6th APSID Congress

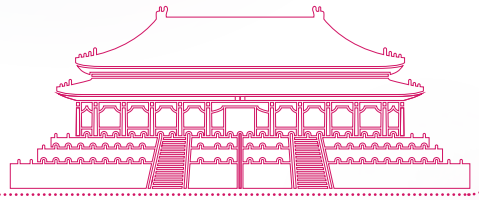
3rd National Congress of Inborn Errors of Immunity & National Forum on Pediatric Immunology

Beijing, China 11-13.04.2025

Event Schedule

APSID School

7:00 - 8:15	REGISTRATION
8:15 - 8:30	INTRODUCTORY SESSION
8:30 - 9:04	LOW AND HIGH ANTIBODIES: STRIKING THE BALANCE
9:18 - 10:12	SCID OR OTHER CONDITIONS REQUIRING TRANSPLANTS
10:30 - 10:50	TEA/COFFEE BREAK
11:00 - 11:42	COMBINED IMMUNODEFICIENCIES
12:00 - 12:42	DEFECTS IN INTRINSIC AND INNATE IMMUNITY
13:00 - 14:00	LUNCH SYMPOSIUM: IMMUNOLOGICAL TESTS
14:00 - 14:42	IMMUNE DYSREGULATIONS
15:00 - 15:42	AUTOINFLAMMATORY AND AUTOIMMUNITY
16:00 - 16:20	TEA/COFFEE BREAK
16:30 - 17:04	IEI IN ADULTS
17:18 - 17:52	GASTROINTESTINAL DISEASES IN IEI
18:06 - 18:26	QUIZ WITH PRIZES
19:06 - 21:00	IEI SCHOOL DINNER



"To view a specific abstract, simply click on the session listed on the agenda page. The link will take you directly to the corresponding abstract page."

Beijing, China 11-13.04.2025

Prof. Hirokazu Kanegane

President, APSID
(2024-2028)

Professor, Department of Child Health and Development, Tokyo Medical and Dental University, Tokyo, Japan.

Our Society, Asia Pacific Society for Immunodefiencies (ASPID) has been in existence for more than 10 years, since its launching in 2015. Our goal is to help more patients in the Asia-Pacific region to be diagnosed and treated appropriately by spreading knowledge of primary immunodeficiency (PID)/inborn errors of immunity (IEI). The first school was held in November 2015 in Hanoi, Vietnam. At that time, 29 young physicians from 10 countries gathered to have lectures from internationally renowned teachers. Subsequently, the school has been held in Kuala Lumpur (2016), Chongqing (2017), Bangkok (2018), Hong Kong (2019), Online (2021) and Tokyo (2024), and this time it will be held in Beijing, China. Many attendants have gathered here so far.

We hope that you will take this opportunity to brush up your knowledge of PID/IEI through discussions with lecturers and young physicians from other countries and take this opportunity to study to become an opinion leader in your own country in the future. Case reports may lead to clinical or basic research. We would be honored if you could take this opportunity to expand research as well as clinical practice.

Prof. Huawei Mao

Chairman, 6th APSID Congress and 3rd National Congress of Inborn Errors of Immunity & National Forum on Pediatric Immunology
Head, Department of Immunology

Beijing Children's Hospital of Capital Medical University, Beijing, China

Dear Colleagues and Friends,

Brimming with anticipation and excitement, on behalf of the Department of Immunology at Beijing Children's Hospital (BCH) and the Department of Paediatrics & Adolescent Medicine at the University of Hong Kong (HKU) as APSID's BCH-HKU Joint Center of Excellence (CoE), we extend to you our most sincere invitation to join us at the upcoming 6th APSID Congress and 3rd National Congress of IEI & National Forum on Pediatric Immunology.

This Congress will be held in Beijing, where history and modernity shine in harmony, blending thousands of years of tradition, cultural enrichment, scientific innovation, technological advancements, and particularly in April, the blooming vitality of the springtime. Together, we gather to share our evolving understanding and knowledge in inborn errors of immunity as well as explore the future of human health from a broader perspective.

At times, our world can be set by boundaries, yet here, we shall transcend them. It is our belief that all nations should collaborate to advance human health and cross disciplines to have impactful discoveries. As the host of this Congress, APSID's BCH-HKU Joint CoE stands alongside our peers to facilitate exchange and collaboration in the field of immunology for the wellbeing of children and adult patients worldwide.

APSID's BCH-HKU Joint CoE is dedicated to providing a people-oriented environment that promotes patient-centered care, individualized trainee-specific education, and acquisition of new information that benefits our society. At this Congress, we will share with each other the latest research findings, under the premise of our respect for life and aspiration for a better future. We will build an open, inclusive, and mutually beneficial academic platform, where every participant can find inspiration and friendship.

We look forward to this 6th APSID Congress and 3rd National Congress of IEI & National Forum on Pediatric Immunology in Beijing, where we aim for each day that our guests spend to be filled with joy and adventure. Let us join hands to forge a bright future for human health!

Welcome to Beijing!

Dr. Jaime S Rosa Duque

Secretary General, 6th APSID Congress and 3rd National Congress of Inborn Errors of Immunity & National Forum on Pediatric Immunology

The University of Hong Kong, Hong Kong, China

Welcome all of you to this 6th APSID Congress and 3rd National Congress of Inborn Errors of Immunity & National Forum on Pediatric Immunology Congress here in 2025! My biggest hope is that this Organizing Committee and I have prepared this platform in the best way for you all to share amongst each other your work, achievements, passion, personal interests, and friendship. Whatever your needs are, let us know and we are here to help you. Please enjoy these 3 days at this conference and your time in Beijing, China!

Dr. Narissara Suratannon

Education and Training Working Party Chair (2023-2026)

Assistant Professor, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

On behalf of the Asian Pacific Society of Immunodeficiency (APSID), it is my great pleasure to welcome you to the APSID School. This gathering represents more than just a meeting—it is a shared commitment to advancing the care, diagnosis, and understanding of inborn errors of immunity (IEI) across the Asia-Pacific region.

As the Educational Chair of APSID, I am deeply proud of how far we've come together. Our school brings together a diverse group of clinicians, scientists, and trainees, all dedicated to improving outcomes for patients with IEIs. Through case discussions, faculty lectures, and discussion, we hope to foster an environment of inquiry, mentorship, and collaboration.

I would like to thank our esteemed faculty for sharing their time and expertise, and to each of you for your enthusiasm and dedication to learn. I encourage you to make the most of this opportunity—not only to absorb knowledge but also to build lasting friends and connections that will strengthen our community for years to come.

Welcome once again, and I look forward to a fruitful and inspiring APSID School ahead.

APSID SCHOOL

6th APSID Congress
3rd National Congress of Inborn Errors of Immunity & National Forum on Pediatric Immunology

LOW AND HIGH ANTIBODIES:
STRIKING THE BALANCE

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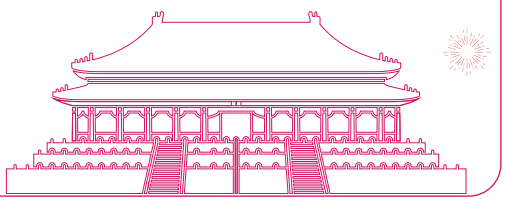


Hyper IgM Syndromes: Whom to Blame, B cells, T cells, or Other Players?

Prof. Hans Ochs

ESID Lifetime Achievement Awardee
and CIS Presidential Awardee
University of Washington Seattle, US

Atypical Kawasaki Illness: Unraveling an Underlying Immunodeficiency

Nura Hulwana Bukhari[1,2], Che Syahida Silmi Che Abdul Rahman[1,2], Syazwani Rahim[1,2], Khairoon Nisa Mohamed Nashrudin[1,2], Mohd Azri Zainal Abidin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA.*

Introduction: Hyper-immunoglobulin M (HIGM) syndrome is a rare primary immunodeficiency disorder characterised by defective immunoglobulin class switch recombination, resulting in low levels of IgG, IgA, and IgE, while IgM levels remain elevated. Affected individuals are at significant risk of recurrent infections and immune dysregulation.

Case Presentation:
We report a case of a 6-year-old Chinese girl with recurrent febrile illnesses and worsening allergic rhinitis since infancy. At 1.5-year-old, she developed persistent high-grade fever and multiple lymphadenopathies. She was treated for atypical Kawasaki disease due to elevated CRP (185 mg/L), coronary artery dilatation, and mild pericardial effusion on echocardiography. She received intravenous immunoglobulin (IVIG) and IV methylprednisolone, leading to improvement and discharge after 10 days. Follow-up imaging showed normalised coronary artery dimensions. Further evaluations for frequent infections revealed persistently elevated IgM, reduced IgG and IgA levels, and significantly decreased class-switched memory B cells and plasmablasts. Genetic analysis identified two heterozygous AICDA mutations (Exon 1 deletion and c.295C>T [p.Arg99*]), consistent with both autosomal dominant and recessive forms of HIGM. Each of her parents carried one of the mutated genes. Four-weekly IVIG therapy was commenced with the aim of maintaining IgG levels above 8 g/L. While the frequency of infections reduced with treatment, she experienced an allergic reaction during one infusion, which was successfully managed with premedication in subsequent cycles.

Discussion: Mutations in the AICDA gene, encoding activation-induced cytidine deaminase (AID), cause HIGM syndrome type 2. Recurrent sinopulmonary infections are common and may progress to bronchiectasis and chronic sinusitis. Immune dysregulation in HIGM2 may also contribute to vascular abnormalities, as seen with coronary artery dilatation in this patient.

Conclusions: This case underscores the importance of early genetic diagnosis to guide therapy. Regular IVIG infusions remain the cornerstone of management, but complications such as adverse reactions, coronary artery involvement, and new symptoms require continuous follow up and multidisciplinary care.

Immunological profiles of the patient

Investigation	Results	Normal range
Inflammatory markers CRP (mg/L)	185	< 5
Autoimmune workup ANA DsDNA	 Negative Negative	
Complement (g/L) C3 C4	 1.19 0.26	 0.5 - 0.9 0.1 - 0.4
Immunoglobulins (g/L) IgG IgM IgA	 <0.07 2.94 <0.27	 4.3 - 13.4 0.2 - 1.8 0.19 - 2.2
IgE (kU/L)	21	<100
Lymphocyte subsets (x 10^6) T cells (CD3+) B cells (CD19+) CD4 (CD4+) CD8 (CD8+) NK cells (CD16+/CD56+)	 3943 1159 2455 955 552	 1800-3000 700-1300 1000-1800 800-1500 200-600
B cell panel (x 10^6) CD19+ B cells Naïve B cells CD19+ IgD+ CD27- Transitional CD38+ IgM++ Total memory CD27+ Class-switched CD27+ IgM- IgD- Non-switched CD27+ IgM+ IgD+ Plasmablasts CD38+ IgM-	 665.8 (15.74%) 307.53 (46.19%) 17.31 (2.6%) 351.41 (52.78%) 3.26 (0.49%) 334.23 (50.2%) 0.47 (0.07%)	 400-1700 (14-29%) 280-1330 (54-88%) 20-200 (3.1-12%) 50-390 (7.8-37%) 20-220 (4.7-21%) 20-180 (2.7-20%) 10-50 (0.6-4%)
Antibody responses to vaccine antigens Tetanus toxoid, IgG (IU/ml) Pneumococcal polysaccharide, IgG (mg/L)	Pre 0.40 17.01	Post 0.27 7.70

What Treatment Should be Used in a Patient with Chronic Mucocutaneous Candidiasis?

Nguyen Ngoc Tin[1], Shu Zhou[2], Sun Jiapeng[2], Ma Jing[2], Han Tongxin[2], Mao Huawei[2]

1 *Children's Hospital No.1, Ho Chi Minh City, Viet Nam*
2 *Beijing's Children Hospital, Capital Medical University, Beijing, China*

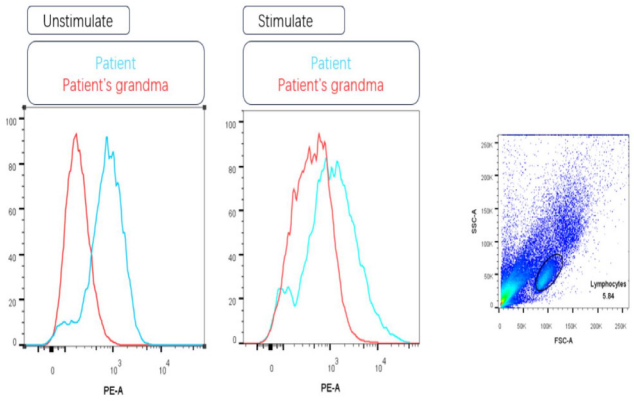
Introduction: Heterozygous AD gain-of-function mutations in STAT1 lead to various clinical presentations, with at least 125 variants reported.

Case Presentation:

We are presenting a 6-year-old girl experiencing chronic onychomycosis, chronic diarrhea, recurrent pneumonia, otitis media, acute malnutrition, anemia, and EBV infection since the age of three without any remarkable family history. Microbiological results identified multiple pathogens from previous infections: P.aeruginosa, S.maltophilia and Mycoplasma in sputum, E.faecium and S.epidermidis in blood, and Candida on nails. Notably, serum gammaglobulin levels were low, with the following results recorded: IgA 0.05g/L, IgG 1.42g/L, and IgM 0.051g/L. The lymphocyte subset showed a significant reduction in the absolute count of B cells (49cells/μL), with their proportion at 2.4%. Additionally, the counts of TCD4+ EM and NK cells were also low with 9 and 90 cells/μL, respectively. KREC could not be detected in the peripheral blood specimen, while TREC assay was normal (48.91copies/ μL). T helper subset (Th1, Th2, Treg, Th17) was within normal range. Laboratory tests for autoimmune seromarkers and endocrinopathies did not detect any abnormalities. Genetic testing requested due to strong suspicion of IEI has revealed a STAT1 variant: c.1169T>C (p.M390T), which is classified as VUS according to ACMG. Therefore, STAT1 phosphorylation assay was ordered, and subsequently yielded hyperphosphorylation of STAT1 in the patient sample compared to healthy control, confirming the gain-of-function of this variant. The patient experienced recurrent episodes of severe diarrhea requiring hospitalization while receiving regular IVIG transfusions. Consequently, she was started on ruxolitinib, which led to significant improvements in her gastrointestinal symptoms.

Discussion&Conclusions:

Hypogammaglobulinemia is among rare manifestations in STAT1 GOF patients, which has been documented to be associated with only 3 variants thus far. The absence of KREC supports the hypothesis of impaired B-cell differentiation. This condition has not been reported to be related to the variant carried by our patient before.



Eczema, Dysmorphism and Pneumatoceles

Ho Wai Koo[1,2], Khairoon Nisa Mohamed Nashrudin[2,3], Ciang Sang Tan[2,4], Mohd Azri Zainal Abidin[2,3], Intan Hakimah Ismail[2,3]

1 *Department of Paediatrics, Hospital Pulau Pinang, Pulau Pinang, MALAYSIA.*
2 *Advanced Medical Research in Allergy & Clinical Immunology (AMRAC), Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA.*
3 *Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA.*
4 *Department of Paediatrics, Hospital Melaka, Melaka, MALAYSIA.*

Introduction: Autosomal dominant Hyper-IgE syndrome (AD-HIES) is an inborn error of immunity caused by dominant negative mutations in the signal transducer and activator of transcription 3 (STAT3) gene, impairing the protein's activity as a transcription factor. Its features include characteristic facies, rash, recurrent skin infections, recurrent pneumonias and a variety of musculoskeletal and connective tissue abnormalities. Recurrent pneumonia leading to the development of pneumatocele is typical and strongly linked to early death in this population.

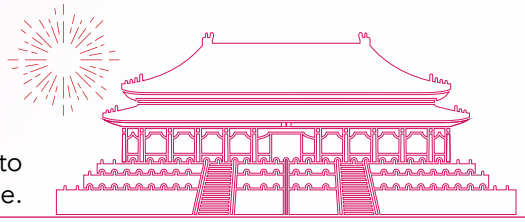
Case Presentation:

We report a case of a 12-year-old Malay girl diagnosed with STAT3-related AD-HIES at the age of 7. She developed bronchiectasis at the age of 4 and has been receiving immunoglobulin replacement therapy with antimicrobial prophylaxis. A surveillance CT scan of the thorax revealed multiple pneumatoceles in both lungs, which were initially managed with 'watchful waiting'. She had a tumultuous clinical progression with recurrent episodes of pneumonias and abscesses, including a severe infection of the left lung pneumatocele, necessitating CT-guided aspiration. Subsequently, she underwent a left lower lobe lobectomy for the multiple pneumatoceles. Unfortunately, she continued to suffer from recurrent lung infections. Her latest spirometry demonstrated a mixed restrictive and obstructive lung disease pattern with moderate small airway obstruction. A recent CT thorax revealed an increase in the number of pneumatoceles.

Discussion & Conclusions: Pneumatoceles are a type of parenchymal lung damage resulting from frequent, severe infections or an exaggerated inflammatory response caused by an aberrant and often dysregulated immune system. The pneumatocele can serve a nidus for colonisation and re-infection by pathogens such as Pseudomonas aeruginosa, Staphylococcus aureus and Aspergillus sp. Despite the severity of pulmonary disease in patients with HIES, there is limited literature available on therapeutic management strategies. Further development in respiratory-targeted therapies that augment the dampened immunological response to infection are an alluring proposition.

	Result (g/L)	Normal Range for Age
IgG	16.2 (g/L)	(N) 4.3 – 13.4 (g/L)
IgA	1.5 (g/L)	(N) 0.19 – 2.2 (g/L)
IgM	1.53 (g/L)	(N) 0.21 – 1.8(g/L)
IgE	>5000 kU/L	(N) mean 16 (+/-56) kU/L
SAR to pneumococcal polysaccharide vaccine	108 (pre)	240 (post)
SAR to tetanus	1.63 (pre)	0.97 (post)

SCID OR OTHER CONDITIONS REQUIRING TRANSPLANTS



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Which STAT-related Diseases Require Hematopoietic Stem Cell Transplantation?

Prof. Michael Albert

ESID Chairperson of Working Party
IEI 2020-2024 and EBMT Secretary of Inborn Error Working Party
Ludwig-Maximilians-Universität München Munich, Germany

Malignancy in Inborn error of immunity

LoganathanSathish Kumar[a], Lennu Lizbeth Josephb, Leni Grace Mathew[b], Phaneendra VenkateswaraRao Datari[c]

a *Division of Pediatric Infectious Disease and Clinical Immunology, Child health 3-unit, Department of Pediatrics, Christian Medical College, Vellore, Tamilnadu, India*
b *Division of Pediatric Hematology and Oncology, Child health 1 unit, Department of Pediatrics, Christian Medical College, Vellore, Tamilnadu, India*
c *Department of Hematology, Christian Medical College, Vellore, Tamilnadu, Indiaa*

Introduction: Inborn errors of immunity (IEI) increase the risk of developing cancer in an individual by ten times in comparison to their peers. We report four patients presented with varied manifestations diagnosed with leukemia and lymphoma and diagnosed as inborn error of immunity

Case Presentation:

CASE DETAILS

	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	15/F	7Y 9m/M	10 Y/M	4 Y/M
Consanguinity	NC	Second-degree consanguineous	NC	NC
Presenting complaints	Bilateral neck swelling and breathlessness for 1 month	Recurrent respiratory tract infections and fever for 1month	Progressive pallor easy fatigability for 1 month.	Excruciating pain in both lower limbs and sub -centimetric cervical adenopathy for 1 week
Past history	Recurrent respiratory tract infections since 3 years of age	Motor developmental delay and recurrent infections	Recurrent epistaxis from 3 years of age	Not significant
System involved	RS	RS / CNS	Hematological	Hematological
Lymph node and bone marrow	Hodgkin lymphoma	Hodgkin lymphoma	BM- acute myeloid leukemia Cytogenetics- Monosomy 7	BM-acute leukaemia
Diagnosis	Hodgkin lymphoma	Hodgkin lymphoma	Acute myeloid leukemia	Acute lymphoblastic leukemia
IEI diagnosis	CD 27	ATM	GATA2 Variant	While on chemotherapy developed painless bilateral parotid swelling Flow cytometry showed elevated double negative T cells
IEI classification	Combined immunodeficiency	DNA repair defect	Congenital defects of phagocyte number or function (Other non -lymphoid defects)	Phenocopies of inborn errors of immunity
Genetics	Homozygous mutation (c.319C>T).	Heterozygous (c.478_482del).	Germline testing (buccal sample) c.655dup (pGlu219GlyfsTer63	Not identified pathogenic variants
Status	Alive/IVIg/antibiotic prophylaxis	Alive/IVIg/antibiotic prophylaxis	Alive underwent a matched sibling allogeneic stem cell transplant	Alive on sirolimus and in remission

Discussion: History of recurrent infections, early age malignancy, and chromosomal aberrations should prompt underlying immune evaluation. Next-generation sequencing should be considered early to facilitate the diagnosis.

Conclusions: Clinicians should be aware of underlying IEI in patients presenting with underlying malignancy.

Unravelling Erythroderma in Neonates

Afrilia Intan Pratiwi, Cahya Dewi Satria, Sumadiono

Departement of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/ Dr. Sardjito General Hospital, Yogyakarta

Introduction: Erythroderma in the neonatal period is an important entity which needs to be properly recognized by dermatologists and pediatricians. It refers to inflammation of the skin with erythema and scaling more than 90% of the surface area of the skin. Neonatal erythroderma can be a sign of severe combined immunodeficiency (SCID)

Case Presentation:
We report a female newborn delivered via caesarean at 40 weeks' gestation. She was the third child of nonconsanguineous parents. Her two siblings were died in infant age with signs of infections.

Since 14 days old, she developed erythroderma and desquamation on her skin. At 4 months old she was referred to our hospital with prolonged fever, prolonged diarrhea, erythroderma, and malnutrition. Examination showed diffuse erythroderma, desquamation, alopecia, absent eyebrows, lymphadenopathy and hepatomegaly.

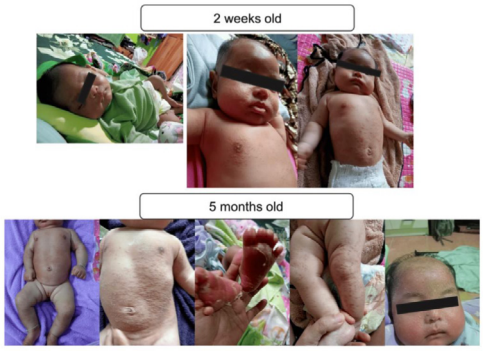
Laboratory tests showed normal leukocyte (7,800/mm^3), normal hemoglobin (12 g/dL), normal platelet count (310.000/mm^3), but eosinophilia (37%).

Immune evaluation confirmed SCID, characterized by low CD4 T-cell count (178 cells/mm^3), low CD8 T cell count (270 cells/mm^3), hypogammaglobulinemia (<12 mg/dL), and elevated IgE (1510 IU/L). Skin biopsy revealed spongiotic dermatitis with focal parakeratosis and lymphocyte infiltration suggestive to Omenn Syndrome.

Genetic testing identify potential compound heterozygous pathogenic and likely pathogenic variants in DCLRE1C. DCLRE1C is associated with autosomal recessive Omenn syndrome.

The fever and the infections causes several hospitalization until she was 9 months old. Despite of antibiotics and intravenous immunoglobulin, her conditions worsened, leading to death before hematopoietic stem cell transplantation (HSCT).

Discussion: Persistent erythroderma may indicate severe combined immunodeficiency, including Omenn Syndrome. Clinical features include exfoliative dermatitis, erythroderma, alopecia, lymphadenopathy, hepatosplenomegaly, recurrent infections, and failure to thrive.



Conclusions: This case highlights the importance of including Omenn Syndrome in the differential diagnosis for neonatal erythroderma. Clinical and genetic assessments, is crucial for early diagnosis and timely hematopoietic stem cell transplantation (HSCT).

COMBINED IMMUNODEFICIENCIES

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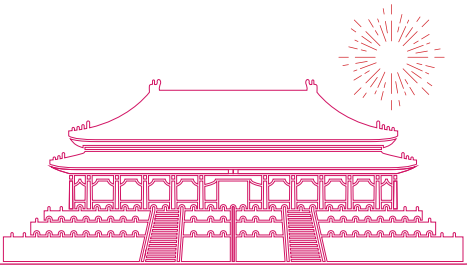


Combined Immunodeficiency:

How to Choose Between Conservative Treatments, Gene Therapy, or Hematopoeitic Stem Cell Transplantation?

Prof. Fabio Candotti

President of European Society for Immunodeficiencies (ESID)
Université de Lausanne
Lausanne, Switzerland

Cohort with Rare Combined Immunodeficiency with Autoinflammation from Resource-limited Settings: A Story of Exploring Founder Gene Effect

Dharmagat Bhattarai[1], Aaqib Zaffar Banday[1], Ramji Baral[3], Pratap Kumar Patra[4], Asmita Neupane[1]

1 *Advanced Centre for Immunology & Rheumatology, Kathmandu, Nepal*
2 *Department of Pediatrics, Government Medical College Srinagar, Srinagar, Kashmir, India*
3 *Pokhara Institute of Health Sciences, Pokhara, Kaski, Nepal*
4 *Department of Pediatrics, All India Institute of Medical Sciences, Patna, Bihar, India*

Background and aims: Inherited ARPC1B deficiency (A1BD) is a rare combined immunodeficiency with a myriad of infective, allergic, and inflammatory features. Very few cases have been reported in the literature. We describe 12 patients with A1BD with unique features from Nepal.

Methods: Data on clinical-epidemiological features, immuno-hematological parameters, treatment, and outcome were included in the analyses. Homozygosity mapping and haplotype analysis were also done.

