest/abdomen/pelvis revealed borderline enlarged bilateral axillary and subpectoral lymph nodes, mild bronchial wall thickening, no enlarged lymph nodes in abdomen or pelvis, no hepatosplenomegaly. Nerve biopsy showed scattered CD8+ cells, little CD4 or CD20. Electron microscopy showed abundant whorled-like formations, generalized small to moderate sized onion bulbs. Additionally, there was some demyelination, with demyelination favoring large myelinated fibers. Whole exome sequencing demonstrated homozygous pathogenic mutation of CASP8 (C.793C>T, p.R265W). Further testing demonstrated decreased FAS-mediated apoptosis, 37% (reference:57–110%) and increased IL-18, 816 pg/mL (reference:< 468 pg/mL).
Discussion: Only eight patients with Caspase-8 Deficiency State (CEDS) have been reported in the literature. Presentations have included very early onset inflammatory bowel disease, lymphadenopathy, splenomegaly, and adult onset multi-organ lymphocytic infiltration. CEDS has been defined by defective T-, B- and NK-cell activation and lymphocyte apoptosis. This case represents a new neurological phenotype of CEDS and indicates the need to consider IEI in the differential for autoimmune or inflammatory neurologic conditions. This case may also indicate the need to consider further evaluation of patients with CIDP for defects in apoptosis as a potential cause.

Keywords: CASP8, CIDP, CEDS, Immune dysregulation, Neuropathy

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(152)

Thymus Hypoplasia in 22q11.2DS (DiGeorge): From Mechanism to Restoration

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Thymus hypoplasia occurs in several clinical conditions including 22q11.2 deletion syndrome (22q11.2DS), the most common human microdeletion disorder, affecting ~1/2150. The 22q11.2DS patients can have multiple congenital malformations; thymus hypoplasia, cardiac defects, hypoparathyroidism and/or dysmorphic facial features. Thymuses from 60–70% of 22q11.2DS patients are smaller than normal, and this results in their T cell lymphopenia. Less than 1% of patients have a severe thymus aplasia, resulting in SCID. An allogenic thymus tissue implant is the preferred clinical treatment for restoring T cell numbers in such athymic individuals. To determine the molecular mechanism(s) leading to thymic hypoplasia/aplasia, embryos from 22q11.2DS mouse models were used. Both reaggregate thymus organ cultures, using different thymic cell subsets involved in tissue growth, and single cell RNA sequencing revealed functional changes in the 5 mesenchymal cell subsets and 1 endothelial cluster in the hypoplastic lobes compared to controls. Altered transcripts in the mesenchymal cells relating to extracellular matrix modeling, collagen deposition and thymus tissue growth were found. These findings were consistent with increased collagen levels found in both the embryonic

thymuses from the mice and postnatal thymic tissues from 22q11.2DS patients, seen with immunohistochemistry. Thymus growth in 22q11.2DS embryos was restored by the administration of minoxidil or PGE2 in pregnant mice. The restoration of the tissue was consistent a reduction in the over-representation of mesenchymal-derived perivascular cells (pericytes) in the hypoplastic tissues. Improved vascularization was also noted, as revealed by immunochemistry with intact thymic lobes. Such findings suggest novel therapeutic strategies aimed at tissue regeneration in utero may have clinical benefits for correcting thymus hypoplasia's in 22q11.2DS.

Keywords: 22q11.2 deletion syndrome, DiGeorge, Immunodeficiency, Thymus hypoplasia, Thymus tissue regeneration

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(153)

Demyelinating CNS Disease: An Unusual Complication of XLA

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Introduction: The patient is a 21-month-old male with developmental delay and X-Linked Agammaglobulinemia (XLA) on monthly immunoglobulin replacement, who presented with refusal to walk for two months, found to have significant white matter signal abnormalities throughout the cerebral hemispheres on brain imaging, concerning for demyelinating CNS disease.

Case Presentation: The patient is a 21-month-old male with XLA on monthly immunoglobulin replacement, and history of left shoulder Neisseria meningitidis septic arthritis, who presented to his regularly-scheduled immunoglobulin infusion with a progressive 2-month-history of refusal to walk. He started walking unassisted at 19 months of age, however only on his tip-toes. Shortly thereafter he stopped walking and preferred to "stand" on his knees. His lower extremities became thin, and alternated between feeling rigid and limp to the touch. He was referred to the emergency department, where his physical exam was notable for axial hypotonia, lower extremity hypertonicity and spasticity with clonus, and abnormal gait. Lumbar puncture provided clear, colorless CSF with 0 RBCs, 1 WBC, 15 mg/dL protein, 46 mg/dL glucose. Brain MRI demonstrated white matter signal abnormalities throughout the cerebral hemispheres, extending into the subcortical gray-white matter junction, and along the periventricular region, suspicious for demyelinating disease. Since no infectious source was identified, and his mental status remained at baseline, this demyelinating condition was thought to be a neurological manifestation of his underlying primary immunodeficiency. He was treated with high-dose IVIG for two days and discharged after modest improvement. He has since continued monthly immunoglobulin replacement, and is receiving intensive physical and occupational therapy.

Discussion: XLA, the most common genetic cause of hypogammaglobulinemia, is caused by a defect in Bruton Tyrosine Kinase (BTK), which leads to arrest in B-lymphocyte maturation at the pre-B cell stage. Patients typically present at 4–12 months of age, once maternal antibodies have waned, with recurrent serious infections due to pyogenic bacteria. While rare, there have been limited reports of progressive neurodegenerative syndromes in patients with XLA. This case illustrates that one should consider demyelinating central nervous system disease in a patient with XLA presenting with new-onset neurological symptoms.

Keywords: X-linked agammaglobulinemia, Neurodegenerative disease, Demyelinating disease, Primary immunodeficiency

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(154)

Neurodevelopmental Outcomes (ND) in Patients with Severe Combined Immunodeficiency (SCID) Following Hematopoietic Cell Transplantation (HCT) in the Era of Newborn Screening. A PIDTC Study

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[22]*Physician/NIH*
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Introduction: Previous studies conducted before newborn screening (NBS) was available have indicated that patients with SCID may be at risk for neurodevelopmental (ND) abnormalities including lower than average IQ, problems with adaptive functioning, and abnormal behavior. We evaluated neurodevelopmental outcomes of a contemporary cohort of patients with SCID who received HCT between 2005–2015 to determine what factors affect post-treatment ND status.

Methods: Seventy-nine patients between the ages of 6–16 years (median age of 8 years) from 17 Primary Immune Deficiency Treatment Consortium (PIDTC) sites throughout the US and Canada were evaluated following HCT (median time post HCT = 7 years) to assess the role of newborn screening, transplant conditioning and genotype on ND outcome. Patient demographics are shown in Table 1. Patients received standardized cognitive, adaptive, and behavioral assessment (Table 2). All patients were previously enrolled on PIDTC SCID protocol 6901 (prospective) or 6902 (retrospective/cross sectional). There were 10 patients with ADA deficiency who were evaluated separately due to established cognitive abnormalities amongst ADA deficient patients.

Table 1.
Patient demographics.

Gender		
	Male	49 (71%)
	Female	20 (29%)
Age		
	Median	8 years
	Range	6–16 years
Race/Ethnicity		
	Asian/Pacific Islander	4 (5.8%)
	Black	5 (7.2%
	White/Hispanic	15 (21.7%)
	White/Non Hispanic	28 (40.6%)
	Unknown	
Mutation		
	DCLRE1C	4 (5.8%)
	IL2RG/JAK3	34 (49.3%)
	IL7R/CD3D	10 (14.5%)
	RAG1/2	11 (15.9%)
	unknown	10 (14.5%)
Trigger for Diagnosis		
	Family History	12 (17.4%)
	Infection/or Clinical Symptoms	24 (34.8%)
	Newborn Screening	33 (48%)
Donor type		
	Autologous (gene therapy)	3 (4.3%)
	HLA identical sibling	4 (5.8%)
	Matched unrelated/other relative	25 (36.2%)
	Mismatched relative	23 (33.3%)
	Mismatched unrelated	14 (20.3%)
Type of conditioning		
	None/immunosuppressive therapy alone	38 (55%)
	Reduced intensity/myeloablative	31 (45%)

Table 2.
Standardized Neurodevelopmental Assessment Screening Battery and Domains Tested.

Test	Domain
Adaptive Behavior Assessment (ABAS-3)	Adaptive Function
Beck Youth Inventory (Depression and Anxiety)	Emotional Adjustment
Beery -Buktenica Development Test-6	Visual-Motor Integration
Behavior Assessment System for Children (BASC-3)	Behaviorial adjustment (parent and patient self report)
Behavior Rating Inventory of Executive Function (BRIEF-2)	Executive Function (parent and patient report)
California Verbal Learning Test (Children's Version (CVLT-C)	Verbal Learning and Memory
Delis Kaplan Executive Function System (D-KEFS Tower Test &Trail Making Test)	Executive Function
Wechsler Intelligence Scales for Children (WISC-V)	Overall intellectual function
Wide Range Achievement Test (WRAT-5) Reading Subtest	Reading achievement

Results: Preliminary analysis of primary ND test variables revealed no statistically significant differences between patients diagnosed by NBS compared to family history or clinical illness (e.g., Full-Scale IQ of patients diagnosed by newborn screening [n = 33, mean score 97.55] vs family history [n = 12, mean score = 96.36] vs clinical illness [n = 24, mean score = 95.5]. IQs were similar among those who received no conditioning/immunosuppressive therapy [n = 38, mean score = 97.89] vs reduced intensity/myeloablative conditioning [n = 31, mean score 95.14]. Further, analysis of the cohort revealed no significant differences in primary test variables relative to the various genotypes.

Conclusion: The evaluation of neurodevelopmental outcomes following allogeneic HCT did not demonstrate any impact of trigger for diagnosis, conditioning regimen or genotype. Median patient scores were in the normal range for all domains. Overall, SCID (excluding ADA) patients did not differ significantly from the normal population in terms of overall intellectual functioning or composite scores of adaptive behavior or executive function.

Keywords: SCID, Neurodevelopment, HSCT

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relevant financial relationships with proprietary interests: Invitae (spouse is employee, spouse is employee). The other authors have no financial relationships or conflicts of interest to report.

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(155)

SARS-CoV-2 Breakthrough Infection Increases the Adaptive Immune Responses of Vaccinated Immunosuppressed Children

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SARS-CoV-2 vaccines licensed for children under 11 years old harbor a reduced dosage compared to adults. Knowing that immunosuppressed (IS) adults were shown to have impaired immune responses to mRNA vaccines, we questioned if the reduced vaccine dosages further restricted immune responses in IS children. To interrogate the impact of vaccination on IS children, we compared a cohort of healthy children (n = 52) receiving the standard two-doses regimen to children affected by primary (PID) or secondary humoral immune deficiencies (n = 30) who received two or three vaccine doses. In the PID group (n = 16), ten children had a humoral immunodeficiency while six others had a combined humoral and cellular immunodeficiency. In the secondary antibody deficiency (SAD) group (n = 14), 11 children were treated with rituximab (four as monotherapy and seven in combination with other immunosuppressive drugs) and three had persistent hypogammaglobulinemia after stem cell transplantation or cell therapy. IgG, IgA, and IgM binding the spike protein, its receptor-binding domain, and nucleocapsid were measured in serum and saliva. Neutralizing antibody titers (nAbs) were determined via live-SARS-CoV-2 micro-neutralizations. Cell-mediated immunity was quantified by assessing interferon-gamma secretion using ELISpot. T CD4+, T CD8+, and B cell populations were characterized through flow cytometry.
After the second vaccine dose, IS children showed reduced circulating binding and nAbs compared to their healthy counterparts. While all healthy children had nAbs after two doses, only 27% of IS children did. Importantly, the third dose significantly increased nAb titers in PID children to levels comparable to healthy children (median [mininum-maximum] nAb titers of 101 [32–403] in PID after three doses compared to 101 [32–254] in healthy children after two doses). In contrast, children with SAD did not develop nAb following vaccination ($p = 0.0002$ compared to healthy children after two doses). In all children, breakthrough (BT) infection induced a profound increase in nAbs, including in children with SAD. Indeed, 80% of SAD children developed nAbs after SARS-CoV-2 infection. As BT infection mimics mucosal challenge, these results support the idea that mucosal vaccination strategies could improve immune responses even in IS children with defective or absent B cells.

Keywords: SARS-CoV-2, COVID-19, Primary immune deficiencies (PID), Secondary antibody deficiency (SAD), Infection, T cells, B cells, Antibodies, Children, Vaccination

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(156)

Novel SAMD9 variant leading to MIRAGE Syndrome treated with subcutaneous immunoglobulin: a case report

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MIRAGE Syndrome is a rare genetic disorder caused by gain-of-function mutations in SAMD9. This multi-organ syndrome was originally characterized by Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy. Phenotypic expansion now includes achalasia, alacrimia, and immune dysregulation with autoinflammatory features. Characterizing the breadth of clinical phenotypes of patients with SAMD9 mutations may provide additional insight into the pathogenesis of MIRAGE Syndrome and expand treatment options.
We report the case of a 5-year-old male with MIRAGE Syndrome driven by a novel SAMD9 variant (p.Asn658Asp), presumed gain-of-function given the clinical presentation of myelodysplasia, infections, restricted growth, chronic diarrhea, achalasia, alacrimia, and chronic hypoxemic lung disease diagnosed as neuroendocrine cell hyperplasia of infancy (NEHI). He has no genital abnormalities and the adrenal insufficiency present in this patient was ultimately thought secondary to frequent exogenous corticosteroids for pulmonary disease, and has resolved. The patient also has a second, presumed somatic, loss-of-function SAMD9 variant (p.Gln30*). The acquisition of secondary loss-of-function SAMD9 variants in MIRAGE Syndrome has been described; these variants are believed to

rescue the gain-of-function activity and correlate with milder disease. Adaption by aneuploidy (monosomy 7) can also be found and is associated with the development of myelodysplastic syndrome, but our patient has normal cytogenetics across serial bone marrow evaluations.

Our patient had frequent hospitalizations for recurrent episodes of fever, often in the absence of an identified infectious source and concerning for sterile autoinflammation. Immune suppression was considered too risky given his history. Normal immunoglobulin levels with poor response to pneumovax defined a specific antibody deficiency in this patient. Accordingly, he started prophylactic azithromycin and subcutaneous immunoglobulin which led to significant improvement in his frequent gastrointestinal symptoms and a reduction in his fever episodes and hospitalizations (Figure 1).

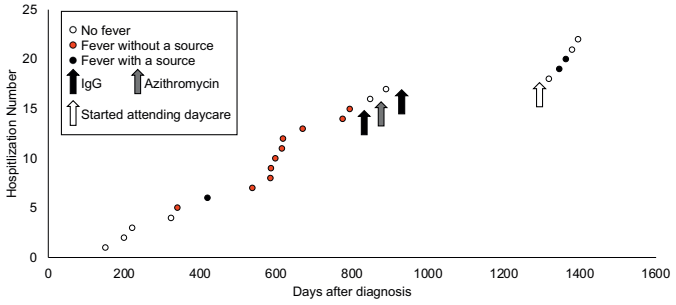

Figure 1. Timeline of hospitalizations. Schematic of hospitalizations following diagnosis of MIRAGE syndrome at 10 months of age (day 0). Open circles represent hospitalizations without fever. Red circles indicate hospitalizations with fever (temperature > 38.0°C) without an identified infectious source. Black circles represent hospitalizations with fever and an identified infectious source. Solid arrows represent introduction of subcutaneous immunoglobulin (4 g bi-weekly, first black arrow), azithromycin (5 mg/kg three times a week, grey arrow), and dose escalation of subcutaneous immunoglobulin (8 g bi-weekly, second black arrow).

MIRAGE Syndrome is a rare disorder of hematopoiesis, immunity, and other features. Given the high infectious mortality in MIRAGE Syndrome, immunoglobulin therapy should be considered and may benefit other patients with MIRAGE syndrome.

Keywords: MIRAGE syndrome, SAMD9, Immunoglobulin

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(157)

The challenges of recognition and diagnosis of APDS2 in a family with novel PIK3R1 variant

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Activated PI3 K delta syndrome (APDS) is a novel inborn error of immunity caused by autosomal dominant variants leading to gain-of-function of the PI3Kδ pathway. Phenotypes are diverse including immunodeficiency, lymphoproliferation, autoimmunity and malignancy. We present a case of two family members with a novel variant on PIK3R1.

Case description: Three-year-old female (Patient 1, P1) was referred to the genetics department after being evaluated by dermatology, endocrinology, and hematology for telogen effluvium, hyperpigmentation, failure to thrive, abdominal pain, fevers, and emotional liability. Extensive work up was negative for endocrinologic and hematologic conditions, autoimmunity, gene analysis for metabolic diseases, porphyria, and a microarray. The only abnormal result was a heterozygous variant in HBA2. At age five, patient returned with concerns for short stature.

Whole exome sequencing showed a novel likely pathogenic truncating heterozygous variant in PIK3R1 gene (c.1083delT: p.T362LfsX11) inherited from mother (Patient 2, P2). Curiously, the patient's older brother (Patient 3, P3) was tested due to history of short stature, developmental delays and learning difficulties and was negative for the variant. The father (Patient 4, P4) has short stature and is not a carrier either. Patient 1 also has a history of speech delay, oral ulcers and recurrent bacterial (otitis media, sinusitis) and fungal infections. Patient's younger sister (Patient 5, P5) has a history of bacterial meningitis, recurrent otitis media, behavioral difficulties, and expressive language delays, P5 has not yet been evaluated for APDS2. Through institutional collaboration immune phenotyping was performed in all family members showing an increase in memory B cells and decrease in naïve B cells in all children, as well as an expansion of senescent CD4+ and CD8+ T cells in P1.

Discussion: APDS2 results from a variant on exon 11 of PIK3R1, the regulatory subunit p85α of p110δ, as the one seen for our patients, except for our variant is not on exon 11 but exon 9. The clinical segregation of carriers

was not clear as the brother has shown some features of APDS2. The deletion and mechanism of variants in exon 9 is unknown. This case represents the importance of multidisciplinary care and prompt genetic screening.

Keywords: APDS, Activated phosphoinositide 3-kinase delta syndrome, PIK3R1 gene, Inborn error of immunity

Disclosures: Manish Butte: I have relevant financial relationships with proprietary interests: ADMA (Scientific Advisory Board); Chiesi (Grants/Research Support Recipient); Grifols (Advisory Board, Consulting Fees (e.g., advisory boards)), Speaker/Honoraria (includes speakers bureau, symposia, and expert witness)); Pharming (Clinical Trial Investigator, Consultant). Jolan Walter: I have relevant financial relationships with proprietary interests: X4 Pharmaceuticals (Grants/Research Support Recipient). The other authors have no financial relationships or conflicts of interest to report.

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(158)

Good Syndrome: A Case of Bowel Perforation, Chronic Diarrhea and Clostridium Difficile Colitis Leading to Detection of a Thymoma

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Case Description: A 60-year-old female with history of hypothyroidism, irritable bowel syndrome, chronic constipation, diverticulosis, asthma and recurrent sinopulmonary infections presented to the emergency department for severe abdominal pain. The pain started a few weeks prior and was initially intermittent, then gradually became worse. Evaluation with an abdominal CT scan showed free air and perforation of the sigmoid colon. She underwent emergency laparotomy with colon resection and temporary colostomy. Postoperative recovery was complicated by Clostridium Difficile colitis. She required multiple courses of vancomycin with tapers and fidaxomicin due to recurrent Clostridium Difficile infections and chronic diarrhea. Repeat colonoscopies showed scattered foci of acute inflammation, cryptitis, paneth cell metaplasia and a lack of plasma cells in the lamina propria. These findings raised the possibility of common variable immunodeficiency, and an immune workup was initiated. Quantitative Immunoglobulins revealed IgG< 33 [694–1618 mg/dL], IgA< 7 [82–453 mg/dL] and IgM< 4 [46–304 mg/dL]. She had undetectable levels of IgG antibodies to 23 Streptococcus pneumoniae serotypes, Tetanus, Diphtheria, and had inadequate Salmonella Typhi vaccination response. Lymphocyte subsets showed undetectable CD19+ cells, but normal CD3+, CD4+, CD8+ and NK cell numbers. IVIG was initiated for presumed CVID. However, chest CT scan obtained 8 weeks later revealed an anterior mediastinal mass which was biopsied and returned as thymoma. She had resection of the mass and a total thymectomy. Despite resection and substitutive immunoglobulins, she developed recurrent sinus infections that eventually led to sinus surgery, and she continues to have intermittent episodes of diarrhea that improve with vancomycin.
Discussion: Good Syndrome (GS) is a rare, thymoma-associated immunodeficiency that is not clearly characterized. A high index of suspicion is required for diagnosis. Clinical manifestations are heterogenous and present with immunological abnormalities that may be accompanied by autoimmune and hematological disorders. Our patient has no history of myasthenia gravis or pure red blood cell aplasia which can be seen in GS. Hypogammaglobulinemia with absent B cells and recurrent infections were her presenting features. GS should be in the differential diagnosis for patients aged 40 or older with recurrent infections, antibody deficiency, hypogammaglobulinemia and few or absent B-cells.

Keywords: Good syndrome, Hypogammaglobulinemia, Recurrent infection, Thymoma, Chronic diarrhea

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(159)

A Case of Eosinophilic Fasciitis Successfully Managed with Benralizumab in a Patient with Hypogammaglobulinemia and B-cell Aplasia

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Case Presentation: A 60-year-old female with a history of Raynaud's symptoms, fatigue, and intermittent joint pain developed non-Hodgkin's follicular lymphoma that evolved into large B-cell lymphoma. She received 6 cycles of R-CHOP. However, two years later, she had a relapse of the lymphoma and developed worsening adenopathy in her neck with night sweats and fatigue. She completed 6 cycles of Fludarabine and Rituximab and received 26 cycles of maintenance Rituximab over 5 years. Treatment was complicated by hypogammaglobulinemia, B-cell aplasia and recurrent infections. Markedly low IgG, IgA, IgM and undetectable B-cells were noted in peripheral blood and bone marrow biopsy. She was started on IVIG.
Over the years, she continued to have night sweats and fatigue, but surveillance imaging studies and biopsies only demonstrated granuloma-like aggregates and no evidence of lymphoma or myelodysplastic syndrome. She then presented with progressive bilateral thigh pain, redness and swelling that limited her ability to walk. Inflammatory markers were elevated with ESR 77 mm/hr and CRP 96 mg/L. CT and MRI showed myositis. Deep muscle biopsy of the right anterior medial thigh revealed dermal fibrosis and septal eosinophils consistent with eosinophilic fasciitis. She was started on daily steroids with a slow taper, then mycophenolate was added a few weeks later. After 15 months on this regimen, mycophenolate was no longer covered by insurance. Benralizumab was subsequently initiated and resulted in symptomatic improvement, and she could be weaned off steroids.
Discussion: Many individuals post-Rituximab will have normalization of B-cells counts within one year. It has been 10 years since our patient last received Rituximab, and B-cell counts have never recovered. Baseline quantitative immunoglobulins should be obtained before initiation of Anti-CD20 immunotherapy, but they were not drawn for this patient. Our patient most likely had undiagnosed CVID that became unmasked by Rituximab. Though the link between CVID and eosinophilic fasciitis (EF) is unclear, we propose that it involves immune dysregulation. CVID patients presenting with persistent limb pain, swelling and redness, should be assessed for possible fasciitis or myositis. Benralizumab may be considered as a treatment option in patients with EF. Benralizumab has been effective in our patient.

Keywords: CVID, Common variable immunodeficiency, Rituximab, B cell aplasia, Eosinophilic fasciitis, Benralizumab, Immunodeficiency, Hypogammaglobulinemia

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(160)

Evolving Clinical Presentation in an Infant with Thrombocytopenia: Insights from a Hispanic Male Baby with Wiskott-Aldrich Syndrome

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Background: Wiskott–Aldrich syndrome (WAS) is an X-linked primary immunodeficiency disorder caused by mutations in the gene located on the short arm of the X chromosome in the Xp11.22-p11.23 loci, which results in aberrance of the Wiskott–Aldrich Syndrome Protein (WASP). Typically, presenting with a triad of severe immunodeficiency, thrombocytopenia, and eczema, the incidence of WAS is about 1 in 100,000 live male births, with no specific ethnic or geographic predilection. Notably, cases in Hispanic populations are infrequently reported, suggesting potential under diagnosis in these communities.
Case Report: We report the case of a 9-month-old Hispanic infant, born to non-consanguineous parents, who initially presented with persistent but mild thrombocytopenia. Genetic testing identified a hemizygous pathogenic variant in the WAS gene (WASP c.777+1 G > A) and the preliminary diagnosis of X-linked thrombocytopenia was considered. However, as the infant aged, he developed more profound thrombocytopenia, along with multiple bleeding episodes, an eczematous rash, and recurrent upper respiratory tract infections. WAS protein expression was obtained and results revealed extremely low levels at only 0.15, which confirmed the diagnosis of Wiskott-Aldrich syndrome. The current treatment regimen includes transfusions, IVIG, and immune modulatory therapy, serving as supportive care as a bridge to a hematopoietic stem cell transplantation with curative intent.
Conclusion: This case highlights the importance of considering Wiskott–Aldrich syndrome in the differential diagnosis for any male child presenting with thrombocytopenia, especially when initial symptoms are mild or atypical. The extremely low WAS protein expression in this patient underscores the severity of the condition. Increasing awareness and access to genetic sequencing in minority communities is crucial for early and accurate diagnosis, thereby improving patient outcomes in rare inborn errors of immunity like WAS.

Keywords: Wiskott-Aldrich syndrome, Thrombocytopenia, Hispanic, WAS

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(161)

Human ITCH E3 Ubiquitin Protein Ligase (ITCH) Deficiency Syndrome Successfully Treated with Hematopoietic Cell Transplant (HCT)

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Introduction: Ubiquitin pathways are important regulators of T cell function in humans. Mutations of the ITCH gene can lead to multisystemic autoimmune disease with facial dysmorphism. Symptomatic treatment by organ system affected has been the rule, given the incomplete understanding of the pathophysiology of the disease. To date, only a single case of successful hematopoietic cell transplant (HCT) in a patient with ITCH deficiency has been described.
Case Description: A 20-year-old female with a medical history of multisystem autoimmune disease involving the skin (psoriasis), muscle (steroid-sensitive juvenile polymyositis), bones (osteochondritis), joints (deforming polyarthritis likely reactive to osteochondritis), gastrointestinal tract (autoimmune enteropathy and inflammatory liver disease), and lungs (ventilator dependent interstitial lung disease vs. emphysema), all related to ITCH deficiency syndrome. Her disease manifestations were only partially responsive to multiple immunosuppressants (infliximab, abatacept, ustekinumab, sirolimus, prednisone). She underwent HCT with the goal of reducing medication and immunosuppression burden. She underwent conditioning with busulfan (AUC of 65), rabbit ATG, and fludarabine preceding unrelated donor BMT. Rituximab and abatacept were continued throughout the transplant process. Prior to discharge on day +23, she received donor lymphocyte infusion to improve T cell numbers and chimerism. The patient tolerated the procedure extraordinarily well, with gradual improvement in multiple organ systems, allowing for the discontinuation of ustekinumab given improved psoriasis, abatacept after improved arthritis and joint stability, and sirolimus given improved enteritis within the first 6–9 months post-transplant. Additionally, there has been a significant reduction of ventilator settings over time, and reduction of prednisone, now replaced with hydrocortisone. Three months post-transplant, the patient developed pericarditis, prompting a switch from tacrolimus to ruxolitinib for graft-versus-host-disease prophylaxis, resulting in subsequent resolution. One year post-transplant, her immunosuppression regimen consists of only hydrocortisone and ruxolitinib.
Discussion: We describe the second reported case of a patient with ITCH deficiency successfully treated with HCT. Due to the incomplete understanding of the pathophysiology of the disease, therapies have largely focused on symptom management. HCT may be considered as a potential therapeutic option for patients with ITCH deficiency in the setting of multisystem immune dysregulation.

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Keywords: ITCH, Stem cell transplant, Autoimmunity

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(162)

Patient with Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID) and Glutaric Aciduria Type 1 (GA1) Successfully treated with delayed Hematopoietic Stem Cell Transplant (HSCT)

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Background: ADA SCID accounts for 10–15% of all SCID (Buckley, 1997). Symptoms occur secondary to the toxic accumulation of deoxyadenosine and deoxyadenosine nucleotide (dAXP) in cells, leading to lymphopenia and systemic symptoms. A temporizing treatment is the use of ERT and curative therapies include HSCT and gene therapy.
GA1 is a rare neurometabolic disorder caused by mitochondrial glutaryl-CoA dehydrogenase deficiency. GA1 metabolic crisis results in irreversible neurological injury with lifelong motor dysfunction. Patients < 3 years are particularly susceptible. Management includes low lysine diet, carnitine supplementation and avoidance of catabolic episodes with augmented emergency treatment during periods of increased metabolic demand such as infections. The Pennsylvania Amish are one of five known communities worldwide with an increased incidence of GA1. We describe the first report of a patient with concomitant diagnoses of ADA-SCID and GA1.
Case: A newborn Amish male with family history of ADA SCID was found to have GA1 and SCID on his newborn screen. Given the increased metabolic demand of HCT which could lead to risk of stroke, he was managed with ERT for 4 years as a bridge to HCT. At 4-weeks he started pegademase (Adagen)with partial recovery of B and NK cells, however, d-AXP levels remained elevated (Figure 1a). At 15-months he transitioned to Recovi with significant increase of ADA activity, undetectable d-AXP levels and improvement in lymphocyte subsets (Figure 2 and Figure 1b). He remained on immunoglobulin replacement and antimicrobial prophylaxis, had four hospitalizations for illness managed with a GA1 protocol and no encephalopathic crisis.

DATE REPORT	3/31/23			*NORMAL VALUES			
st PADA:	Date HSCT	Nominal	Plasma	Erythrocyte Nucleotides			Erythrocyte
10/9/17?	6/1/22	weekly dose	ADA	AXP	dAXP		ADA activity
	Weeks of	PEG-ADA	µmol/h/ml	µmol/ml RBC	µmol/ml RBC	% dAXP	nmol/h/mg
Date	Therapy	U/kg/inj	*<0.5**	*1.465 ± 0.38**	*<0.002**	*<0.2**	*63.0 ± 41.4*
8/30/17	-	-		0.871	1.067	55.0	0.0
10/22/17	1.9	?	14.37	1.449	0.179	11.0	
12/12/17	?	?	79.09	1.719	0.017	1.0	
2/14/18	18	?	38.18	1.604	0.008	0.5	
2/20/18	19	?	42.79	1.635	0.005	0.3	
4/11/18	26	?	71.28	1.858	0.013	0.7	
7/10/18	39	?	33.47	1.726	0.015	0.9	
Recovi Initiated 3/4/19	73	?	136.38	1.438	0.000	0.0	
5/21/19	84	?	168.48	1.121	0.000	0.0	
12/3/19	112	?	198.66	1.341	0.008	0.6	
10/14/20	157	?	116.56	1.607	0.000	0.0	
5/10/21	187.0	?	143.83	1.761	0.000	0.0	
Pre HCT	238.4	?	173.94	1.512	0.006	0.4	
Day +100	261.3	0	0.21	2.196	0.008	0.4	26.3
Day +250	285.4	0	0.00	2.311	0.009	0.4	32.8

Figure 2. Table of ADA activity and dAXP levels.

After four years of ERT he underwent a 10/12 HLA-mismatched unrelated PBSCT with CD34 selection and T-cell add-back. His conditioning included Campath, Fludarabine and Busulfan (AUC 50). ERT was stopped six weeks post-transplant. Patient experienced adenovirus reactivation that responded to Cidofovir and an infusion of adenovirus specific-cytotoxic T cells with complete resolution. No significant organ toxicity or metabolic crisis. He is 2.5y out of HCT, has stable mixed donor chimerism and has achieved T and B cell immune reconstitution.

Keywords: Adenosine deaminase, SCID, GA1 deficiency

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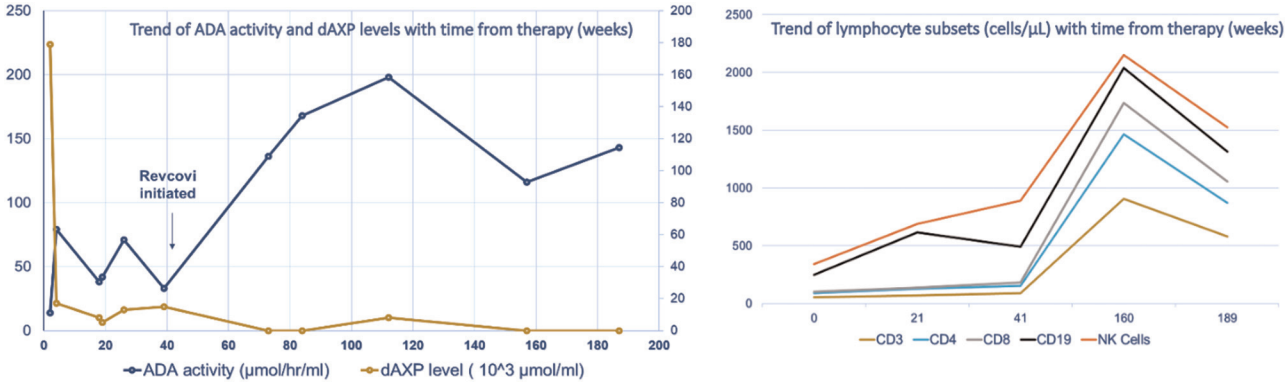

Figure 1. (abstract: 162) (**a**) Trend of ADA activity and dAXP levels. (**b**) Trend of lymphocyte subsets.

(163)

Biallelic splice variants in NHEJ1 deficiency causing primary hematologic and oncologic manifestations: A Tale of Two Patients

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NHEJ1 deficiency is a rare genome instability syndrome associated with defects in double strand break repair (DSBR) by nonhomologous end joining (NHEJ) with less than 50 reported individuals world-wide. It has historically been associated with adaptive immunodeficiency (primarily SCID) and neurological abnormalities. Here, we present two adolescent patients with predominant hematologic problems arising from adjacent NHEJ1 splice site mutations. DNA repair assessment in lymphocytes by DDRFL assay confirmed the presence of DSBR defect in both patients' cells. These cases highlight our emerging understanding that many genome maintenance disorders are capable of causing defects in both hematopoiesis and immunity. This suggests that both primary hematologic and immune-mediated etiologies need to be considered when patients present with cytopenias, and emphasizes the importance of obtaining head circumference measurements on these patients. Finally, it highlights the value of combining available genetic and non-genetic tools for achieving molecular diagnosis.

Patient A was an African-American boy with history of pre- and post-natal growth failure, microcephaly, sinopulmonary infections, and recurrent thrombocytopenia, found to have myelodysplasia. Inherited bone marrow failure syndrome (iBMFS) gene panel returned negative but chromosomal microarray showed a region of homozygosity on chromosome 2 that included NHEJ1, a gene not included on the gene panel sent. Subsequent NHEJ1 sequencing confirmed a Likely Pathogenic homozygous variant, c.530-1G>A, predicted to affect the consensus splice acceptor site for Intron 4. Unfortunately, our patient developed CMML during his bone marrow transplant (BMT) workup and ultimately passed away from refractory AML. Patient B is a previously healthy Southeast Asian girl presenting with recent onset pancytopenia and found to have microcephaly and severe clinodactyly on Genetics evaluation. DNA repair assessment in lymphocytes supported a DSBR defect and labs found subtle adaptive immune abnormalities, though she had no clinical history of immune problems. WES revealed a homozygous NHEJ1 c.530-3C>G variant, initially classified as a VUS but revised to Likely Pathogenic status after results of the DDRFL assay were presented to the laboratory. This variant is located adjacent to two other known patient splice site mutations affecting the invariant -1 and -2 splice acceptor sites. She is currently undergoing allogenic BMT workup.

Keywords: NHEJ1, XLF, Cernunnos, Myelodysplasia, Bone marrow failure, Double strand break repair, DDRFL, Genome instability, NHEJ, Immunodeficiency

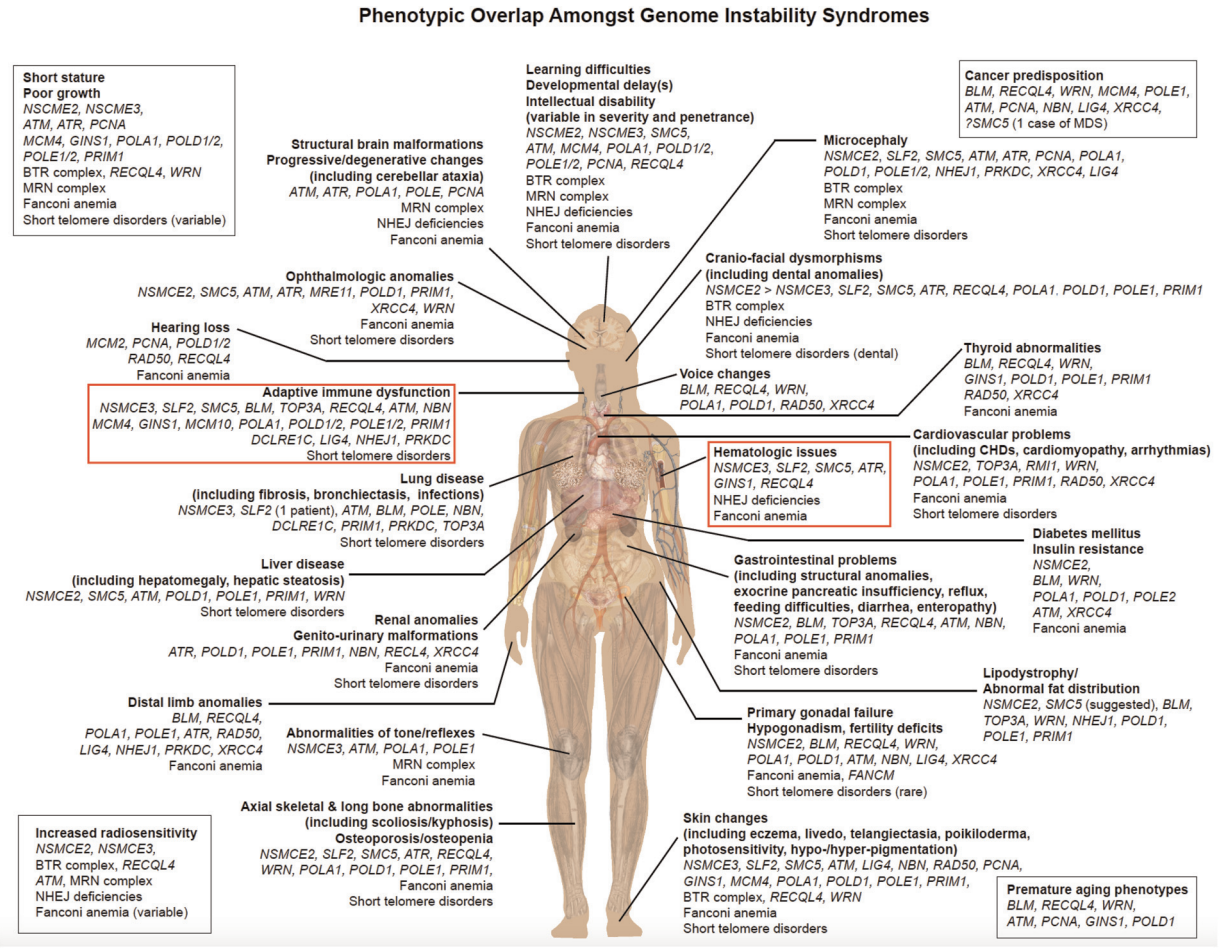

Figure. (abstract: 163)

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(164)

Enteropathy in Patients with Common Variable Immunodeficiency: A Dutch Cohort Study

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Background: CVID is the most common symptomatic primary immunodeficiency, often accompanied by immune dysregulation and complications like enteropathy. The optimal management of CVID-enteropathy (CVID-E) remains poorly understood. Here, we describe the clinical characteristics, disease progression and treatment outcomes in a Dutch cohort of CVID-E patients.
Methods: Conducted as a single-center retrospective cohort study, we analyzed electronic health records to collect patient demographics, along with endoscopic and histological data. Additionally, we gathered data regarding the course of enteropathy-related symptoms and treatment efficacy.
Results: We included 32 patients with CVID-E (mean age at CVID diagnosis: 31.7 years; 50% female). Frequent endoscopic findings included nodular lymphoid hyperplasia (37.9%), colitis (44.8%), ulcerative lesions (31%) and gastritis (56%). Histologically, the most prevalent findings were IBD-like colitis (n = 10) and intra-epithelial lymphocytosis (n = 9). Common clinical manifestations were lymphoproliferation (43.8%), splenomegaly (34.3%), autoimmune disorders (31.3%), gastrointestinal infections (65.6%), and bronchiectasis (65.6%). In total, 17 patients received immunosuppressive treatment: budesonide (n = 14), systemic corticosteroids (n = 10), DMARD monotherapy (n = 13), biologic monotherapy (n = 4), and combination therapy (n = 7). Combined treatment consisted of systemic corticosteroids, biologicals and/or systemic DMARDs. Of all treatment options, combined therapy was associated with the highest response rate (6/7 patients).
Conclusion: In this study, we describe a cohort of CVID-E patients, detailing associated comorbidities, the clinical course and their responses to therapy. Our findings emphasize the high occurrence of severe comorbidities in CVID-E patients. Moreover, the study highlights the effectiveness of using combination therapy in managing CVID enteropathy.