Results: Similar to previous reports, we noted infective and autoimmune/allergic manifestations in all of our patients. Unique features noted in our study include rheumatoid factor (RF) positive chronic arthritis (mimicking RF+ juvenile idiopathic arthritis), significantly elevated anti-tissue transglutaminase antibody titers, generalized skin hyperpigmentation, distal phalangeal enlargement, frontal bone hypertrophy, hypertrophic skin scars, and hyperkeratosis. Ten cases harbored the founder splice-site variant c.64+2T>A in the ARPC1B gene. Two cases have unique compound heterozygous mutations. Long-term outcomes in our patients were significantly worse than reported previously. Comparative phenotypic analysis showed significantly greater proportions of otitis, gastroenteritis, lymphadenopathy, arthritis, inflammatory bowel disease-like manifestations, and elevated IgA.

Conclusions: This is the first and largest cohort of A1BD ever reported from a single center. c.64+2T>A is a founder variant in Nepalese patients with A1BD.

Mutation at a Novel Gene Site and the Phenotypic Findings in a Case of Combined Immunodeficiency and Cardiomyopathy

Han Yang, Yan Li, Fei Sun and Huawei Mao

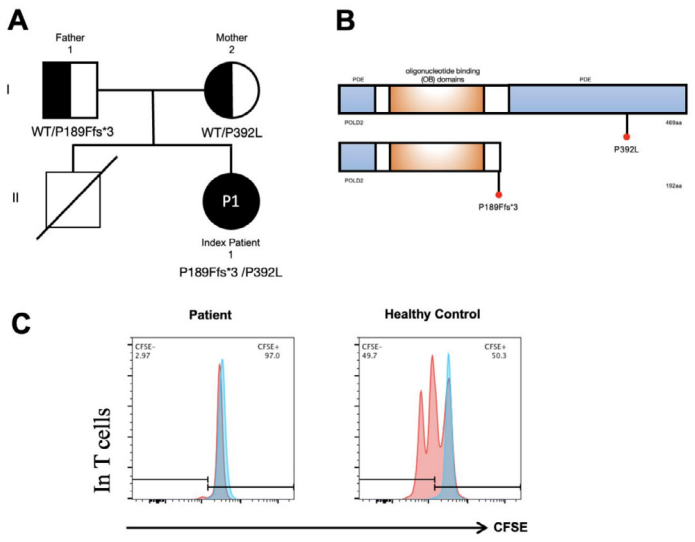
Department of Immunology, Beijing Children's Hospital of Capital Medical University, National Center for Children's Health of China, Beijing, China

Introduction: The DNA polymerase δ complex (PolD), a heterotetrameric enzyme composed of the catalytic subunit POLD1 and accessory subunits POLD2, POLD3, and POLD4, is crucial for the replication and maintenance of eukaryotic genomes. Recent research has associated mutations in POLD1, POLD2, and POLD3 with CID syndrome, characterized by T-cell lymphocytopenia, which may be accompanied by intellectual disability and sensorineural hearing loss.

Case Presentation:
We present a case of a girl with compound heterozygous mutations in the POLD2 gene (p. P392L, p. P189Ffs*3) identified by whole-exome sequencing. The patient exhibited combined immunodeficiency, neurodevelopmental delay, sensorineural deafness, and cardiomyopathy. Her brother had a history of leukopenia and recurrent pneumonia, leading to death at the age of one.

Discussion: While PolD2 deficiency is known to reduce the numbers of CD4+ T cells, B cells, and NK cells, the impact on CD8+ T cell counts has not been previously documented. In our case, we observed a reduction in the absolute numbers of CD4+ T cells, CD8+ T cells, B cells, and NK cells, with decreased IgG and IgA but normal IgM levels, and impaired T-cell proliferative function. Additionally, the patient had left ventricular enlargement, irregular papillary muscle morphology, and multiple coarse muscle bundles in the left ventricular chamber, with an unclear association with the disruption of the PolD.

Conclusions: This report marks the first description of a novel POLD2 mutation site, expanding the phenotypic spectrum associated with POLD-related disorders. Our findings contribute to the understanding of the complex activities of polymerase δ and its accessory subunits, which is constrained by the importance of polymerase δ, limiting the generation of gene knockout cell lines or model organisms.



What We Knew, And What Is New?

Ira Gautam[a],Sathish Kumar Loganathan[a], Arul Premanand Lionel[b], Mary Purna Chako[c]

a *Division of Pediatric Infectious Disease and Clinical Immunology, Child health 3 unit, Department of Pediatrics, Christian Medical College, Vellore, Tamilnadu, India*
b *Division of Pediatric Gastroenterology and Hepatology, Child health 1 unit, Department of Pediatrics, Christian Medical College, Vellore, Tamilnadu, India*
c *Department of Cytogenetics, Christian Medical College, Vellore, Tamilnadu, India*

Introduction: Immunodeficiency, centromeric instability and facial anomalies (ICF) syndrome(s) are a rare category of combined immunodeficiency. This entity with its immunological profile, characteristic facies, and karyotypic features, is inherited in an autosomal recessive inheritance and is seen to have 4 subclasses (ICF 1-4)

Case Presentation:

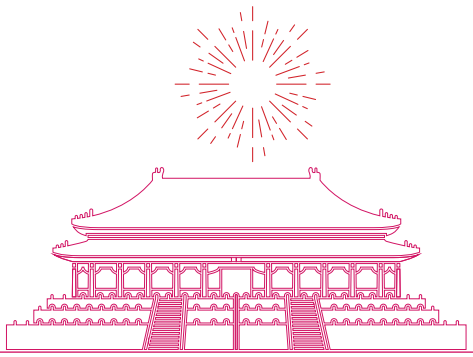
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/sex	6yr/m	19yr/f	18yr/m	10yr/m	3yr/m
Consanguinity	3rd degree	present	present	2nd degree	present
Initial Presentation	Recurrent respiratory tract infections	Recurrent respiratory tract infections	Recurrent hematemesis; portal hypertension and cough	Recurrent respiratory tract infections	Recurrent seizures and loose stools
Initial diagnosis	Combined immunodeficiency	Combined immunodeficiency	Non-cirrhotic portal hypertension	Common variable immunodeficiency	Acute encephalitis
Final Diagnosis	ICF2	ICF1	ICF2	ICF1	ICF2
Delay in diagnosis (months)	67	3	180	50	10
Genetics	ZBTB24	DNMT3B	ZBTB24	DNMT3B	DNMT3B
Status	Alive/on IVIG	Alive/on IVIG	Alive/on IVIG	Alive/on IVIG	Alive/on IVIG

Discussion: Respiratory tract infections and facial anomalies are clinically seen in more than 80 % of the patients. Reduction in B cell number and reduction in at least one isotype of Immunoglobulin is seen, especially IgG and IgA. Additionally, psychomotor and cognitive impairment, intrauterine growth retardation, café au lait macules and scleral telangiectasia are also seen. The same is detectable by metaphase chromosomal analysis of mitogen-stimulated lymphocytes, and additionally on next-generation sequencing. Intravenous immunoglobulin replacement, antimicrobial prophylaxis and hematopoietic stem cell transplant are the backbones of therapy.

Aberrations involving pericentromeric regions of chromosomes 1 and 16 of mutagen-stimulated lymphocytes are consistent with ICF (immunodeficiency, centromere instability, and facial anomalies) syndrome.

Conclusions: In every case of hypogammaglobulinemia, clinical examination suggestive of facial dysmorphism should alert one towards the possibility of ICF syndrome. Also, CVID mimics this entity, hence hypogammaglobulinemia very early in childhood should prompt us to evaluate for ICF syndrome.

DEFECTS IN INTRINSIC AND INNATE IMMUNITY



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Management Strategies for Gain-of-Function Innate Immune Defects besides HSCT/Cellular Therapies

Prof. Manish Butte

E. Richard Stiehm Endowed Chair and Division Chief of Immunology, Allergy and Rheumatology
University of California Los Angeles (UCLA) Los Angeles, US

Recurrent BCG Abscesses and Severe Immunodeficiency in a 2-Year-Old Girl

Tanatchabhorn Soponkanabhorn, MD.

Center of Excellence for Allergy and Clinical Immunology, Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Abstract:

STAT1 gain-of-function (GOF) mutation is an autosomal dominant condition characterized by excessive STAT1 pathway activation, leading to immune dysregulation and heightened susceptibility to chronic infections, particularly chronic mucocutaneous candidiasis (CMC) and mycobacterial infections. STAT1 GOF typically present in adults and are often associated with chronic mucocutaneous candidiasis or milder immune dysregulation. However, our case highlights an atypical presentation in a toddler with severe immunodeficiency, emphasizing the importance of considering STAT1 GOF mutations in young patients presenting with unusual or severe infections.

We describe a 2-year-old Thai girl with a two-week history of a BCG abscess at her left shoulder. Her clinical course included multiple severe infections: pneumonia with isolation of Klebsiella pneumoniae and Pseudomonas aeruginosa at 3–4 months of age. By age one, she had experienced ten episodes of pneumonia episodes. She also developed oral

mucocandidiasis, and recurrent BCG abscesses. PCR testing of the latest abscess confirmed Mycobacterium tuberculosis complex.

Immunologic evaluation revealed normal serum immunoglobulins but low CD4, CD8, and B-cell counts, with markedly impaired T-cell proliferation. Whole-exome sequencing identified a de novo heterozygous STAT1 GOF variant, c.1154C>T (p.Thr385Met). Delayed STAT1 dephosphorylation confirmed the diagnosis. The patient's pathogenesis likely stems from aberrant STAT1 activation, leading to immune subset exhaustion and impaired response to type II interferon, contributing to mycobacterial susceptibility.

Treatment included a three-month course of isoniazid and rifampicin for the BCG abscess, alongside antifungal therapy, resulting in clinical improvement. Hematopoietic stem cell transplantation is planned as curative therapy, with JAK inhibitors considered as a potential adjunctive therapy.

Early genetic testing in children with unusual infections as shown in this STAT1 GOF mutation case enables timely detection of this disorder, and guides tailored immunomodulatory and antimicrobial strategies to improve outcomes and reduce complications.

Refractory mediastinal purulent lymphadenitis-associated chronic mucocutaneous candidiasis

Ryohei Watanabe[1], Ryosuke Wakatsuki[1], Yohei Nishiyama[2], Satoshi Miyamoto[1], Akihiro Hoshino[3], Takahiro Kamiya[4], Takeshi Isoda[2], Shota Okamoto[5], Yoshifumi Ito[5], Yuki Mizuno[5], Kentaro Okamoto[5], Aiko Honda[6], Megumi Okawa[6], Toshiyuki Takagi[6], Kosei Yamashita[6], Masatoshi Takagi[2], Hirokazu Kanegane[3]

1 *Department of Pediatrics, Institute of Science Tokyo Hospital, Tokyo, Japan*
2 *Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo, Japan*
3 *Department of Child Health and Development, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo, Japan*
4 *Health Science Research & Developmental Center, Institute of Science Tokyo Hospital, Tokyo, Japan*
5 *Department of Pediatric Surgery, Institute of Science Tokyo Hospital, Tokyo, Japan*
6 *Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan*

Introduction: Chronic mucocutaneous candidiasis (CMCD) is an inborn error of immunity, mainly caused by gain-of-function variants in STAT1, characterized by persistent and recurrent Candida infections. Most cases of candidiasis in CMCD are localized to mucocutaneous tissues. While patients with CMCD are generally not associated with other pathogens, some may present with invasive infections by non-Candida pathogens including bacteria. Here, we report a case of CMCD complicated by refractory mediastinal purulent lymphadenitis.

Case Presentation:
A 4-year-old boy presented with persistent oral and periungual Candida infections, and was diagnosed with CMCD caused by STAT1 variant at the age of 3. After the diagnosis, oral fluconazole administration ameliorated Candida infections.

The patient developed a fever and was admitted to a hospital. Contrast-enhanced computed tomography (CT) revealed a 22-mm mass with surrounding enhancement in the superior mediastinum. Broad-spectrum antibiotics were administered, but fevers persisted. Thus he was transferred to our hospital.

He suddenly developed oxygen requirements two days after the admission, and chest CT revealed bilateral pleural effusion. Exudative pleural fluid (350 mL) was collected from thoracentesis. Bacterial cultures of the pleural fluid were negative. After thoracentesis, his oxygen requirements gradually diminished, and there was no recurrence of pleural effusions.

Broad-spectrum antibiotics reduced the mediastinal mass, later diagnosed as suppurative lymphadenitis via magnetic resonance imaging. After 7 weeks of intravenous and 4 weeks of oral antibiotics, the patient was free from infections.

Discussion: Few papers have been published showing a patient with CMCD complicated by an invasive infection other than Candida. In this patient, no specific pathogen was identified by any of the culture tests. However, the lymphadenitis may have been due to a bacterial infection, since antibiotic treatment was successful.

Conclusions: Patients with CMCD may be susceptible to bacteria as well as Candida albicans.

An Adolescent Girl with Recurrent Respiratory Tract Infections and Bronchiectasis

Diadra Annisa[1], Rizqi Amalia[1], Yu-Lung Lau[2], Dina Muktiarti[1]

1 *Allergy Immunology Division, Department of Child Health, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia*
2 *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China*

Introduction: Loss-of-function mutation in the IL-21R gene causes severe primary immunodeficiency. However, reports on IL-21R deficiency are scarce. We presented a case of an adolescent girl with recurrent respiratory tract infections with a possible diagnosis of IL21R deficiency.

Case Presentation:
A twelve-year-old girl presented with chronic cough since the age of three years. At the age of five, she was diagnosed with tuberculosis and received antituberculosis drugs; however, the cough persisted. Her symptoms continued to worsen, including tuberculosis relapse, as well as multiple inpatient admissions due to pneumonia, atelectasis, and pleural effusion. Other notable features were a small secundum atrial septal defect, long extremities, and high level of IgE (reaching 48,775 ng/dL). She was of middle east descent and was the third child of three siblings. Her older sister died at the age of thirteen due to unknown cause of cirrhosis. Both her sister and brother had tuberculosis and multiple respiratory tract infections. Her parents had third degree consanguinity. After loss to follow up due to the COVID-19 pandemic, she was readmitted with pneumonia at the age of 16 years. Her CT-Scan showed bronchiectasis and fibrosis. Genetic testing revealed an autosomal homozygous missense mutation I246K in IL21R (c.737T>A, po.I246K, RefSeq:NM_021798.4). In addition to antibiotics, she began receiving routine intravenous immunoglobulin. Subsequently, her condition improved, and she did not experience any further infections.

Discussion: Interleukin-21 is a cytokine that mediates the JAK/STAT signaling pathway which regulate effector functions. Multiple reports revealed that patients with loss-of-function mutations in IL-21/IL-21R developed autosomal recessive combined immunodeficiency with variable presentations. Most patients had recurrent respiratory infections; while others had cryptosporodium infection associated with chronic cholangitis. IL-21R mutation in our patient may be a variant of uncertain significance; hence further evaluation is needed.

Conclusions: Our report provides additional awareness to IL-21R deficiency to improve the survival of patients with similar phenotypes. Sanger sequencing on family members and further functional studies are needed.

Unraveling a Mystery: Recurrent *Streptococcus pyogenes* Septicemia in an 11-Year-Old with Congenital Lymphedema

Apichaya Kriengwatanasiri, MD.

Center of Excellence for Allergy and Clinical Immunology, Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand

Abstract:

Recurrent Streptococcus pyogenes septicemia is rare and often signifies an underlying immunological predisposition. This report describes an 11-year-old boy with recurrent Streptococcus pyogenes septicemia and congenital lymphedema, highlighting a rare pathogenic mutation in the MDFIC gene.

An 11-year-old Thai boy born as a late preterm infant with a prenatal diagnosis of hydrops fetalis, followed by a postnatal diagnosis of bilateral chylothorax with generalized lymphedema due to congenital lymphedema. There was no family history of consanguinity or early infant death.

Physical examination revealed generalized non-pitting edema with hyperpigmented scars. At the age of 3 and 7, he was hospitalized with fever and hypotension, diagnosed with Streptococcus pyogenes septic shock, and Streptoccocus pyogenes sepsis from cellulitis of the right arm, respectively.

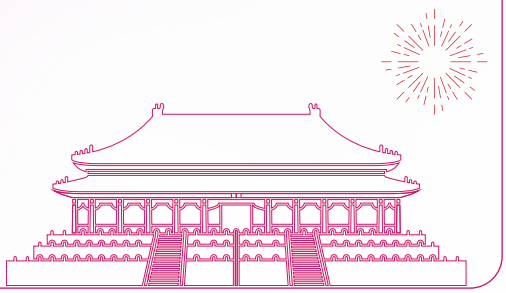
Immunological investigations demonstrated reduced number of CD3, CD4, and CD8 T lymphocytes. Trio-genome sequencing identified a known homozygous c.391dup (p.Met131fs*) variant in MDFIC gene, which is classified as pathogenic (PVS1, PM2_supporting, PM3) according to ACMG guidelines.

MDFIC (MyoD Family Inhibitor Domain Containing) is a protein encoded by the MDFIC gene (NM_001166345.3), located at 7q31.1-q21.3. It regulates the activity of transcription factors, including the glucocorticoid receptor (GR), HAND1, and members of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family.

Loss-of-function mutations in MDFIC are rare. However, these markedly increase susceptibility to Streptococcus pyogenes infections. Recognizing and understanding this mutation is essential for identifying at-risk individuals and tailoring care strategies.

Although specific treatment guidelines are not yet established, vigilant monitoring and early management of complications are essential for improving patient outcomes.

IMMUNE DYSREGULATIONS



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Immune Dysregulation in Inborn Errors of Immunity: Targeted Treatment Approaches and Possible Pitfalls

Dr. Anna Shcherbina

Chief of Immunology Dmitry Rogachev Center of Pediatric Hematology Oncology and Immunology Moscow, Russia

Think Early and Act Fast: Pyrexia of Unknown Origin in a Young Infant Could be an Inborn Error of Immunity

Rajkumar Kundavaram[1], Mohinish Darshan[1], Amber Kumar[1], Narendra Kumar Chaudhary[1], G C Bhatt[1], Bhavna Dhingra[1], Shikha Malik[1]

1 *Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, India*

Introduction: Hemophagocytic lymphohistocytosis (HLH) is a disorder of immune dysregulation characterized by increased inflammatory response and hypersecretion of proinflammatory cytokines leading to severe organ damage and death. It can be primary (familial) or secondary (triggered by infection, cancer, and rheumatological disease). Familial hemophagocytic lymphohistiocytosis (FHL) is a potentially fatal disease that presents in infancy.

Case Presentation:
Eight-month-old male infant presented with high-grade fever for two weeks. Past history was significant for unremitting fever and packed red cell transfusion. Elder sibling died at the age of four months with fever, seizures and bleeding. At admission, child had high grade fever (temperature 104 F) with pallor and hepatosplenomegaly (liver span 11 cm and spleen 5 cm below left costal margin). Empirical broad-spectrum antibiotics were started and was worked up for infective, neoplastic and metabolic causes. Hemogram revealed bicytopenia (hemoglobin 7.3gm% and platelets 14000/mm3). Bone marrow examination ruled out leukemia.

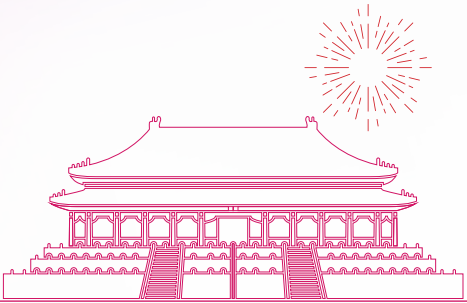
Persistence of fever despite antimicrobials with history of sibling death made the possibility of inborn errors of immunity more likely. Serum immunoglobulins, DHR, NBT and lymphocyte subset analysis were normal. As the clinical criteria and laboratory parameters of HLH were being met, FHL was considered and genetic analysis was done (given the age and family history). Perforin assay was normal. Fever persisted despite upgrading antibiotics and initiation of anti-fungal agents. Whole exome sequencing confirmed the diagnosis of FHL type 2. Dexamethasone and Etoposide was initiated. The clinical condition deteriorated with liver failure and disseminated intravascular coagulation setting in. Genetic counselling was given to family and the role of pre-natal diagnosis in next pregnancy was explained.

Discussion: The treatment of familial HLH is mainly supportive with HSCT being the only curative option. Early diagnosis and prompt initiation of immune suppressive therapy is the key. In our case there was no time window to prepare the child for HSCT. This case underscores the non-specific clinical presentation of a potentially fatal disease where thinking early and acting fast could alter the prognosis.

Conclusions: Prompt initiation of immune suppressive therapy and early HSCT will prevent mortality in FHL. The role of genetic counselling and prenatal diagnosis in further pregnancies should be emphasized.

GENE/ REFSEQ	COORDINATE	VARAINT	EXON	VARAIANT	ZYGOSITY/ INHERITANCE	OMIM/ PHENOTYPE	CLASSIFICATION
PRF1/ NM_0010831163	Chr10 70600736	c.167C>A p.Ser56	Exon 2	Nonsense	Homozygous/ AR	Hemophagocytic Lymphohistiocyto-sis, Familal, 2 (OMIM # 603553)	Likely pathogenic

AUTOINFLAMMATORY AND AUTOIMMUNITY



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Type I Interferon Signature in Autoinflammatory Diseases

Dr. Kazushi Izawa

Member of the JSIAD PID and Autoinflammatory Diseases Database Project Kyoto University
Kyoto, Japan

Recurrent Oral Infections, Otitis, Sinusitis, Pneumonia, and Chronic Diarrhea in a 13-Year-Old Boy

Moahmmadreza Shafiei[1], Zahra Chvooshzadeh[2]

1 *Alborz University of Medical Sciences*
2 *Shahid Beheshti University of Medical Sciences*

Introduction: Transcription factor BTB and CNC homolog 2 (Bach2), is a transcription factor Located on human chromosome 6 (6q15) comprising 841 amino acids protein that regulates the differentiation of Th2 cells, B cells, and Treg cells. Bach2 deficiency reduces the number of regulatory (Treg) cells and increases the number of Th2-type effector memory T cells.

Herein, we aim to report the clinical, immunological, and genetic features of a 12-year-old Iranian boy, harboring a novel heterozygous nonsense mutation in Bach2 with recurrent infections and hospitalization due to prolonged infections.

Case Presentation:
A 13-year-old boy was referred to our hospital with a history of recurrent oral infection (recurrent oral plagues, aphthous lesions, and gingivitis), otitis, recurrent sinusitis, and pneumonia from 12 years of age. He also had a history of hospitalization due to prolonged diarrhea.

Family history of immunodeficiency, malignancy: No recognized immunodeficiency, or malignancy in his relatives, but a history of recurrent stomatitis and recurrent sinusitis was positive in his mother.
Drug History: Acyclovir, Co-trimoxazole
Vaccination History: No Problem
Allergy History: No
Rheumatology and autoimmune diseases: No
Hematology and Oncologic disease: No
Physical exams: Normal

Discussion: R outine laboratory data and primary immunologic screening tests were obtained from patients. The primary screening test for immunodeficiency was normal in patients. The total serum level of antibodies IgM, IgA, and IgG was normal in patients. Only an elevated level of IgE was observed in the patient. To rule out any type of immunodeficiency, the whole exome and Sanger sequencing was obtained from the patient's DNA which showed a novel heterozygous nonsense mutation in Bach2. The WOS and Sanger showed a similar mutation in the mother, while his father was wild type. A reduced number of CD4+CD25+FOXP3 was seen in the patient and his mother. Nevertheless, the patient's mother showed no clinical symptoms.

Conclusions: This is the first report of a patient with this mutation and the clinical presentation is unique among previously reported patients. This study enhances our understanding of the phenotypic spectrum and clinical manifestations of Bach2 deficiency and paves the way to elucidate underlying immunopathogenesis. In contrast to the previously reported patients with bach2 deficiency, our patient did not develop any autoimmunity and her mother was intact. This may be due to the penetrance phenomena.

Lab data:

	Date: 2021.07.03		Normal range
WBC	4900		4000 - 11000
Lymph	51%	2499	34%
PMN	43%	2107	56%
PLT	259000		150000 - 450000
Hb	13.6		14 - 17.5
CD3	62%		35 - 78%
CD4	32%		22 - 62%
CD8	27%		12 - 36%
CD4/CD8	1.18		1 - 3%
CD16	16.05%		3-22%
CD56	16.11%		5–24%
CD19	17.49%		6–23
CD20			
CD27	15.35%		
HLA DR	19.71%		

	Date: 2021.07.14	Normal range
IgG (mg/dl)	1007	700 - 1400
IgA (mg/dl)	129	51 - 297
IgM (mg/dl)	94	40 - 150
IgE (IU/ml)	> 500	< 144

Arthritis and Rashes: A Case Study

Jing Yin, Jijun Ma, Chongwei Li

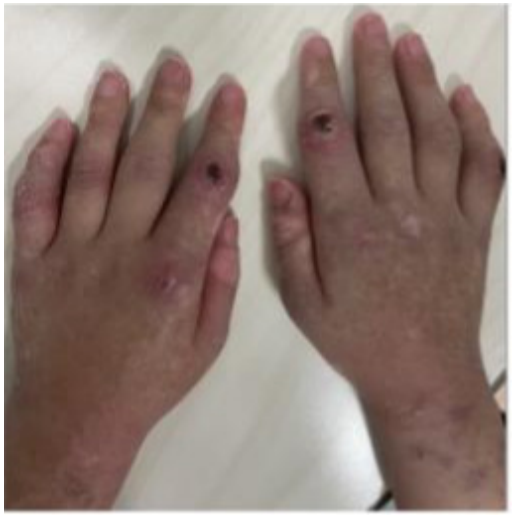
Department of Rheumatology and Immunology, Tianjin Children's Hospital, Tianjin University, Tianjin, China

Introduction: Aicardi-Goutières syndrome (AGS) is a rare neuro-immunologic disorder associated with elevated levels of type I interferon. Gain-of-function mutations in IFIH1 were identified as AGS7 and characterized by early-onset encephalopathy. There are also some patients have no neurological symptoms, exhibiting a phenotypic heterogeneity.