Keywords: Common variable immunodeficiency, Enteropathy, Inborn errors of immunity, Primary immunodeficiency, Antibody deficiency

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(165)

The neuroimmunological network in cancer-induced HPV Infections

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Although neuroimmunological relationships have been characterized as playing a critical role in cancer development and patients' outcomes, their involvement in cancer-induced Human Papillomavirus (HPV) infections remains unexplored. Hence, to provide a comprehensive landscape of the neuroimmunological molecular signatures, we conducted an integrative analysis (meta-analysis using the Fisher method and batch effect correction) of 471 publicly available transcriptomes (429 microarrays and 42 bulk RNAseq) from 3 individual groups (195 controls, 187 cervical, 54 head and neck, 35 penile patients). The highest transcriptional activity was found in cervical cancer groups with the highest number of differentially expressed genes (meta-DEGs), including several neuroimmune genes (NRP1, NF1, HDAC, MECP2). Functional enrichment of meta-DEGs from cervical cancer revealed a robust and interconnected network of neuroimmunological pathways, including negative regulation of the immune response, neuronal death, regulation of neurogenesis, synaptic organization. These results underscore an intriguing previously unreported systemic interconnection involved in the HPV immunopathogenesis that includes the interaction between the nervous system and the immune response. Hence, this ongoing work paves the way for the development of new therapies for patients with HPV infections

Keywords: HPV carcinogenesis, Neuroimmune response, Meta-analysis

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(166)

PRF1-Related Isolated CNS Hemophagocytic Lymphohistiocytosis Successfully Treated with Ruxolitinib Monotherapy

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Introduction: Biallelic mutations in the PRF1 gene are among the most common genetic defects leading to familial hemophagocytic lymphohistiocystosis (HLH) type 2 (FHL2). PRF1 encodes for perforin; a protein essential for regulation of lymphocyte and natural killer cell mediated cellular destruction. Pathogenic PRF1 variants may lead to systemic HLH, and rarely isolated central nervous system (CNS) HLH. Our case highlights effective treatment of familial CNS-isolated HLH via JAK inhibition.
Case: A previously healthy 13-year-old male presented with a four-month history of headaches, intermittent aphasia, and cognitive decline. Initial radiographic findings were concerning for acute disseminated encephalomyelitis (ADEM). Evaluation revealed subclinical seizures and cerebral spinal fluid (CSF) analysis noting lymphocytic pleocytosis but negative for autoimmune antibodies. He was treated with 1 g methylprednisolone over 5 days and 2 g of intravenous immunoglobulin (IVIG) resulting in stabilization of neurologic symptoms. Two years later, he was hospitalized for altered mentation. CNS imaging revealed new demyelinating lesions without signs of vasculitis. He received 1 g methylprednisolone over 3 days, increased IVIG infusions and was initiated on Rituximab. Following six months of Rituximab therapy, he was re-hospitalized for cognitive decline and respiratory distress; found to have non-specific pulmonary nodules. He was treated for Pneumocystis pneumonia given high clinical suspicion despite negative bronchoalveolar lavage and biopsy. Genetic testing revealed homozygous pathogenic PRF1 c.1228C>T; p.(Arg410Trp) variants. Immunologic testing revealed elevated CXCL9 15,545 (pg/mL), increased CSF neopterin 89 (nmol/L), and markedly decreased perforin expression on NK cells. Systemic HLH evaluation showed normal ferritin and sCD163. He was diagnosed with CNS-isolated HLH and started on oral dexamethasone 8 mg twice daily and Ruxolitinib 10 mg twice daily with wean and cessation of dexamethasone after one month. No intrathecal therapy was administered given overall well appearance. He remains on Ruxolitinib monotherapy while awaiting potential bone marrow transplantation (currently lacks adequate donor matches) with improvement in neurologic symptoms/CNS imaging and normalization of CXCL9.
Conclusion: Isolated CNS-HLH should be considered in the differential of demyelinating disease, particularly in patients not responding to conventional therapies. Additionally, our case highlights the effective novel use of Ruxolitinib monotherapy in a patient with familial CNS-isolated HLH.

Keywords: CNS HLH, Hemophagocytic lymphohistiocytosis, Familial hemophagocytic lymphohistiocystosis, Ruxolitinib, Jakafi, Novel treatment, FHL2, PRF1, HLH, Isolated CNS HLH

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(167)

Differentiating IPEX- like syndrome from other causes of autoimmune enteropathy

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We report a 5-month-old full-term male with history of eczema born to consanguineous parents presenting with chronic diarrhea and failure to thrive (weight 3% tile, length 38% tile). Initial endoscopy revealed diffuse villous atrophy, gastritis, crypt hyperplasia, and granulomas, with FOXP3 +cells identified throughout. In the setting of enteropathy and eczema, this finding raised concern for IPEX-like syndrome.
IPEX (immune dysregulation, poly-endocrinopathy, enteropathy, X-linked) is an inborn error of immunity (IEI) caused by mutations in FOXP3 which controls the production and function of regulatory T-cells (Tregs). IPEX is characterized by protracted diarrhea, autoimmune endocrinopathies (commonly involving the pancreas or thyroid), and dermatitis. Patients can also have autoimmune cytopenias and elevated IgE and IgA. Notably, there are normal levels of circulating T- and B-cells but a paucity of Tregs. While IPEX-like syndromes can mimic the clinical presentation of IPEX, they result from monogenic defects in genes including LRBA, CTLA4, MALT1, DOCK8, TTC7A, STAT1, and STAT3 rather than FOXP3.
Our patient had elevated levels of IgG (1,920 mg/dL) and IgE (763 IU/mL) with mildly elevated IgA (62 mg/dL). Lymphocyte enumeration revealed a markedly lower proportion of naïve T-cells than expected for age (CD45RA +CD3 40.6%). However, the absolute count and percentage of peripheral Tregs was normal with elevated FOXP3 protein expression. Whole genome sequencing was also non-revealing. Additionally, the patient lacked signs of endocrinopathy, and serum thyroid and islet cell antibodies were negative. Together, these findings did not support an IPEX or IPEX-like diagnosis. Evaluations for other pathologies including microvillus inclusion disease, tufting enteropathy, and chronic granulomatous disease were negative. Ultimately, anti-enterocyte antibodies were identified, and the patient was treated with steroids and infliximab with improvement in symptoms and tissue pathology but with new acute sigmoid/rectum colitis suggestive of inflammatory bowel disease (IBD).
Such cases highlight the importance of thorough immunologic evaluations including gene sequencing in patients with early-onset enteropathy or IBD, as this presentation can occur in various IEIs. Additionally, early confirmation of systemic versus tissue-specific involvement is essential in recognizing the risk for developing further manifestations such as endocrinopathy and cytopenias. Finally, identification of a molecular cause can assist in guiding pathway-specific targeted therapies.

Keywords: Inborn error of immunity (IEI), IPEX, Enteropathy, Inflammatory bowel disease (IBD)

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(168)

Autoimmunity and neoplasia in a cohort of adult patients with inborn errors of immunity and the implications of having a positive molecular diagnosis

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Background: Human Inborn Errors of Immunity (IEI) commonly present not only increased susceptibility to infections but also immune dysregulation events, defined as autoimmunity, autoinflammation, lymphoproliferation/neoplasia, granuloma or eczema. Notably, autoimmune manifestations and neoplasia are observed in a significant percentage of patients with IEI, sometimes representing the first sign of disease. Although the mechanisms underlying the development of these clinical manifestations are not completely elucidated, a specific genetic and environmental background is generally a necessary precondition. The aim of this study is to explore the molecular mechanisms, immunophenotypes and inheritance in adult patients with autoimmunity and neoplasia events in the context of an IEI.
Methods: This work is a retrospective study including 173 adult patients with a clinical picture strongly suggesting an IEI. Immunophenotyping and Next Generation Sequencing were performed for the phenotypical and molecular characterization of these patients.
Results: Disease-causing variants were identified in 44 of the 173 (25.43%) patients with suspicion of IEI. Autoimmune features were found in 18 of the 44 (40.91%) patients with genetic diagnosis. These patients harbored variants in genes as CD8A, CTLA4, FAS, FASL, GATA2, MAGT1, NFKB1, PIK3R1, TBX1, TET2 or TNFRSF13B. Regarding neoplasias, 15 out of 44 (34.09%) patients developed lymphomas of any kind associated to the partial deletion of chromosome 22 (22q11.2) or pathogenic variants in ADA2, FAS, FASL, GATA2, RAB27A and TET2 genes.
Forty (31.01%) and seventeen (13.18%) of 129 patients without confirmed molecular diagnosis also presented symptoms related to autoimmunity and neoplasia, respectively.
The Jeffrey Model Foundation (JMF) warning signs consist of a list of 10 clinical symptoms related to IEI. In this work, we added a new JMF criterion (immune dysregulation) and this modified JMF list (JMF_dys) was compared to the classic one. After carrying out a pairwise comparison of both models, our results confirmed that this new proposed JMF_dys better predicts which patients will be genetically diagnosed.
Conclusions: The knowledge of the genetic background of IEI can help to characterize the defects that link immunodeficiency to autoimmunity and neoplasia, thus providing important implications for diagnosis, prognosis and treatment with novel target therapies.

Keywords: Inborn errors of immunity (IEI), Immune dysregulation, Genetic diagnosis, Autoimmunity, Neoplasia, Jeffrey Model Foundation (JMF)

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(169)

Long Term Management of Transplanted Patients with Chronic Granulomatous Disease, Wiskott-Aldrich Syndrome, and Primary Immune Regulatory Disorders: A PIDTC Survey

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Introduction: Significant improvements in understanding early post-transplant supportive care and survival of patients with CGD, WAS, and PIRD1-3 have been observed, but long-term management remains challenging given the lack of standard of care guidelines for these patients with very rare immune deficiency/dysregulatory diseases who have received allogeneic hematopoietic cell transplantation (HCT).
Methods: A survey developed by a committee of immunologists and transplanters was completed by 41 of 44 (93.1%) PIDTC sites from March-June 2023. Responses were stratified by disease and specialty. Data analysis was performed using the dplyr package and graphs were plotted using the ggplot package. All code was implemented in R version 4.3.1.
Results: Fifty-eight responders from 41 PIDTC institutions contributed to the survey. The majority (95%; n = 55 of 58) recommended life-long follow-up following HCT. Importantly, the majority recommended long term monitoring of peripheral whole blood, T, B, NK, and/or myeloid chimerism regardless of post-HCT donor chimerism degree. In addition, >75% of responders recommended disease specific monitoring for at least 2 or more years. Regarding immune reconstitution, >60% recommended annual immunoglobulin monitoring for 5 years post-HCT or until immunoglobulin levels normalize. Recommendations regarding the duration of peripheral blood lymphocyte subsets monitoring were more varied ranging from annual monitoring through 2 years (40%, n = 23 of 58), through 5 years (26%, n = 15 of 58), or >5 years (26%; n = 15 of 58), and 9% (n = 5 of 58) do not recommend monitoring at all. Challenges in the care of patients with these rare diseases included difficulty in obtaining insurance approval for disease specific functional testing (i.e. DHR; 59%, n = 19 of 32) and other supportive labs/imaging following HCT (38%, n = 12 of 32).
Discussion: There was widespread agreement on the need for life-long follow-up with subspecialists following HCT, but other areas were less clear. Efforts to obtain a consensus on standard of care follow-up are warranted, along with assessments to define tests and examinations need for optimal long-term care. Implementation of standard of care procedures through multi-specialty collaborative efforts are needed to better define how best to manage these medically complex patients with very rare diseases long-term following HCT.

Keywords: Long-term, CGD, WAS, PIRD, Transplant, PIDTC

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(170)

Celiac disease in selective IgA deficiency patients is associated with T-cell defects

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Introduction: Selective Immunoglobulin A deficiency (sIgA-def) is a relatively common subtype of immunodeficiency with a prevalence between 0.1 and 1%. Although most of them remain asymptomatic, sIgA-def patients are at higher risk of celiac disease and allergy. However, the pathophysiologic mechanisms underlying these complications remains largely unknown.
Objective: We aimed to investigate in detail the potential patterns of immune cell alterations in sIgA-def patients presenting with these complications.
Material and methods: Blood samples from 76 sIgA-def individuals (serum IgA< 7 mg/L) referred to 7 different hospitals were analyzed using high sensitive flow cytometry techniques validated by the Euroflow consortium.
Results: Among our patients, respiratory infections (22%), followed by celiac disease (14%) and allergy (21%) were the most frequent complications. As previously proposed, these sIgA-def patients were further classified based on the specific memory B-cell defects as mild sIgA-def (group 1) when circulating IgA+ memory B cells (MBC) were detected, or severe sIgA-def (group 2), when no IgA+ MBC were detected at a sensitivity limit of < 0.02 cells/uL. However, the severity of the IgA+ MBC defect did not show an impact on the prevalence of celiac disease or allergy, with a similar frequency of both complications of the disease in group 1 vs. group 2 cases: 16% vs. 19% of patients presenting celiac disease, and 34% vs 21% of allergic patients, respectively ($p > 0.05$). In contrast, detailed dissection of the T-cell compartment showed that sIgA-def patients presenting with celiac disease had increased counts of total TCR$\gamma\delta$+ T cells ($p = 0.03$), and significantly lower TCD4+ central/transitional memory cell ($p = 0.02$) and total Th17 TCD4+ cells ($p = 0.03$) counts in blood. In contrast, allergy did not appear to be associated with any specific T-cell immune profile among sIgA-def patients.
Conclusions: Our results suggest that sIgA-def patients presenting with celiac disease might have an uniquely altered T-cell immune profile consistent with increased counts of TCR$\gamma\delta$ cells, and decreased memory T cells and Th17 TCD4+ T-cells. Larger studies, including in vitro functional tests, might contribute to define whether the lack of IgA antibodies in celiac patients is the primary defect or a symptom of a more broad T-cell defect.

Keywords: Selective immunoglobulin A deficiency, Celiac disease, B cells, Th17, TCRgd, Allergy, IgA antibodies

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(171)

Assessment and Characterization of Tbet+ B Cells in Various Inborn Errors of Immunity (IEIs)

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Introduction: Originally detected as tissue resident memory cells in influenza infection, B cells exhibiting the CD21low CD11c+ Tbet+ phenotype have garnered attention due to their association with autoimmunity. This study aims to understand their presence in different B cell developmental stages and their characteristics in patients with various Inborn Errors of Immunity (IEIs).
Methods: Patients with a monogenic IEI were enrolled through our IRB-approved protocol and data was collected by retrospective chart review. Utilizing a 24-color full spectrum flow cytometry panel, we comprehensively evaluated B cell immunophenotypes in peripheral blood mononuclear cells (PBMC) from these patients. Unsupervised clustering techniques (FlowSOM) were employed for subset identification and quantification, while the t-distributed Stochastic Neighbor Embedding method (tSNE) was used for visualization. Additionally, a detailed assessment of T cell composition was performed using an 18-color panel.
Results: 55 patients with CTLA4 deficiency ($n = 24$), NFKB1 deficiency ($n = 13$), or Activated PI3K-delta Syndrome (APDS)/Phosphoinositide 3-kinase/PI3Kδ, p85α deficiency ($n = 18$) were included in the cohort, along with healthy controls ($n = 26$). A total of 94 patient samples were collected at various timepoints. Individuals with repeated samples were analyzed to assess the correlation with disease status and severity. In this analysis 16 distinct developmental B cell subsets were discerned. Among these, Tbet+ B cells were detected within three naive and a double-negative population. Notably, the majority of patients had Tbet+ B cell expansion at least one of their timepoints. Interestingly, these cells exhibit dynamic plasticity and correlate with disease severity. Unrelated to the underlying monogenic disorder, Tbet + cells expanded similarly in symptomatic patients.
Conclusions: In patients with CVID-associated monogenic disorders, we noted remarkable expansion of Tbet+ B cells, especially among symptomatic patients. Tbet+ B cells emerge at early stages of B cell development and display similar characteristics among monogenic IEIs. For the shared characteristics, these cells may serve as candidates for targeted therapy.

Keywords: Tbet+ B cells, Inborn errors of immunity, CVID-associated monogenic disorders

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(172)

Identification of TNFa-Related Biomarkers in Patients and Carriers with Adenosine Deaminase 2 Deficiency (DADA2)

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Overproduction of TNFα is implicated in the pathogenesis of DADA2 and TNFα inhibition (TNFαi) is used for treatment. TNFα and its receptors, TNFR1 and TNFR2, exist as transmembrane (tm) forms or are cleaved into soluble forms by TNFα-converting enzyme (TACE/ADAM17). The response to TNFαi is variable in DADA2 with some patients manifesting relapse after a period of clinical stability. It is unclear if TNFαi serves only to remove excess soluble TNFα or whether it exerts a dynamic effect on signaling via tm-TNFαreceptors, TNFR1/R2. It is also unknown if soluble or transmembrane (tm) TACE or TNFR1/R2 or TNFα can serve as biomarkers for disease activity or response to treatment. Evaluation of DADA2 carriers and patients – untreated and receiving different types of TNFαi treatment may offer additional insight into the mechanism of action of different TNFαi in DADA2. Therefore, serum or plasma and PBMCs were obtained from DADA2 patients (n = 22), DADA2 carriers (n = 4–9) and healthy adult and pediatric controls [HCs] (n = 46–85 and n = 12–65 respectively). The DADA2 patients in this study included those receiving treatment with TNFαi. ADA2 activity in serum or plasma were measured with an assay currently being validated in our clinical laboratory. TACE levels were measured by ELISA. Flow cytometry was utilized to investigate the frequency and expression of tmTACE, tmTNFα, tmTNFR1 and tmTNFR2 in different leukocyte subsets (monocytes, NK cells, B Cells, CD4+/CD8+ T cells). As expected, ADA2 levels were absent in DADA2 patients and decreased in carriers (median = 5mU/mL) relative to HCs (median = adult, 11.78 mU/mL; pediatric, 15.02 mU/mL). Soluble TACE levels were significantly lower in pediatric DADA2 carriers relative to healthy controls ($p = 0.02$). Cellular analysis showed a significant increase in the amount and frequency of tmTACE MFI (median fluorescence intensity) on monocytes between DADA2 carriers compared to patients ($p = 0.03$). Transmembrane TNFR1/R2 was decreased in patients compared to controls in lymphocyte subsets and monocytes. Transmembrane TNFα MFI on monocytes was significantly decreased in carriers ($p = 0.014$) and patients ($p = 0.006$) relative to controls. Clinical correlation and inclusion of additional patients and carriers is ongoing.

Keywords: Adenosine deaminase 2 deficiency (DADA2), Tumor necrosis factor alpha (TNFα), TNFα converting enzyme (TACE), TNFα inhibitors, DADA2 biomarkers

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(173)

Spatial mapping of immune cells in barrier tissues of immunocompromised patients affected by human papillomavirus-related disease

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Background: Inborn errors of immunity (IEI) are rare, genetic disorders that compromise the immune responses, leading to increased susceptibility to infections, immune dysregulation and increased risk of malignancy. GATA2 deficiency, an IEI caused by heterozygous mutation of the hematopoietic transcription factor GATA2, is characterized by an increased susceptibility to skin and mucosal HPV-related diseases. GATA2 deficiency is treated with hematopoietic stem cell transplantation (HSCT), which results in resolution of HPV-related diseases.
Methods: We assessed myeloid and lymphoid cell populations in biopsies of lesional and non-lesional verrucuous lesions and anogenital condylomas from GATA2 deficiency patients pre- and post- HSCT via confocal microscopy, characterizing the immunological landscape resulting in regression of HPV- related disease at epithelial surfaces.
Results: Our preliminary data show that following HSCT, long lived Langerhans cells, recruited dendritic cells and other myeloid cells help orchestrate the innate and adaptive immune response during the critical early period of immune reconstitution post-HSCT.
Conclusions: After HSCT, innate immunity and myeloid reconstitution play a central role in regression and clearance of HPV related skin lesions in GATA2 deficiency patients. Further imaging and functional studies will help elucidate the role that different immune cell types play in lesion regression, allowing us to devise better strategies for effector cell-based therapies or vaccines for humans. (Funded by the National Institute of Allergy and Infectious Diseases and the National Cancer Institute).

Keywords: Spatial mapping, HPV, GATA2

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(174)

Age-associated distribution of TH subsets in blood of LOCID vs CVID patients

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Background: Several alterations of CD4+ T-cell subsets have been reported in common variable immunodeficiency (CVID) patients, although none of previous studies discriminated patients with an underlying defect in CD4+ T-cell production fulfilling the diagnostic criteria for late-onset combined immunodeficiency (LOCID). In addition, these studies have not taken into consideration the CD4+ T-cells age-associated changes.

Aims: To investigate the potential association between the defects in the CD4+ T-cells and the clinical manifestations in CVID and LOCID patients.

Methods: CD4+ T-cell subsets were analyzed in 44 CVID and 27 LOCID patients, and 150 healthy donors, using EuroFlow-based flow cytometry methods.

Results: We defined the normal age-matched reference ranges for each Th subset (TFH, Treg, Th1, Th2, Th17, Th1/Th2, Th1/Th17), using ≥20 healthy donors per age-group (4–9y, 10–19y, 20–39y, 40–59y, 60–69y, ≥70y). Compared to age-associated reference values, LOCID and CVID patients showed defects of circulating Tregs (94% and 58% of patients, respectively), Th2 (88% and 46%), Th17 (84% and 42%), and Th1/Th2 (62% and 24%) TCD4+ cells. In contrast, few LOCID and CVID patients showed decreased TFH (6% and 4%), Th1 (25% and 17%), and Th1/Th17 (25% and 19%) counts. Interestingly, multivariable analysis identified a subgroup of LOCID patients with expanded Th1 cell counts who showed a higher frequency of autoimmune cytopenia (100% vs. 38%, $p < 0.001$) and interstitial lung disease (73% vs. 19%, $p = 0.008$), together with a lower frequency of non-respiratory infections (55% vs. 94%, $p = 0.03$). In addition, a subgroup of CVID patients with higher Th1 cell counts also emerged, associated with a higher frequency of autoimmune cytopenia (71% vs. 14% $p < 0.001$), but not interstitial lung disease (17% vs. 6% $p > 0.05$). No other clinical complications were associated with the Th cell profile of LOCID and CVID patients.

Conclusion: LOCID patients showed more severe T-cell defects than CVID patients, which particularly affected Tregs, Th2, Th17, and Th1/Th2 TCD4+ cells, while TFH, Th1, and Th1/Th17 cells were usually preserved in both groups of patients. Interestingly, the presence of autoimmune cytopenia in both LOCID and CVID cases, and of interstitial lung disease in LOCID patients, was strongly associated with increased Th1 counts in these patients.

Keywords: CVID, LOCID, CD4 T-cell, Autoimmune cytopenia, Interstitial lung disease, Age, Non infectious complications, Th1, Treg, TFH

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(175)

Immune response after anti-SARS-CoV-2 mRNA repeated boosters vaccination in patients with Common Variable Immunodeficiency

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Background: Common Variable Immunodeficiency (CVID) disorders have a spectrum of B and T cell defects that cause a defective antibody response. Both the response and the durability of humoral and cellular responses to the currently used COVID-19 mRNA vaccines remain to be elucidated.

Aim: This study evaluates the immune response along time after SARS-COV-2 mRNA vaccines primary cycle plus three boosters' vaccine and/or COVID-19 infection in patients with Common Variable Immunodeficiency (CVID).

Results: We analysed 65 patients with CVID. All the patients who had SARS-COV-2 infection had no need of hospitalization.

Before receiving the first vaccine dose, 13 patients had COVID-19. The time of positive swab was 33.8 days (±37.87).

mRNA-1273 was administered in 45 patients as primary cycle and 20 ones BNT162b2. As first booster, 14 received mRNA-1273 vaccine and 51 BNT162b2. After that, 27 patients had COVID-19. The time of positive swab was 25.3 days (±20.71).

As second booster, 6 received mRNA-1273 vaccine and 45 BNT162b2. After the second vaccine booster, 15 patients had COVID-19. The time of positive swab was 16.3 days (±10.74).

As third booster two patients had mRNA-1273 vaccine and 23 BNT162b2.

4-weeks after the primary cycle, 46 were responders. The median Ig anti-S level was 609 U/mL. It was higher in the 11 previously infected patients than in the uninfected (4302 vs 297.5 U/mL). Six months after the primary cycle, the Ig anti-S titre of the overall subjects dropped to a median level of 313 U/mL. After the vaccine booster dose, the overall median Ig anti-S level raised to 3442 U/mL and the differences between the previously infected and uninfected patients reduced (3680 vs 2867.5, respectively). Nine patients remained not-responders after 3 vaccine doses.

The SARS-CoV-2-T-cell responses analysis showed that 78.3% patients maintained a positive cellular response before the booster, almost unchanged after it. Six subjects remained not-responders. 3–4 months after the booster dose, 21 patients (35%) got SARS-CoV-2 infection, mostly omicron variant.

Conclusion: The sequentially booster doses produced both an antibody and cellular response in severals and was higher in those who had SARS-COV-2 infection.

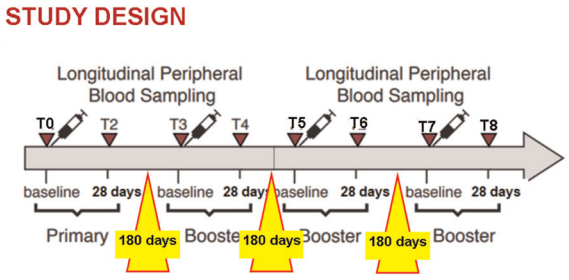

Figure 1. Study design.

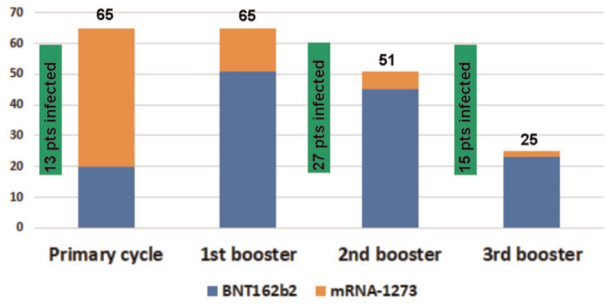

Figure 2. Type of vaccines administered and number of patients vaccinated and infected.

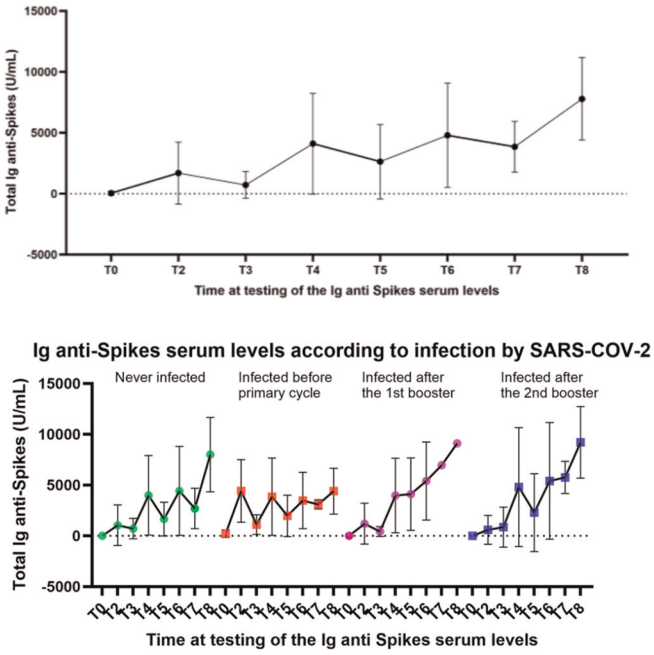

Figure 3. Humoral responses after vaccination/infection.

Keywords: Common variable immunodeficiency, Vaccine, SARS-COV-2, Immune response, Immune dysregulation, Coviferon, Humoral response, Anti-spike, COVID-19

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(176)

JAK1-selective inhibitor upadacitinib induced dynamic immunologic alterations and clinical response in treatment-resistant CVID gastrointestinal disease

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Case Study: Enteropathy is among the most severe and intractable complications of CVID. Here, we report the therapeutic response and immune dissection of JAK1-selective inhibition in a 31-year-old male CVID patient with recalcitrant enteropathy. At baseline, the patient had biopsy-confirmed small and large intestinal disease, 10–20 watery diarrhea/day, a nadir BMI of 15 kg/m^2, and severe malnutrition requiring total parenteral nutrition (TPN). His gastrointestinal disease had previously failed topical steroids, anti-α4β7 integrin, anti-IL12/23, CTLA4-Ig, and anti-TNFa agents. JAK1-selective inhibition with upadacitinib (30–45 mg/day) led to enhanced clinical response, with reduced stool frequency to 3–4/day, mixed formed stools, 8.2 kg weight gain (BMI 19.6 kg/m^2), and termination of TPN-dependence. No associated adverse events or infectious complications had been observed for the duration of therapy to-date (1.2 years).

Serum high-dimensional cytokine profiling pre and post-upadacitinib revealed dynamic immunologic alteration by JAK1-selective inhibition in

association with clinical response. These included pronounced reduction of circulating proteins related to 1) type 2 interferon pathway (IFN-g, CXCL9), 2) IL-17 axis (IL-17A, IL-17C), 3) gut chemotaxis (CCL19, CCL20), and 4) IL-5. Clinical response to JAK1 inhibition was also associated with increased expression of CX3CL1 and FGF19 back to normal ranges seen in healthy controls, with both proteins previously linked to modulation of intestinal inflammation in murine models.

Conclusion/Impact: Upadacitinib led to enhanced clinical response in a case of treatment-resistant CVID enteropathy. Therapeutic benefits and safety profile of JAK1-selective inhibition in CVID enteropathy warrant further study. Immune dissection herein additionally revealed immune pathways of interest in the investigation and development of targeted therapeutics for CVID enteropathy.

Keywords: CVID, Enteropathy, Biologics, JAK1, Proteomic

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(177)

ClinGen Framework for PIK3CD Variant Classification: Use of Adapted ACMG/AMP Guidelines

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Background: Inborn errors of immunity (IEIs) encompass a diverse range of diseases, with Activated PI3K Delta Syndrome (APDS) being particularly noteworthy. APDS is associated with variants in the PIK3CD gene, responsible for encoding the p110δ catalytic subunit of phosphoinositide 3-kinase delta (PI3Kδ). This rare immunodeficiency disorder presents challenges due to its varied clinical manifestations, complicating the accurate classification of PIK3CD variants and subsequent clinical management. Acknowledging the importance of precision in variant classification, this study details the adaptation of PIK3CD-specific guidelines from the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) as part of the ClinGen framework. The aim is to improve understanding and classification of PIK3CD variants, thereby enhancing diagnosis, risk stratification, and targeted therapeutic interventions for individuals affected by APDS.

Methods: The Antibody Deficiencies Variant Expert Panel (AD-VCEP) adapted twenty specification codes for PIK3CD. A total of 37 PIK3CD variants, including well-known pathogenic variants, likely pathogenic ones, variants with uncertain significance (VUS), and benign or likely benign variants, were evaluated.

Results: During the pilot phase, crucial gene-specific modifications to ACMG/AMP codes impacting variant classification were identified. These modifications included specific population frequency considerations for codes (BA1, BS1, and PM2), a point system defining probands with a phenotype highly specific to APDS (PS4 and PP4), and detailed descriptions of well-established functional studies in vitro and in patient's cells (PS3). The specifications successfully resolved the ambiguity of 18 PIK3CD variants in ClinVar, resulting in the reclassification of one pathogenic variant and twelve variants as likely benign or benign, with only five variants remaining classified as VUS. Notably, 12 PIK3CD variants initially considered pathogenic were revised, with only seven ultimately classified as Pathogenic or Likely Pathogenic.

In summary, this collaborative effort between ClinGen and AD-VCEP comprehensively adapts ACMG-AMP guidelines for IEIs, with the goal of standardizing PIK3CD variant curation and resolving ambiguities in classification.

Keywords: PIK3CD, APDS, Variant classification, ClinGen

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(178)

Case Study: IgG deficient patient receiving immune globulin intravenous, human-slra 10% demonstrates improvement in quality of life

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Rationale: Immunoglobulin replacement therapy (IgRT) is proven to be effective in preventing the occurrence of serious bacterial infections in patients with immunodeficiencies, but quality of life is not frequently studied in IgRT clinical trials. This case study highlights the effect of IgRT on quality of life. A 68-year-old female was referred to this complex specialty pharmacy to initiate IgRT infusions in the home for selective IgG deficiency, selective deficiency of immunoglobulin A, pemphigus, and mild asthma. She was prescribed immune globulin intravenous, human-slra 10%, an Ig product that is manufactured using plasma from donors that possess high antibody titers against RSV and other common pathogens including influenza, parainfluenza, metapneumovirus, and seasonal coronaviruses.

Methods: A retrospective analysis of the patient's medical records was performed. The review consisted of data contained within a customized

Table 1. (abstract: 178)
PADQOL-16 results.

Date Interviewer	5/2/2023 Pharmacist	5/4/2023 Nurse	5/24/2023 Pharmacist	6/1/2023 Nurse	6/29/2023 Nurse	7/27/2023 Nurse	8/24/2023 Nurse	9/21/2023 Nurse	10/19/2023 Nurse
1. I get infections between infusions	2	0	1	0	0	0	0	0	0
2. I am more than tired than normal	2	2	1	2	0	0	0	0	0
3. My cough has worsened	0	0	0	0	0	0	0	0	0
4. I have flare-ups and symptoms of sinusitis	2	0	2	0	0	0	0	0	0
5. I have to seek unscheduled medication visits for my PIDD	2	0	2	0	0	0	0	0	0
6. I have nausea and bloating	0	0	0	0	0	0	0	0	0
7. I have trouble with infections	2	0	1	0	0	0	0	0	0
8. The effects of my treatment wears off between infusions	0	0	0	0	0	0	0	0	0
9. I have trouble with shortness of breath	0	0	0	0	0	0	0	0	0
10. I struggle to keep up with others	1	1	1	1	1	1	1	1	1
11. I have trouble sleeping	0	1	0	1	1	1	1	1	1
12. I feel downhearted and depressed about my PIDD	0	0	0	0	0	0	0	0	0
13. I have missed school or work due to my PIDD	0	1	0	1	0	0	0	0	0
14. I feel that I am a burden to others	0	0	0	0	0	0	0	0	0
15. I require help from others frequently	1	0	1	0	0	0	0	0	0
16. I avoid certain places and situations because of my PIDD	1	2	1	2	0	0	0	0	0
PADQOL-16 Total Score	**13**	**7**	**10**	**7**	**2**	**2**	**2**	**2**	**2**

Table 1 details the patient's PADQOL-16 scores while receiving intravenous immunoglobulin therapy from this national complex specialty pharmacy. The patient was interviewed either via telephone by a pharmacist prior to the infusion or at the bedside by a registered nurse at the time of immunoglobulin administration. PIDD = primary immunodeficiency diseases.

clinical assessment created by this complex specialty pharmacy, including the Primary Antibody Immune Deficiency Quality of Life (PADQOL-16), a validated quality of life measure specific to primary immunodeficiency. Additional items collected and analyzed from the customized clinical assessment included drug tolerability, side effect management, infection history, and anti-infective use.

Results: After 148 days of therapy, the patient experienced an 11-point improvement in the PADQOL-16. The most significant improvement in the PADQOL-16 total score was obtained at day 58 of therapy (score = 2), which was then sustained through the remainder of the available clinical documentation at day 148. The patient did not experience any infections while on therapy and reported side effects were chills/rigors with one infusion. Differences in the PADQOL-16 scores around the same infusion were observed depending on the interviewer – a pharmacy team member via telephony versus a registered nurse during IgRT administration.

Conclusions: Immune globulin human-slra 10% is well-tolerated and effective in preventing infections in IgG deficient patients, and this case study demonstrates the added quality of life benefit this IgRT provides. The addition of a validated, disease-specific quality of life measure, such as the PADQOL-16, in routine clinical assessments allows the opportunity for this complex specialty pharmacy to collect and analyze real-world data for IgRT beyond single case reports in future studies.

Keywords: Primary immunodeficiency, Quality of life, PADQOL, Immunoglobulin therapy

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(179)

Expanded phenotypic presentations in CADINS disease associated with novel CARD11 dominant interfering variants that impact NF-kB and AP-1 signaling

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CARD11 encodes a critical scaffold protein linking antigen receptor (AgR) engagement to signaling pathways required for effector lymphocyte survival, proliferation, and differentiation, including nuclear factor kappa B (NF-κB), c-Jun N-terminal kinase (JNK), and mechanistic target of rapamycin complex 1 (mTORC1). Genetic mutations in CARD11 are

associated with a spectrum of inborn errors of immunity - here we focus on the characterization of CARD11 variants suspected to be causative of CARD11-associated atopy with dominant interference of NF-κB signaling (CADINS) disease. CADINS disease is attributed to impaired AgR signaling caused by heterozygous dominant interfering (DI) variants in CARD11. From a total of 133 referred patients with 117 unique genetic mutations in CARD11, we identified 32 novel DI CARD11 variants in 41 patients. Prior studies demonstrated that ~89% of patients with DI CARD11 variants presented with some form of atopic disease (AD), whereas 73% of the new patient cohort described here presented with AD. Intriguingly, we noted an expanding spectrum of phenotypic presentations within this cohort including autoimmunity (e.g. inflammatory bowel disease; 20%; 8/41) and neutropenia (5%; 5/41). Based on our recent work characterizing the function of the CARD11-JNK signaling axis in T cells, we expanded our mechanistic studies to quantify the effects of heterozygous DI CARD11 mutations on these pathways, revealing marked defects in AP-1-dependent transcription congruent with quantitative impairment of NF-κB signaling. Furthermore, our identification of 32 novel impactful CARD11 DI variants prompted us to reassess the previously described Mutation Significance Cutoff (MSC) for CARD11 based on updated Combined Annotation Dependent Depletion (CADD) scoring metrics. Including all published pathogenic mutations in CARD11, we found that the MSC for CARD11 substantially increased from 22.9 to 25.24. Our work provides a comprehensive update on deleterious CARD11 variants and associated clinical presentations in CADINS disease, helping to refine potential genotype-phenotype correlations and illuminating a new avenue for mechanistic investigations of pathogenesis related to abnormal AP-1 activity.