Case Presentation:
A 5-year-old girl presented as frostbite-like rash on her face, auricles, hands and feet when she was one year old. Her rashes became worse in the winter and were less severe in the summer. After topical herbal treatments, rashes partially developed into blisters, which later transformed into skin depigmentation. Symmetrical spindle-shaped swelling around proximal interphalangeal joints in both hands was observed when she was 4 years old. Recently, joint swelling has progressed with ulcers formation on the dorsal aspect of the joints. The patient has no developmental delay and no history of recurrent infections. Computed tomography showed intracranial calcification. Anti-nuclear antibodies were negative. Rheumatoid factor and C-reactive protein were normal, and erythrocyte sedimentation rate was slightly elevated. A spontaneous heterozygous c.2380G>A mutation in *IFIH1* was identified by genetic testing. AGS7 is considered and the expression of interferon stimulated genes is being tested.

Discussion: We reporte a case of AGS7 presenting with cutaneous vasculitis and arthritis without typical neurologic clinical features. For AGS patients with completely normal psychomotor development, skin lesions may be the major diagnostic clue. The most common skin manifestation is frostbite, which is also the primary diagnostic clue of this case. The patient has intracranial calcification but no neurological symptoms. Whether delayed neurological manifestation will occur remains to be seen. In addition, rheumatoid-like arthritis is not frequency in AGS.

Conclusions: AGS is a heterogeneous disease. Recognition of phenotypic diversity is helpful in the early diagnosis of AGS.



The Hidden Peril of Dual Immune Disorders: A Diagnostic and Therapeutic Challenge

Yamini Sharma, Ahmed Jamal, Rakesh Kumar Pilania, Vignesh Pandiarajan, Amit Rawat, Surjit Singh

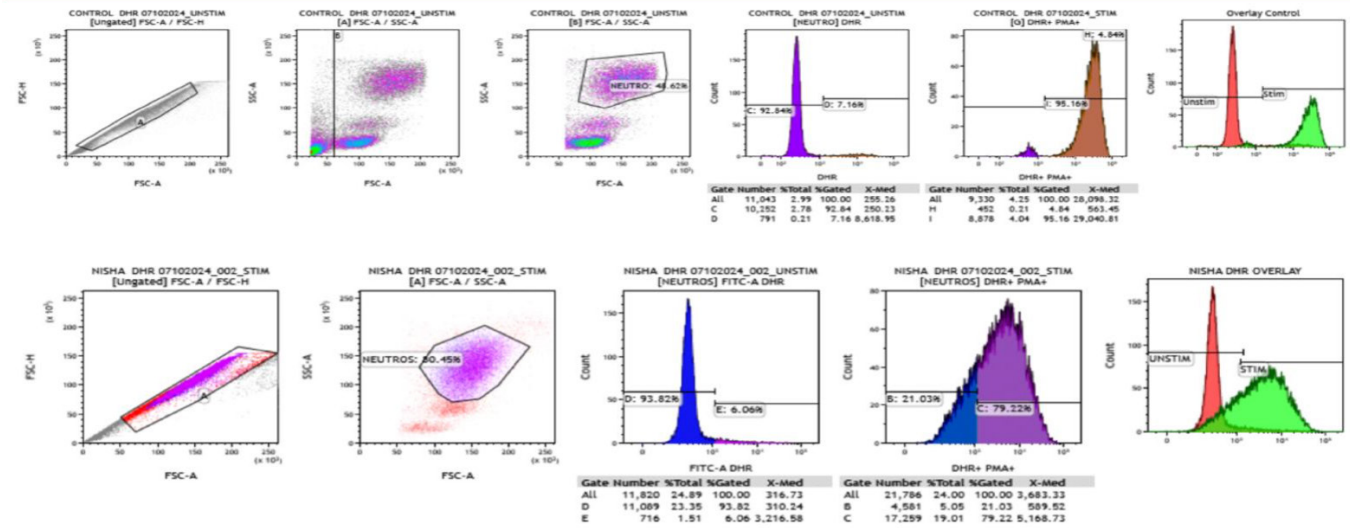
Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and research, Chandigarh, India

Introduction: Chronic Granulomatous Disease(CGD) has been associated with various autoimmune disorders, including Systemic Lupus Erythematosus(SLE).We report a unique case of 12-year- old girl diagnosed with SLE and following non-resolving necrotising pneumonia

Case Presentation:
A 12-years-old girl born to a non-consanguineous marriage presented with polyarticular arthritis, recurrent oral ulcers, alopecia , right sided pneumonia. On general physical examination she had alopecia, palatal ulcer, malar rash and digital tip ulcers and had tachycardia, tachypnoea and hypertension with bronchial breath sounds and diffuse crepitations in right lung. Laboratory investigations revealed anaemia, neutrophilic leucocytosis, thrombocytopenia, nephrotic range proteinuria and deranged renal function test (urea/creatinine-211/ 26.3 mg/dl). ANA was strongly positive (4+ homogenous)with low C3/C4 while antiphospholipid antibodies and G6PD tests were negative. Nitroblue tetrazolium test was negative, and a Dihydro-rhodamine assay confirmed CGD(figure 1). B 558 expression on granulocytes was normal. CT chest revealed fibrocavitary changes in right lung with pneumothorax. Sputum cultures grew Enterbacter cloacae and Klebsiella and Pseudomonas aeruginosa while empyema pus cultures revealed Aspergillus Fumigatus. Despite treatment, she developed recurrent pneumothorax, empyema, and ultimately succumbed to her illness. Genetics testing is awaited.

Discussion: This case highlights a rare presentation of SLE with underlying CGD, an inborn error of immunity (IEI). Severe autoimmune manifestations such as SLE can mask underlying immunodeficiencies, making early recognition crucial. The interplay between CGD and SLE remains poorly understood but may involve immune dysregulation due to defective NADPH oxidase activity.

Conclusions: Primary immunodeficiencies, including CGD, can present with severe autoimmunity and recurrent infections. Few cases of SLE with CGD, particularly autosomal recessive CGD, have been reported. Early diagnosis and tailored management are essential to prevent complications.



Neutrophils were gated on FSc vs SSc

S. No		MFI UNSTIMULATED	MFI STIMULATED	Δ MFI	STIMULATION INDEX	% Positivity
1.	Control	255.26	28098.32	27843	110.07	95.16
3.	Patient	316.73	3683.33	3366.6	11.63	79.22

Panniculitis and IgA Deficiency in a 6-Year-Old Girl with Polyarthritis

Sihao Gao[1], Yongwang Shi[2], Xu Meng[3], Juan Ding[1], Zhuo Li[1], Jingjing Jiang[1], Yanyan He[1], Sirui Yang[3], Hongmei Song[1]

1 *Department of Pediatrics, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China*
2 *4 + 4 Medical Doctor Program, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China*
3 *Pediatric Rheumatology, Immunology, and Allergy, The First Hospital of Jilin University, Changchun 130021, China*

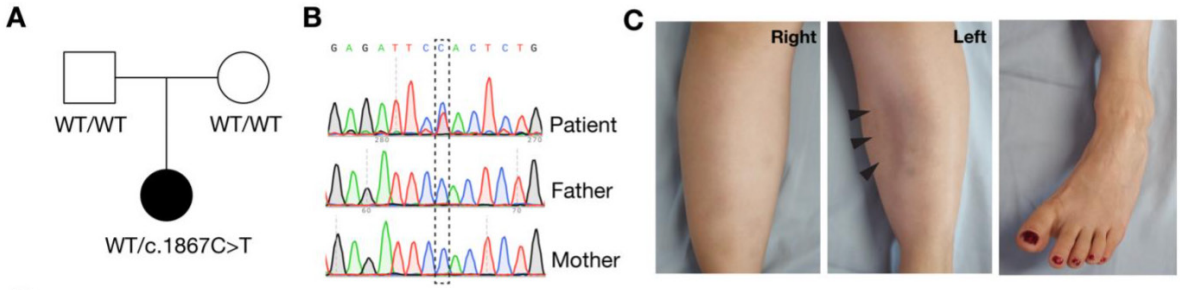
Introduction: JAK-STAT signaling regulates cytokine and immune responses, cell growth and differentiation, cell survival, apoptosis, and oncogenesis. Variants in STAT4 have recently been identified to cause an autoinflammatory disease (AID) with disabling pansclerotic morphea (DPM). Only four patients from a single report have been published. This study aims to report the presentations and phenotypes of the first Chinese patient with STAT4 variant and to raise the recognition of this disease.

Case Presentation:

A 6-year-old girl presenting with rash, joint swelling and tenderness in bilateral lower limbs for 7 weeks was admitted to our hospital. She developed multiple painful erythema nodosum in the pretibial regions of both lower limbs 7 weeks ago. Both ankle joints are tender and swollen. She had no fever or any respiratory, and gastrointestinal symptoms. She had been initially treated with oral prednisone at the local hospital but the symptoms persisted. A comprehensive analysis by a local hospital revealed normal blood count, urinalysis, and stool. CRP was elevated (38.47 mg/L) but ESR and ferritin were normal. Infections were excluded. The IgG was 6.46 g/L, IgA was 0.01 g/L and IgM was normal. Antibody screening returned all negative. She had a decreased lymphocyte lineage (7%) in bone marrow aspiration with 1% phagocytes. Coagulation, blood lipids, and muscle enzymes were all normal. Ultrasound showed joint swelling and synovitis in ankles, elbows, hips, and knees. Bilateral cervical lymphadenopathy was found (maximum 6.5*2.9mm). She also had a thickened spleen (27mm in thickness). She was diagnosed with erythema nodosum, common variable immunodeficiency, suspected selected IgA deficiency and arthritis on discharge. She was started on prednisone 50mg/d and the dosage was gradually tapered. The rash and arthritis symptoms were relieved. On discontinuation of steroids, her rash and arthritis resurged and extended, and she started to have fever. On examination by our hospital, her pretibial skin was soft but showed a marked depression with lipoatrophy. Both CRP and ESR were found to be elevated. Repeated IgA levels were still low. Polyarthritis was reconfirmed by ultrasound. A pretibial skin biopsy was done and pathology was consistent with panniculitis with lymphocyte infiltration. Uveitis was ruled out by ophthalmologists. She was re-initiated with prednisone and treated with methotrexate for her arthritis. A detailed family history was collected. She experienced recurrent deep oral ulcers at 3–5 years old and recurrent respiratory infections were also noted. Whole exome sequencing for the family was done and revealed a de novo variant c.1867C>T (p.H623Y) in STAT4, which was classified as pathogenic according to ACMG guidelines (PS4+PM2_Supporting +PS2). Lymphocyte phenotyping showed decreased CD4+ T lymphocytes and NK cells but normal CD8+ T lymphocytes and B cells. She was diagnosed with STAT4-associated autoinflammatory disease and started on ruxolitinib treatment and followed.

Discussion: DPM is a severe form of scleroderma with progressive deep fibrosis and poor prognosis. In 2023, Baghdassarian et al identified the first genetic cause of DPM from three independent families. In their study, all patients share STAT4 germline variants with varying ages of onset ranging from 9 months to 5 years. All reported patients were male, and one patient deceased. The patient in our study is the first female patient reported. Although our patient shares the same variant with the third pedigree in the previous study, her onset age was later and had different chief complaint. All STAT4-AID patients (including the girl in our study) showed similar histopathological findings with classic DPM. However, the laboratory findings varied. DPM is commonly associated with eosinophilia and IgG could be elevated. All patients (except the one with no immunoglobin data) showed IgA deficiency, and 3/5 had history of recurrent infections, suggesting the immunodeficiency and autoinflammation overlapping phenotype. In vitro, these variants led to enhanced phosphorylation of STAT4 and overactivation of IL6 promoter detected by the luciferase assay, confirming the gain-of-function phenotype. Patient-derived fibroblasts also showed increased IL-6 secretion and impaired wound healing and contraction. These phenotypes could be rescued with Janus kinase inhibition ruxolitinib. Considering the above evidence, our patient was started on ruxolitinib and no flares occurred over the past 5 months.

Conclusions: STAT4-associated autoinflammatory disease is a rare inborn error of immunity characterized by panniculitis rash, arthritis, and low IgA levels. To our knowledge, this is 1st Chinese patient and the 2nd report of STAT4-autoinflammatory disease since the genetic discovery. Early intervention with JAK inhibitors may be crucial to halt the progression to disabling pansclerotic morphea.



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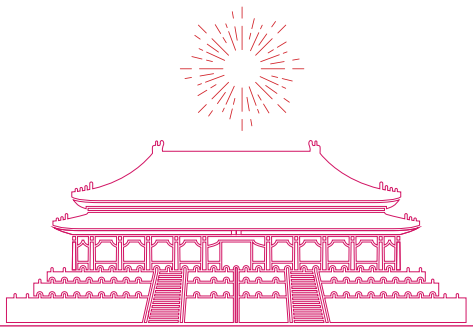
Case	1	2	3	4	5 (This study)
Variant	p.A635V	p.A635V	p.A650D	p.H623Y	p.H623Y
Sex	M	M	M	M	F
Age of onset	3y	5y	3y	9m	6y
Growth restriction	Unknown	+	Unknown	–	–
Oral ulcers	+	Unknown	Unknown	Unknown	+
Typical skin lesions	+	+	+	+	+
Skin ulcers	+	+	+	+	–
Arthritis	+	+	+	+	+
Joint contracture	–	+	+	+	_
Muscle atrophy	+	+	+	–	–
Bone damage	Unknown	+	Unknown	–	–
Squamous carcinoma	–	+	–	–	–
Recurrent infections	–	–	+	+	+
Eosinophilia	–	–	+	–	–
CRP or ESR elevation	+	+	+	–	+
IgG	Normal	Low	Unknown	Normal	Normal
IgA	Low	Low	Unknown	Low	Low
IgM	Normal	Low	Unknown	Unknown	Normal
Autoantibodies	Unknown	Unknown	–	Unknown	–
Treatment	Ruxolitinib	Ruxolitinib	Unknown	MTX→ADA	MTX→Ruxolitinib
Outcome	Remission	Remission	Dead	Remission	Remission

IEI
IN ADULTS



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Primary Immunodeficiency Diseases Are not Only Diseases of Children

Prof. Kazushi Izawa

Professor, Department of Child Health and Development,
Tokyo Medical and Dental University, Tokyo, Japan

Thymoma-associated Immunodeficiency: A Case Report from Vietnam

Tung Lam Do Thi, Hieu Chu Chi, Nguyet Nguyen Nhu, Hang Vu Thi

Tam Phuc Allergy & Clinical Immunology Clinic; Bach Mai Hospital

Introduction: Good syndrome (GS) is a rare immunodeficiency disorder characterized by hypogammaglobulinemia and thymoma, typically diagnosed in individuals aged 40 – 70 years. Its prevalence is estimated at 1/700000 – 1.5/1000000, primarily from Europe and Asia. GS is defined by critically low or absent peripheral B cell counts, CD4+ T lymphopenia, elevated CD8+ T cell counts, inverted CD4+/CD8+ cell ratios, and impaired T cell proliferative responses to mitogens. These immunological abnormalities lead to hypogammaglobulinemia predisposing patients to recurrent severe infections, autoimmune diseases, and malignancies. So, it progresses worse than other adult immunodeficiencies.

Case Presentation:
A 39-year-old Vietnamese male with no prior medical history presented with severe pneumonia due to SARS-CoV-2, followed by recurrent fever and pneumonia episodes for about 3 months. The workup excluded influenza, HIV, CMV, Epstein-Barr virus, and fungal infections. Laboratory investigations revealed profound hypogammaglobulinemia with an IgG level of 73.8 mg/dl, lymphopenia (particularly CD4+T cells count of 54 cells/μL), decreased CD4:CD8 ratio of 0.45, and B-cells level approximately 0. Serological tests for autoimmune disease were negative. However, a chest CT scan identified a 6 cm anterior mediastinal mass with features suggestive of thymoma, confirmed histopathological as thymoma type AB. The diagnosis of Good syndrome was established. Therefore, management included antibiotics, IVIG (400mg/kg when IgG < 600mg/dl), and thymoma resection. One year postoperatively, the patient demonstrated stable IgG levels (700-800 mg/dL) with monthly monitoring.

Discussion: Recognition of hypogammaglobulinemia in thymoma-associated secondary immunodeficiency is critical to reducing infection-related complications. The immunodeficiency in GS can improve after thymectomy, however adjustive IVIG therapy may be required to manage severe hypogammaglobulinemia.

Conclusions: Early identification and comprehensive management of GS, including timely thymoma resection and long-term immunoglobulin replacement, are crucial for favorable outcomes in affected patients.

Good Is Bad: Repeated Infections and Intrathoracic Mass in a 44-Year-Old Woman

Sharmen S. delos Santos-Gallon, MD; Maria Socorro L. Agcaoili-de Jesus, MD; Emerita Brigino -Buenaventura, MD; Christine P. Manalili-Trinidad, MD

University of the Philippines – Philippine General Hospital, Department of Internal Medicine, Division of Allergy & Immunology

Introduction: Good syndrome is a rare adult-onset immunodeficiency with thymoma, hypogammaglobulinemia, and increased susceptibility to encapsulated bacteria, opportunistic viral, or fungal infections.

Case Presentation:

A previously healthy 44-year-old female had an incidental detection of a benign thymoma which was resected in 2019.

Three years after the thymectomy, the patient experienced recurrent and difficult-to-treat pneumonia with encapsulated organisms such as *Hemophilus parainfluenza*, as well as Covid-19 infection and oral thrush. She was brought to our hospital in July 2022 due to progressive cough and shortness of breath for eight months. Serial immunological tests showed hypogammaglobulinemia, very low CD19 and CD20 B cells, and low CD4 T cells *(Table 1)*. She was diagnosed with Good syndrome (GS) and prescribed intravenous immunoglobulin (IVIG) 400mg/kg monthly.

Discussion: Dr. Robert Good first identified the connection between adult-onset hypogammaglobulinemia and the presence of a thymoma in 1955. Good syndrome's clinical presentation varies greatly, ranging from recurring bacterial and opportunistic infections to autoimmune disorders and even malignancies. Recognizing this condition can be difficult due to its diverse clinical manifestations and insufficient diagnostic criteria. This is a rare and understudied category of a phenocopy of inborn errors of immunity with uncertain pathogenesis. Immunoglobulin replacement and supportive antibiotics are recommended treatments for this condition in order to prevent infection.

Conclusions: Patients over the age of 40 with a history of thymectomy, recurrent infections with encapsulated bacteria, opportunistic viral and fungal infections, and unexplained antibody deficiency should be investigated for Good syndrome. Hypogammaglobulinemia, decreased or absent B cells, and cell-mediated immune defects are immunological abnormalities that are seen in this disease. To date, this is the third known case of Good syndrome in the Philippines. With increased awareness by reporting this case, recognition of this disease and implementation of current management can help future clinicians and patients in the Philippines.

TABLE 1. Immunological Tests & Radiographic Imaging

IMMUNOLOGICAL TESTS				
	April 2022	**July 2022**	**December 2022**	**February 2024**
CD3 (Reference Value: 1220-2256 cells/cu.mm)	1066 cells/ cu.mm	1116 cells/ cu.mm	1036 cells/ cu.mm	---
CD4 (Reference Value: 581-1177 cells/cu.mm)	294 cells/cu.mm	346 cells/cu.mm	310 cells/cu.mm	---
CD45 (Reference Value:500-1400 cells/cu.mm)	---	1312 cells/ cu.mm	---	---
CD8 (Reference Value:490-1031 cells/cu.mm)	658 cells/cu.mm	730 cells/cu.mm	670 cells/cu.mm	---
CD16+56 NK Cell (Reference Value:142-523 cells/cu.mm)	126 cells/cu.mm	198 cells/cu.mm	192 cells/cu.mm	---
CD19 (Reference Value:118-323 cells/cu.mm)	3 cells/cu.mm	4 cells/cu.mm	2 cells/cu.mm	---
CD20 (Reference Value:139-347 cells/cu.mm)	5 cells/cu.mm	---	---	---
CD4:CD8 ratio (Reference Value:0.9-4.5)	---	0.47	---	---
Serum IgG	69.1 IU/ml (Ref Value: 90.1-187 IU/ml)	---	---	5.14 g/L (Ref Value: 6.1-16.1 g/L)
Serum IgA	42.3 IU/ml (Ref Value: 57.4-317 IU/ml)	---	---	---
Serum IgM	12 IU/ml (Ref Value: 54.3-359IU/ml)	---	---	---

RADIOGRAPHIC IMAGING	
RADIOGRAPHIC IMAGING	**FINDING/S**
PET CT SCAN (July 2022)	• s/p thymectomy with no evidence of mass to suggest tumor recurrence
HRCT (December 2021)	• Findings in the lungs are commonly reported imaging features of COVID-19 pneumonia (CORADS 6) • Bilateral lung fibrosis • Post-sternotomy changes

Sarcoidosis-associated Immunodeficiency

Vu Thi Hang[1], Chu Chi Hieu[1], Nguyen Nhu Nguyet[1], Nguyen Thi Van Anh[2], Nguyen Dinh Giang[2], Ha Phuong Anh[2], Bui Thuy Quynh[2].

1 *Center of Allergy and Clinical Immunology, Bach Mai Hospital.*
2 *Viet Nam National Children's Hospital.*

Introduction: GATA 2 deficiency is a rare disorder of the immune system with wide-ranging effect. GATA2 deficiency is diagnosed based on clinical findings, laboratory tests, and genetic testing.

Case Presentation:
A 35-year-old female was admitted for joint pain and red papules on the right arm. She was initially diagnosed with erythema nodosum and treated with diclofenac. Immunology evaluation demonstrated normal immunoglobulin level; the ANA test was negative. There was no lymphocytosis, the CD4/CD8 ratio was normal, and bone marrow examination was normal. A CT scan of the thorax showed interstitial pulmonary infiltrates, with a patchy, subpleural pattern of increased reticulation. Extensive culture and PCR analysis of BAL fluid did not reveal active infectious disease. The result of the skin biopsy showed granulomatous inflammatory, including semi-permeable and giant cells, that are suggestive of sarcoidosis. Notably, her son suffers from GATA2 deficiency, so genetic examination was indicated for her. Her genetic testing revealed heterozygous pathogenic mutations for an inversion on p.(Arg337) encompassing the *GATA2* (NM_001145661.1) gene. These findings were consistent with a diagnosis of GATA2 deficiency with sarcoidosis-like disease.

Discussion: The clinical features of GATA2 deficiency are wide-ranging in both type and severity. Apart from haematologic and infectious phenotypes, additional clinical presentations have been described, such as aplastic anaemia, pulmonary alveolar proteinosis, dermatological, autoimmune, or vascular features. Autoimmune or chronic inflammatory disorders, such as lupus, sarcoidosis-like disease, Sweet's syndrome, and panniculitis, are recurrent. Mutations for an inversion on p.(Arg337) encompassing the GATA2 (NM_001145661.1) gene have been described as causing primary lymphoedema with myelodysplasia. However, our patient presented with erythema nodosum and pulmonary involvement, without haematologic abnormalities.

Conclusions: Sarcoidosis-like disease was a rare clinical feature of GATA 2 deficiency. No correlation between the type or location of the GATA2 mutation and the clinical/biological phenotype has been established.

GASTROINTESTINAL DISEASES IN IEI

Please click this picutre to return to the agenda page.

Advanced Therapies for Inflammatory Bowel Disease Due to Inborn Errors of Immunity

Prof. Holm Uhlig

Professor of Paediatric Gastroenterology and Lead Clinician of NIHR Paediatric IBD BioResource University of Oxford
Oxford, UK

When EBV-Associated Visceral Tumors Meet IBD: Rare Etiological Links in Dual Pathological Manifestations

Qiling Xu,Xi Yang

Children's Hospital of Chongqing Medical University

Introduction: CARMIL2 deficiency is a rare combined immunodeficiency (CID) characterized by defective CD28-mediated T cell co-stimulation, altered cytoskeletal dynamics, and susceptibility to Epstein Barr Virus smooth muscle tumors (EBV-SMTs). Case reports associated with EBV-SMTs are limited. We describe herein a novel homozygous CARMIL2 variant(c.2105 A>G) in a Chinese male born in unconsanguineous parents who developed EBV-SMTs and IBD.Here we analyzed the clinical, genetic, and immunological features of this patient.

Case Presentation:
The major manifestation observed in the patient was recurrent pneumonia, Epstein Barr Virus smooth muscle tumors and inflammatory bowel disease dignosed by biopsy and colonscopy.Whole-exome sequencing indicated novel homozygous N702S mutation of CARMIL leading to low of CD28 expression. The immunological features of this patient showed low percentage of CD4, memory B and Treg..

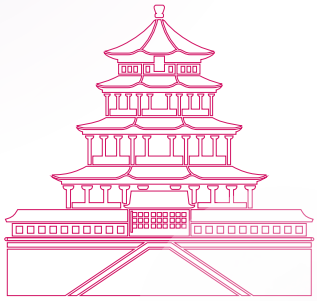
Discussion: CARMIL2 deficiency is a rare combined immunodeficiency (CID) characterized by defective CD28 -mediated T cell co-stimulation, altered cytoskeletal dynamics, and susceptibility to Epstein Barr Virus smooth muscle tumors (EBV-SMTs). Case reports associated with EBV-SMTs are limited. We describe herein a novel homozygous CARMIL2 variant(c.2105 A>G) in a Chinese male born in unconsanguineous parents who developed EBV-SMTs and IBD.Here we analyzed the clinical, genetic, and immunological features of this patient. These findings expand the clinical spectrum of CARMIL deficiency, reinforce its diversity.