Keywords: CARD11, CADINS, Atopic disease, NF-kB, JNK, AP-1, T cell receptor signaling, Autoimmunity, Neutropenia

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(180)

Anti-IL12 autoantibodies in a teenage girl with multiple recurrent abscesses

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More frequent among adults, phenocopies may be caused by somatic mutations or anti-cytokine autoantibodies, mimicking the phenotypes of primary immunodeficiencies. A fourteen-year-old girl was referred for a 2-year history of weight loss and multiple recurrent abscesses, as well as complicated recurrent pneumonia, pyelonephritis, osteomyelitis, and septic shock, without fever. She had started with nausea, hyporexia, and weight loss (21 kg), then with abscesses in her hands, knee, ankle, and spleen. She also developed a rib fracture and left thoracic herpes zoster. The patient was cachectic, with normal vital signs, crackles on chest auscultation, tumefaction of the knee joint, and poorly healed wounds in hands and chest, oozing a yellowish fluid. Chest computed tomography revealed multiple bilateral bronchiectases. Laboratory workup reported chronic anemia, leukocytosis, neutrophilia, mild lymphopenia, thrombocytosis, hypergammaglobulinemia, and elevated acute serum reactants. Lymphocyte subsets were low but present. Mycobacterium tuberculosis was detected via polymerase chain reaction in a bone biopsy specimen from ankle osteomyelitis. Whole-exome sequencing failed to identify a monogenic defect. IL-12 was found markedly elevated in serum from our patient. Phosphorylation of STAT4, induced by increasing doses of IL-12, was neutralized with serum from the patient, thus confirming the presence of anti-IL12 autoantibodies. IL-12 and IL-23 are crucial cytokines in the defense against intracellular microorganisms, the induction of interferon-gamma production by lymphocytes, and other inflammatory functions. Patients who develop neutralizing serum autoantibodies against IL12 manifest late in life with weight loss, multiple recurrent abscesses, poor wound healing, and fistulae. Treatment with anti-CD20 monoclonal antibodies might be effective.

Keywords: Phenocopy, Multiple recurrent abscesses, Late-onset, Teenage, Anti-cytokine autoantibodies, Inborn errors of immunity, Anti-CD20 monoclonal antibody

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(181)

Incidental Diagnosis of NFKB2 Mutation in Patient with ACTH Deficiency and Low IgA

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Introduction: Deficient anterior pituitary with variable immune deficiency (DAVID) syndrome is a rare disorder characterized by adrenocorticotropic (ACTH) deficiency and common variable immunodeficiency (CVID) due to NFKB2 mutations. We report a pediatric patient who initially presented with GI symptoms and weight loss.
Case: A 6-year-old female with history of recurrent otitis media presents with abdominal pain, recurrent vomiting for 2 weeks, and weight loss. Patient's initial work-up showed hypoglycemia (47), and celiac work-up with low IgA level (18). Endocrinology work-up for ketotic hypoglycemia revealed isolated ACTH deficiency, which was diagnosed as central adrenal insufficiency (CAI) and treated with hydrocortisone supplementation. Patient's Immunology visit for low IgA showed no history of serious infections but revealed father's CVID. While isolated low IgA levels would not typically warrant extensive work-up, immunoglobulins were collected due to patient's family history. These revealed severe hypogammaglobulinemia (IgA 12, IgM 21, IgG 226) and additional workup showed low, but protective, tetanus titers and immunity to only 1/23 of the pneumococcal titers. Patient was diagnosed with CVID, which was treated with IgG replacement. Given patient's new diagnosis of CAI and CVID, genetic testing confirmed NFKB2 pathogenic heterozygous variant (c. 2557 C > T).
Conclusion: DAVID syndrome may have various clinical presentations. It is classically considered with adrenal crisis and severe recurrent infections. This prompt diagnosis of the NFKB2 mutation was due to the accidental finding of low IgA from the celiac work up. The patient's initial presentation

with weight loss can likely be attributed to her adrenal insufficiency. Extensive immunologic workup for a slightly low IgA is not usually conducted, but due to the emphasis placed on the family history of CVID, genetic work up confirmed the diagnosis. Had the celiac workup, including IgA levels, was not obtained, there would have likely been a significant delay in diagnosis. This case shows the importance of considering NFKB2 mutations for patients with CAI, especially with relevant family history but lacking a significant infection history.

Keywords: NFKB2, CVID, Central adrenal insufficiency, Hypogammaglobulinemia, DAVID syndrome

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(182)

Inherited POMP-Related Autoinflammation and Immune Dysregulation Disease Treated with Baricitinib Prior to Hematopoietic Stem Cell Transplant

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Introduction: Proteasome maturation protein (POMP) is a chaperone protein critical for proteosome assembly. Heterozygous truncating variants in POMP have been shown to cause POMP-related autoinflammation and immune dysregulation (PRAID) via escape of non-sense mediated decay. PRAID has been characterized by neonatal onset neutrophilic dermatitis, autoimmunity, and immunodeficiency.
Case: Our patient is a female born at full term and she was admitted at 7 weeks of age with severe dermatitis. Skin culture grew Escherichia coli and Enterococcus. She was also noted to have an absolute eosinophil count of 12,150 (cells/μL), anemia, thrombocytopenia, B-cell lymphopenia, elevated CD4/CD8 ratio, and hypogammablogulinemia. Skin biopsy showed neutrophilic dermatitis. Family history was significant for mom having undergone a hematopoietic stem cell transplant (HSCT) at 7 months of age for a genetically undefined combined immunodeficiency. Rapid whole genome sequencing in our patient revealed a heterozygous known pathogenic variant in POMP (c.334_335del). She was started on prophylactic azithromycin, trimethoprim-sulfamethoxazole, acyclovir, fluconazole and intravenous immunoglobulin G replacement. Baricitinib was initiated 9 weeks prior to HSCT. Baricitinib was then stopped 3 weeks prior to HSCT when conditioning was started. While on baricitinib soluble IL2 receptor (CD25) was monitored and decreased from >5000 pg/mL to ~2000 pg/mL. Prior to baricitinib, she was treated for cutaneous aspergillus and bilateral Pseudomonas aeruginosa otitis media infections. At 6 months of age, our patient underwent a 5/6 match unrelated cord blood transplant with alemtuzumab, fludarabine, thiopeta, and melphalan. Post transplant course was complicated by venocclusive disease, transplant associated thrombotic microangiopathy and acute graft versus host disease. Five weeks post-transplant, serum CD25 was within normal limits at 608 pg/mL. Sanger sequencing on buccal swab from mom also demonstrated the same POMP variant (c.334_335del).
Discussion: To our knowledge, this is the first familial case PRAID. With the early onset of the inflammatory phenotype, we elected to initiate pre-HSCT JAK-inhibition and monitored serial CD25 for effect. No adverse events from JAK inhibition were noted and successful transplant in this patient. More research is necessary to fully understand the role of pre-HSCT JAK inhibition in patients with PRAID and other autoinflammatory diseases.

Keywords: PRAID, POMP, JAK inhibitor, HSCT, Autoinflammatory

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(183)

Resolving Variants of Unknown Significance (VUS) in PIK3CD and PIK3R1

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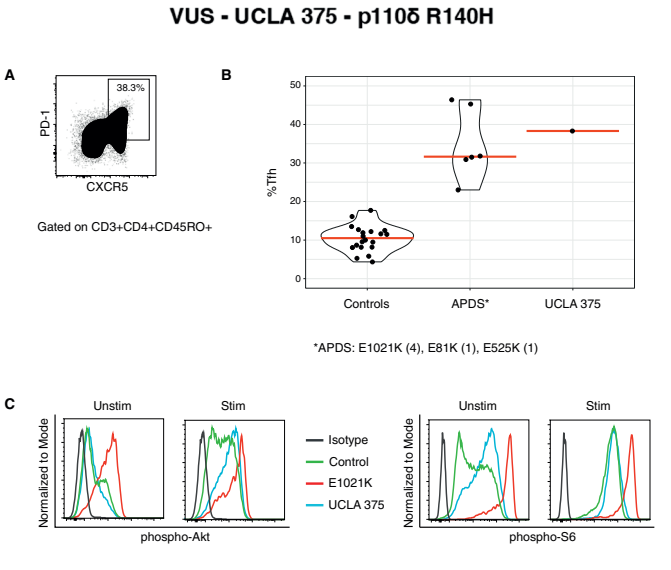
Diagnosis of Activated PI3K Delta Syndrome (APDS) requires the presence of a heterozygous, pathogenic germline variant in either PIK3CD or PIK3R1 that confers a gain of function of the p110δ kinase activity. Variants of unknown significance (VUS) require validation to understand their biochemical impact on PI3K function, for example on the downstream mTOR pathway and consequently on the development of immune cells. There are no existing services that offer such clinical validation. The degree of phenotypic immune dysregulation can be quite variable and no existing source identifies the cutoffs for immune or metabolic parameters that we might expect to see to make a diagnosis of APDS.
Here, we demonstrate an approach that combines clinical phenotype, immunological phenotype, and a flow cytometric assay to diagnose APDS from those with genetic VUS. We received blood after informed consent from over a dozen subjects who bore VUS in PIK3R1 or PIK3CD. We compared samples to those with bona fide pathogenic variants such as p.E1021K in PIK3CD. We found all subjects showed an increase in circulating T follicular helper cells. We found markers of dysregulated maturation in the B cells. We made T cell blasts and activated them while testing their mTOR pathway using flow cytometry. Overall, these tests can be run within one week. Results of validation studies were deposited in ClinVar to facilitate future classification of these variants. Our results reveal the ability to diagnose APDS among those bearing genetic variants of unknown significance using research laboratory tests.
Funding: This work was supported by Pharming, Inc., which did review the results but was not permitted to make edits.



(A and B) Percentage of T follicular helper (Tfh) cells among CD3+CD4+CD45RO+ cells was determined by flow cytometry of PBMCs. The result is compared to healthy controls and known APDS patients. **(C)** Flow cytometry of resting CD4+ T cell blasts with or without stimulation with anti-CD3 for 10 min. Cells were stained for phosph o-Akt and phospho-S6.

Figure. R140H variant validated as gain of function.

Keywords: APDS, mTOR, Gain of function, T cell

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(184)

RECQL4 mutation is associated with a hematopoietic-cell-intrinsic severe T cell deficiency and is amenable to treatment with unconditioned, unmanipulated hematopoietic stem cell transplant

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RECQL4 is a DNA helicase involved in DNA replication, recombination, and repair [1]. Mutations in RECQL4 cause three distinct but overlapping rare syndromes, BGS, Rothmund-Thomson Syndrome, and RAPADILINO syndrome [1]. All three share features of slow growth, radial ray defects, and cancer predisposition. BGS additionally manifests with craniosynostosis and rash [1]. In general, immune deficiency has not been described as a prominent clinical feature in RECQL4 diseases. However, there are four case reports in the literature describing various immune defects in these diseases [2–5]. RECQL4 is strongly expressed in the thymus but has an unclear role [6].

Our patient was noted to have growth restriction and multiple congenital anomalies (including craniosynostosis, dysmorphic facies, severe foreshortening of the limbs, oligodactyly, and small thymus) on prenatal ultrasound, prompting genetic testing. Whole genome sequencing revealed homozygous pathogenic mutations in RECQL4 (c.2464-1G>C) and TYR (c.1037-7T>A). After birth, the prenatal ultrasound findings were confirmed. He was also noted to have faltering growth and severe diarrhea requiring parenteral nutrition. His SCID newborn screen was abnormal. Confirmatory testing demonstrated a T-B+NK- SCID phenotype without evidence of maternal engraftment (Table 1).

Table 1.
Lymphocyte cell counts pre- and post-transplant.

Age at Testing	CD3	CD4	CD8	CD4/CD45RA	CD19	CD3-/CD56+ and/or CD16+
10 days old	28	24	1	No data	310	6
1 month old	52	49	3	31	160	23
2 months old	71	67	3	41	229	4
2.5 months old	60	54	3	34	642	10
Post transplant						
7 months old (2 weeks post transplant)	247	165	51	93	353	177
7.5 months old, (1 month post transplant)	315	222	67	No data	424	69
8 months old, (2 months post transplant)	509	194	239	No data	282	238

Although his RECQL4 defect was known, it was initially unclear whether his T cell deficiency was hematopoietic cell intrinsic or extrinsic. To clarify this, the potential of his CD34+ cells to differentiate into mature T cells was analyzed using an artificial thymic organoid (ATO) system [7]. These results confirmed the presence of a hematopoietic intrinsic defect (Figure 1).

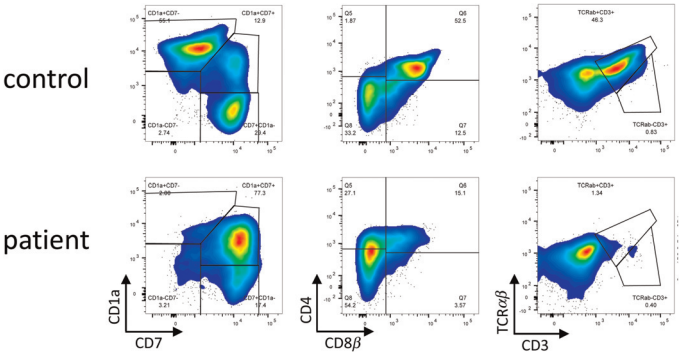

Figure 1. Defective T cell differentiation from CD34+ stem cells in our patient compared to control after 7 weeks in an Artificial Thymic Organoid (ATO) system. The ATO system is made by aggregating a DLL4-expressing stromal cell line (MS5-hDLL4) with CD34+ cells isolated from mobilized peripheral blood of either our patient or a healthy control. Plots shown are gated on CD45+CD56- cells.

Due to the radiosensitivity associated with RECQL4 mutation and compromised respiratory capacity from body habitus, our patient was deemed to be too high risk for conditioning. A donor search revealed that two of his siblings were matched donors. He underwent unconditioned, unmanipulated matched sibling donor transplant at 6 months of age. He is currently 2.5 months post-transplant, with emerging T cell development (Table 1) and at 60 days post-transplant demonstrated 83% T cell donor chimerism.

Keywords: RECQL4, SCID, Artificial thymic organoid (ATO) system, Unconditioned hematopoietic stem cell transplant, Baller-Gerold syndrome

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(185)

Complex Acquired Angioedema Case in a 46-Year-Old Emirati Female with a History of Breast Cancer

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This report examines a challenging case of acquired angioedema (AAE) in a 46-year-old Emirati female, a rare condition with a prevalence of less than 1 in 500,000. The patient's AAE, characterized by recurrent, severe swelling due to C1 esterase inhibitor deficiency, manifested subsequent to her breast cancer diagnosis in 2012, complicating her medical history intertwined with autoimmune disorders.

The patient experiences frequent angioedema attacks affecting her extremities, face, abdomen, and occasionally the throat, leading to multiple intensive care unit admissions. Despite extensive diagnostic efforts, including PET CT scans and biopsies, the specific trigger of her angioedema attacks remains elusive. Her treatment regimen includes C1 inhibitor esterase infusion prophylaxis, administered three times a week, which significantly alleviates symptoms when initiated early in the onset of attacks.

Her medical history is complex, with an initial diagnosis of breast cancer in 2012, treated with chemotherapy and radiotherapy. Following a relapse in 2015, she underwent further surgery and reconstruction. The temporal association between her cancer diagnosis and the onset of AAE suggests a potential link between her autoimmune condition and her oncological history.

The patient's case, marked by diagnostic and management challenges, highlights the need for a comprehensive, multidisciplinary approach. This approach is essential to investigate the multifaceted relationship between her AAE, breast cancer, and autoimmune disorders, aiming to optimize her treatment and improve her quality of life.

In summary, this case underscores the importance of an integrated, multidisciplinary approach in the management of AAE, particularly in patients with coexisting complex medical conditions. Understanding the interplay between various health factors is crucial in developing effective treatment strategies and enhancing outcomes for patients with similar profiles.

Keywords: Acquired angioedema (AAE), Breast cancer, C1 esterase inhibitor deficiency, Multidisciplinary approach, Diagnostic challenges

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(186)

Traversing Immunodeficiency Complexity: Profound Ureaplasma infection in Agammaglobulinemia with TCF3 Mutation

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This case study presents an in-depth clinical overview of a 32-year-old female patient marked by a recurrent history of sinopulmonary infections, agammaglobulinemia, and a longstanding immunoglobulin replacement therapy initiated since early childhood. In her early twenties, she encountered significant perineal tissue damage attributed to a challenging-to-diagnose and treat infection, subsequently identified as Ureaplasma urealyticum. The management of this complication necessitated collaboration across multiple medical teams. Additionally, a recent discovery of a TCF3 gene mutation further contributes to the complexity of the case. This case underscores the importance of precise diagnosis, individualised treatment, and multidisciplinary care in the management of complex immunodeficiency disorders.

Keywords: Agammaglobulinemia, TCF3 gene mutation, Ureaplasma infection, Multidisciplinary care

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(187)

Diagnostic approach in a young adult with RAG1 variants initially diagnosed with specific antibody deficiency and bronchiectasis

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Rationale: Adult patient with antibody deficiency syndromes are increasingly recognized with inborn errors of immunity including partial RAG deficiency (pRD). RAG1/2 genes are highly polymorphic. Hence, when variant of uncertain significance (VUS) is found, diagnostic approach linking the variants to pRD clinical phenotypes is essential. Through describing our adult case we aim to raise awareness and improve diagnostics for this vulnerable and underreported population.
Methods: We conducted a retrospective chart review for data on demographics, clinical features, laboratory evaluation, and treatment. Research laboratory testing included flow cytometry on T and B cell developmental subsets and autoantibody detection via ELISA.
Results: Our patient is 32 years old female with clinical history of asthma, allergic rhinitis on immunotherapy, recurrent bronchitis with mild bronchiectasis, viral infections include history of EBV, RSV and severe COVID-19 and autoimmunity (Sjögren's syndrome). Clinical immune evaluation revealed normal immunoglobulins with low IgG2 and IgG4 subclasses, declining pneumococcal titers after repeated vaccinations and normal T, B and NK lymphocyte counts. Diagnoses included IgG subclass and specific antibody deficiencies. Genetic evaluation revealed three RAG1 variants including pathogenic c.1420C>T p.Arg474Cys (Allele 1) and likely pathogenic (c.1A>G p.Met1?) and variant of uncertain significance c.310C>G (p.Gln104Glu). Detailed immune phenotyping revealed a low naïve (CD4+CD45RA+) T cell fraction for age (20%), low mucosal associated invariant (MAIT) (TCRVα7.2+) T cells (1% of CD3+ T cells), and detectable autoantibodies against IFNα, all hallmarks of pRD. Among immune subsets reflecting immune dysregulation, we only noted expansion of follicular helper T cells. The patient is naïve to immunomodulatory and immunoglobulin replacement therapies (IgRT).
Conclusions: Although RAG-CID is increasingly detected among adults, genetic diagnosis can be delayed due to incomplete evidence for pathogenicity in novel variants. Disease burden in adult pRD is often high, including inflammatory lung disease and systemic autoimmunity that complicates the potential hematopoietic stem cell transplant (HSCT). Immune phenotyping for biomarkers of pRD such as low MAIT and anti-IFNα autoantibodies supports a pRD diagnosis. Monitoring immune dysregulation is of importance to prevent end organ damage and determine when HSCT is indicated. Prompt genetic screening may combine with such biomarkers to expedite pRD diagnosis and proper management.

Keywords: Partial recombination activating gene deficiency, Specific antibody deficiency, Anti-cytokine antibodies, Adult immunodeficiency

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(188)

Novel Hypomorphic BTK Variant in X-Linked Agammaglobulinemia of a Kindred

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Introduction: X-Linked Agammaglobulinemia (XLA) is a primary immunodeficiency disorder due to a pathogenic mutation of the Bruton Tyrosine Kinase (BTK) gene, resulting in a full or partial block in early B cell development. Classical XLA displays full absence of immunoglobins and tonsils, whereas partial XLA can present with common variable immunodeficiency with decreased but not completely absent immunoglobulin levels.
Methods: Clinical and laboratory data was obtained from retrospective chart review.
Case Series Presentation: Our index case is a 6-year-old male who was admitted for two separate episodes of left lobar pneumonia 3 months apart. Past medical history is notable for multiple episodes of ear infections, pneumonia, and chronic intermittent diarrhea treated as outpatient. His specialist team includes otolaryngologist (adenoidectomy, tympanostomy, sleep apnea) and pulmonology (reactive airway disease/asthma). At one year of age, he underwent imaging that discovered he has normal caliber of adenoids and tonsils. With the latest admission, his other laboratory findings displayed low levels of immunoglobulins and near absence of antibody responses to vaccines and very low B cell count. Family history was concerning for XLA. Genetic report from his cousin highlights a missense variant of uncertain significance (VUS) in BTK c.1574G>A p.Arg525Gln. Currently the variant is not listed in ClinVar or gnomAD. Intracellular BTK protein expression is decreased in monocytes with a Mean Fluorescent Intensity (MFI) of 2.43, relative to the experimental control of MFI of 7.35. Currently we have identified 10 patients with hypomorphic XLA in this kindred. Once diagnosed, members with confirmed XLA have often missed clinical care and experienced gaps in immunoglobulin replacement therapy leading to chronic lung disease and death among adults.