Conclusions: We reported one chinese patient with a novel CARMIL mutation. This patients showed recurrent pneumonia, Epstein Barr Virus smooth muscle tumors and inflammatory bowel disease. These findings expand the clinical spectrum of CARMIL deficiency, reinforce its diversity, and identify a therapeutic method for this rare disease.

APSID Congress

Day1 12.04.2025

7:00 - 7:45	REGISTRATION
7:45 - 8:00	WELCOME CEREMONY
8:00 - 9:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 1
9:00 - 10:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 2
10:00 - 11:00	POSTER WALK WITH TEA/COFFEE: RESEARCH POSTERS I
11:00 - 12:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 3
12:00 - 13:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 4
13:00 - 14:00	LUNCHEON SEMINARS
14:00 - 14:30	TEA/COFFEE BREAK
14:30 - 15:15	THE 5TH PROFESSOR YU LUNG LAU ORATION
15:15 - 15:30	AWARD PRESENTATION: APSID MEDAL OF HONOR FOR LIFETIME ACHIEVEMENT
15:30 - 16:30	POSTER WALK WITH TEA/COFFEE: IEI SCHOOL POSTERS
16:30 - 17:30	SYMPOSIUM WITH PRESENTATIONS OF CLINICAL CASES: SESSION 1
17:30 - 18:30	SYMPOSIUM WITH PRESENTATIONS OF CLINICAL CASES: SESSION 2
18:30 - 19:00	APSID ANNUAL GENERAL MEETING
19:30 - 21:30	CONGRESS DINNER

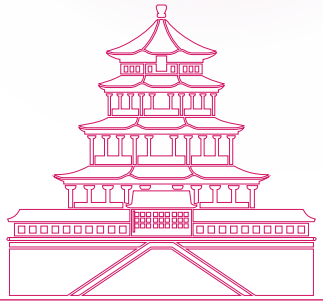


"To view a specific abstract, simply click on the session listed on the agenda page. The link will take you directly to the corresponding abstract page."

Beijing, China 11-13.04.2025

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 1



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Mendelian Disease Discovery: From Inherited Skin Conditions to Inborn Errors of Immunity

Dr. Xue Zhang

X-Linked Agammaglobulinemia, the Oldest Primary Immunodeficiency/Inborn Error of Immunity, Yet Still Reluctant to Reveal Its Secrets

Prof. Hans Ochs

Improving Patient Care and Treatment through the Primary Immunodeficiency Registry in Malaysia

Intan Hakimah Ismail[1,2*], Jalilah Jamaluddin[1,2], Mohd Azri Zainal Abidin[1,2], Khairoon Nisa Mohamed Nashrudin[1, 2]

1 *Advanced Medical Research in Allergy & Clinical Immunology, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Malaysia.*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Kuala Lumpur, Malaysia.l.*

Background and aims: A national primary immunodeficiency (PID) registry is an essential tool for tracking and managing information about individuals diagnosed with PID. While countries like the US, UK, Japan, and South Korea have established such registries, Malaysia lacks an official national PID registry, despite the existence of the Malaysian Primary Immunodeficiency Network (MyPIN) since 2009. PID is under-reported in Malaysia and the true prevalence and diversity of these diseases remain unclear. This study aims to establish a national PID registry for better documentation and research. Paediatric Immunology at Universiti Putra Malaysia (UPM), a major referral center for PID, provides both clinical and laboratory support dedicated for PID patients.

Methods: The registry is designed for long-term use incorporating demographic and clinical data from UPM's Paediatric Immunology clinical notes. Data collected include patient details, PID diagnosis, age at symptom onset and diagnosis, clinical manifestations, family history, treatment types, and laboratory test results (e.g., immunoglobulins, IgG subclasses, lymphocyte subsets, specific antibody responses, lymphocyte proliferation, and B cell profiling). PID diagnoses are made according to the criteria set by the International Union of Immunological Societies (IUIS).

Results: From 2012 to 2022, data from 409 patients were entered into the registry. The number of PID cases referred for investigations increased annually. The most common PID category was predominant antibody deficiencies (12.96%), followed by immunodeficiencies affecting both cellular and humoral immunity (11.25%), congenital defects of phagocytes (9.78%), and combined immunodeficiencies with syndromic features (7.09%). X-linked agammaglobulinemia was the most frequent condition with antibody deficiencies (28.3%). Additionally, 183 cases are still under investigation, and 25 cases were not classified as PID.

Conclusions: The registry emphasizes the importance of establishing a national PID registry to improve the understanding of PID epidemiology, prevalence, and clinical features. Such data are crucial for research, treatment development, and enhancing practitioners' knowledge of PID.

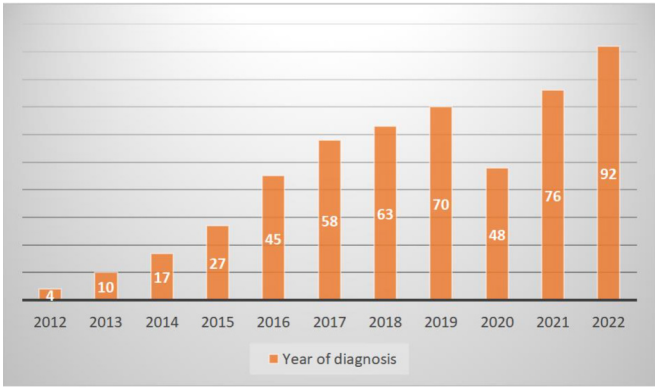


Figure 1: Case of possible PID to be investigated according to year

Epidemiology of primary immunodeficiency identified from the Korean Immunodeficiency Network (KiNET) and registry project

Sohee Son[1], Hwanhee Park[2,14], Doo Ri Kim[1], Kiwook Yoon[3], Eun Hwa Choi[3], Dayun Kang[3], Ji-man Kang[4], Hyeonmi Kang[5], Dae Chul Jeong[5], Hye-kyung Jo[6], Hyeonjoo Lee[7], Jaehong Choi[8], Gahee Kim[9], Hun Kook[10], Hee-jo Baek[10], Yun-seon Yoon[11], Su-Eun Park[12], Kyo-jin Jo[12], Areum Shin[1], Soyeon Kim[1], Sungbin An[1], Youngjun Choi[13], Eun Young Cho[15], Joon Kee Lee[16], Youn-soo Hahn[16], Yae-Jean Kim[1,2]

1 *Samsung Medical Center*
2 *Sungkyunkwan University School of Medicine*
3 *Seoul National University Children's Hospital*
4 *Severance Children's Hospital*
5 *Seoul St. Marys Hospital*
6 *Ewha Womans University Mokdong Hospital*
7 *Seoul National University Bundang Hospital*
8 *Jeju National University Hospital*
9 *Chosun University Hospital*
10 *Chonnam National University Hospital*
11 *Korea University Guro Hospital*
12 *Pusan National University Yangsan Hospital*
13 *Korea University Anam Hospital*
14 *Soonchunhyang University Bucheon Hospital*
15 *Chungnam National University Hospital*
16 *Chungbuk National University Hospital*

Background and aims: Inborn error of immunity (IEI) is a group of rare diseases caused by a singlegene defect in the immune system. Due to limited epidemiological data on IEI in Korea, we attempted to develop a registry program and establish a national multicenter network.

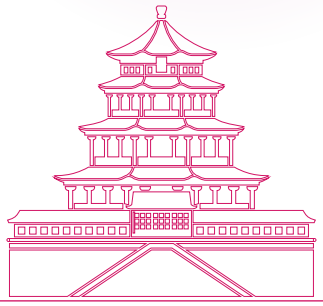
Methods: Korean Immunodeficiency Network (KiNET) was established in March 2022, funded by the Lee Kun-hee Child Cancer and Rare Disease Project (Grant number: 22B-002-0100). The web-based IEI registry was developed, adhering to the "2019 International Union of Immunological Societies (IUIS)" and updated to the most recent version of "2022 IUIS". In order to analyze the residence and disease distribution of all IEI patients registered in KiNET, IUIS Table, Disease, and Disease subclass items of "Region of current residence" and "IEI Diagnosis" among the baseline items were collected.

Results: A total of 180 IEI patients (Male 126, Female 54) were identified in 13 centers. The region of residence was reported, with Gyeonggi Province having the highest number of cases (68 patients), followed by Seoul (35 patients) and Incheon (17 patients); all within the metropolitan area. An additional 60 patients were identified in other provinces.The IEIs sorted by 2022 IUIS were reported in 18 patients for Immunodeficiencies affecting cellular and humoral immunity, 26 patients for Combined immunodeficiencies with associated or syndromic features, 57 patients for Predominantly antibody deficiencies, 18 patients for Diseases of immune dysregulation, 35 patients for Congenital defects of phagocyte number or function, 6 patients for Defects in intrinsic and innate immunity, 10 patients for 7. Autoinflammatory disorders, 2 patients for Complement deficiencies, 2 patients for Bone marrow failure, 6 patients for Phenocopies of inborn errors of immunity.

Conclusions: In this study, we established a systematic IEI registry for the first time in Korea which will provide a solid foundation for future research.

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 2



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Updates in the Diagnosis and Treatment of Hemophagocytic Lymphohistiocystosis

Dr. Tianyou Wang

Respiratory Syncytial Virus Infection and Immunodeficiency

Prof. Hirokazu Kanegane

PTPN2 deficiency modulates STAT3 signaling and induces muscle damage in Juvenile Dermatomyositis

Zheng Qi; Wang Zhaoling; Lu Meiping

Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China.

Background and aims: Janus-kinase signal transducer and activators of transcription 3 (JAK/STAT3) pathway was over-activated in juvenile dermatomyositis (JDM). How JAK/STAT3 signaling modulated was not fully understood. To verify the mechanism by which protein tyrosine phosphatase non-receptor type 2 (PTPN2) negatively regulates the JAK/STAT3 signaling pathway.

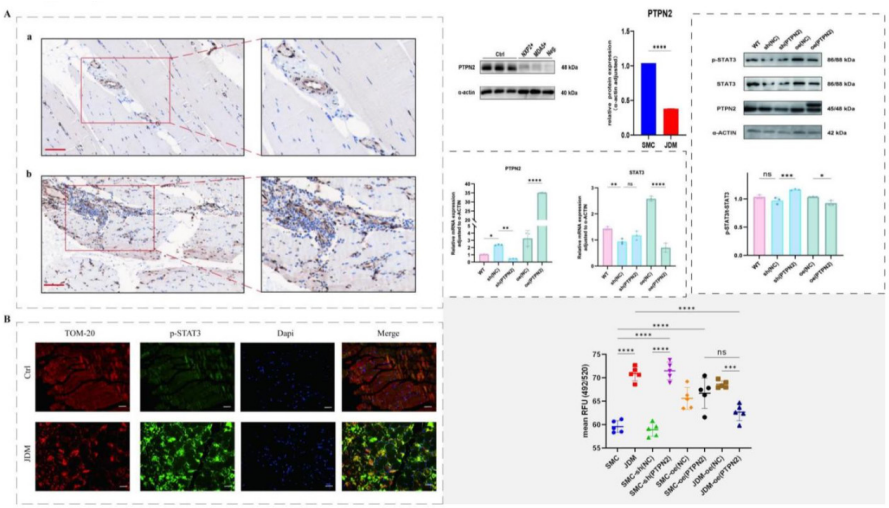
Methods:

PCR was used to screen the levels of transcription factors negatively regulate JAK/STAT3 signaling pathway, and the transcription of PTPN2 was found significantly decreased. Immunohistochemistry showed that the expression of PTPN2 in the muscle tissue of JDM patients was decreased. Skeletal muscle cell models (PTPN2+ or PTPN2-) were established, and the differential expression of pSTAT3 in cytoplasm and mitochondria was compared, and the localization detection was carried out by confocal microscopy. Sensitivity to IFN assay was conducted through the cell models.

Results:

ScRNA-seq analysis of muscle biopsies from patient with JDM revealed abnormal activation of the JAK/STAT3 pathway in skeletal myocytes, macrophages, and vascular endothelial cells. The phosphorylation levels of STAT3 were elevated in active JDM cases. Transcription of PTPN2 was found significantly decreased in patients with JDM. Knock-down PTPN2 induces enhanced phospharylation of STAT3 (pSTAT3) in cytoplasm, but not the expression of STAT3. Over-expressed PTPN2 induces decreased pSTAT3 in both cytoplasm and mitochondria. Skeletal muscle cell (PTPN2-) showed increased sensitivity to IFN-a and IL-6 as well as increased ROS production.

Conclusions: PTPN2 negatively regulates JAK/STAT3 signaling pathway in JDM and plays a critical role in the muscle damage of patients with JDM..



Hematopoietic Stem Cell Transplantation for children with leukodystrophy : A single center retrospective study

Wenjin Jiang, Xiaowen Qian, Ping Wang, Quanli Shen, Hongsheng Wang , Shuizhen Zhou, Yi Wang and Xiaowen Zhai

Children's Hospital of Fudan University, Shanghai

Background and aims: Leukodystrophies and genetic leukoencephalopathies comprise a growing group of inherited white matter disorders.The majority of these genetic diseases are asso- ciated with specific enzyme defects, with each enzyme responsible for the degradation of particular substrates. These enzymatic deficiencies lead to the accumulation of substrate, which directly or indirectly contributes to toxicity. Disorders such as metachromatic leukodystrophy(MLD) and globoid cell leukodystrophy(GLD) are caused by lysosomal enzyme deficiencies, and are in- herited in an autosomal recessive fashion. In contrast, adrenoleukodystrophy(ALD) is a peroxisomal disorder and is X-linked in inheritance.

These three conditions are the primary disorders currently treated with allogeneic hematopoietic stem cell transplantation (HSCT).

Methods: A retrospective study was performed in patients with

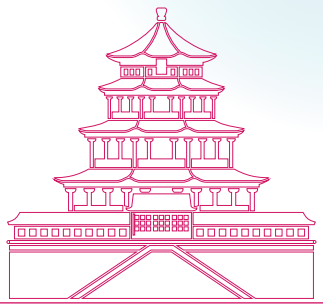
leukodystrophy who underwent HSCT after myeloablative chemotherapy in Children's Hospital of Fudan University between April 2015 and October 2024.

Results: The study cohort included 41 pediatric patients (thirty three males), twenty six with cerebral ALD,thirteen with GLD and two with MLD. One patient received a haploidentical donor, two patients received matched sibling donors, and the rest received unrelated umbilical cord blood(UCB). There were no cases of graft rejection. Median neutrophil engraftment time was 17 days [9–33 days] and median platelet engraftment time was 29 days [8–65 days]. Median follow-up was 31 months [1–117 months], and the overall survival rate for patients with cerebral ALD, juvenile GLD and the congenital or late infantile form MLD after HSCT were 88.4% (23/26) ,100% (13/13) and 100% (2/2) ,respectively.Two patients died from severe pneumonia, and one patient died from severe infection and grade IV graft-versus-host disease(GVHD).Seven patients with ALD, twelve patients with GLD and all patients with MLD showed stable neurologic function score and performance status after transplantation.

Conclusions: In patients with cerebral ALD, patients with no or mild neurological symptoms can benefifit from HSCT. In patients with juvenile GLD and the congenital or late infantile form MLD,HSCT is safe and contributes to stabilize neurological function.

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 3



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Newborn Screening of IEI in China

Dr. Wei Li

Mild Wiskott-Aldrich Syndrome: Does It Exist? And How Should We Treat It?

Prof. Michael Albert

A new tecnique of manipulation in Haploidentical Transplantation: Report of a single center group of patients with primary immunodeficiencies

Fulvio Porta[1], Marianna Maffeis[1], Giulia Albrici[1], Giulia Baresi[1], Stefano Rossi[1], Vincenzo Pintabona[1], Fabian Richard Schumacher[1], Alessandra Beghin[2], Federica Bolda[2], Marta Comini[2], Elena Soncini[1], Arnalda Lanfranchi[2]

1 *Pediatric Oncohematology and Bone Marrow Transplant Unite, Children's Hospital, ASST Spedali Civili, Brescia, Italy*
2 *Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Diagnostic Department, ASST Spedali Civili, Brescia, Italy*

Introduction: Allogeneic hematopoietic cell transplantation is a therapeutic option not only for malignant diseases but also for inborn errors of immunity.

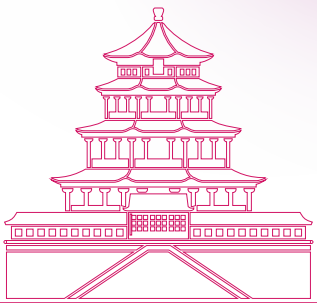
Case Presentation: Here we report our experience, the evolution in transplantation techniques that have contributed to making haploidentical BMT an alternative source of HSC in the absence of an HLA-compatible donor, overcoming one of the main limitations of this type of transplantation: the risk of GvHD. Indeed, the most important problem of CD34+ isolated selection on both bone marrow and PBSC is the risk of no take and delayed reconstitution. As a result, in recent years, an original manipulation technique has been developed in our Center that involves the positive selection of CD34+ stem cells on PBSC and the addback of a controlled number of CD3+ T lymphocytes (20-30 x106 cells/kg recipient). The limitations of pure selection of CD34+ stem cells in terms of immunological engraftment and reconstitution were overcome by involving a controlled number of CD3+T lymphocytes.

Results and discussion: Recently our new techniques allowed to achieve relevant results in the engraftment rate and in incidence and severity of GVHD also in Matched Unrelated Donor (MUD) BMT. Analyzing our last years, from January 2019 to July 2023 we retrospectively collected our data on bone marrow transplants with CD34+ selection and CD3+ addback performed at our Centre for both malignant and non malignant diseases: 31 patients (18 MUD, 13 Haplo). We dind't see any graft failure. Only one patient developed grade III acute GVHD, no patients developed grade IV aGVHD, only 1 patient developed chronic GVHD with cumulative incidence of aGVHD grade III-IV<10%. The immunological exams revealed that in haplo cohort 20% reached 200/ml CD4+ and 1000 ml CD3+ cell counts on D+100, >50% reached 200/ml CD4+ and 1000/ml CD3+ on D+180, no significant differences there were between Haplo and MUD BMT.

Conclusions: Haploidentical transplantation using CD34+ selection/CD3+ addback/PT-Cy and serotherapy is feasible and safe, we had good engraftment rates, low rates of GVHD. The continuous improvement of manipulation strategies has made possible to obtain excellent results not only in terms of GvHD control, but also in survival with an overall survival for the last transplanted patients almost 100%.

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 4



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CCL2: Old Molecule as a Novel Candidate for Mendelian Susceptibility to Mycobacterial Disease

Dr. Xiaodong Zhao

Respiratory Syncytial Virus Infection and Immunodeficiency

Prof. Manish Butte

The response to abatacept therapy in children with immune dysregulation syndromes – T-regopathies (LRBA and CTLA4 deficiencies)

D. Bogdanova, Y. Rodina, E. Raykina, D.Yukhacheva, V. Burlakov, N. Kan, A. Avedova, A. Moiseeva, I. Abramova, E. Deripapa, Z. Nesterenko, A. Mukhina, D. Pershin, G. Tereshchenko, A. Shcherbina

Dmitry Rogachev National Research Center of Pediatric Hematology - Oncology and Immunology, immunology, Moscow, Russia

Background and aims: T-regopathies (TR) are a subgroup of immune dysregulation syndromes. They are characterized by autoimmunity involving different organs, infectious and oncological manifestations. Abatacept is a biologically modified CTLA4 molecule and a potent therapeutic option for this cohort.

Case Presentation: Here we report our experience, the evolution in transplantation techniques that have contributed to making haploidentical BMT an alternative source of HSC in the absence of an HLA-compatible donor, overcoming one of the main limitations of this type of transplantation: the risk of GvHD. Indeed, the most important problem of CD34+ isolated selection on both bone marrow and PBSC is the risk of no take and delayed reconstitution. As a result, in recent years, an original manipulation technique has been developed in our Center that involves the positive selection of CD34+ stem cells on PBSC and the addback of a controlled number of CD3+ T lymphocytes (20-30 x106 cells/kg recipient). The limitations of pure selection of CD34+ stem cells in terms of immunological engraftment and reconstitution were overcome by involving a controlled number of CD3+T lymphocytes.

Results and discussion: Recently our new techniques allowed to achieve relevant results in the engraftment rate and in incidence and severity of GVHD also in Matched Unrelated Donor (MUD) BMT. Analyzing our last years, from January 2019 to July 2023 we retrospectively collected our data on bone marrow transplants with CD34+ selection and CD3+ addback performed at our Centre for both malignant and non malignant diseases: 31 patients (18 MUD, 13 Haplo). We dind't see any graft failure. Only one patient developed grade III acute GVHD, no patients developed grade IV aGVHD, only 1 patient developed chronic GVHD with cumulative incidence of aGVHD grade III-IV<10%. The immunological exams revealed that in haplo cohort 20% reached 200/ml CD4+ and 1000 ml CD3+ cell counts on D+100, >50% reached 200/ml CD4+ and 1000/ml CD3+ on D+180, no significant differences there were between Haplo and MUD BMT.

Conclusions: Haploidentical transplantation using CD34+ selection/CD3+ addback/PT-Cy and serotherapy is feasible and safe, we had good engraftment rates, low rates of GVHD. The continuous improvement of manipulation strategies has made possible to obtain excellent results not only in terms of GvHD control, but also in survival with an overall survival for the last transplanted patients almost 100%.

Barriers and challenges to healthcare access in patients with Primary Immunodeficiency Diseases: a phenomenological qualitative study

Adamu Sa'idu Adamu[1], Zarina Thasneem Zainudeen[1], Fahisham Taib[2], Izzal Asnira Zolkepli[3], Azizah Omar[4], Intan Juliana Abd Hamid[1*]

1 *Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Institut Perubatan dan Pergigian Termaju, Universiti Sains Malaysia, Bertam, Pulau Pinang, Malaysia,*
2 *Paediatric Department, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia,*
3 *School of Communication, Universiti Sains Malaysia, Pulau Pinang, Malaysia,*
4 *School of Management, Universiti Sains Malaysia, Pulau Pinang, Malaysia*

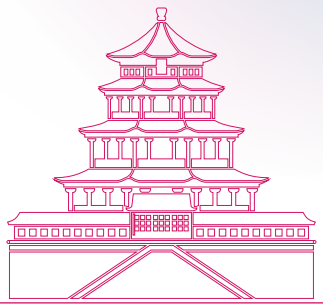
Background and aims: There has been progress in the diagnosis and treatment of Primary Immunodeficiency Disease (PID). However, this progress significantly varies between countries, causing wide regional disparities in PID care and eliciting the need for country-specific policies to improve the care of PID patients. We aimed to appraise the barriers to PID care in Malaysia through stakeholders' involvement, hoping to set a framework for PID care quality improvement in Malaysia.

Methods: This is a preliminary result of a Phenomenological qualitative design. Using a constructivist paradigm, we conducted an In-depth Interviews (IDIs) with Pediatricians directly involved in managing PID cases in Malaysia. The interviews were conducted via online, recorded, and transcribed verbatim into written records. The transcripts were analysed using ATLAS.ti® (LUMIVERO LLC) version 25. Data were coded in three cycles. The first coding used QDA Artificial Intelligence (AI coding), followed by 2 additional cycles by the researchers. An inductive thematic analysis was performed using Braun and Clarke's six phases.

Results: This study enrolled eight pediatricians, four of whom are clinical immunologists. The age of respondents ranged 42-78 years with mean: 52 ± 13 years. Respondents had a mean clinical experience of 16 ±11 years. A total of 137 codes were generated from 8 IDI documents. Several themes emerged as barriers to access for PID healthcare delivery, including governance and policy, such as the absence of recognition and policy, which results in a shortage of clinical immunologists, barriers to treatment access and low disease awareness.

Conclusions: The study finding highlight the urgent need for targeted policy intervention, capacity building and enhanced stakeholder involvement to address gaps in PID care. Developing a comprehensive framework for PID care in Malaysia, based on the identified barriers, is crucial for enhancing health outcomes and minimizing disparities in care delivery.

LUNCHEON SEMINARS



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Poliovirus Excretion Among Patients with Primary Immunodeficiency Disorders

(Format: Virtual)

Dr. Ondrej Mach and
Dr. Syeda Kanwal Aslam

Poliovirus Surveillance Among Patients with Primary Immunodeficiency Disorders

(Language: Chinese)

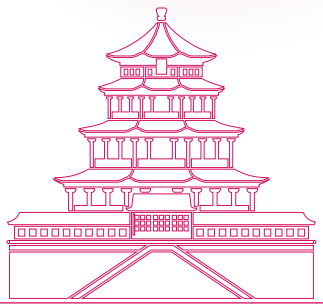
Dr. Hong Yang

Application of New Generation Immunoglobulin G Preparations in Rheumatic and Immune Diseases

(Language: Chinese)

Prof. Huawei Mao

THE 5TH PROFESSOR YU LUNG LAU ORATION



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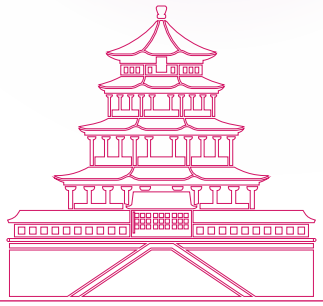
Gene Therapy and Enzyme Replacement Therapy for Inborn Errors of Immunity Around the World and What Lies Ahead for the Asia Pacific?