Discussion/Conclusions: Our findings conclude that a novel pathogenic hypomorphic BTK variant has been discovered in a large kindred that presented with low, but not absent, immunoglobulin levels, low B cells, however presence of tonsils and adenoids, which presented a diagnostic challenge. Full understanding of the partial XLA by medical teams and the family led to delayed interventions and social challenges that hindered proper medical care and resulted in high mortality and morbidity.

Keywords: X-linked agammaglobulinemia, Hypomorphic Bruton tyrosine kinase variant, Recurrent infections, Immunodeficiency, Inborn error of immunity

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(189)

Disseminated cryptococcal lymphadenitis in a patient with STAT1 gain-of-function: diagnostic and therapeutic challenges

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Background and objective: Patients carrying STAT1-GOF mutations display a wide range of immune dysregulatory features. Chronic mucocutaneous candidiasis is the most common infectious manifestation, however patients may suffer from viral, bacterial and other fungal invasive infections, and present with aneurisms and malignancy. We present a case of disseminated colliquative lymphadenopathy that revealed the STAT1-GOF.
Methods: Genetic diagnosis was performed throughout NGS (STAT1: c.863C>T; p.Thr288Ile). STAT1 mutation GOF effect was based on the Tyrosine-701 increased phosphorylation in response to IFN.
Case presentation: The patient is a female, that was investigated at the age of 16 years for a persistent bilateral cervical lymphadenopathy associated with fever, night sweat and weight loss. In her past medical history she had autoimmune thyroiditis and type 1 diabetes. Imaging showed multiple lymphadenopathies in the mediastinal, supra and sub clavicular districts, with PET CT also showing radiopharmaceutical accumulation. Lymph node excisional biopsy revealed granulomatous lymphadenitis, with colliquative necrosis and positive PCR for Mycobacterium tuberculosis. First line quadruple antitubercular therapy was started, but after 12 months, despite the negative PCR, imaging showed a progression with abdominal lymph nodes involvement. Further microbiological analysis of the lymph node biopsy identified Cryptococcus neoformans; antigenemia resulted positive (1:2048) whereas MRI and lumbar puncture ruled out pulmonary and neurological involvement, respectively. The patient was treated with an induction therapy with fluconazole 15 mg/kg/die and amphotericin B 4 mg/kg/die for 4 weeks, followed by a consolidation phase of fluconazole 12 mg/kg/die that is still ongoing. The infection resolved, and antigenemia progressively decreased.
Conclusions: We described a challenging presentation of IEI with immune dysregulation secondary to STAT1 GOF mutation with infectious granulomatous disseminated lymphadenopathy, for which a complex multidisciplinary management was required for the diagnostic definition and therapeutic management. Patients with STAT1-GOF exhibit increased susceptibility to intracellular pathogens, and we suggest investigating this rare IEI in cases of Cryptococcus neoformans infections, particularly in patients with concomitant manifestations of autoimmunity.

Keywords: Lymphadenopathy, STAT1-GOF, Cryptococcus neoformans

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(190)

What is needed to diagnose an autoinflammatory disease? From clinical manifestations to genomic sequencing: the Brazilian experience

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Introduction: Autoinflammatory diseases in real life are much more than the periodic fever syndrome. Although genetics is central to the final diagnosis, various immunologic tests may be needed to support both clinical suspicion and genetic results, either for novel mutations, variants of uncertain significance, or in case of negative results.
Patients and Methods: We retrospectively analyzed clinical data of 350 patients with confirmed autoinflammatory diseases sent to our department during the last 5 years. We also collected data on immunologic tests performed in our laboratory to support the clinical diagnosis. All patients underwent whole genome sequencing.
Results: Recurrent fever was observed in 98% of patients, 53% were female, we observed a 7-year delay in diagnosis, and patients from all over Brazil were seen. Patients were subdivided into recurrent fever with a clear monogenic or multifactorial autoinflammatory or immunodysregulatory condition (48%): 20% monogenic autoinflammatory condition; 2%

immunodysregulatory; and 16% multifactorial. A definitive clinical diagnosis could not be made in 52% of the patients. Double negative T cells were positive in 21% of patients, peripheral Foxp3 expression was low in 56% of patients, and the interferon signature was positive in 80% of patients sent for analysis. Inflammasome activation for NLRP3, NLRC4 and NLRP1 was positive in all patients with clinical suspicion of CAPS, AIFEC and NAIAD. Pyrin/MEFV inflammasome activation was inconclusive for heterozygous MEFV mutations and non-exon 10 mutated patients. Whole genome sequencing was positive and clinically relevant in 17% of all patients. Novel mutations in NLRP3, XIAP, WASp and ADA2 were found after functional analysis and genome sequencing. 8 patients died during the last 5 years and 4% were diagnosed with systemic amyloidosis.

Conclusions: We demonstrate here the complexity of establishing a clinical diagnosis of autoinflammatory disease and the broad clinical spectrum observed in different scenarios. We also demonstrate the low positivity of genetic sequencing even with large-scale sequencing such as genome sequencing. Finally, we demonstrate the need for complex laboratory analysis for patients with autoimmune diseases during the diagnostic process.

Keywords: Autoinflammatory diseases, Immunodysregulatory disease, Genome sequencing, Type-1 interferon, Inflammasome

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(191)

CMV-specific adaptive immune response in U.S. Mennonite patients with hypomorphic RAG1 or RAG2 mutations presenting with clinical variability

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Hypomorphic mutations in recombinase activating genes 1 and 2 (RAG1/RAG2) lead to defective lymphocyte development and variable clinical and immunological presentation, including difficulty to contain viruses such as cytomegalovirus (CMV). We propose that low virus-specific adaptive immune response is associated with immune dysregulation and clinical decline in partial RAG deficiency (pRD).

Patients were consented to IRB-approved protocol. Immunophenotyping was performed with flow cytometry for T and B cell developmental subsets. Viral load was measured via qPCR, virus-specific antibodies were detected by Viracor's Immucor Capture-CMV, and CMV-specific lymphocyte proliferation was quantified with the tritiated thymidine assay upon exposure to CMV antigens.

Our cohort of CMV-exposed U.S. Mennonite pRD patients (n = 6) aged 3 months to 24 years included 5 patients with homozygous RAG1 (p.C176F, 25.8% recombinase activity) (n = 5) or RAG2 (p.G461A, 66.3% recombinase activity) (n = 1). Only two young siblings experienced severe clinical disease with infections and autoimmunity and concomitant elevation in CMV viral load. The youngest symptomatic sibling seroconverted from CMV-specific IgM to IgG at 11 months of age. Among the asymptomatic adults off immunoglobulin therapy (IgT), one patient had CMV-specific IgG (remaining cohort pending testing). CMV-specific antibody evaluation is hindered by maternal antibody (<6mo) and IgRT in some individuals. The CMV-exposed clinically ill pediatric female had a low CMV-specific proliferation response (18 mo). Repeated samples during clinical decline with CMV worsening viremia revealed an expansion of T follicular helper cells (Tfh) and CD19hiCD21loCD11c+ B cells. However, three CMV-exposed clinically well patients were able to mount a robust CMV-specific immune response and had no sign of expanding Tfh or CD19hiCD21loCD11c+ B cells. The rest are yet to be tested.

In a cohort with divergent clinical phenotypes, a CMV-exposed clinically ill patient initially was able to create CMV-specific IgM and IgG, but worsening viremia was associated with low lymphocyte proliferation to CMV. Throughout this time immune dysregulation escalated. These abnormalities were absent in CMV-exposed clinically well patients. This indicates the potential for evaluation of dysregulated immune subsets and virus-specific lymphocyte proliferation as indicators for clinical well-being in pRD and may serve to guide indication of immune modulation and/or definitive therapies.

Keywords: Combined immune deficiency, Recombinase activating gene (RAG), Cytomegalovirus (CMV), Mennonite, Immune competence, Immune dysregulation

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(192)
Subtle Presentation of Fungal Disease in X-CGD

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X-linked chronic granulomatous disease (X-CGD), manifests with increased susceptibility to severe infections with fungi due to pathologic variants in gp91phox (CYBB), resulting in a non-functional NADPH oxidase complex. Below, we describe two patients presenting with very mild clinical symptoms despite invasive fungal disease.
Patient 1: 3-year-old with X-CGD (CYBB c.742dupA), who presented with a "lump" on his upper back, but no other subjective complaints or clinical sign of illness. Lab testing demonstrated increased WBCs, CRP, ESR; ultrasound was suggestive of a lipoma. Five days later, he developed malaise and decreased oral intake. Excisional biopsy of the lump was performed; fungal culture grew Aspergillus fumigatus. A whole body CT revealed two mediastinal masses and liver abscesses; brain MRI showed multiple parietal abscesses (Figure 1a & b). He was treated with voriconazole and methylprednisolone, which eventually resulted in improvement.

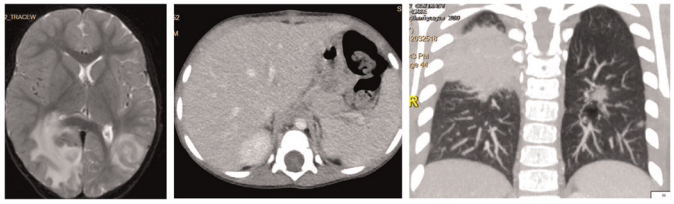

Figure 1a-c.

Patient 2: 7-year-old with X-CGD (CYBB c.1272G>A), who was noted to have cough and bilateral wheezing at a routine follow-up appointment, but no subjective complaints or other sign of illness. A chest x-ray (CXR) was notable for a consolidation in the right upper lobe. His ESR and CRP were elevated. He was started on empiric therapy with treatment dosing of Bactrim and Ciprofloxacin due to concern for bacterial pneumonia. Minimal improvement was seen on CXR obtained after 14 days, therefore chest CT was obtained and demonstrated multifocal bilateral lung consolidation, predominantly in the right upper lobe (Figure 1c). Fungal culture obtained from bronchoalveolar lavage grew Scedosporium species. He was treated with voriconazole and terbinafine.
Patients with X-CGD have greater mortality with respiratory or disseminated fungal infection. These cases highlight that the initial presentation with severe fungal infection can be quite subtle, with diagnosis requiring advanced imaging and tissue sampling to ensure proper treatment. Overall, for patients with X-CGD it is important to consider fungal infection when there is a lack of response to conventional bacterial therapies or radiologic evidence of disseminated disease even in relatively well appearing patients.

Keywords: Chronic granulomatous disease, Aspergillus, Scedosporium, Fungal pneumonia

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(193)
A Case of Chronic Rhinosinusitis with Nasal Polyps in a Patient with a Single Heterozygous RNU4ATAC Pathogenic Variant

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Introduction: Roifman Syndrome is a rare, autosomal recessive syndrome caused by RNU4ATAC gene mutation that typically presents with dysmorphic features, intellectual delay, skeletal abnormalities, growth retardation, and B-cell immunodeficiency. Serum immunoglobulin (Ig) levels are typically normal or low-normal, however, patients fail to mount an appropriate antibody response to both protein and polysaccharide vaccines. We describe a patient with short stature and chronic rhinosinusitis with nasal polyps (CRSwNP), who was found to have humoral immune deficiency and a heterozygous pathogenic variant in RNU4ATAC.
Case description: A 19-year-old Bangladeshi male presented for evaluation of CRSwNP. He was born small for gestational age (36 weeks gestation) and had slow growth. His immunizations are up to date. There was no prior history of severe/recurrent infections, hospitalization, or asthma. On presentation to our office, he was short (third percentile for height) and had biphasic wheezing. Spirometry revealed reversible obstruction. Sinus cultures grew Haemophilus influenzae, Stenotrophomonas maltophilia, and Streptococcus pneumoniae. Skin testing to environmental allergens was negative, there was no peripheral eosinophilia, and IgE was low (6 KU/L). Immune work up was significant for low IgG (454 mg/dL), non-protective tetanus, and pneumococcal titers. IgA, IgM levels and lymphocyte immunophenotype were normal. CT Chest revealed right upper lobe ground glass opacity with mild bronchial wall thickening. Genetic testing identified a pathogenic variant (n.13C>T) in the RNU4ATAC gene.
Discussion: As genetic testing is becoming an essential tool in diagnosis and management of immunologic diseases, our understanding of phenotype and pathogenicity of heterozygous variants deepens. Compound heterozygous RNU4ATAC variants have been reported. Here, we present a subject with a single heterozygous RNU4ATAC pathogenic variant, who manifested clinical features of Roifman syndrome, including premature birth, short stature, and humoral immune deficiency. He also has CRSwNP

with features of both T2 and non-T2 endotypes. Absence of atopy and peripheral eosinophilia, low IgE, and positive sinus cultures are suggestive of non-T2 endotype of CRSwNP, while nasal polyposis and asthma are features of T2 inflammation. To our knowledge, symptomatic carriers and association with CRSwNP in patients with Roifman syndrome haven't been previously reported.

Keywords: Roifman syndrome, Nasal polyps, RNU4ATAC gene, Humoral immune deficiency

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Characterizing a unique B-cell precursor population as a potential diagnostic tool for WHIM syndrome and APDS

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Introduction: Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare combined immunodeficiency disease that is caused by pathogenic variants in the cytoplasmic C-terminus of the C-X-C chemokine receptor type 4 (CXCR4) gene and may manifest in incomplete clinical penetrance. The variable clinical presentation prompts the need for confirmatory procedures such as invasive bone marrow biopsies for the assessment of myelokathexis. Genetic testing to confirm a diagnosis through identification of a pathogenic CXCR4 variant is an alternative but may result in a variant of uncertain significance. We have identified a unique B-cell precursor (BCP) subset in treatment-naïve WHIM patients and may prove to be a less invasive diagnostic method. Moreover, an equivalent subset has been identified within patients with activated phosphoinositide 3-kinase delta syndrome (APDS), another immune deficiency characterized by dysregulated B-cell signaling activation. The significance of the BCP has yet to be identified but may prove to be a useful diagnostic tool.

Objectives: We aim to characterize the unique BCP population (CD19+CD10+CD38+IgM–IgD–) and the apoptotic tendencies of B-cells among WHIM and APDS patients and correlate the presence of the population with clinical status.

Methods: We analyzed the peripheral blood B-cell compartments and their tendency for apoptosis among patients with WHIM syndrome and APDS using flow cytometry. Medical record review was completed to gather demographic and treatment-related information.

Results: We identified expanded BCP subsets in blood of WHIM and APDS patients. Affected WHIM patients did not express an expansion in this compartment when on respective targeted therapies. We observed the recurrence of BCP subset in two WHIM patients nearly a year after targeted treatment was completed. Premature apoptotic tendencies of the B-cell compartment in select WHIM patients were additionally noted.

Conclusions: We identified a unique early B-cell subset that could be a noninvasive diagnostic tool and serve to monitor treatment progression in WHIM syndrome and APDS. We also characterized the premature apoptotic tendencies of B-cells in WHIM syndrome. The pathomechanism and clinical relevance that the BCP subset may offer new indirect insight in the diagnosis and management of myelokathexis and other early B-cell blocks.

Keywords: WHIM, APDS, B-cells, B-cell precursor, CXCR4

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DHR-based Flow Cytometry Beyond CGD

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DHR flow cytometry is a frequently used test to assess for NADPH oxidase function. A 6-year-old male presented with a two-year history of chronic cough unresponsive to asthma medications. Other than an occasional fever, he was otherwise asymptomatic without major infections. A chest x-ray (CXR) demonstrated interstitial and multifocal bilateral pulmonary opacities multiple times. These were repeatedly treated as pneumonia with appropriate antibiotics, but symptoms and CXR findings persisted. A CT scan demonstrated bilateral peripheral multilobar, crazy paving pattern of ground glass density with interlobular septal thickening. A limited bronchoscopy was normal. Immunological evaluation revealed normal lymphocyte subset quantitation, immunoglobulin levels and specific vaccine antibodies. A DHR test (x2) revealed an anomalous pattern consistent with what is observed in complete myeloperoxidase (cMPO) or p40phox deficiency or a hypomorphic gp91phox defect for both PMA and fMLP stimulation. Maternal evaluation of DHR was normal and genetic testing for CGD-specific genes was unrevealing. Further studies on a research protocol for specific NADPH oxidase subunit protein expression by flow cytometry (gp91, p22, p47 and p67phox) was normal. Neutrophil function was assessed by ROS (reactive oxygen species) production, which revealed a significant reduction (>90%) in intracellular ROS after stimulation with serum-opsonized zymosan (SOZ) and IgG-coated beads. Subsequent genetic testing revealed compound heterozygous variants in MPO, (c.1705C>T; c.2031-2A>C), which was confirmed as pathogenic due to absent myeloperoxidase protein expression in neutrophils by flow cytometry. Myeloperoxidase is a key regulator of the neutrophil oxidative burst and amplifies ROS production downstream of NADPH oxidase activation. The patient's clinical phenotype was atypical for cMPO deficiency and CGD. Evaluation for pulmonary alveolar proteinosis (PAP) was negative, genetically and for GM-CSF autoantibodies. This case highlights the importance of accurate interpretation of DHR results and using appropriate genetic panels to obtain a diagnosis. MPO deficiency can be confirmed by a peripheral smear analysis of neutrophils or flow cytometry.

Keywords: cMPO, Myeloperoxidase, NADPH oxidase, Flow cytometry, DHR, CGD, Reactive oxygen species, ROS, Neutrophil oxidative burst, Genetic testing

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Unique Presentation of Mycobacterium haemophilum, Associated with T-cell dysfunction after Nelarabine Administration

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Introduction: Mycobacterium haemophilum (MH), a slow-growing, fastidious microorganism, infrequently causes human infection. Yet, this non-tuberculous mycobacterium manifests as ulcerating cutaneous or subcutaneous nodular skin lesions, predominantly affecting immunocompromised individuals. Disseminated cutaneous infections with MH are exceedingly rare, documented primarily in severely immunosuppressed patients. Nelarabine, a purine nucleoside analog antineoplastic agent, leads to DNA fragmentation and T-lymphocyte/T-lymphoblastoid cytotoxicity. Yet, mycobacterium infection has not been reported in, or associated with, nelarabine use. Herein, we describe a unique case of disseminated MH in a male with T-cell acute lymphoblastic leukemia (T-ALL).
Case: A 16-year-old male with a past medical history of asthma presented with T-ALL treated with vincristine/dexamethasone/daunorubicin/PEG-ASP/methotrexate/mercaptopurine/nelarabine with remission. The last dose of nelarabine was at month 19. Prior to T-ALL, the patient denied frequent infections/hospitalizations and also denied family history of autoimmunity, consanguinity or immunodeficiency. After 34 months, the now 19-year-old presented with an erythematous skin nodule, 2-weeks of worsening shoulder pain, and development of numerous similar suppurating lesions throughout the body. Biopsies of multiple lesions revealed positive AFB-smears. Karius Test® liquid biopsy was positive for MH and Pneumocystis jiroveci. MRI revealed left shoulder cellulitis/abscess, left elbow septic arthritis, distal humeral osteomyelitis, and right tibial avascular necrosis, requiring numerous washouts in various joints. He was initially treated with ciprofloxacin/clarithromycin/rifabutin, subsequently developed septic shock, and was successfully managed with ciprofloxacin/clarithromycin/rifabutin/amikacin/imipenem. Immune evaluation included low immunoglobulins (IgG = 561/IgA = 17/IgM = 43), normal anti-IFNg, anti-GM-CSF, and HIV Ag/Ab/NAAT. Moderate lymphopenia (CD3+ = 207, CD4+ = 118, CD8+ = 99, CD19+ = 5, CD16+56+ = 12), with normal B-cell subpopulations, was accompanied by absent lymphocyte proliferative response to candida and tetanus. Primary Immunodeficiency (PIDD) Panel for 474 genes (Invitae) was negative for known mutations.

Discussion: Disseminated mycobacterium infection is uncommon with CD4>50 cells/ml. Given the patient's CD4 = 118 cell/ml, T-cell dysfunction is important to explore. Although pre-chemotherapy immunologic workup was not performed, PIDD is less likely due to history and genetics obtained. No studies have examined nelarabine-induced T-cell dysfunction. Given nelarabine's mechanism-of-action this case highlights the association of, and suspicion of, nelarabine-induced, long-term T-cell dysregulation. Further studies are needed to confirm and characterize this association. Additionally, the findings emphasize the importance of conducting a thorough immunological workup before initiating chemotherapy.