Prof. Fabio Candotti

SYMPOSIUM WITH PRESENTATIONS OF CLINICAL CASES:

SESSION 1



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First Results of Neonatal Screening Utilizing TREC/KREC in Russia: Statistics and Treatment Outcomes

Dr. Anna Shcherbina

Novel gene causing Severe Congenital Neutropenia

Vaishnavi V Iyengar[1], Akshaya Chougule[1], Prasad Taur[1], Vijaya Gowri[1] , Mukesh Desai[1]

1 *Department of Immunology, Bai Jerbai Wadia Hospital for Children, Parel.*

Introduction: Severe congenital neutropenia (SCN) comprises a heterogeneous group of genetically determined disorders characterized by decreased neutrophils in the peripheral blood and severe skin and deep bacterial infections.

Case report:

A 4 year old male child, born of nonconsanguineous marriage; presented with recurrent sinopulmonary infections starting from 5 months age. He was admitted at 15 months with bronchopneumonia, pyoderma gangrenosum and sepsis. He subsequently also suffered multiple episodes of impetigo and abscess. Immunological tests including lymphocyte enumeration, nitroblue tetrazolium test and immunoglobin levels were normal. Neutrophil count persisted at <500 cells/cumm. Bone marrow examination revealed hypocellular marrow with sequential maturation of neutrophils. He was started on GCSF to maintain ANC>1500/cumm along with antibiotic and antifungal prophylaxis. We performed exome sequencing which did not reveal any pathogenic or likely pathogenic variants in any known genes associated with neutropenia. On follow up he developed acquired microcephaly with delayed speech development and was diagnosed with autism spectrum disorder. Neurological evaluation revealed subclinical epileptic discharges and cerebellar atrophy suggestive of possible neurodegenerative disorder. On re-analysing the data we found a novel homozygous variant in VPS52 gene which was confirmed by Sanger sequencing in index patient. The variant is a splice variant in intron 10 and likely pathogenic according to ACMG guidelines with a CADD score of 29. Both parents are heterozygous for this variant. RNA sequencing showed an aberrant transcript with loss of intervening exons.VPS52 is a vacoular transporting protein existing as a complex with VPS51 and VPS53. Defects in VPS51 and VPS53 also have neurodegenerative phenotype and mild neutropenia.

Conclusions: We present a novel genetic cause of SCN, which combines features of a neurodegenerative disorder with heightened susceptibility to severe infections. In today's era, clinical immunologists must equip themselves with the skills for raw data analysis to uncover novel genes underlying complex phenotypes.

A girl with ipsilateral temporal atrophy- A Case of Parry-Romberg syndrome in Korea

Ji Young Lee[1], Yongjae Lee[2], Ji Young Oh[1], Jee Yeon Baek[1], Hye-Jung Choi[1], Hyun-Soo Seo[1], Jong-Gyun Ahn[1,3], Jeong Seok Lee[2,3], Ji-Man Kang[1,4]

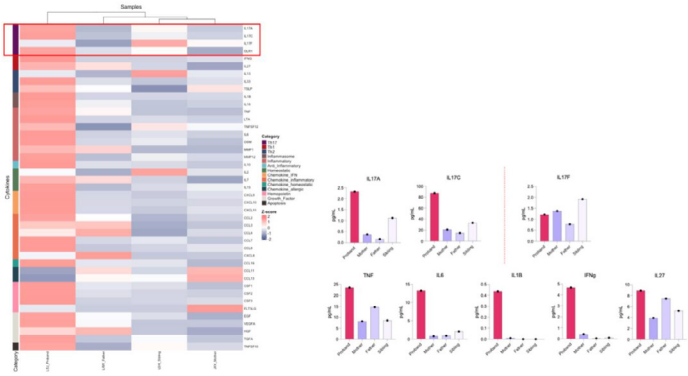
1 *Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Republic of Korea*
2 *Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Republic of Korea*
3 *Genome Insight, Inc., San Diego, La Jolla, CA, USA*
4 *Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Republic of Korea*

Introduction: Parry-Romberg syndrome (PRS) is a craniofacial disorder characterized by progressive hemifacial atrophy associated with neurological, ophthalmologic, and dental impairment with unknown origin. We present a case of a 9-year-old girl with right temporal area atrophy, whose diagnostic process was challenging.

Case Presentation:
A 9-year-old was referred to our IEI clinic by the department of orthodontics and clinical genetics due to depressed right temporal area. She was born at full-term pregnancy to non-consanguineous parents with insignificant family history. She grew up with normal development until she experienced anterior crossbite and cleft alveolus since the age of 8. She was treated at our dental hospital until atrophy in the right temporal area was noted in 3 months prior to the consultation under the impression of PRS. Laboratory results were normal including complete blood count, lymphocyte subset, CRP, ANA, and mitogen function on IGRA; however, whole body bone scan revealed bilateral maxilla, involvement indicating ongoing inflammation. Whole genome sequencing (WGS) of PBMC and saliva samples were unremarkable as well as trio germline WGS. Meanwhile, flow cytometry showed two-fold increase in Th17 cell compared to her family with half the expression of Th1 cells. Multiplex cytokine analysis demonstrated heightened levels of IL-17A, IL-17C, TNF, and IL-1. She has been taking methotrexate and follow-up bone scan three months after treatment showed no chang. Currently, we're considering secukinumab, a monoclonal antibody against IL-17.

Discussion: PRS has traditionally been recognized by orthodontic surgeons and ophthalmologists. However, its pathogenesis might involve immunologic phenomenon. Although a specific genetic cause remains unidentified, could IL-17 inhibition potentially alleviate disease progression? Additionally, what would be the optimal approach for monitoring the patient's disease activity?

Conclusions: Awareness and suspicion of PRS by the orthopedic surgeon allowed further diagnostic work-up and treatment to prevent further bone disruption. Multidisciplinary management in PRS patients is warranted.



a) b)

a) Multiplex cytokine analysis
b) Proband analysis of inflammatory expression

Homozygous p.Arg90His of NCF1 in a twin-sister presenting as mixed connective tissue disease

Xiaoxue Liu, Chongwei Li

Department of Rheumatology & Immunology, Tianjin Children's Hospital, Tianjin, China

Introduction: Null mutation in NCF1 lead to reactive oxygen species(ROS) deficiency and chronic granulomatous disease . A single nucleotide polymorphism in the NCF1 gene (NCF1-339, p.Arg90His), reducing partial ROS ,is associated with systemic lupus erythematosus (SLE),rheumatoid arthritis and Sjögren's syndrome. This study demonstrates the association of homozygous p.Arg90His variant with mixed connective tissue disease(MCTD) in a twin-sister.

Case report:

P1 was a 12-year old girl presented with a 3-month history of Raynaud's phenomenon .She also had fatigue and shortness of breath,diffuse rash and puffy hand . ANA was 1:1280, anti-U1RNP IgG+++, anti-Ro52 IgG++,IgG 25.96 g/L. Chest CT revealed interstitial lung disease. P2 was the twin sister of P1.She had atrial septal defect and repaired when she was five. Presented with 1-year history of Raynaud's phenomenon, difussue rash and puffy hand, elevated ANA and anti-U1RNP antibody, consolidation and effusion in chest CT.They were diagnosed with MCTD and found to carry the homozygous p.Arg90His variant in NCF1, coming from the asymptomatic parents . After 2-month treatment with prednisone,Methotrexate, Tofacitinib and Nifedipine,they get partial remission and still under close follow-up.

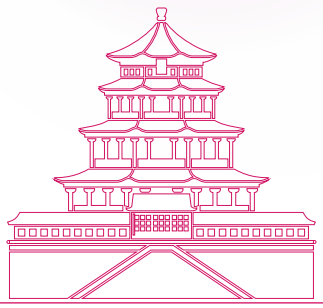
Discussion:

ROS production and gene expression of type 1 interferon-regulated genes including ISG15, SIGLEC1, RSAD2, IFI27, IFI44L and IFIT1 were measured in isolated cells from the family. They showed lower limits of normal in Neutrophil respiratory burst test and a strong upregulation of IFN-regulated genes.

Conclusions: This report is the first on MCTD causing by NCF1 p.Arg90His homozygous mutation in a twin-sister. MCTD is rare and poorly studied at the molecular level by GWAS.Close to NCF1 are two pseudogenes NCF1B and NCF1C, decreased and increased copy numbers of NCF1 was found predispose to and protect against SLE. The complex genomic organization of NCF1 poses a difficulty for high-throughput genotyping techniques and variants in this gene should be carefully evaluated.

SYMPOSIUM WITH PRESENTATIONS OF CLINICAL CASES:

SESSION 2



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Clinical Study Driven by the Diagnosis and Treatment of Patients with Rheumatic Diseases

Dr. Xuan Zhang

A Rare Case of Combined Immunodeficiency with Immune Dysregulation in a 4-Month-Old Infant

Alhana A. Ayaon, M.D, Mary Anne R. Castor, M.D

University of the Philippines- Philippine General Hospital

Introduction: Combined immunodeficiency (CID) refers to a group of rare genetic disorders characterized by defects in T cell development or function, along with variable abnormalities in B cell activity. The clinical spectrum of CID ranges from mild to severe susceptibility to infections, with some cases also presenting immune dysregulation leading to autoimmune diseases and inflammation. Diagnosis can be challenging, especially when genetic causes remain unidentified.

Case Presentation:
We report a 4-month-old male infant with a history of recurrent opportunistic infections, fever, failure to thrive, hepatosplenomegaly, and features of autoimmunity, including severe atopic dermatitis, bicytopenia, and alopecia. Initial laboratory investigations revealed elevated CD3, CD4, and CD19 lymphocyte subsets, with normal CD8 and NK cells, suggesting a functional defect. Despite supportive therapy, systemic antibiotics and intravenous immunoglobulin, the infant\'s condition deteriorated, culminating in multiple organ dysfunction and death. A customized exome panel was conducted, revealing no identifiable variants, suggesting a potentially unknown genetic mutation.

Discussion: Combined immunodeficiency can present with a range of clinical features depending on the underlying genetic defect. In this case, the presence of immune dysregulation and autoimmune manifestations complicates the diagnosis and management of the condition. The absence of identifiable variants in the exome panel highlights the need for further genetic exploration to uncover potentially unknown mutations responsible for the condition. CID cases without clear genetic findings can pose significant diagnostic challenges, especially when presenting with features of both immunodeficiency and autoimmunity.

Conclusions: This case underscores the importance of early suspicion and comprehensive diagnostic workup in infants with recurrent infections and autoimmune symptoms. It also highlights the complexity of CID, especially when genetic mutations remain unidentified. Further research into the genetic causes of CID and immune dysregulation is necessary to improve diagnostic accuracy and management strategies.

Severe COVID-19 Infections In Three *SAMD9* (Mirage) Patients

Ciang Sang Tan[1,2], Maaike Kusters[2], Paul Torpiano[2], John Achermann[3], Matthew Buckland[4], Kimberly Gilmour[4], Rainer Doffinger[5], Catherine O'Sullivan[6]

1 *Department of Paediatric, Hospital Melaka, Malaysia*
2 *Department of Paediatric Immunology, Great Ormond Street Hospital, UK*
3 *Department of Genetics and Genomics, UCL Great Ormond Street Institute of Child Health, UK*
4 *Department of Immunology, Great Ormond Street Hospital, UK*
5 *Department of Clinical Biochemistry, Cambridge University Hospital, UK*
6 *Department of Immunology, Cambridge University Hospital, UK*

Introduction: MIRAGE syndrome (due to gain-of-function variants in SAMD9) is a complex multisystem disorder with features including myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. SAMD9 is an interferon-stimulated gene (ISG) essential in cell-intrinsic antiviral defense through type 1 interferon signaling. We report 3 MIRAGE infants with severe COVID-19 infections.

Case report:

1. An 18-month-old girl with recurrent chest infections and chronic lung disease (CLD) experienced severe COVID-19 chest infection requiring extracorporal membrane oxygenation (ECMO), steroids, and antivirals. Bloods showed thrombocytopenia, lymphopenia, and low IgG levels. She started immunoglobulin replacement treatment (IgRt), unfortunately, she succumbed at the age of 4 due to sepsis with multiple organ failure.
2. A 13-week-old with congenital anomalies suffered from fever and uncontrolled seizures during severe COVID-19 chest infection requiring ventilation; she was discharged with CLD on home oxygen. Bloods showed temporarily pancytopenia. She had 2 further ICU admissions due to chest infections. Currently alive, on IgRt and antibiotic prophylaxis.
3. A 5-month-old girl, who experienced three COVID-19 chest infections with prolonged hospitalization and multiorgan failure during first hospital admission (aged 5-11 months); discharged with CLD on home oxygen and Ig Rt and prophylaxis. She had another two more severe COVID-19 infections (4^{th}&5^{th}) aged 27-28 months requiring ventilation. Sadly, she passed away from cardiorespiratory arrest at home at 30 months old.

Analysis of patient 3 with 2 GOF SAMD9 mutations showed upregulated type I interferon signaling at baseline (no COVID), with further dysregulation during COVID-19 infection, abnormal interferon signature panel and highly elevated anti-COVID antibodies.

Conclusions: Our MIRAGE patients showed ineffective viral clearance and increased inflammation in response to COVID-19 leading to increased morbidity and mortality. These cases highlight the association between MIRAGE syndrome and severe COVID-19 in immunodeficient patients, despite the mild presentations in the broader population.

Crescentic glomerulonephritis in a 6-year-old boy leading to the diagnosis of X-linked agammaglobulinaemia

Matthew HL Lee[1,2], Janice CY Chow[1,2], Kai-Ning Cheong[2,4], Florence Choi[4], Crystal K Lam[3], Brian HY Chung[2,5], Jaime S Rosa Duque[1,2,4], Elaine YL Au[3], Eugene YH Chan[4,5], Alison LT Ma[2,4], Yu Lung Lau[1,2,4]

1 *Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong*
2 *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong*
3 *Department of Pathology, Queen Mary Hospital, Hong Kong*
4 *Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong*
5 *Hong Kong Genome Institute, Hong Kong*
5 *Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong*

Introduction: Rapidly progressive crescentic glomerulonephritis (RPGN) is a medical emergency that warrants prompt diagnosis and treatment. Here we report a boy with such presentation that led to the diagnosis of X-linked agammaglobulinaemia (XLA).

Case report:
A 6-year-old boy presented with gross haematuria and oedema. He reported recurrent productive cough requiring multiple courses of empirical antibiotics since 4 years old despite receiving all childhood vaccinations. Family history was unremarkable. On examination, he had hypertension, pallor, generalised oedema, and ascites. Investigation revealed elevated serum creatinine 209 μmol/L, equivalent to a glomerular filtration rate (GFR) of 20 ml/min/1.73m^2, azotaemia, hyperkalaemia, hyperphosphataemia, hypoalbuminaemia, anaemia, reduced C3, and no ANA. Pretreatment IgG, IgA, and IgM levels were 1073 mg/dL, 175 mg/dL, and 48 mg/dL, respectively. Continuous renal replacement therapy was commenced, and the renal biopsy showed immune complex-mediated RPGN, with positive immunofluorescent staining for IgG, IgM, IgA, C3 and C1q. He was given pulse corticosteroid, rituximab, and cyclophosphamide. Subsequently, he developed fever, and blood culture yielded *Streptococcus pneumoniae*. Whole genome sequencing found maternally inherited, likely pathogenic hemizygous genetic mutation in *Bruton tyrosine kinase*. Lymphocyte subset showed CD19 count of <0.1%, and functional antibodies against vaccines were absent. These confirmed the diagnosis of XLA. CT thorax showed patchy ground glass opacity, while bronchoscopy was unremarkable. Overall, the patient had immune-mediated glomerulonephritis and interstitial lung disease associated with XLA. Balancing immunosuppression and infection risk, long-term prednisolone, mycophenolate, and Ig replacement were started. He improved and no longer required renal replacement. His GFR after 3 months was 65 ml/min/1.73m^2.

Discussion: Up to 20% of XLA patients can develop autoimmunity, mostly involving joints, gut and rarely kidneys, as oligoclonal B lymphocytes produce autoantibodies rather than functional antibodies. Balance with immunosuppressants and Ig replacement to control the autoimmunity and infection risks is necessary.

Conclusions: Antibody-mediated glomerulonephritis can occur in XLA.

Encephalitis Due to Enterovirus in XLA Patients: Challenges in Diagnosis and Treatment

Anh Thi Van Nguyen, Quynh Thi Thuy Bui, Giang Dinh Nguyen, Anh Phuong Ha, Nhu Thi Huynh Nhu, Mai Thi Phuong Nguyen, Van Thi Nguyen, Huong Thi Minh Le

Vietnam National Children's Hospital

Introduction: Encephalitis due to Enterovirus (EV) represents a significant clinical challenge, particularly in patients with underlying immunodeficiencies such as X-Linked Agammaglobulinemia (XLA). XLA is characterized by a lack of functional B lymphocytes, leading to increased susceptibility to infections and complications from viral pathogens.

The association between EV and encephalitis in Primary immunodeficiency patients is well-documented, yet the prognosis remains poor, with a persistently high mortality rate despite various available treatments

Case Presentations:
Among 65 XLA patients, we identified three cases of EV encephalitis, with two fatalities at ages 5 and 10. The third patient, a 15-year-old male diagnosed with XLA at age 10 due to recurrent respiratory infections and a BTK mutation, has been treated with IVIG every 4-5 weeks. The patient experienced his first encephalitis at age 10, presenting with generalized seizures and no identifiable pathogens. He was treated with methylprednisolone (20 mg/kg/day for 3 days) and IVIG, leading to improvement after 7 days. At age 12, he had a second episode with PCR positive for EV in cerebrospinal fluid, treated with IVIG at 1 g/kg/day for 2 days and antiepileptic drugs. At age 14, he presented the third episode of acute encephalitis with cognitive disturbances, loss of balance, and recurrent seizures. Cerebrospinal fluid analysis revealed WBC=8 cells/ml and protein=0.35 g/L, while PCR for EV was negative. Despite IVIG 1 g/kg/day for 2 days the patient continued to have seizures and worsening brain injury. He was subsequently treated with Favipiravir and Fluoxetine along with IVIG every 4 weeks. Outcome: After 6 months, the patient's condition stabilized, improved, and he could walk better without further progression of brain injury.

Discussion: When should we stop the Favipiravir and Fluoxetine?

Conclusions: High-dose IVIG and Favipiravir and Fluoxetine may effectively treat encephalitis due to EV in XLA patients.syndrome and severe COVID-19 in immunodeficient patients, despite the mild presentations in the broader population.

APSID Congress

Day2 13.04.2025

7:00 - 8:00	REGISTRATION
8:00 - 9:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 5
9:00 - 10:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS BY RECIPIENTS OF APSID YOUNG INVESTIGATORS AWARD: SESSION 1
10:00 - 11:00	POSTER WALK WITH TEA/COFFEE: RESEARCH POSTERS II
11:00 - 12:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS BY RECIPIENTS OF APSID YOUNG INVESTIGATORS AWARD: SESSION 2
12:00 - 13:00	SYMPOSIUM WITH RESEARCH PRESENTATIONS BY RECIPIENTS OF APSID YOUNG INVESTIGATORS AWARD: SESSION 3
13:00 - 14:20	LUNCHEON SEMINARS
14:20- 14:30	TEA/COFFEE BREAK
14:30 - 15:30	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 6
15:30 - 16:30	POSTER WALK WITH TEA/COFFEE: CLINICAL CASES POSTERS
16:30 - 17:30	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 7
17:30 - 18:30	SYMPOSIUM WITH RESEARCH PRESENTATIONS: SESSION 8
18:30 - 19:00	CONGRESS CLOSING CEREMONY
19:30 - 21:30	APSID EB MEETING AND DINNER

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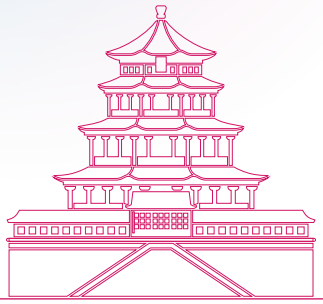
SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 5



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Inborn Errors of Immunity in Interleukin-6 Cytokine Family Signalling

Prof. Holm Uhlig

Genetic Mutations in Pediatric Patients with Inflammatory Bowel Disease

Dr. Yuxia Zhang

Comprehensive genetic and immunological analyses reveal the involvement of inborn errors of immunity in pediatric IBD: a Japanese multicenter study

Yoji Sasahara[1], Takashi Uchida[1], Tasuku Suzuki[1], Daiki Abukawa[2], Dan Tomomasa[3], Hirokazu Kanegane[4]

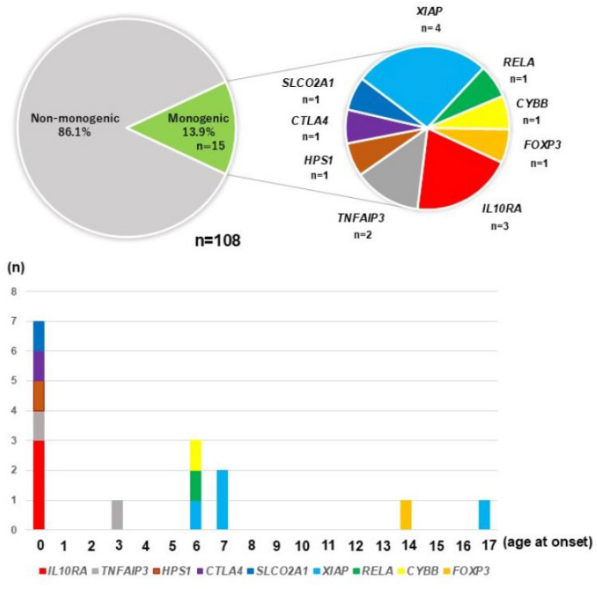
1 *Department of Pediatrics and Pediatric Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan.*
2 *Department of General Pediatrics, Gastroenterology and Hepatology, Miyagi Children's Hospital, Sendai, Japan.*
3 *Department of Pediatrics and Developmental Biology, Institute of Science Tokyo, Tokyo, Japan.*
4 *Department of Child Health and Development, Institute of Science Tokyo, Tokyo, Japan.*

Background and aims: Pediatric inflammatory bowel disease (IBD) is a heterogeneous disorder caused by multiple factors. Clinical significance of inborn errors of immunity (IEIs)-associated IBD has been investigated as genetic factors.

Methods: We established targeted gene panels covering all responsible genes for pediatric IBD. In total, 108 patients under 18 years of age suffering from refractory IBD were enrolled in this Japanese multicenter study. Exome and targeted gene panel sequencing was performed for all patients. Variants in genes responsible for IEIs, clinical and immunological parameters were evaluated according to disease type.

Results: A total of 15 out of the 108 enrolled patients (13.9%) were identified as monogenic. We identified 4 patients with *XIAP, 3* patients with *IL10RA, 2* patients with *TNFAIP3, 1* patient with *RELA, CTLA4, SLCO2A1, HPS1, FOXP3*, and *CYBB* variants, respectively. Using assays for protein expression levels, IL-10 signaling, and cytokine production, we confirmed that the variants resulted in loss of functions. A patient with compound heterozygous *IL10RA* variants, who was the first case diagnosed in Japan, ameliorated her bowel symptoms spontaneously. A patient with heterozygous truncated *RELA* variant was the first case worldwide who complicated with IBD, and immunological analysis revealed that the variant affected nuclear factor kappa B signaling. Allogeneic hematopoietic stem cell transplantation was performed in patients with XIAP, IL-10RA deficiency, or other IEIs, and the preferable outcome of reduced-intensity conditioning and complete resolution of IBD symptoms and dysbiosis were achieved.

Conclusions: Our results indicated that the genes responsible for IEIs are frequently involved in the pathogenesis of pediatric IBD and play critical roles in the gastrointestinal tract immunity. Comprehensive genetic analysis, including targeted gene panel analysis which is covered by health insurance in Japan, has been widely applied to screen for patients with IEIs-associated IBD and contributed to selecting appropriate therapies and better prognosis.



The mechanism of a novel variant in TCIRG1 on mouse model of infantile malignant osteopetrosis

Zhe Cai [1, 2], Ping Wu[3], Juan Zhou[2], Ping Zeng[2]

1 *Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China*
2 *Department of Allergy, Immunology and Rheumatology, Guangzhou Women and Children's Medical Center, Guangzhou, Guangzhou Medical University, Guangdong, China*
3 *Department of Pediatrics, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China*

Background and aims: Infantile malignant osteopetrosis (IMO) is a rare autosomal recessive disease characterized by a higher bone density in bone marrow that caused by the dysfunction of bone resorption. The gene variant of TCIRG1 is one of the main causes for IMO infants. We previously reported a novel variant of TCIRG1 (c.1371delC/p.G458Afs*70) in an IMO child. However, the functional and regulatory mechanism of this variant is not clear. Therefore, our aim of the present study is to investigate the mechanism of this variant in IMO.

Methods: Based on this aim, the TCIRG1 gene knockout, overexpression and variant (c.1371delC) Raw264.7 cells were established for the functional study of osteoclasts. The cell viability and osteolytic activity of osteoclasts were verified by CCK-8 and ELISA assay. The effect of osteoclasts on cell autophagy was verified by western blot. The potential mechanism of TCIRG1 variant was analyzed by the protein structure prediction. The dysfunctional osteoclast with this novel variant was verified in the IMO mouse model.

Results: The cell viability and osteolytic activity of osteoclast with TCIRG1 variant were decreased. The bone resorption marker CTX-I was down-regulated, while the autophagy related proteins like p62 and LC3BII were upregulated in the TCIRG1 mutated osteoclasts. Further analysis of the protein structure revealed that this variant would result in a loss of the transmembrane domain of TCIRG1 protein. It may lead to the inactivation of its regulated ATPase proton pump. Accordingly, we verified that the mutated TCIRG1 leads to a dysfunction of osteoclast in the dynamic balance between osteolysis and bone remodeling in IMO mouse.

Conclusions: In this study, we provided a new insight into the pathogenesis of IMO with TCIRG1 variant by various verifications in vitro and in vivo. We hope our founding of the mechanism in mutated TCIRG1 could be a novel therapeutic target for IMO in future.

SYMPOSIUM WITH RESEARCH PRESENTATIONS BY RECIPIENTS OF APSID YOUNG INVESTIGATORS AWARD:

SESSION 1

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Type-1 Interferonopathy

Dr. Xiaochuan Wang

JAK Inhibitor Treatments for Inborn Errors of Immunity

Prof. Yae-Jean Kim

Screening Programme Providing Outreach for Testing Hereditary Angioedema (SPPOT-HAE): Validation and Utilizing Dried Blood Spots for Family Screening

Jane CY Wong MBBS[1], Dorothy LY Lam MSc[1], Jackie SH Yim MSc[1], Elaine Lee MSc[1], Weihong Shi MMed[1], Valerie Chiang MBBS[2], Philip H Li MD[1,3]

1 *Division of Rheumatology & Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China.*
2 *Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital, Hong Kong SAR, China.*
3 *Division of Rheumatology & Clinical Immunology, Department of Medicine, University of Hong Kong-Shenzhen Hospital, China.*

Background: Hereditary angioedema (HAE) is a rare genetic disorder with potentially life-threatening consequences, traditionally diagnosed by conventional laboratory methods which can be resource-intensive and inconvenient. Incorporating dried blood spot (DBS) tests may be a promising alternative for diagnosing HAE and family screening.

Objective: This study aimed to validate DBS with conventional laboratory assays among confirmed C1INH-HAE patients and assess the utility of DBS in a Screening Programme Providing Outreach for Testing Hereditary Angioedema (SPPOT-HAE).

Methods: In Part I, 16 Chinese C1INH-HAE patients from 7 families participated in the validation of DBS for detecting C4, C1INH, and fC1INH. The results were compared with conventional laboratory assays. In Part II, DBS was utilized in family screening for HAE in a large Chinese family with relatives previously refusing testing.

Results: The study found strong correlation between conventional assays and DBS in measuring C4 ($r=0.957$, $p<0.0001$), C1INH ($r=0.946$, $p<0.0001$), and fC1INH ($r=0.981$, $p<0.0001$). There were no false negative results from the DBS for C4, C1INH or fC1INH.

SPPOT-HAE successfully recruited 9 additional relatives for family screening, of which 22% were confirmed to have HAE. The use of DBS in an outreach programme overcame barriers of prior family screening initatives.

Conclusions: This is the first study to validate measurement of fC1INH using DBS in C1INH-HAE with conventional assays. An outreach programme using DBS is a promising strategy overcoming previously barriers of family screening. Further large-scale, multicenter studies are required to establish the role of DBS, compare cost-effectiveness with prior strategies and maximize diagnosis in resource-constraint countries.

Combined immunodeficiency caused by *PTPRC* mutation

Yulu Li, Yue Li, Mengyue Deng, Yan Li, Huawei Mao

Department of Immunology, Beijing Children's Hospital of Capital Medical University, National Center for Children's Health of China, Beijing, China

Background and aims: PTPRC, also known as CD45, is required for T-cell activation through the antigen receptor. To our knowledge, only three cases reported to date, all presenting with severe combined immunodeficiency (SCID) that necessitates early bone marrow transplantation for life-saving treatment.

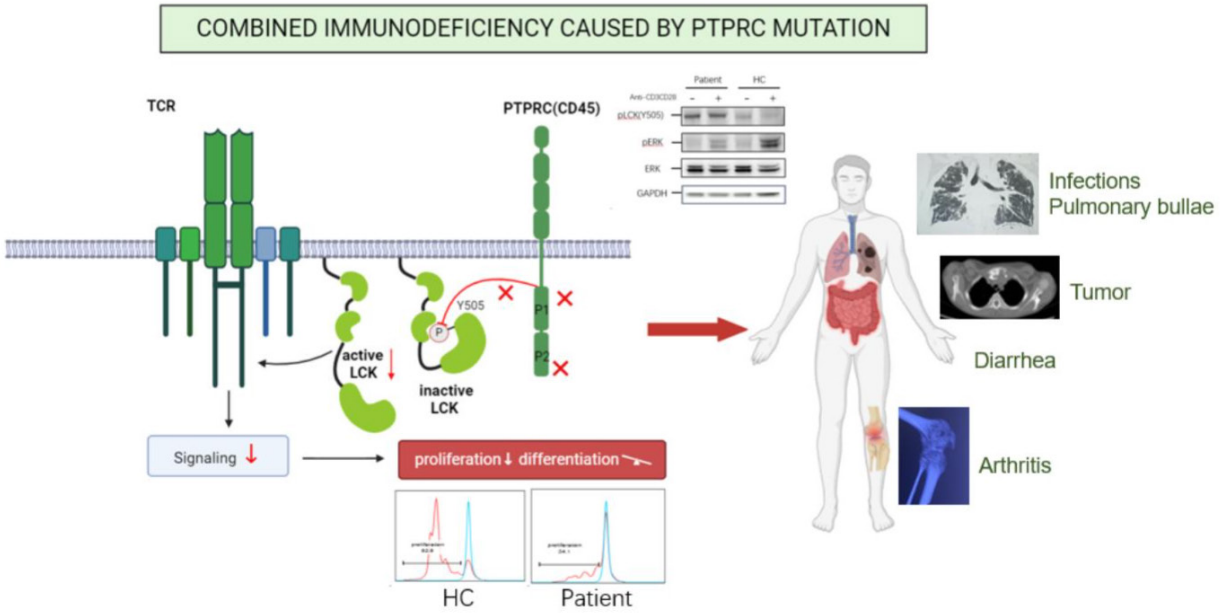
In this study, we reported two patients with novel PTPRC compound heterozygous mutations. The aim of this study is to expand the clinical and immune phenotype spectrum of CD45 deficiency.

Methods: The clinical characteristics of the children were summarized through clinical data collection. The variants were identified by whole exon sequencing and verified by Sanger sequencing. PTPRC expression, lymphocyte subsets, cytokine production and functional assays were explored by flow cytometry. TCR Signaling were detected by Western Blot.

Results: Two patients with novel compound heterozygous mutation have been identified. P1 was an 11-year-old boy suffered from otitis media, diarrhea, and joint pain since childhood. The joint symptoms have gradually worsened, affecting the ability to walk. P2, a 9-year-old boy, has suffered from recurrent respiratory infections since birth. CT scans indicated interstitial pneumonia and pulmonary bullae.

The mutation led to reduced PTPRC expression and damage the phosphatase activity domain of PTPRC. The proximal TCR signaling pathway was found to be impaired, as evidenced by an increase in pLCK(Y505) and a decrease in pERK levels. These findings explain the reduced proliferation capacity of P1's T cells and the abnormal T cell development. In addition, mutations also affect the development and function of B cells, manifesting as a decrease in naive B cells and reduced secretion of IgG, IgM, and IgA.

Conclusions: Our findings expand the previous reports of PTPRC in human T-cell development and function.

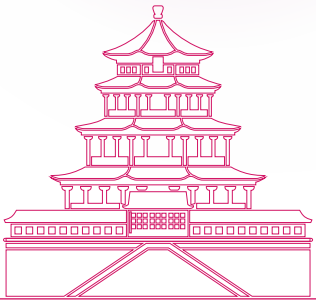


Patient	sex	Age of onset	Mutation	Clinical phenotype	Immunophenotype	Ig	Diagnoses	Therapy
P1*	male	1y	c.3709_3710dupAA p.K1238Rfs*19 c.2032C>T p.Q678X (compound heterozygous)	Recurrent fever, polyarthritis, upper respiratory tract infection, otitis media, sinusitis, watery stools	T-B-NK-	IgG↓ IgM↓ IgA↓	CID	Regular immunoglobulin infusion; Adalimumab; Antimicrobials; PCP prophylaxis
P2*	male	1mo	c.3301C>T, p.L1101F c.646A>C, p.T216P (compound heterozygous)	recurrent upper respiratory tract infection, interstitial lung disease, gastroesophageal reflux, EBV infection	T-B+NK-	IgG↓ IgM↓ IgA↓	CID	Regular immunoglobulin infusion; oxygen therapy; Antimicrobials; PCP prophylaxis
P3	male	2mo	c.1450+1G>A & Large deletion	NA	T-B+NK-	IgG↓ IgM↓ IgA↓	SCID	Died of lymphoma at 2 years-old
P4	female	2mo	c.1090_1095del p.E364_W365del (Homozygous)	Fever, pneumonia, rash, hepatosplenomegaly, lymph node enlargement, pancytopenia, CMV infection	T-B+NK+	IgM↓ IgA↓	SCID	died of CMV recurrence after bone marrow transplantation at 8 months old
P5	male	6mo	c.1624A>T p.K542X (Homozygous)	Feeding difficulties, developmental retardation, gastroesophageal reflux, and pneumocystis pneumonia	T-B+NK+	IgG↓ IgM↓ IgA↓	SCID	survived bone marrow transplantation at 10 months of age

*This study

SYMPOSIUM WITH RESEARCH PRESENTATIONS BY RECIPIENTS OF APSID YOUNG INVESTIGATORS AWARD:

SESSION 2



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A Multi-omics Understanding of Thymus Development and Function

Prof. Georg A Holländer

The Potential Applications of Extracellular Vesicles in Inborn Errors of Immunity

Dr. Wenwei Tu

Inborn errors of immunity in the Himalayan region – a multi-center study

Aaqib Zaffar Banday[1], Aneek Farooq[1], Dharmagat Bhattarai[2], Phub Tenzin[3], Asmita Neupane[2], Syed Tariq Ahmad Bukhari[1]

1 *Government Medical College, Srinagar, Kashmir, India*
2 *Advanced Centre for Immunology & Rheumatology, Kathmandu, Nepal*
3 *Jigme Dorji Wangchuk National Referral Hospital, Thimpu, Bhutan*

Background and aims: Data on inborn errors of immunity (IEIs) from (resource-limited) regions located in the challenging terrain of the Himalayas are lacking. Herein, we provide a multi-center description of the spectrum of IEIs in this large geographic area.

Methods: Patients with IEIs from Northernmost India, Nepal, and Bhutan (diagnosed from August 2020 to September 2024) were included. Patients with variant-proven IEI were grouped according to the 2022 International Union of Immunological Societies Classification. In the absence of molecular diagnosis, the European Society of Immunodeficiencies criteria were used for clinical diagnoses of IEIs.

Results: During 4 years of study duration, 262 patients were diagnosed with IEIs. Predominant antibody deficiency was the most common (18.7%) group of IEIs diagnosed. Combined immunodeficiencies with associated/syndromic features (15.3%) and quantitative/qualitative phagocytic defects (14.5%) were the other common IEIs identified. Other IEIs diagnosed are summarized in **Figure 1.**

Regular antimicrobial prophylaxis was administered in all patients. Overall, regular immunoglobulin replacement therapy (IgRT) could be arranged in less than half of patients with humoral and combined immunodeficiencies with significant inter-center variability. Targeted therapy in the form of sirolimus or Janus kinase inhibitors was used in ten patients. Logistics for performing a hematopoietic stem cell transplantation (HSCT) could be arranged in only four patients.

Conclusions: Our study highlights enhanced diagnosis of a wide spectrum of IEIs in our region. Greater awareness and increasing availability of immunological/genetic testing are the notable factors resulting in improved diagnostic rates of IEIs. However, significant hurdles impede the optimal management of these patients. Regular IgRT and routine employment of HSCT is specifically hindered given the substantial costs borne by the patients' caregivers in the absence of universal health insurance or federal support. Besides, only a few targeted therapeutic agents are available at affordable costs in our region.

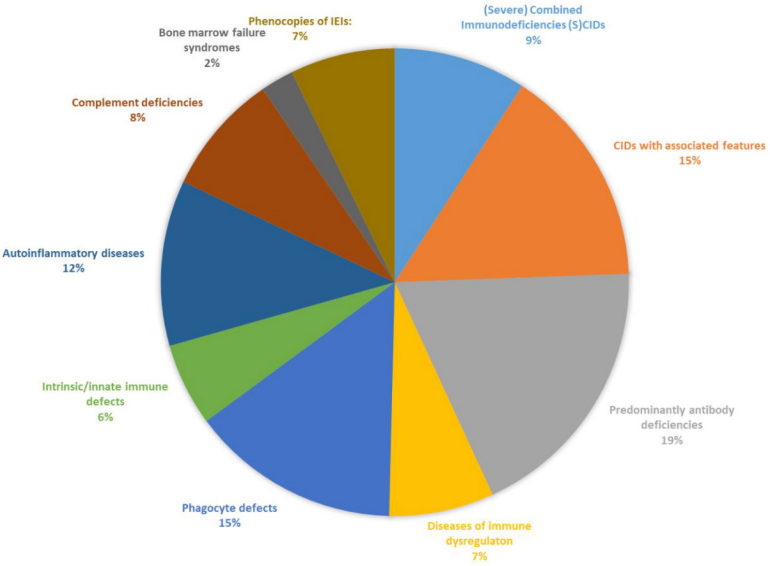


Figure 1: Spectrum of IEIs diagnosed in our multi-center study.

Transcriptional Regulatory Mechanism of Autoimmunity Promoted by STAT1-GOF Mutation

Ran Chen, Huilin Mu, Yunfei An, Yanjun Jia, Xiaodong Zhao

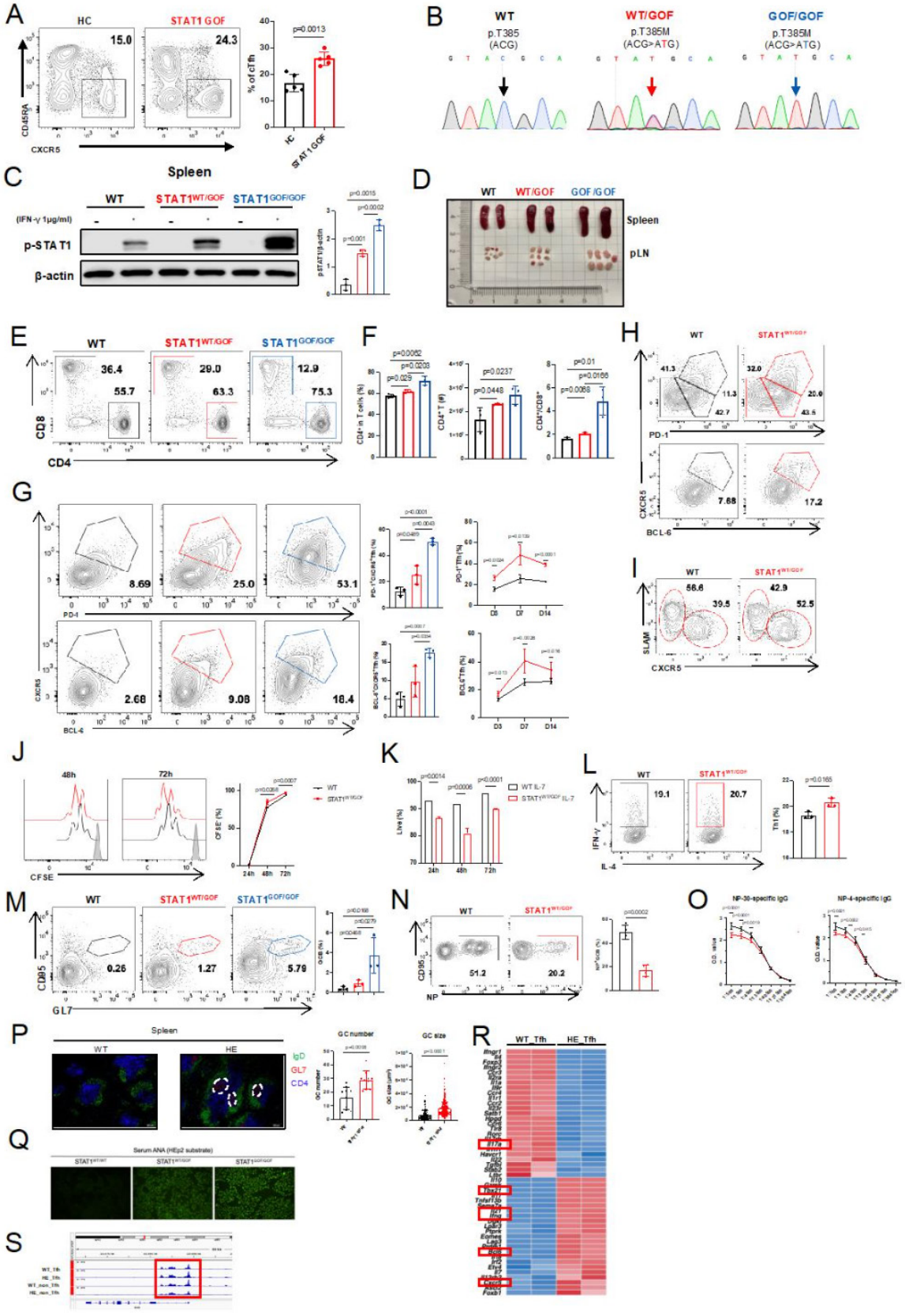
National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Child Rare Diseases in Infection and Immunity, Children's Hospital of Chongqing Medical University, Chongqing, China.

Background and aims: STAT1 gain-of-function (GOF) mutations have been increasingly linked to autoimmune diseases in patients. However, the precise mechanisms by which STAT1-GOF mutations contribute to autoimmunity remain unclear. This study aims to elucidate the transcriptional mechanisms underlying STAT1-driven autoimmune pathology, focusing on the role of T follicular helper (Tfh) cells and associated signaling pathways.

Methods: Samples from STAT1-GOF patients were collected. STAT1 knock-in mice was generated. Various analytical techniques, including Sanger sequencing, flow cytometry, ELISA, immunofluorescence, CUT&Tag, and RNA sequencing, were employed to assess immune cell profiles and gene expression patterns.

Results: In STAT1-GOF patients, an increased proportion of circulating Tfh cells was observed (A). STAT1-GOF mice showed elevated STAT1 expression and spontaneous splenomegaly (B-D). These mice exhibited expansion of CD4+T and Tfh cells (E-I). Naïve CD4+ T cells showed increased proliferation, weakened survival and skewed differentiation (J-L). Expanded GCB, impaired antigen-specific antibody production and positive auto-antibody were observed (M-Q). Transcriptome analysis revealed a Tfh1-like phenotype, with STAT1 directly binding BCL6 (R-S).

Conclusions: Our findings reveal that STAT1-GOF mutations promote autoimmunity by enhancing a Tfh1-like population that drives pathological immune responses through IFN-γ signaling. These results suggest that dysregulation of Tfh cells contributes significantly to the development of autoimmunity in STAT1-GOF diseases, further providing insights into targeted therapeutic strategies for these conditions.


A
HC
STAT1 GOF
15.0
24.3
CD45RA
CXCR5
p=0.0013
% of cTfh
HC
STAT1GOF
B
WT
p.T385
(ACG)
WT/GOF
p.T385M
(ACG>ATG)
GOF/GOF
p.T385M
(ACG>ATG)
C
Spleen
WT
STAT1WT/GOF
STAT1GOF/GOF
(IFN-γ 1μg/ml)
p-STAT1
β-actin
D
WT
WT/GOF
GOF/GOF
Spleen
pLN
E
WT
STAT1WT/GOF
STAT1GOF/GOF
36.4
55.7
29.0
63.3
12.9
75.3
CD8
CD4
F
CD4+ in T cells (%)
CD4+ T (#)
CD4+/CD8+
H
WT
STAT1WT/GOF
41.3
11.3
42.7
32.0
20.0
43.6
PD-1
7.68
17.2
CXCR5
BCL-6
I
WT
STAT1WT/GOF
56.6
39.5
42.9
52.5
SLAM
CXCR5
G
8.69
25.0
53.1
2.68
9.08
16.4
PD-1
CXCR5
BCL-6
J
48h
72h
CFSE
CFSE (%)
WT
STAT1WT/GOF
K
Live (%)
WT IL-7
STAT1WT/GOF IL-7
24h
48h
72h
L
WT
STAT1WT/GOF
19.1
20.7
IFN-γ
IL-4
Th1 (%)
M
WT
STAT1WT/GOF
STAT1GOF/GOF
0.26
1.27
5.79
CD95
GL7
GCB (%)
N
WT
STAT1WT/GOF
51.2
20.2
CD95
NP
O
NP-30-specific IgG
NP-4-specific IgG
O.D. value
P
Spleen
WT
HE
IgD
GL7
CD4
GC number
GC size
R
WT_Tfh
HE_Tfh
Q
Serum ANA (HEp2 substrate)
S

SYMPOSIUM WITH RESEARCH PRESENTATIONS BY RECIPIENTS OF APSID YOUNG INVESTIGATORS AWARD:

SESSION 3

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Management of Inflammasomopathy

Prof. Huawei Mao

Deficiency of Adenosine Deaminase 2: Consensus and Controversies in 2025

Dr. Pui Y Lee

Unraveling the Genetic Landscape of Early-Onset Systemic Lupus Erythematosus in India: Insights from a Large Cohort Study of 365 Patients

Rakesh Kumar[1], Madhubala Sharma[1], Ankur Jindal[1], Vignesh Pandiarajan[1], Deepti Suri[1], Saniya Sharma[1], Manpreet Dhaliwal[1], Surjit Singh[1], Amit Rawat[1]

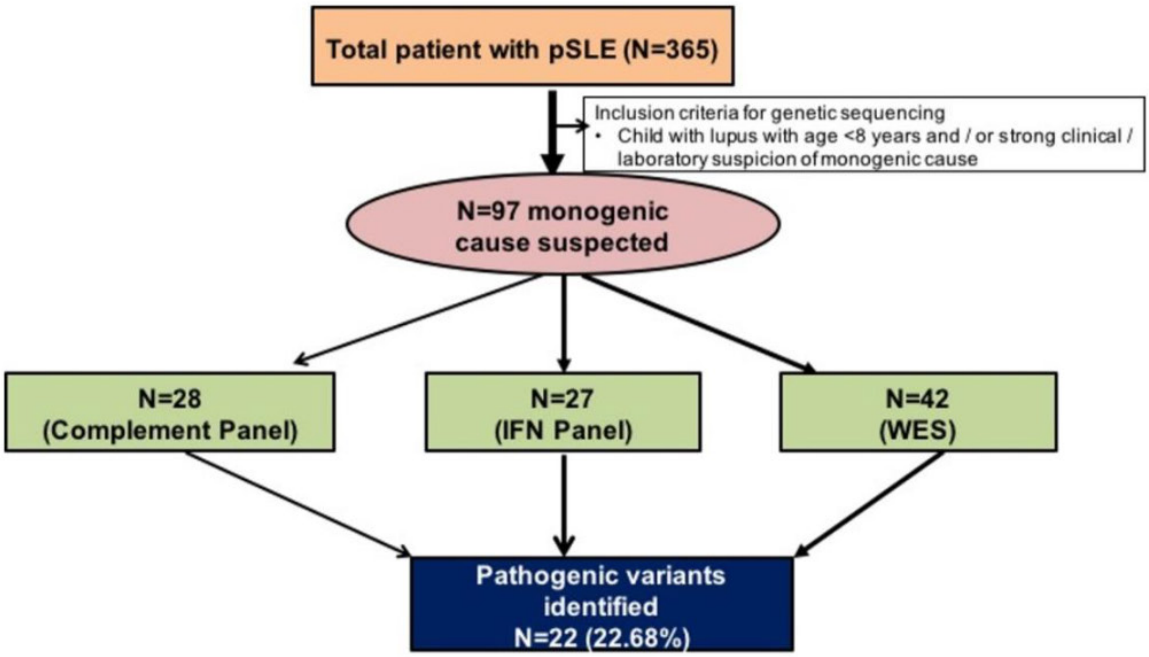
Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh, India

Background and aims: Early-onset systemic lupus erythematosus (EOSLE) is a rare autoimmune disorder with significant morbidity in children. Monogenic lupus, caused by single-gene mutations, often presents with early-onset and severe phenotypes, requiring specialized diagnostic approaches. This study explores the genetic basis of EOSLE in the largest cohort of patients with pediatric SLE (pSLE) from India.

Methods: This prospective observational study investigated monogenic causes in 97 of 365 pSLE patients. Inclusion criteria for study comprised patients with EOSLE (age ≤8 years) and/or those with a clinical suspicion of monogenic lupus. Monogenic cause was suspected in 97 patients. Genetic screening was performed using targeted next-generation sequencing on the Ion S5 system in 55 of 97 patients [complement defect gene panel in 28 and type 1 interferonopathy gene Interferon (IFN) panel in 27]. Remaining 42 patients underwent whole exome sequencing (WES).

Results: Results: Among 97 patients who underwent genetic sequencing, 22 (22.68%; 11 boys and 11 girls) were found to carry pathogenic or likely pathogenic variants. Median age of symptom onset in patients with monogenic lupus was 2 years (range: 2 months - 9 years). Consanguinity was reported in 7/22 (31.8%) patients. Variants were detected in *C1QA (n=7), C1QC (n=2), C1R (n=1), C1QB (n=1), C3 (n=2), ACP5 (n=2), TMEM173 (n=1), DNASE2 (n=1), ADAR (n=1), TREX1 (n=1), DNASE1L3 (n=1), PEPD (n=1), SLC7A7 (1)* genes. Functional complement deficiencies and elevated Type 1 interferon signatures were consistent with genetic findings.