Keywords: Disseminated Mycobacterium haemophilum, T-cell dysfunction, Nelarabine

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A Quality Improvement Approach for Transition of Immunodeficiency Patients to Adult Healthcare

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Background: The Transition to Adulthood Program at Children's Mercy Kansas City is administered hospital wide to eligible patients. Patients starting at age 15 complete the annual transition readiness assessment and the medical team completes the transition discussion details form. We evaluated the compliance of the transition process in Immunology clinic. We also evaluated the effectiveness of Transition program in improving health care transition at the hospital level.
Method: We designed Post-Transition Readiness Evaluation surveys to assess program effectiveness. Surveys were designed using REDCap database for caregivers and young adults. Starting August 1, 2022, surveys were sent via text message 120 days after a transition to adult care order was placed at the last pediatric medical appointment. REDCap allowed responses to be automatically updated and text messaging helped surveys to be user friendly. We updated the functionality and frequency of survey administration. We implemented Plan-Do-Study-Act cycles to improve the completion rate of forms and surveys in Immunology clinic.
Results: To date a total of 39 surveys within seven hospital divisions have been completed: 22 by caregivers and 17 by young adults. Thirteen young adults (59.1%) attended their first medical appointment with an adult provider. Twelve (54.5%) caregivers and eight (47%) young adults stated that transition was always explained in a way that they could understand. Seven (31.8%) caregivers felt their child was very ready and ten (45.5%) felt their child was somewhat ready to transition to an adult provider. Seven (41.2%) young adults felt very ready and three (17.6%) felt somewhat ready to transition to an adult provider.
This project improved the completion of Transition Readiness survey from 0% to 44% and completion of Transition Discussion forms from 0 to 25% (Target goal 20%) from October 2022 to May 2023 in Immunology clinic.
Conclusion: Through the Transition to Adulthood Program young adults and caregivers feel prepared to transition to an adult medical provider and attend their initial medical appointment. The more complex a young adults medical care the less confident caregivers felt about transition readiness, indicating a need for on-going transition services.

Keywords: Immunodeficiency, Transition, Quality improvement

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(198)

Activated PI3Kδ Syndrome (APDS) associated with G6PD deficiency and reaction to BCG

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EGSS patient, male, cesarean section due to pre-eclampsia, term, non-consanguineous parents. Patient 1 month old hospitalized due to BCGitis associated with bicytopnea (Hb:5.6 g/dl, platelets:38000/mm3) treated with isoniazid and antibiotics. At the age of 1 year, he was hospitalized due to persistent fever, petechiae on the face, hepatosplenomegaly, cervical lymphomegaly and persistent bicytopenia. Myelogram, lymph node biopsy and several serologies were performed. He was diagnosed with Epstein-Barr virus and Cytomegalovirus infection.
During follow-up, he had tonsillitis with an ulcer-necrotic lesion treated at home with antibiotics for 14 days. After 3 weeks he developed severe diarrhea. Hospitalized with positive Clostridium difficile and with USG and CT of the abdomen with splenic nodular images. Treated with broad-spectrum antibiotics.
A 1-year-old patient presented immunoglobulin values with IgA 1.7 (< P3); IgG 1077 and IgM 183.5 (P75–97) (mg/dL) with adequate vaccine serology, associated with inversion of CD4 and CD8 with reduction of CD4 -TCD4 307; TCD8 1251; CD19 574 and NK 690 (cell/mm3) - with reduction of G6PD and high inflammatory tests (ESR = 110 mm/h (nl< 15), G6PD = 2.8 U/gHb (nl>6.7).
Genome performed with heterozygous mutation in the PIK3CD gene (c.3061G>A p.(Glu1021Lys) and homozygous mutation in G6PD (c.292G>A p.(Val98Met). Diagnosed with PI3 activated kinase delta syndrome (APDS) associated with deficiency of G6PD.
G6PD deficiency is an enzymopathy that favors the hemolysis of red blood cells, which is caused by exposure to an oxidative stressor such as infections and some drugs, which is why treatment is aimed at avoiding these agents. APDS is an inborn error of immunity associated with autosomal dominant inheritance with onset in childhood. Heterozygous gain-of-function (GOF) mutations are identified in PIK3C, which encodes the p110d catalytic subunit of phosphoinositide 3-kinase d (PIK3Kd), resulting in immune dysregulation. Characterized by the occurrence of recurrent respiratory tract infections, herpesvirus infections (mainly Epstein-Barr and

Cytomegalovirus), benign lymphoproliferation and a high incidence of lymphoma and autoimmune manifestations, such as cytopenias.
The clinical presentation of this patient suggested research into an inborn error of immunity, however, a molecular genetic study was necessary for the diagnosis. The use of selective PI3Kd inhibitors may be indicated in cases like this patient.

Keywords: APDS, G6PD, BCGitis, Activated PI3Kδ syndrome

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(199)

Provider Perspectives of Long-Term Follow-Up Care of Patients with Severe Combined Immunodeficiency

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Background: Patients with Severe Combined Immunodeficiency (SCID) remain at risk for late effects following hematopoietic cell transplantation due to factors such as genotype-specific complications, conditioning regimens, or associated immune dysregulation. However, there are limited SCID-specific long-term follow-up (LTFU) programs and characteristics of these services are poorly understood.
Objective: The purpose of this needs assessment was to query heath care providers primarily serving patients with SCID (primary SCID providers) to characterize approaches and barriers to LTFU care.
Methods: The California Severe Combined Immunodeficiency Consortium (CalSCID) provider needs assessment was a cross-sectional survey conducted online in the United States (US) in June 2022. Primary SCID providers were queried with respect to demographics, current practices, transition of care, and informational needs regarding LTFU care.
Results: A total of 75 health care providers representing 24 states completed the survey. Most health care providers (95%) practiced at an academic center (57% for at least 10 years) with 36% following more than 10 patients with SCID, 32% following 4–10 patients with SCID, and 21% following 1–3 patients with SCID. Less than half of the providers felt patients could get referrals or care coordination when needed. More than half of the practices (59%) required patients to transition care from a pediatric to an adult allergy/immunology provider. Perceived barriers to the transition from pediatric to adult care included identifying knowledgeable providers, and the lack of support staff to coordinate the transition of care. Few (< 50%) centers had LTFU SCID-specific program. Barriers to LTFU care included: lack of staff and time, distance to providers, loss to follow-up, knowledgeable subspecialists, and family resources. Participants were knowledgeable regarding LTFU needs; however, areas primary SCID providers would benefit from additional information included psychosocial impact of SCID on the patient, and how patients with SCID function in adulthood.
Conclusion: Providers highlight gaps in the SCID-specific LTFU care underscoring the need for the development of a LTFU program specific to the needs of patients with SCID and their families.

Keywords: Severe combined immunodeficiency, Long-term follow-up, Providers, Needs assessment, CalSCID

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Morna Dorsey: I have relevant financial relationships with proprietary interests: Horizon (Advisory Board); Up to Date (Royalties). The other authors have no financial relationships or conflicts of interest to report.

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(200)

Characterization of CD4+ T lymphocytes in STAT3-DN hyper-IgE syndrome patients

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Introduction: Autosomal dominant Hyper-IgE syndrome (AD-HIES) is caused by dominant negative (DN) mutations of STAT3 gene, a transcription factor that is critical for T-cell differentiation and consequently for the correct functioning of the immune system. AD-HIES patients present recurrent, severe and chronic infections by S. aureus and C. albicans, severe chronic eczema and serum high levels of Ige. While the reasons for the aberrant IgE production are incompletely understood, pathogens persist

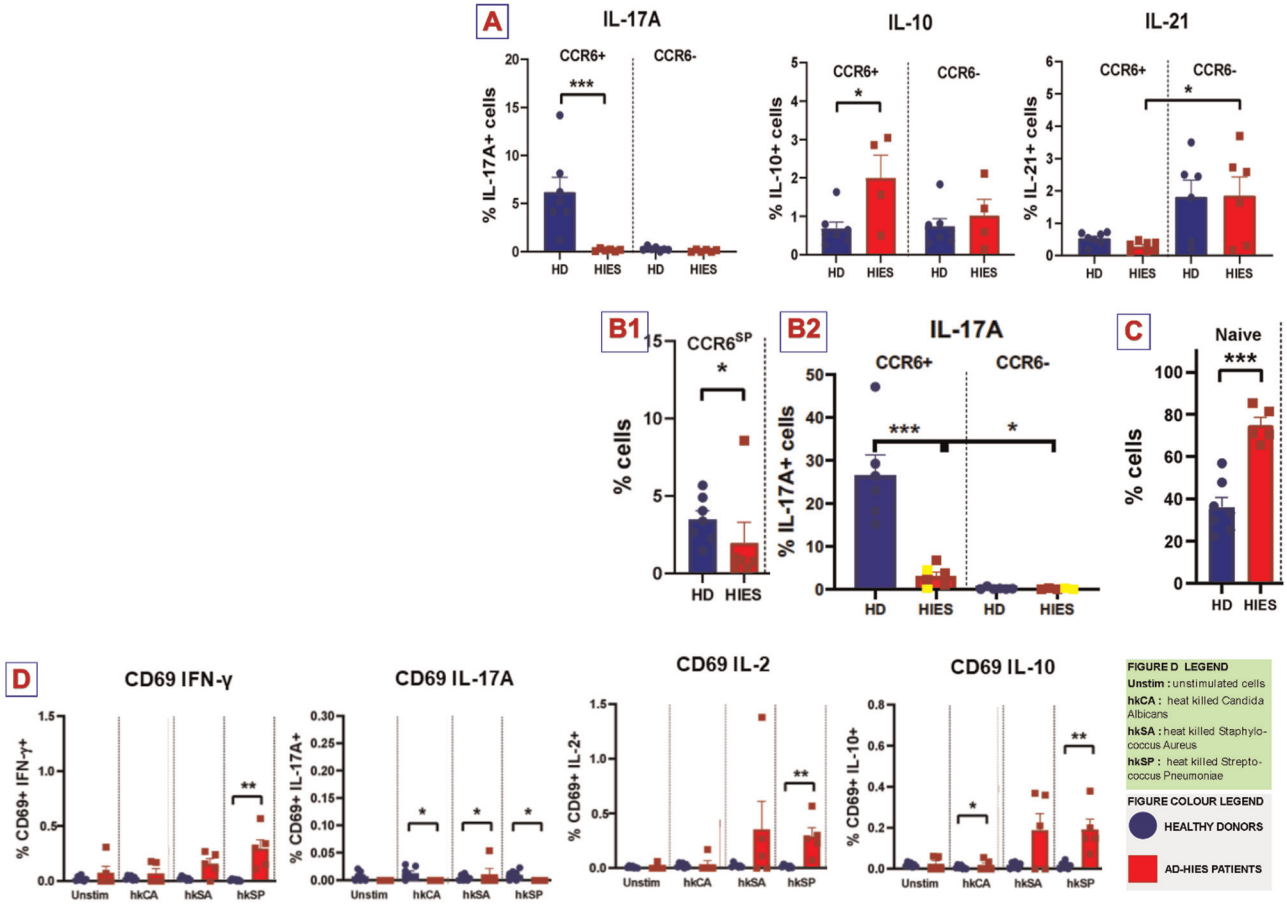

Figure. (abstract: 200) Figure A, B1 and B2, C, D - see abstract text.

because T-cells of AD-HIES patients are unable to produce key pro-inflammatory cytokines, namely Interleukin (IL)-17.

Aims:

- Characterize whether the reduced IL-17 production and uncontrolled infections with pathogens in AD-HIES patients could be caused by an incomplete Th17 differentiation of CCR6+ "pre-Th17" T-cells.
- Assess pathogen specific responses of STAT3-DN CCR6+ T-cells.

Results: In five AD-HIES patients, STAT3-DN CD4+ cells had impaired IL-17A production as expected, but produced B-helper cytokines like IL-10 and IL-21 normally. (Figure A) Furthermore, STAT3-DN CD4+ cells expressed reduced but detectable Th17 associated surface markers such CCR6 and CD161 (Figure B1). CD4+ T cells could acquire IL-17A production in vitro, although with a lower efficiency than STAT3-sufficient cells (Figure B2).
AD-HIES patients have a severe, but not complete defect in Th17-cell differentiation. Unbiased analysis indicated that there was an increased number of naïve CD4+ T cells in AD-HIES patients compared to healthy donors, suggesting a defect in the differentiation of CD4+ lymphocytes. (Figure C)
To better understand the defects of STAT3-DN cells, we evaluated their ability to response to antigens belonging to pathogens, such as S. Aureus, S. Pneumonia and C. Albicans, that cause recurrent infections in AD-HIES patients. Compared to healthy donors, STAT3-DN CD4+ cells
show an increased production of both pro- (IFN-γ and IL-2) and anti- (IL-10) inflammatory cytokines in response to heat killed S. Aureus and S. Pneumoniae. (figure D)
Conclusion: These data suggest that STAT3-DN CD4+ cells are not unresponsive to pathogens but, at the same time, underline the presence of an altered cytokine production compared to healthy donors.

Keywords: AD-HIES, STAT3-DN, CD4+, CCR6, Hyper-IgE syndrome, Pathogens, Infections, IL-10, IL-17

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(201)

Novel pathogenic MAGT1 variant identified in an adult patient with XMEN disease

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X-linked MAGT1 deficiency with increased susceptibility to Epstein–Barr virus (EBV) infection and N-linked glycosylation defect (XMEN) disease is a combined immunodeficiency with variable clinical presentation which

typically presents in childhood. Common clinical features include lymphoproliferation, autoimmune cytopenias, frequent sinopulmonary infections. Here, we describe a case of a 36-year-old man with a history of chronic lymphadenopathy and immune thrombocytopenia purpura (ITP), found to have a novel variant in MAGT1. He had no notable medical issues until two episodes of unilateral lymphadenopathy at age 15 and 17, both surgically removed with pathology indicative of Castleman's disease. At age 31 he developed chronic ITP with multiple flares despite use of multiple treatment regimens and splenectomy. Pathology from multiple bone marrow biopsies, excisional lymph node biopsies and excised spleen were negative for malignancy. Family history is negative for immune deficiency. Further studies showed increased number and percentage of CD19+ B cells, and mildly decreased CD4+ and CD8+ T cells with a normal CD4/CD8 ratio. Prior polymerase chain reaction (PCR) testing for serum EBV was negative, but low level EBV viremia has been intermittently detected with more frequent monitoring. Recent lymph node biopsy was notable for the presence of EBV and an expanded CD5+ CD20+ B cell population, suggestive of XMEN disease. Genetic testing uncovered a missense mutation in MAGT1 (NM_032121.5:c.97A>G, p.Met33Val), classified as a variant of unknown significance, but predicted to impact expression; this variant was detected in patient's mother but not in an asymptomatic maternal uncle. Notably, a different mutation at this site has been previously reported in a patient with XMEN disease. Subsequent functional testing with Carbohydrate Deficient Transferrin (CDT) showed elevated mono-oligo/di-oligosaccharide ratio, which is a pattern seen in patients with pathogenic MAGT1 variants, suggesting the mutation found was pathogenic and diagnostic of XMEN disease. This case highlights the importance of maintaining a broad differential in adults with presentations of rare diseases (i.e. Castleman's) and the need for further characterization of immune deficiencies.

Keywords: MAGT1, XMEN, EBV, Lymphoproliferation, ITP, Immunodeficiency

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(202)

Two siblings with autoinflammation and combined immunodeficiency due to autosomal recessive RNF31-loss of function

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Introduction: The linear ubiquitin chain assembly complex (LUBAC) plays crucial roles in immune NFkB signaling and cell death. Few patients with HOIL and HOIP deficiencies have been described, from consanguineous families with myopathy, combined immune deficiency and autoinflammation.

Case: A 6-year-old female patient, third child of non-consanguineous Mexican parents. Her brother died at 15 months with ganglionic tuberculosis, diarrhea, hepatosplenomegaly, anemia, and hyperleukocytosis.

She started at age one month with fever, diarrhea, extensive eczema, and cortical blindness. She was hospitalized on several occasions for persistent fever, recurrent gastrointestinal and respiratory infections, and Cytomegalovirus chronic viremia. Other isolates included: Klebsiella sp, E. coli, Giardia lamblia, and Staphylococcus haemolyticus. On physical examination, she had low weight, pallor, oral candidiasis, small cervical, retroauricular, and submandibular lymphadenopathies; hepatomegaly, and diaper rash.

Laboratory workup reported anemia, leukocytosis, neutrophilia, eosinophilia, monocytosis, and thrombocytosis, and elevated serum acute reactants; serum immunoglobulin levels were increased: IgG (913 mg/dL), IgM (115 mg/dl), IgA (179 mg/dl), with normal IgE (25 IU/ml), and IgD (5 mg/L). Flow cytometry for lymphocyte subsets were normal, as were lymphoproliferation assays.

She started on steroids, colchicine, immunoglobulin, and anti-mycobacterial antibiotics, on which she improved. Subsequently, the patient developed severe and recurrent viral, bacterial, and fungal infections: pneumoniae, gastroenteritis, esophageal candidiasis, chronic CMV hepatitis, pulmonary aspergillosis, and catheter-associated infections, as well as: epilepsy, failure to thrive, renal tubular acidosis, and exogenous Cushing syndrome. Currently, she receives monthly IVIG, colchicine, prednisolone, valganciclovir, ambulatory prophylaxis with trimethoprim/sulfamethoxazole, itraconazole, and levetiracetam. HSCT was declined by her parents.

In 2015, a sequencing panel of around 200 genes at the NIH came back negative. In 2021, whole-exome sequencing identified a compound-heterozygous genotype consisting of two single-nucleotide variants in RNF31 (HOIP): a splice-site transversion in intron 15 (c.870-1C>G), and a missense transversion in exon 16 (c.2615C>G, p.Pro782Arg), highly conserved (GERP++ RS 5.45), not found in population databases, and classified as deleterious by nearly all in silico predictors.

Discussion: HOIP deficiency has been described to cause a Combined/Autoinflammatory syndrome with pyogenic bacterial infections, with or without amylopectinosis and lymphangiectasia. Our patient and her dead brother are, to our knowledge, the third and fourth patients identified with HOIP-LOF.

Keywords: HOIP deficiency, LUBAC pathway, Inborn errors of immunity

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(203)

Seronegative Autoimmune Hepatitis Complicated by Severe Aplastic Anemia

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Case Description: A 9-year-old boy presented to the emergency department for jaundice. He had no other complaints, but initial evaluation revealed elevated liver enzymes concerning for hepatitis and he was hospitalized for further evaluation. Infectious workup was negative for Hepatitis A/B/C, EBV, CMV, adenovirus, and enterovirus. Autoimmune workup was negative for anti-liver-kidney, anti-smooth muscle, anti-mitochondrial, and ANA antibodies. However, liver biopsy showed inflammatory infiltrate consistent with seronegative autoimmune hepatitis (SAIH). Labs and jaundice improved with IV steroids and ursodiol. He was discharged with oral steroids and ursodiol. Approximately 8-weeks after

initial presentation, liver enzymes remained normal, but he was found to have thrombocytopenia and leukopenia. Despite a steroid wean and a trial off ursodiol, platelets and WBC continued to downtrend. The patient underwent a bone marrow biopsy that was hypocellular (< 10%), consistent with severe aplastic anemia (SAA). He required prophylactic antimicrobials and multiple hospitalizations for blood product transfusions and treatment for neutropenic fevers. After conditioning with cyclophosphamide and total body irradiation, the patient then underwent hematopoietic stem cell transplant (HSCT).

Discussion: This case highlights SAA as a potential complication following acute hepatitis, despite an unclear etiology. Despite the negative infectious and autoimmune work-up, liver biopsy findings were consistent with autoimmune hepatitis. Seronegative refers to when no autoantibodies are identified, but features of autoimmune hepatitis still present. It remains unclear if SAIH is due to laboratory error or a different clinical entity that requires further understanding. Hepatitis-associated aplastic anemia (HAAA) is a rare, life-threatening complication that occurs weeks to months after the onset of hepatitis. It is believed to be secondary to inappropriate T-cell-mediated immune response. Despite the rarity of HAAA, it appears more frequently in seronegative cases. Though early corticosteroid treatment may prevent SAA, HSCT remains 1st-line treatment if SAA develops.