Conclusions: This study highlights the genetic heterogeneity of EOSLE in India, with monogenic causes identified in 22.68% of cases, with C1q deficiency caused by genetic defects in *C1QA*, *C1QC*, and C1QB being the most common defect. Overall, C1QA was the most common single gene defect detected in 7/97 (7.2%) patients screened. Our findings support the need to evaluate underlying genetic causes in childhood lupus.



Details of pathogenic variants in patients with monogenic defect in pediatric systemic lupus erythematosus from India

Patient. No.	Gene	Transcript ID	Variation	Zygosity/ Inheritance	Pathogenicity	ACMG criteria applicable for variant
1	C1QA	NM_015991.4	c.622C>T p.Gln208*	Homozygous/AR	Pathogenic	PVS1, PS3, PM2, PP5
2	C1QA	NM_015991.4	c.622C>T p.Gln208*	Homozygous/AR	Pathogenic	PVS1, PS3, PM2, PP5
3	C1QA	NM_015991.4	c.622C>T p.Gln208*	Homozygous/AR	Pathogenic	PVS1, PS3, PM2, PP5
4	C1QA	NM_015991.4	c.374del p.Pro125Glnfs*157	Homozygous/AR	Pathogenic	PVS1, PS3, PM2
5	C1QA	NM_015991.4	c.284G>A p.Gly95Asp	Homozygous/AR	Likely pathogenic	PS3, PM2, PP3
6	C1QA	NM_015991.4	c.44delT plle1fs*7	Homozygous/AR	Likely Pathogenic	PVS1, PM2
7	C1QA	NM_015991.4	c.622C>T p.Gln208*	Homozygous/AR	Pathogenic	PVS1, PS3, PM2, PP5
8	C1QC	NM_172369.5	c.100G>A p.Gly34Arg	Homozygous/AR	Likely Pathogenic	PS3, PP3, PM2, PP5
9	C1QC	NM_172369.5	c.118G>A p.Gly40Ser	Homozygous/AR	Likely Pathogenic	PS3, PM2, PP3
10	C1R	NM_001733.7	c.1138C>T p.Arg380*	Homozygous/AR	Likely Pathogenic	PVS1, PM2
11	C1QB	NM_001378156.	c.227G>T p.Gly76Val	Homozygous/AR	Likely Pathogenic	PS3, PM1, PM2, PP3
12	C3	NM_000064.4	c.1003+1G>A	Homozygous/AR	Pathogenic	PVS1, PS3, PM2
13	C3	NM_000064.4	c.2943_2945del p.Leu982del	Homozygous/AR	Likely pathogenic	PS3, PM2, PM4
	ADAR	NM_001111.5	c.577C>G (p.Pro193Ala)	Heterozygous/AD	Pathogenic	PS1, PS3, PP3
14	ADAR	NM_001111.4	c.3019G>A p.Gly1007Arg	Heterozygous/AD	Pathogenic	PS1, PS3, PP3
15	ACP5	NM_001611.5	c.680_720del p.Leu227Argfs*10	Homozygous/AR	Pathogenic	PVS1, PS3, PM2
16	ACP5	NM_001611.5	c.550C>T p.Gln184*	Homozygous/AR	Pathogenic	PVS1, PS3, PM2, PP5
17	STING1/ TMEM173	NM_198282.4	c.463G>A, p.Val155Met	Heterozygous/AD	Pathogenic	PS3, PS4, PM1, PM2, PP3, PP5
	STING1/ TMEM173	NM_198282.4	c.463G>A, p.Val155Met	Heterozygous/AD	Pathogenic	PS3, PS4, PM1, PM2, PP3, PP5
	STING1/ TMEM173	NM_198282.4	c.463G>A, p.Val155Met	Heterozygous/AD	Pathogenic	PS3, PS4, PM1, PM2, PP3, PP5
18	DNASE2	NM_001375.3	c.1040G>A, p.Cys347Tyr	Homozygous/AR	Likely Pathogenic	PS3, PM2, PP3
19	DNASEIL3	NM_004944.4	c.151C>T p.Arg51Cys	Homozygous/AR	Likely Pathogenic	PS3, PM2, PP3
20	TREX1	NM_033629.6	c.716_717delCTinsGA p.Ala239Gly	Homozygous/AR	Likely Pathogenic	PM2, PP2, PP1, PP4, PM1
21	PEPD	NM_000285.4	c.1244T>A p.Ile415Asn	Homozygous/AR	Likely Pathogenic	PM2, PM3, PP3, PP4
22	SLC7A7	NM_003982.4	c.1307T>G p.Leu436Arg	Heterozygous/AR	Likely Pathogenic	PM2, PP3, PP4, PM1
			c.323del p.Leu108ArgfsTer62		Pathogenic	PVS1, PM2, PP4

Figure 1: Flow diagram of genetic Sequencing in pediatric systemic lupus erythematosus and genetic variant details from India

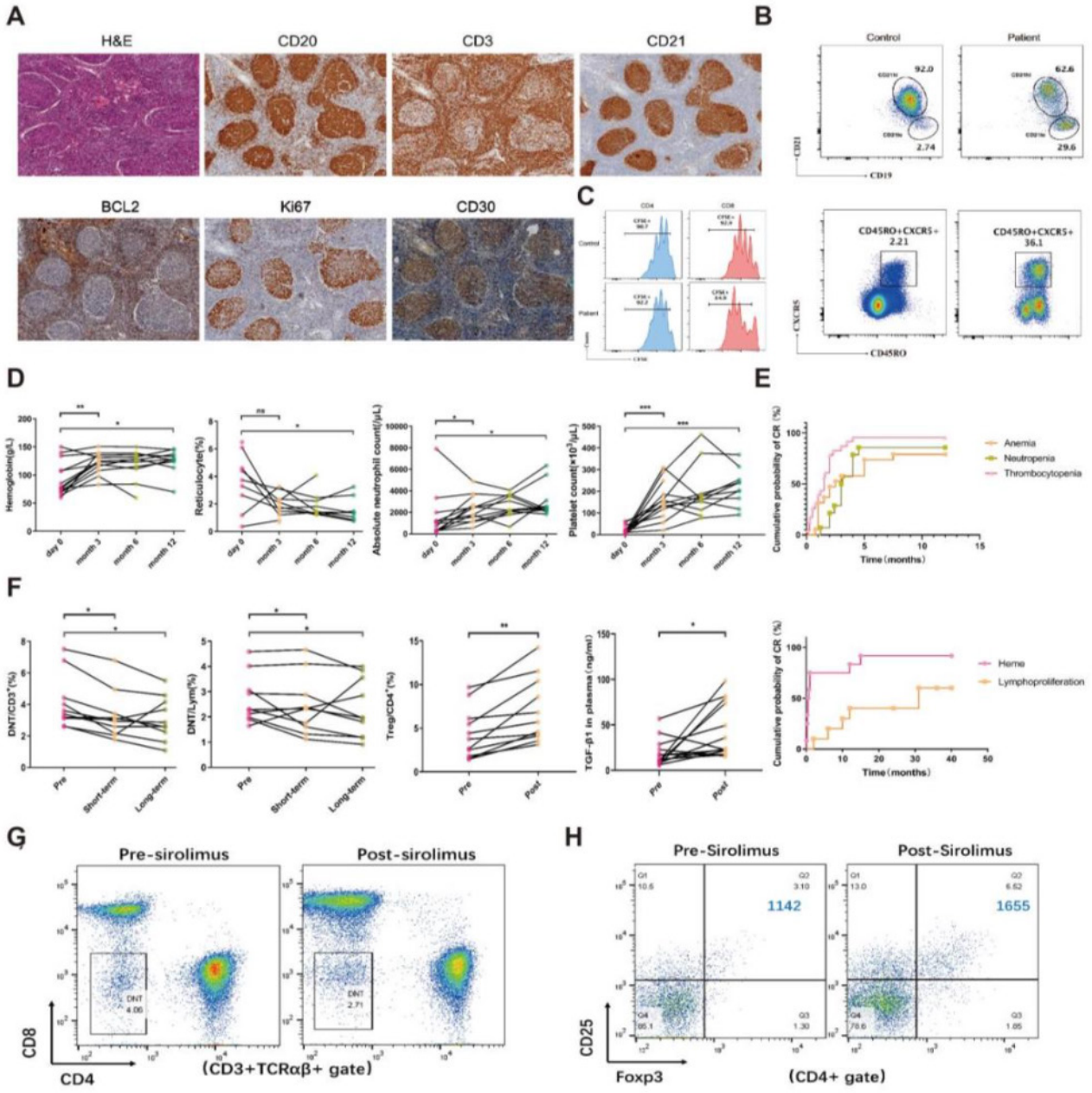
Effectiveness of Sirolimus in Early On-Set Autoimmune Cytopenias of Autoimmune lymphoproliferative immunodeficiencies (ALPIDs)s

Hao Gu[1], Zhou Shu[1], Mengyue Deng[1], Dan Lu[1], Zhenping Chen[3], Runhui Wu[2*], Huawei Mao[1*]

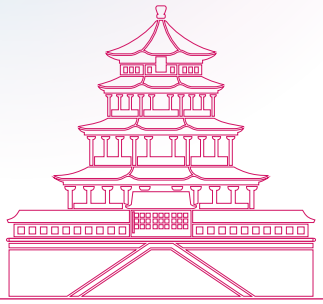
1 *Department of Immunology, Ministry of Education Key Laboratory of Major Diseases in Children, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045*
2 *Department of Hematology, Beijing Key Laboratory of Pediatric Hematology Oncology; Ministry of Education Key Laboratory of Major Diseases in Children, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045*
3 *Hematologic Disease Laboratory, Beijing Key Laboratory of Pediatric Hematology Oncology; Ministry of Education Key Laboratory of Major Diseases in Children, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045*

Background and aims: Pediatric autoimmune-lymphoproliferative immunodeficiencies (ALPIDs) patients with autoimmune cytopenias were often diagnosed with immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) and Evans syndrome (ES) requiring chronic immunosuppression with medications with limited efficacy and high toxicity. In this real-world case series study, we presented 23 pediatric ALPIDs with autoimmune cytopenias as the initial manifestation, who received sirolimus monotherapy. All children with ALPIDs achieved a durable complete response (CR), including rapid improvement in autoimmune cytopenias, lymphadenopathy, and splenomegaly within 1 to 3 months of starting sirolimus. Cytopenias showed a higher CR rate than lymphoproliferative manifestation. Thrombocytopenia achieve CR earlier than anemia and neutropenia. The proportion of $CD4^+CD25^+Foxp3^+$Treg and serum TGF-β elevated after sirolimus

treatment, a significant decreased DNT ratio was observed as well. Sirolimus led to CR and durable responses in a majority of pediatric ALPIDs patients, suggesting that sirolimus should be considered as a first-line, steroid-sparing treatment of patients needing chronic therapy. The elevation of Treg and reduction of DNT after sirolimus treatment may provide a direction for investigating the mechanism of sirolimus in ALPIDs.


A
H&E
CD20
CD3
CD21
BCL2
Ki67
CD30
B
Control
Patient
92.0
2.74
62.6
29.6
CD21
CD19
C
CD45RO+CXCR5+
2.21
CD45RO+CXCR5+
36.1
CXCR5
CD45RO
D
Hemoglobin(g/L)
Reticulocyte(%)
Absolute neutrophil count(/μL)
Platelet count(*10^3/μL)
day 0
month 3
month 6
month 12
E
Cumulative probability of CR (%)
Anemia
Neutropenia
Thrombocytopenia
Time (months)
F
DNT/CD3+(%)
DNT/Lym(%)
Treg/CD4+(%)
TGF-β1 in plasma (ng/ml)
Pre
Short-term
Long-term
Post
Heme
Lymphoproliferation
G
Pre-sirolimus
Post-sirolimus
DNT
4.06
2.71
CD8
CD4
(CD3+TCRαβ+ gate)
H
Pre-Sirolimus
Post-Sirolimus
1142
1655
CD25
Foxp3
(CD4+ gate)

LUNCHEON SEMINARS



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Unlocking the Frontier Progress and Clinical Practice of Clinical Diagnosis and Treatment of Pediatric Vasculitis

(Language: Chinese)

Prof. Huawei Mao

Centralized Rare Disease Diagnosis Service and Decentralized Product Solution for Screening Applications

(Language: Chinese)

Dr. Jian Wu

Changing the Outcome of Disease Treatment and Opening a New Chapter in Childhood Lupus Disease Modification

(Language: Chinese)

Dr. Tongxin Han

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 6

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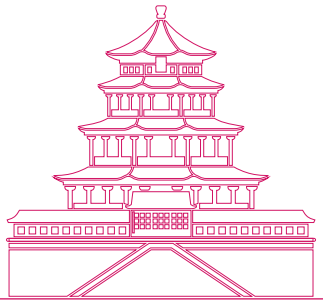


Management of IgG4-related Diseases

Dr. Yanying Liu

Cryopyrin-associated periodic fever syndrome in Japan

Dr. Kazushi Izawa

Genetically defined systemic autoinflammatory diseases in pediatric patients with Behçet's disease

Shaoling Zheng , Pui.Y Lee, Xu Hand, Xiaolin Fang, Changhua Zhou, Xuechan Huang, Yukai Huang, Jiajun Chen , Chun Zheng, Xia Pan, Qing Zhou, Tianwang LI

Guangdong Second provincial General Hospital
Boston Children Hospital
Academy of Life Sciences, Zhejiang University Key Laboratory of Major Diseases in Children, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045

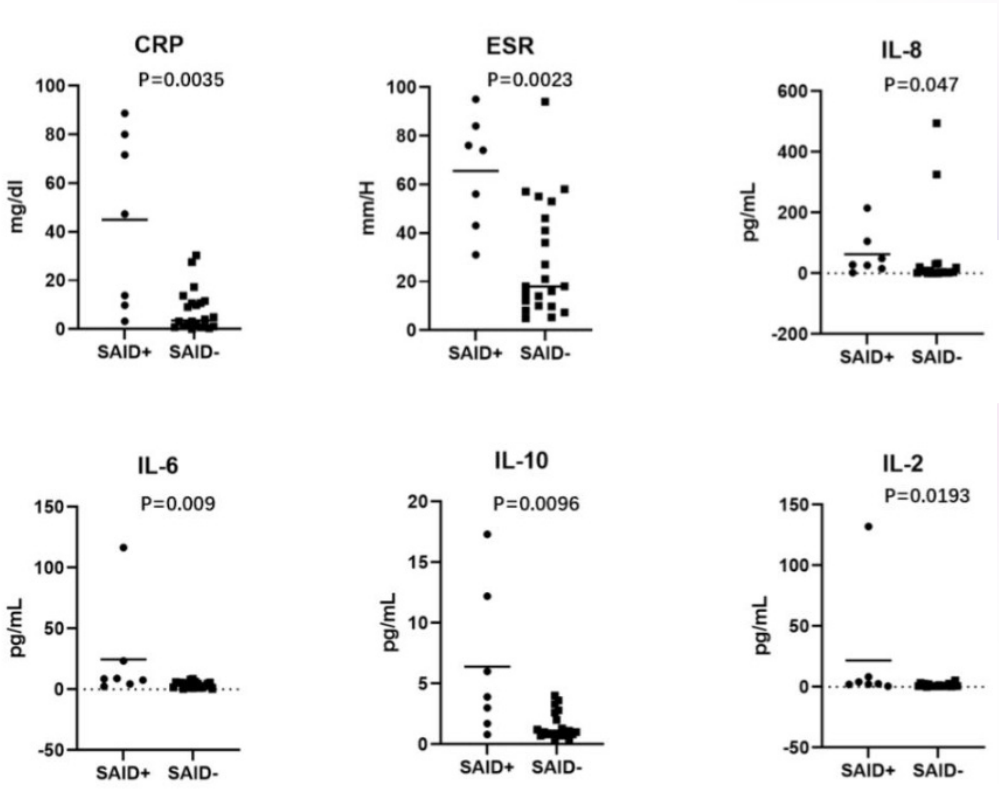
Background and aims: The aim of this study is to characterize genetically defined systemic autoinflammatory diseases (SAID) in a cohort of children with Behçet's disease (BD).

Methods: We studied 31 cases of pediatric BD treated in our center from 2020 to 2024. All cases fulfilled the 2015 classification criteria for paediatric BD. Whole exome sequencing was performed to identify potential genetic causes of disease. Clinical characteristics of cases with or without genetically defined SAID were compared.

Result: We performed whole exome sequencing on 31 patients with pediatric BD and identified 7 cases with genetic findings associated with SAID (SAID+ group). Six patients possessed pathogenic or likely pathogenic germline variants in RELA, TNFAIP3 (encoding A20), and GATA2, compatible with the diagnoses of RELA haploinsufficiency (3 cases), haploinsufficiency of A20 (HA20; 2 cases), and GATA2 deficiency (1 case), respectively. One patient was found to have trisomy 8.

Three of the 7 cases exhibited parentally inherited variants (2 case with RELA haploinsufficiency and 1 case with HA20) while the remainder possessed de novo variants. Compared to pediatric BD patients without genetically determined SAID (SAID- group; n = 24), the SAID+ group exhibited earlier disease onset (3.55±3.33 vs. 7.38±4.26, P=0.034) and greater prevalence of recurrent fever episodes, intestinal involvement, and hematologic abnormalities. Oral ulceration affected all patients and was the initial symptom in the majority of cases in both groups. Laboratory studies revealed higher levels of C-reactive protein (44.92±36.08 vs. 7.47±8.58, P=0.0035), erythrocyte sedimentation rate (65.57±23.03 vs. 28.47±23.45, P=0.0023), and multiple cytokines including IL-8, IL-6, IL-10, and IL-2. Corticosteroid treatment was commonly utilized in both groups while the use of biologic DMARDs was more common in the SAID+ group (85.71% vs. 33.33% in the SAID- group, P=0.028). SAID+ patients were treated with adalimumab (3 cases), etanercept (3 cases), tocilizumab (1 case), and Infliximab (2 case).

Conclusion: Genetic evaluation of pediatric-onset BD is important as genetically defined SAID account for a substantial proportion of cases. Pediatric BD patients with SAID display greater levels of systemic inflammation and require more aggressive immunosuppressive therapy.


CRP
P=0.0035
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SAID+
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IL-6
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SAID+
SAID-
IL-10
P=0.0096
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IL-2
P=0.0193
pg/mL
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SAID+
SAID-

Monogenic Pediatric Systemic Autoinflammatory diseases in Nepal– Maiden Himalayan cohort

Dharmagat Bhattarai[1], Aaqib Zaffar Banday[2], Asmita Neupane[1], Pratap Kumar Patra[3]

1 *Advanced Centre for Immunology & Rheumatology, Kathmandu, Nepal*
2 *Government Medical College, Srinagar, Kashmir, India*
3 *All India Institute of Medical Sciences, Patna, India*

Background and aims: The availability of advanced courses, subspecialists, diagnostics, and therapeutics has shifted the paradigm for diagnosing and managing pediatric systemic autoinflammatory diseases (PSAIDs) including autoimmune diseases in developing countries. We describe the profile of patients diagnosed with PSAIDs at a tertiary care center in Kathmandu during 2020-2024.

Methods: Case records of patients diagnosed and treated (including HSCT) for PRDs at the tertiary private care center in Kathmandu from Aug 2020 to November 2024 were analyzed. Lead author (DB) collated data from all patients. Diagnosis and treatments were based on internationally acclaimed criteria.

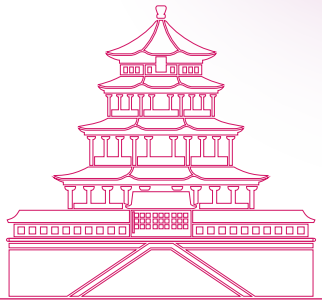
Result: Monogenic PSAIDs were diagnosed in 48 patients. Three cases were referred from the border area of Bihar, India, and one was from Assam. Monogenic PSAIDs included various etiologies including A20 haploinsufficiency, *ARPC1B* deficiency, Blau syndrome, MVK mutation, familial cold autoinflammatory syndrome, neonatal-onset multisystem autoinflammatory disease, *PIK3CD* mutation, TRAP syndrome *(TNFRSF1A)*, PSMB8 mutation, STX11 mutation, and PAPA syndrome. Almost 60% of children with autoinflammation and/or arthritis/vasculitis had visited dermatologists or orthopedicians before referral. Three children have undergone bone marrow transplantation in an Indian centre.

Three of the 7 cases exhibited parentally inherited variants (2 case with RELA haploinsufficiency and 1 case with HA20) while the remainder possessed de novo variants. Compared to pediatric BD patients without genetically determined SAID (SAID- group; n = 24), the SAID+ group exhibited earlier disease onset (3.55±3.33 vs. 7.38±4.26, P=0.034) and greater prevalence of recurrent fever episodes, intestinal involvement, and hematologic abnormalities. Oral ulceration affected all patients and was the initial symptom in the majority of cases in both groups. Laboratory studies revealed higher levels of C-reactive protein (44.92±36.08 vs. 7.47±8.58, P=0.0035), erythrocyte sedimentation rate (65.57±23.03 vs. 28.47±23.45, P=0.0023), and multiple cytokines including IL-8, IL-6, IL-10, and IL-2. Corticosteroid treatment was commonly utilized in both groups while the use of biologic DMARDs was more common in the SAID+ group (85.71% vs. 33.33% in the SAID- group, P=0.028). SAID+ patients were treated with adalimumab (3 cases), etanercept (3 cases), tocilizumab (1 case), and Infliximab (2 case).

Conclusion: We present the first cohort of PSAIDs from Nepal. Significant phenotypic variations were noted. There are substantial challenges to the diagnosis and treatment of PSAIDs in resource-limited settings. Various socioeconomic factors coupled with a lack of awareness of PSAIDs accounted for a late presentation with severe state, increased morbidity, and mortality.

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 7



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The Role of Innate Immunity in Pediatric Neurological Disorders

Tingting Chu

Severe Combined Immunodeficiencies Due to Defects in V(D)J Recombination

Brahim Belaid

Implementation of a territory-wide Newborn Screening Program for Severe Combined Immunodeficiency in Hong Kong: experience from our 3-year program

Kai-Ning Cheong[1,3], Florence Choi[1], Toby Chan[4], Daniel Ka-Leung Cheuk1, Pamela Lee[1,2,3], Lau Yu-Lung[1,2,3], Rosanna Wong[1], Janette Kwok[5], Matthew Yeung[4], Edgar Hau[6], Chloe Mak[4]

1 *Department of Paediatrics & Adolescent Medicine, Hong Kong Children's Hospital*
2 *Department of Paediatrics & Adolescent Medicine, University of Hong Kong*
3 *Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital*
4 *Department of Pathology, Hong Kong Children's Hospital*
5 *Department of Transplantation and Immunogenetics, Queen Mary Hospital*
6 *Department of Clinical Genetics, Hong Kong Children's Hospital*

Introduction: Newborn screening (NBS) SCID programs have transformed the landscape of diagnosis and treatment. The incidence of SCID in Hong Kong is 1: 50,000 – 65,000. We present our 3-year experience implementing a territory-wide NBS SCID program between October 2021-2024, in conjunction with an integrated diagnostic and therapeutic pathway to HSCT at Hong Kong Children's Hospital.

Results: Hong Kong's NBS SCID program commenced in the Hospital Authority's 8 hospitals with maternity services, achieving >99% coverage of babies born in the public sector. 67,857 samples had enumeration of T-cell receptor excision circles (TRECs) from Guthrie cards, with a recall rate of 0.21% (Enlite technique) and 0.18% (ddPCR technique). Confirmatory lymphocyte subset and next-generation sequencing (NGS) identified 3 cases of SCID (X-linked IL2RG, X-linked JAK3, and X-linked RAG1). All were screened to have 0 TRECS by day 7 of life, received a genetic diagnosis by day 10, admitted immediately to neonatal ward for reverse isolation, received curative HSCT and discharged by 3 months with 100% engraftment. No patients had non-SCID T-lymphopenia (e.g. DiGeorge Syndrome) severe enough to be detected on NBS. The false positive rate was 0.188%.

Discussion: With >99% coverage in public hospitals, recall rates were comparable to overseas cohorts. However, with anticipated program expansion to cover private hospitals, further refinement of our TRECs recall threshold and protocol will be needed to maximize sensitivity, specificity and reduce unnecessary call-backs. With increased utilization of NBS whole-genome screening (WGS) programs internationally, further discussions are needed on the ethical, medical, legal and societal impacts that will arise.

Conclusion: The Hong Kong NBS SCID program demonstrated strong collaboration with regional obstetric and neonatal care units, a robust TRECs screening protocol, and streamlined implementation of integrated diagnostic and multidisciplinary care pathways. 3 SCID cases identified had successful early HSCT by 3 months of life. Further longitudinal data collection, program evaluation, screening protocol refinement and discussion on future screening methodology e.g. NBS-WGS is needed.

Developing laboratory supports for the diagnosis of PIDs in Bangladesh: Past, present and futur

1. Chandan Kumar Roy, Associate Professor, Department of Microbiology & Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh.
2. Mohammad Imnul Islam, Professor, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh.
3. Ismet Nigar, Associate Professor, Department of Microbiology & Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh.
4. Kamrul Laila, Assistant Professor, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh.
5. Mohammed Mahbubul Islam, Associate Professor, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh.

Introduction: Several advances have been made in the diagnostic and therapeutic research related to PIDs and the field of PIDs has rapidly evolving in Asia as well as in Bangladesh. Few years back diagnosis of the PIDs in Bangladesh was done mostly based on clinical criteria, CBC with differential count and estimation of serum immunoglobulins level and was virtually impossible to detect all of the cases.