Conclusion: Seronegative autoimmune hepatitis remains a relatively unknown entity in regards to its diagnosis and treatment. Severe aplastic anemia appears to be a frequent life-threatening complication of SAIH. Thus, close monitoring for signs and symptoms of aplastic anemia is crucial. Corticosteroids may be considered, but patients who develop SAA will likely require treatment with immunosuppressive therapy and HSCT.

Keywords: Autoimmunity, Seronegative, Immune dysregulation, Aplastic Anemia, T-cell mediated, Hepatitis

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(204)

Diagnostic Approach to complex Common Variable Immunodeficiency Patient With Phosphoinositide 3-Kinase Catalytic Domain Variant of Uncertain Significance

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Introduction: Activated phosphoinositide 3-kinase delta syndrome (APDS) comprises a variable combination of immunodeficiency, immune dysregulation, and lymphoproliferation. Due to improved genetic testing accessibility, the diagnoses of variants of uncertain significance (VUS) have markedly increased among patients with inborn errors of immunity (IEI), notably in the PIK3CD and PIK3RD genes associated with APDS. Here, we present a 59-year-old female with complex Common Variable Immunodeficiency (cCVID) harboring a novel PIK3CD VUS. We aim to assess the pathogenicity of the VUS and connection to cCVID.

Case Presentation: Our 59-year-old patient has been followed by a multidisciplinary care team comprised of hematologist, immunologist, oncologist, and endocrinologist for a myriad of medical complications since early childhood. Immunodeficiency was reflected in recurrent bacterial infections and a diagnosis of hypogammaglobulinemia alongside features of immune dysregulation such as arthritis. Diagnosed with cCVID at age 53, she required treatment utilizing monthly immunoglobulin replacement and azithromycin prophylaxis. Persistent symptoms of frequent infections, chronic pain and fatigue prompted further investigation. Genetic testing at age 54 revealed a heterozygous PIK3CD VUS (c.2320G>A; p. Val774Met) with autosomal dominant inheritance. This variant is observed in the general population at an overall allele frequency of 0.0033%. Computational algorithms yielded conflicting results on the effect on protein function, necessitating immunophenotyping and functional analysis. Immune evaluation unveiled hallmark features of active APDS, including increase in transitional B cells (8.7%), diminished memory B cell subset (9.62%), a dominant IgMhi IgDlo non-switched subset (2.9%), and a reduced naïve CD4 compartment (25%). Family testing revealed the same VUS in the patient's 35-year-old son, exhibiting relatively benign symptoms including recurrent ear infections. Comparative immunophenotyping and functional testing for phosphorylated AKT (pAKT) are planned to establish pathogenicity of this VUS.

Discussion/Conclusion: APDS is a rare syndrome which typically incurs a 12-year delay of diagnosis. Yet, with improved access to genetic screening more patients may emerge with a VUS requiring immunophenotyping and functional testing. Comprehensive immunophenotyping and functional assays are important precursors to patient advancement to targeted therapy with PI3K inhibitor. Post-treatment, ongoing immunophenotyping can monitor response to therapy and provide further evidence for APDS.

Keywords: Activated phosphoinositide 3-kinase delta syndrome, Complex common variable immunodeficiency, Variant of uncertain significance

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(205)

Prospective identification of inborn errors of immunity in a 104-patient autoimmune cytopenia cohort

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Introduction: We describe a prospective cohort of autoimmune cytopenia (AIC) patients at an academic center. Early identification of IEI among AIC patients allows early targeted therapy and reduces morbidity from immune dysregulation. Among those with AIC, biomarkers are needed to identify patients with IEI who may benefit from genetic testing.
Methods: IEI was defined by laboratory results, genetic testing, and clinical phenotype. IEI genetic panels were obtained through Invitae/Blueprint. Flow cytometry protocols were developed to assess specialized lymphocyte subsets that may correlate with AIC and/or IEI. Lipopolysaccharide (LPS) and soluble IL-2 receptor (sIL2-R) serum levels were measured by ELISA as biomarkers for antigen load and immune activation, respectively.
Results: We enrolled 104 patients. Fifty-three (51%) of AIC patients had IEI; 51 (49%) had AIC-only, without IEI. Seventy-nine percent of patients underwent genetic testing for IEI. Among all AIC patients, 20%, 5% and 13% had a pathogenic variant, likely pathogenic variant, or variant of uncertain significance, respectively; 41% tested negative; 21% were not tested. Pathogenic variants, in order of frequency were partial DiGeorge syndrome, FAS, NFKB1, CTLA4, KMT2D, PI3K, POLE-1, and CYBB. Flow cytometry revealed expansion of T follicular helper (Tfh), TCRαβ-DNT, and CD19hi21lo cells in IEI compared to AIC-only or healthy donors. Expansion of Tfh cells was found primarily in CVID (genetically undefined), NFKB1, and CTLA4 patients. Expansion of TCRαβ-DNTs was seen in ALPS/ALPS-like and CVID-undefined patients. CD19hi21lo expansion was seen in NFKB1 and CVID-undefined patients. Soluble IL2-R distinguished genetically defined vs undefined IEI, and IEI vs. AIC-only patients. LPS did not distinguish AIC-IEI from AIC-only but did distinguish AIC from healthy donors. Evans syndrome and autoimmune hemolytic anemia (AIHA) were more common in IEI vs AIC-only patients ([45% vs 29%] and [9.4% vs. 6%], respectively).
Conclusions: Panel genetic testing for IEI, flow cytometry for specific immune cell subsets (Tfh, TCRαβ-DNTs, and CD19hi21lo cells), and sIL2-R assay aids identifying IEI in AIC patients, thus facilitating targeted and possibly definitive therapy. Over half of AIC patients had underlying IEI; 25% had pathogenic or likely pathogenic IEI variants. LPS was a marker for AIC but not for AIC patients with IEI.

Keywords: Autoimmune cytopenia, Inborn errors of immunity, Evans syndrome, Immune dysregulation, Anemia, Thrombocytopenia, Neutropenia

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(206)
Oral Pathology in STAT3DN Hyper IgE Syndrome

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Background and Aims: STAT3 dominant negative (DN) Hyper IgE Syndrome is a primary immunodeficiency resulting in frequent sinopulmonary infections, eczema, musculoskeletal and vascular changes. Well described oral manifestations include retained primary teeth and high arced palate. We have increasingly recognized that these patients also have oral lesions requiring biopsy and painful aphthous ulcers that interfere with quality of life. Aphthous ulcers are well described in STAT1 GOF disease and in part may be similar due to increased STAT1 expression in those with STAT3 DN HIES and/or due to abnormal tissue remodeling. The aim of this project is to determine the frequency and types of oral pathology.
Methods: Medical records were retrospectively reviewed for 164 patients with STAT3 DN HIES.
Results: Aphthous ulcers were seen in 83/158 (53%); Herpes simplex virus (HSV) was excluded by PCR in 12 patients; one had a positive HSV lesion. 9 of 83 (11%) patients with oral ulcers also had autoimmune disease. Aphthous ulcers were treated with topical steroids for 39 patients. Oral biopsies were obtained for 15 patients. 6 of 15 (40%) biopsies showed chronic inflammation, 4 showed hyperkeratosis, 2 traumatic ulcerative granuloma with stromal eosinophilia, 2 with squamous papilloma, and 2 with pyogenic granuloma. One patient with concurrent eosinophilic esophagitis was treated with mepolizumab with resolution of eosinophilic oral lesion. One squamous papilloma resolved with allogeneic bone marrow transplant.
Conclusions: Aphthous ulcers are common in STAT3DN Hyper IgE Syndrome and are frequently painful leading to decreased oral intake. Similar ulcers are seen in STAT1 GOF disease suggesting that the ulcers are related to increased STAT1 expression. Oral lesions related to abnormal inflammation and proliferation were also seen, some with increased eosinophils. Aberrant wound healing may contribute to the development of these lesions. Oral cancer has not been described in this population, but biopsy should be done to confirm diagnosis.

Keywords: STAT3 DN Hyper IgE syndrome, Aphthous ulcer, Oral pathology

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(207)
The Use of Tofacitinib and Upadacitinib in Very Early Onset IBD

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Over the past decade, the incidence of inflammatory bowel disease (IBD) onset under 6 years (very early onset IBD or VEOIBD) is increasing. When compared with conventional onset IBD, VEOIBD has distinct characteristics such as higher likelihood of underlying inborn errors of immunity (IEI),

severe disease, and poor response to conventional IBD medications. Here, we describe our experience with oral JAK-inhibitors in managing patients with VEOIBD. We performed a retrospective chart review of patients with VEOIBD on JAK-inhibitors followed at a multidisciplinary pediatric intestinal immunology clinic. We identified five (n = 5) patients with VEOIBD on JAK-inhibitors tofacitinib or upadacitinib. All patients in our cohort presented with bloody stools, anemia, elevated fecal calprotectin, elevated CRP and hypoalbuminemia. All five patients had pancolitis with one having upper GI tract involvement.

All patients in our cohort failed to respond to several medications, such as tacrolimus and sirolimus (3/5), sulfasalazine (5/5), azathioprine (1/5), anti-TNF antibody (5/5), vedolizumab (3/5), and ustekinumab (5/5). Four patients are on combination therapy with ustekinumab and tofacitinib and one patient is on monotherapy with upadacitinib. The duration of treatment with tofacitinib ranged from 34 to 507 days. Duration of exposure to upadacitinib is 124 days.

After initiation of JAK inhibitor, patients showed a brisk clinical response within 2 weeks. Four had an improvement in hemoglobin, albumin, CRP and calprotectin. Weight and height improved in all patients.

Genetic analyses in our cohort did not identify any IEI. Two patients have mutations thought to be suspicious. This includes one patient with a small duplication on chromosome 10 causing copy number gain in IL2RA and IL15R which has been seen in another VEOIBD patient. Another patient has RAB27A mutation shown to have a partial dominant negative effect.

In our cohort, use of JAK inhibitors tofacitinib and upadacitinib for patients with severe and refractory disease has been both safe and effective. This effect seems to be independent of the location, extent of intestinal involvement, and the genetic cause of disease given that no clear monogenic disorders have been found.

Keywords: Primary immunodeficiency, Inflammatory bowel disease, Tofacitinib

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(208)

A Subtle Clinical Presentation of LAD1 Deficiency

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Background: Leukocyte adhesion deficiency (LAD-1) is an autosomal recessive in disorder of the innate immune system caused by pathologic variants in ITGB2., leading to decreased surface expression of CD18. CD18 is critically important in the ability of neutrophils to appropriately migrate from the blood vessels to the extravascular space. LAD-1 typically presents early in infancy with infections of the mucosa, skin and soft tissues caused by Staphylococcus and gram-negative species.

Case Presentation: Here, we report the case of a 3-month-old male who was transferred to our hospital following multiple presentations to an outside hospital He initially reported to the outside hospital at 6 weeks due to fever. The initial CBC was significant for leukocytosis to 51.7×10^3/uL with predominant neutrophilia (ANC 39.8×10^3/uL). Of note, he continued to have umbilical cord attachment, without signs or symptoms of omphalitis. He was ultimately found to have acute otitis media. By the time of transfer, he had had 3 total episodes of otitis media including ruptured tympanic membrane. Imaging was performed and was found to be significant for some opacification of his mastoid cells. Though patients of his age typically do not have formed sinuses, imaging showed signs of sinusitis. Genetic testing revealed a homozygous change in intron 6 of the ITGB2 gene, specifically c.741+1G>A (splice donor). This represents a loss of function mutation of the beta-2 integrin protein. Confirmatory, flow cytometry demonstrated 0% CD11b and 0.3% CD18. CD18 activity less than 2% activity of CD18 are classified as severe and suffer significant infections. These patients often die in infancy without transplant. He underwent matched sibling donor bone marrow transplant at 5 months of age. His initial engraftment studies at 30 days were: 94% total, 100% myeloid, 6% T cells, insufficient quantity B cells.

Discussion: Although patients with severe LAD-1 have classically been described to present with skin and other soft tissue infections such as omphalitis associated delayed umbilical cord separation, this is patient's primary presenting symptom was recurrent otitis media. However, his marked leukocytosis led to clinical suspicion for primary immune deficiency and genetic testing.

Keywords: Leukocyte adhesion deficiency, Leukocyte adhesion deficiency-type 1, Primary immunodeficiency, Leukocytosis, Omphalitis

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(209)

Aggressive immunosuppressive therapy is beneficial early on in reducing autoreactive T cell proliferation in Omenn syndrome/Severe combined immunodeficiency

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Omenn syndrome (OS), a subset of severe combined immunodeficiency (SCID), results from hypomorphic missense mutations in recombinase activating genes 1 and 2 causing reduced oligoclonal T cell development and uncontrolled autoreactive T cell proliferation. This autosomal recessive disorder manifests in infancy with exfoliative erythroderma, alopecia, eosinophilia, lymphadenopathy, hepatosplenomegaly, and elevated IgE levels. Treatment involves immunosuppression, nutritional optimization, and bone marrow transplant (BMT). positive outcomes after the BMT and lead to rejection. Due to various toxicities with immunosuppression especially in newborns, providers are usually cautious with aggressive treatment. Our case, a 34w1d preterm female infant with a strong family history of OS demonstrated significant improvement with aggressive immunosuppressive therapy.

The patient was born with significant erythroderma with sloughing, hepatomegaly and alopecia. Given her exam findings and strong family history of RAG 1 SCID (5 of 9 siblings, 2- s/p BMT), SCID with OS was strongly suspected. Genetic testing confirmed homozygous RAG1 mutation, T-B-NK+ SCID phenotype with normal T and B cells, concerning for maternal engraftment. Skin biopsy revealed extramedullary hematopoiesis with an eczema-like rash seen in OS/SCID. Despite initial IVIG and isolation

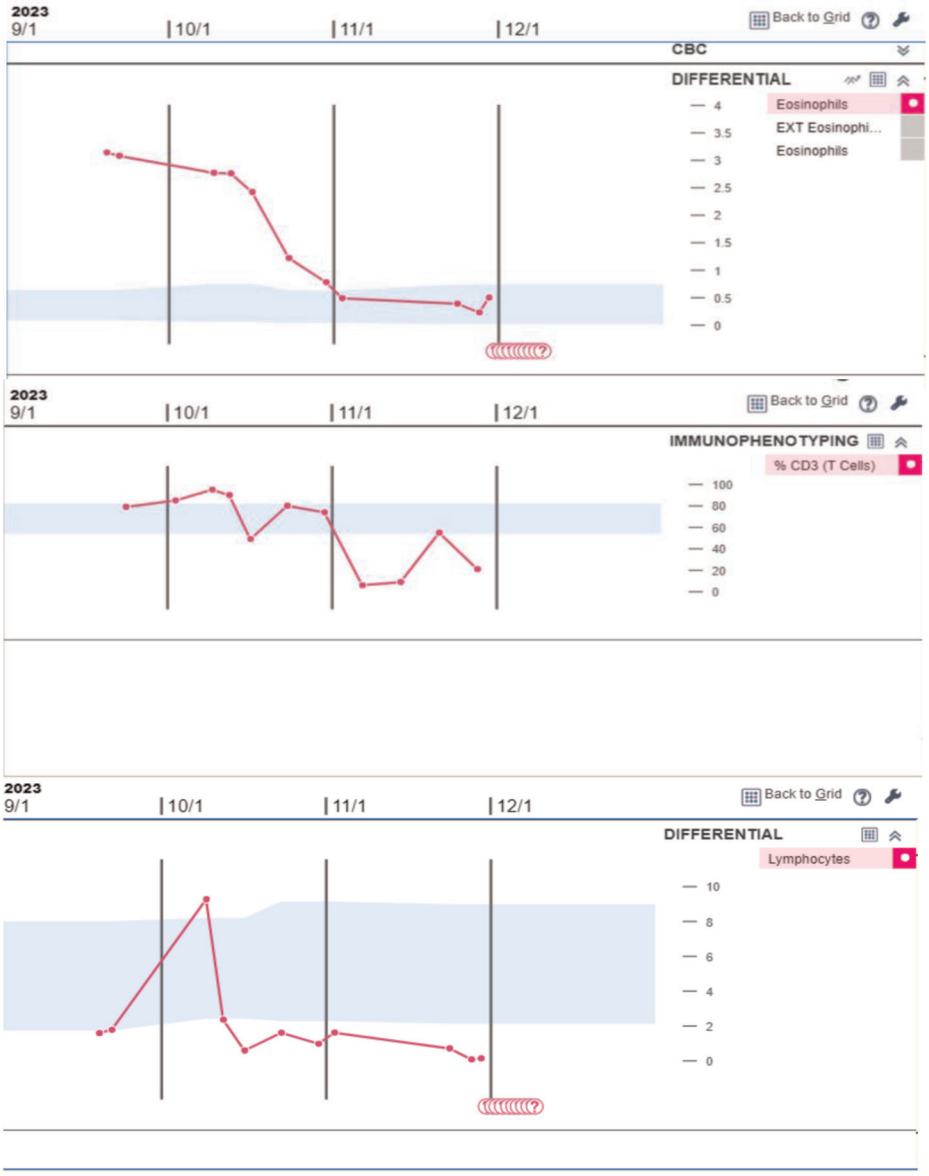

Figure 1. (abstract: 209) Trend of various immune cells over time.

measures, progressive T cell lymphocytosis and erythroderma persisted. Prednisone, antimicrobials, and IVIG provided no relief, prompting the addition of tacrolimus and later anti-thymocyte globulin (ATG) (figure 1 & 2). ATG was increased based on modest clinical improvement, to further achieve undetectable cell counts. Labs were obtained to differentiate between maternal engraftment and autoreactive T cells. Eventually, the quantitative lymphocyte panel appeared to be her own cells, however, this did not change management nor the goal for immunosuppression. Clinical improvement followed, and the patient underwent a successful matched sibling donor BMT at 9 weeks. She was conditioned with fludarabine, Campath and melphalan instead of busulfan given the high risk of VOD.

In conclusion, OS/leaky SCID's severe autoreactive T cell proliferation necessitates early aggressive immunosuppressive therapy before transplant to curtail tissue infiltration and organ damage, and rejection post transplant. This could significantly improve outcomes for SCID patients pre and post transplant.

Keywords: Severe combined immunodeficiency, Omenn syndrome, Immunosuppressive therapies

Disclosures: The authors have no financial relationships or conflicts of interest to report.

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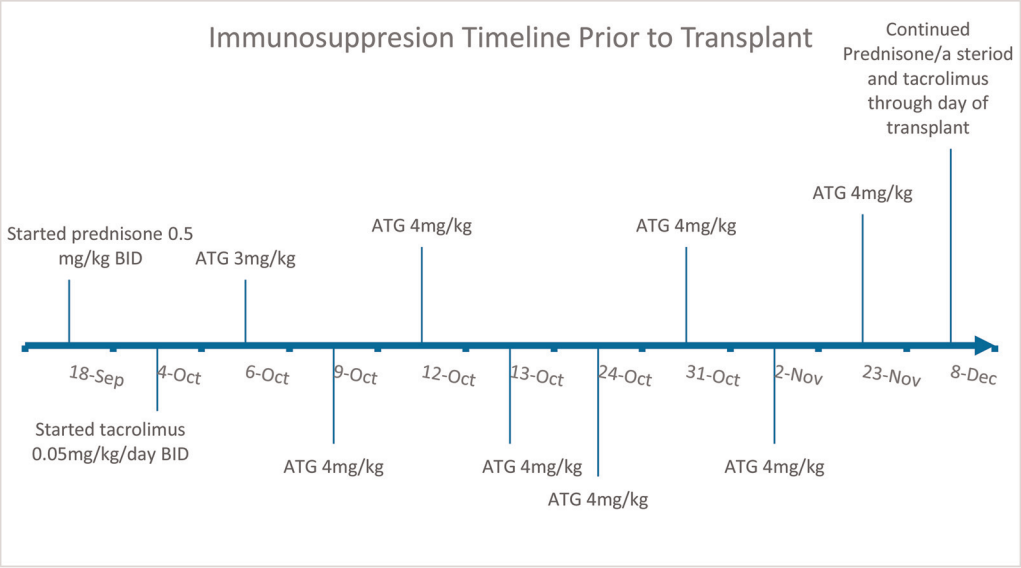

Figure 2. (abstract: 209) Immunosuppression timeline. When matched with figure 1, it shows that when more immunosuppression was on board, the immune cells remained low to undetectable.

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