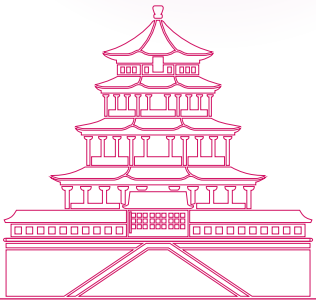
Presentation: Introduction of T-B-NK cell immunophenotyping in 2016 was the breakthrough laboratory investigation to the diagnosis of PIDs in Bangladesh. Subsequently by next years, detection of PIDs cases has increased with the use of Naïve (CD45RA+) and memory (CD45RO+) T cell, switched memory B cell (CD27+IgD-) markers, detection of intracellular BTK, LRBA, DOCK8 protein expression, NBT and DHR123 assay of neutrophils. Flowcytometry introduction for gp 91-phox protein assay in Neutrophils, detection CD18 & CD11a proteins of leukocyte and detection of Th 17 cells contributing in the specific diagnosis of X-linked CGD, LAD and HIES accordingly. Laboratory support is at place for exome sequencing of TACI/TNFRSF13B and BTK genes to make the specific diagnosis of CVID and XLA cases among the PIDs patient in Bangladesh.

Discussion: Currently the immunology laboratory of BSMMU is planning to set-up the capacity to measure the antibody response to protein and carbohydrate antigens, such as tetanus or diphtheria toxoids and pneumococcal polysaccharide vaccine. The laboratory has also taken initiative to establish CH50, NK cells perforin expression and degranulation assay. On the other hand, there are several barriers that need to be overcome, such as cost, access to tests and interpretation of genetic results.

Conclusion: The laboratory diagnostic supports for PIDs are developing in Bangladesh since last decade on the basis of clinical demand of the physicians and contributing in the diagnosis and management of the cases very efficiently.

SYMPOSIUM WITH RESEARCH PRESENTATIONS:

SESSION 8



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Monogenic Lupus

Dr. Mingsheng Ma

Current Therapeutic Approaches to Activated PI3K Delta Syndrome (APDS)

Dr. Jaime S Rosa Duque

Type-1 Interferon Signature in patients with Chronic Granulomatous Disease

Vignesh Pandiarajan[1], Ridhima Aggarwal[1], Aditya Dod[1], Saniya Sharma[1], Amit Rawat[1], Surjit Singh[1]

1 *Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh, India.*

Background and aims: Pathogenesis of hyperinflammation in patients with Chronic Granulomatous Disease (CGD) is not clearly understood. We hypothesized increased type-I interferon signature to be an important cause for hyperinflammation in CGD. Our objectives are to evaluate type-I interferon signature using RNA sequencing analysis of peripheral blood mononuclear cells in CGD patients, and, subsequently, to calculate an interferon score and measure Siglec-1/CD169 expression on monocytes and compare the two.

Methods: mRNA sequencing in 5 CGD patients and 3 controls was analyzed for differentially expressed genes. Subsequently, 20 patients with CGD, 10 carriers of CYBB, 11 healthy controls and 11 patients of systemic lupus erythematosus (disease controls) were enrolled. Expression of CD169 on monocytes was measured using flow-cytometry. Expression of 5 interferon signature genes (ISG) was measured using RT-PCR.

Results: On transcriptome analysis, increased expression of ISGs was seen in CGD patients. Monocyte CD169 expression was compared across subgroups of CGD patients (10=Inflammatory disease, 5=Infectious disease, 5=Asymptomatic). CD169 expression on monocytes (percentage and ΔMFI) was significantly high in inflammatory disease subgroup in comparison to asymptomatic subgroup ($p<0.001$ and $p<0.001$) and infectious disease subgroup ($p=0.033$ and $p=0.017$) (Figure). In accordance, elevated type-I interferon score by RT-PCR was found in inflammatory disease subgroup in comparison to healthy controls ($p=0.021$) and infectious disease subgroup ($p=0.029$). Percentage CD169 monocytes and ΔMFI correlated with type-I interferon scores, $rp=0.38$ ($p=0.049$) and $rp=0.46$ ($p=0.017$), respectively.

Conclusion: Type-I interferon signature is elevated in CGD patients, significantly more in patients with hyperinflammation in comparison to those with infections or those that are asymptomatic. CD169 is a reliable surrogate marker for estimation of Type-I interferon signature.

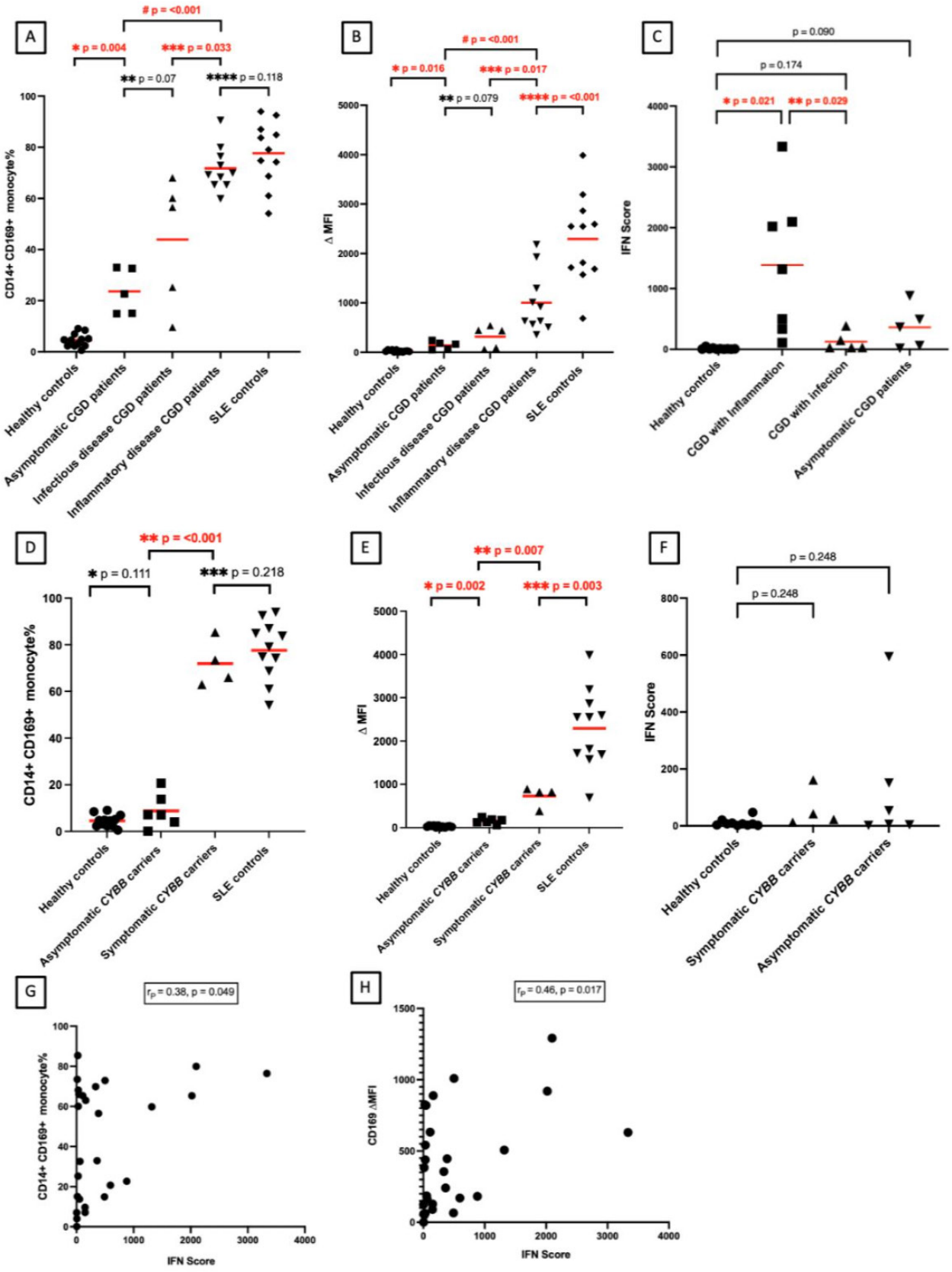


Figure 1: SIGLEC-1 expression in monocytes and comparison with type-1 interferon signature in patients with Chronic Granulomatous Disease

The efficacy of dupilumab in treatment of atopic dermatitis in children with STAT3-loss-of-function hyper-immunoglobulin E (STAT3-HIES) syndrome.

A. Moiseeva[1], A. Mukhina[1], N. Nikitin[1,2], D. Yukhacheva[1], A. Avedova[1], N. Kan[1], D. Bogdanova[1], V. Burlakov[1], Z. Nesterenko[1], V. Bludova[1], A. Ogneva[1], I. Abramova[1], E. Deripapa[1], Y. Rodina[1], A. Shcherbina[1].

1 *Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Department of Immunology, Moscow, Russian Federation*
2 *Center of Theoretical Problems of Physico-Chemical Pharmacology, Russian Academy of Science, Moscow, Russian Federation*

Background and aims: HIES is rare inborn error of immunity characterized by recurrent skin and lung infections, chronic mucocutaneous candidiasis and atopic dermatitis-like eczema. Autosomal dominant loss-of-function STAT3 pathogenic variants are the most common genetic cause, leading to a deficiency of Th17 lymphocytes with a shift of the immune response towards type 2 inflammation and the T helper 2 (Th2) pathway, with elevated levels of IL-13 and IL-4. Dupilumab is a humanized monoclonal antibody directed against the alpha chain subunit of the interleukin-4 receptor (IL-4R) and the interleukin-13 receptor (IL-13R), which blocks signaling of respective pathways and results in the inhibition of Th2-type responses..

Methods: We analyzed a group of 11 patients, median age 9 years (3-17) with STAT3-HIES complicated by atopic dermatitis (moderate to severe, SCORAD (SCORing Atopic Dermatitis) score >25) who were treated with dupilumab for median 22 months (8 - 31 months).

Results: Improvement of cutaneous lesions was noted in all patients after initiation of dupilumab. At baseline, the mean SCORAD score was 43,35 (35,6-55,3). After 3-6 months of treatment, the mean SCORAD score reduced to 9,55 (5,2-23,1), at 12 months of treatment decreased to 5,9 (4,4-9,3). The mean SCORAD score reduction was 77.9% at 3-6 months and 86.4% at 12 months. No adverse effects were observed.

Conclusion: Treatment with dupilumab in STAT3-HIES patients results in a dermatitis remission and demonstrates potential as a long-term treatment option for the cutaneous symptoms of HIES, although longer follow-up is required.

APSID POSTER

Day 1

PER1 Plays a Pivotal Role in the Pathogenesis of Patients with STAT1 Gain-of-Function Mutations

Lingxin Meng[1#], Ran Chen[2#], Bo Zhou[1#], Yue Pan[1], Yuting Sun[1], Huilin Mou[2], Chenhui Wang[3], Yi Zhang[4], Zhihua Ruan[5], Lei Fei[1], Yuzhang Wu[1], Xiaodong, Zhao[2], Yongwen Chen[1*], Yunfei An[2*]

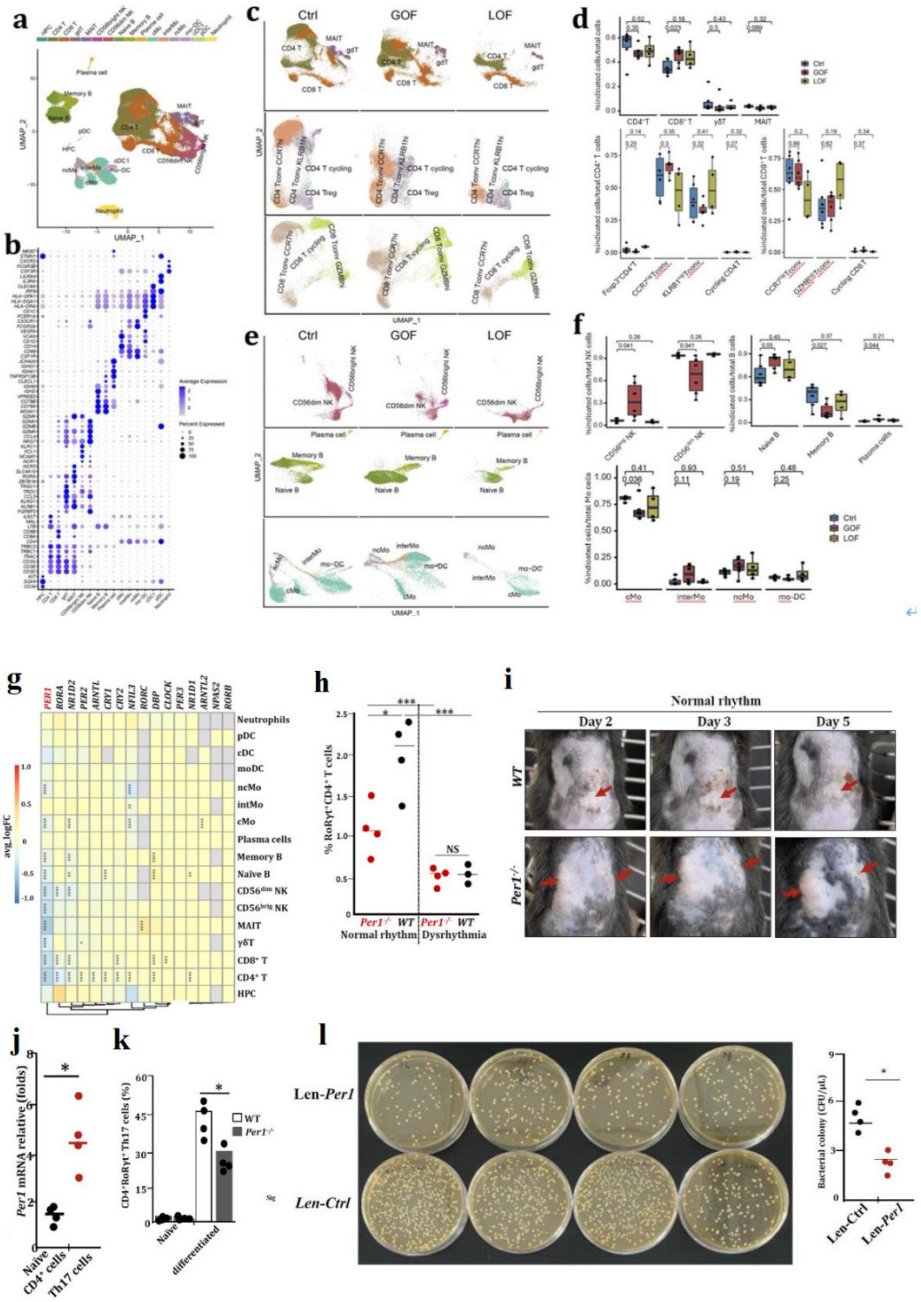
1 *Institute of Immunology, PLA, Third Military Medical University, Chongqing, 400038, People's Republic of China.*
2 *Department of Rheumatology and Immunology, Children's Hospital of Chongqing Medical University, Chongqing, China.*
3 *Beijing Institute of Microbiology and Epidemiology, Beijing 100071, China*
4 *Chongqing International Institute for Immunology, Chongqing, 400026, People's Republic of China.*
5 *Department of Oncology and Southwest Cancer Centre, Southwest Hospital, Third Military Medical University, Chongqing 400038, People's Republic of China.*

Background and aims: Patients with signal transducer and activator of transcription-1 (STAT1) gain-of-function (GOF) mutations display a range of clinical manifestations, including increased susceptibility to infections and severe immune dysregulation. However, the precise pathophysiology of these conditions remains incompletely understood. This study aims to investigate the underlying immune mechanisms in STAT1-GOF patients, focusing on the role of the circadian gene Period-1 (PER1) and its impact on immune responses.

Methods: Peripheral blood mononuclear cells (PBMCs) from five STAT1 GOF patients were analyzed using single-cell RNA sequencing (scRNA-seq) to explore gene expression patterns and immune cell profiles. Per1 knock-out mice was generated and utilized for functional detection.).

Results: We observed that the expression of PER1, a circadian rhythm gene, was significantly downregulated in PBMCs from STAT1 GOF patients. In Per1 gene knockout (Per1-/-) mice, there was a marked reduction in several immune cell populations, including RoRγt+ CD4+ Th17 cells, CD3-NK1.1+ NK cells, and CD45+ CD11b+ monocytes, which led to increased susceptibility to C. albicans infection and heightened autoinflammation. Mechanistically, Per1 deletion impaired Th17 cell differentiation by reducing STAT3 phosphorylation and triggered the release of proinflammatory cytokines IL-6 and IL-1β from macrophages through activation of the p38MAPK-ERK signaling pathway. Remarkably, forced overexpression of PER1 alleviated C. albicans invasion and improved inflammation in vivo.

Conclusions: Our findings suggest that PER1 plays a critical role in modulating immune responses in the context of STAT1-GOF mutations and highlight PER1 as a potential therapeutic target for managing STAT1-GOF disorders, offering a novel avenue for treatment.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Naïve
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Bacterial colony (CFU/μL)

Potential relation between a novel variant of FAM111A gene and KCS2-like syndrome

Zhe Cai[1, 2], Ping Wu[3], Juan Zhou[1], Chun Kwok Wong[4, 5], Ping Zeng[1]

1 *Department of Allergy, Immunology and Rheumatology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China.*
2 *Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China.*
3 *Department of Pediatrics, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China.*
4 *Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China.*
5 *Institute of Chinese Medicine and State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants, The Chinese University of Hong Kong, Hong Kong, China.*

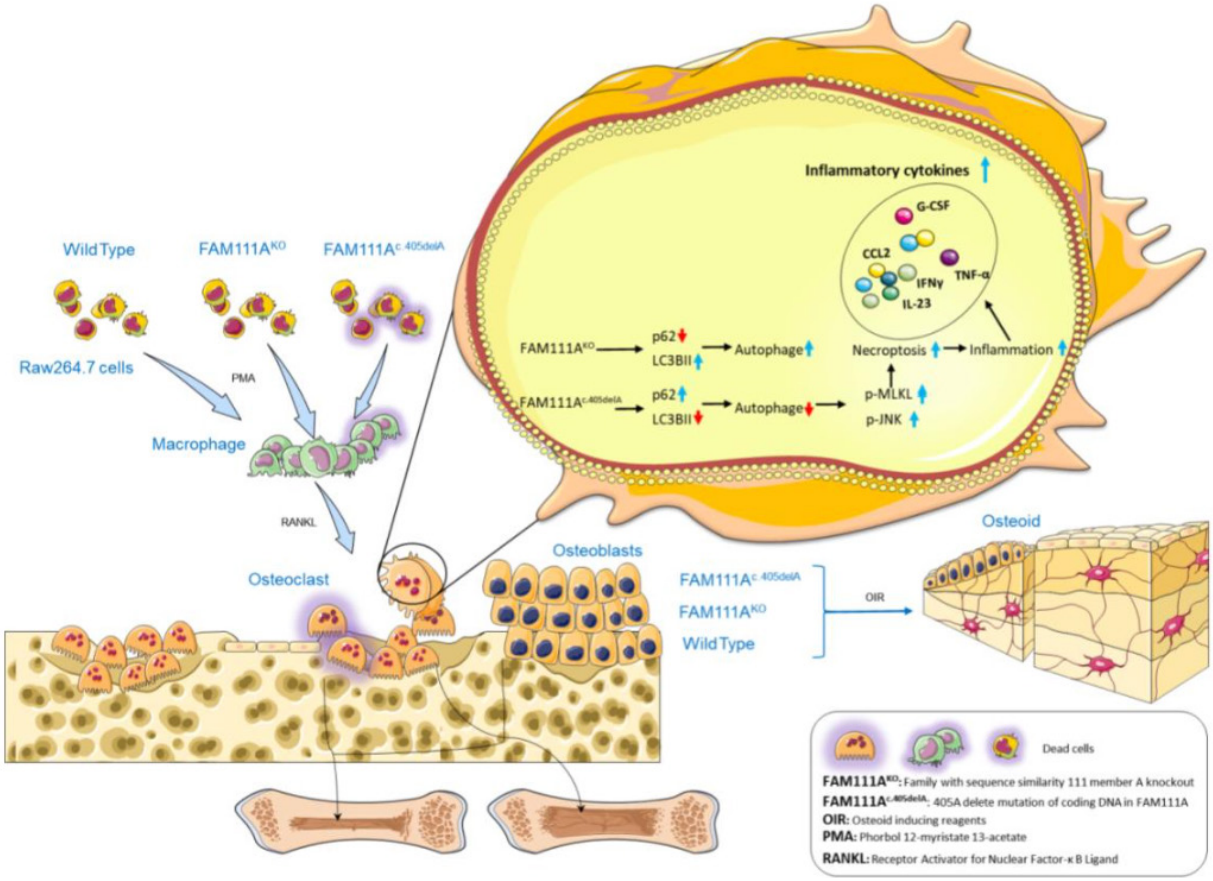
Background and aims: Kenny-Caffey syndrome type II (KCS2) is a rare genetic disorder characterized by skeletal abnormalities, impaired growth, and developmental delay. Our research focuses on exploring the contribution of a novel heterozygous variant in the FAM111A gene to the clinical features of a patient exhibiting KCS2-like syndrome. The exome sequencing, in vitro experiments, and protein structure analysis were conducted to explore the contribution of this variant to the clinical features of KCS2-like syndrome.

Methods: The exome sequencing, *in vitro* experiments, and protein structure analysis were conducted to explore the contribution of this variant to the clinical features of KCS2-like syndrome.

Results: In order to confirming the diagnosis, through whole exome sequencing, a novel heterozygous variant (c.405delA/p.E136Sfs*3) in FAM111A gene was discovered in an 11-year-old patient. Additionally, we found the clinical features of this patient were consistent with KCS2-like syndrome. Our in vitro study revealed that the variant led to a significant increase in necroptosis of osteoclasts. Furthermore, variant osteoclasts displayed a significant down-regulation of autophagy, potentially contributing to the onset of KCS2-like syndrome. Consequently, the augmented necroptosis may result in the up-regulation of inflammatory cytokines such as G-CSF, IL-17A, IL-23, CCL2, IFN-γ, and TNF-α. Considering the protein structure analysis, it is hypothesized that the truncated FAM111A (p.E136Sfs*3) retains the ubiquitin-like domain, which might explain the up-regulated ubiquitination in variant osteoclasts. Therefore, the enhanced ubiquitination in variant osteoclasts may lead to the excessive degradation of intracellular proteins, causing irreversible necroptosis.

Conclusions: Our study comprehensively investigates the potential relations between the novel variant of FAM111A (c.405delA) and clinical features of KCS2-like syndrome. We propose that this novel variant could be one of the pathogenic factors for KCS2-like syndrome.

Graphic Abstract:



Study of Knowledge, Attitude and Perception of Knowledge Gap in Expanded Newborn Screening Among Medical Practitioners in Universiti Sains Malaysia

Muhammad Khairil Azizi Bin Che Omar[1], Intan Juliana Abd Hamid[1] and *Zarina Thasneem Zainudeen[1]

1 *Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam 13200, Kepala Batas, Penang, Malaysia.*

Introduction: The study assesses and investigate knowledge, attitude, and perception regarding expanded Newborn Screening Program (NBS) in Malaysia.

Methods: This study was conducted from 1st July 2024 until 31st October 2024 at HPUSM and PPUSMB. The participant was invited to join this study via invitation text using communication application WhatsApp and a validated questionnaire.

Results: The study found that the proportion of medical practitioners having favourable knowledge score is low, with highest among the category of others specialty 16.67%, surgical specialty 14.61% and medical specialty 14.61%. For the attitude score, majority has favourable score, with medical specialty 75.00%, Others specialty 69.23% and surgical specialty 67.42%. For the Practices the score, majority has favourable MPL score medical specialty 83.33%, surgical specialty 78.65% and 'Others' specialty 76.92%.Analysis of knowledges and attitudes score showed there is no significant predictors found. Analysis of practice scores showed that specialty and years of practice are significant predictors.

Discussion: The participants lack of knowledge on expanded NBS can be improved by continuous education and training. Participants favorable score on attitude and can play a major factor in successful implementation of expanded NBS in Malaysia. There is no significant predictor on studied variables for knowledge and attitude. Years of practice and specialty show as significant predictors on practices which play important role in implementation of expanded NBS in Malaysia.

Conclusions: Study provided valuable insights into the knowledge, attitudes, and practices of medical practitioners, highlighting how the studied variables influence these outcomes.

(Keywords: expanded NBS, Malaysia, knowledge, attitude and perception)

Challenges and Community-Directed Interventions for Immunodeficiencies in Underdeveloped and Resource-constrained Countries

Dharmagat Bhattarai[1], Aaqib Zaffar Banday[2], Radha Neupane[1], Phub Tenzin[3], Asmita Neupane[1], Pratap Kumar Patra[4]

1 *Advanced Centre for Immunology & Rheumatology, Kathmandu, Nepal*
2 *Government Medical College, Srinagar, Kashmir, India*
3 *Jigme Dorji Wangchuk National Referral Hospital, Thimphu, Bhutan*
4 *All India Institute of Medical Sciences, Patna, India*

Background and aims: Immunodeficiencies (IDs) and inborn errors of immunity (IEIs) remain grossly undiagnosed and untreated in resource-constrained settings. We studied socio-economic determinants and the effect of community-directed interventions (CDIs) for IDs/IEIs in underdeveloped countries.

Methods: Direct patient questionnaires and web-based community and healthcare provider-directed surveys were performed to assess the baseline awareness regarding IEIs in 2 phases in the Himalayan regions of South Asia including Nepal and Bhutan. CDIs were implemented from January 2022 up to May 2023. Applied interventions included health camps, media promotions, articles, videos, television interviews, awareness talks, college classes, and society formation.

Results: Having only 1 clinical immunologist, Nepal is facing several challenges in specialized immunological care. Patients are either misdiagnosed or mistreated or face poor outcomes due to numerous challenges like lack of a nationalized health system, poverty, educational gap, and gross lack of awareness, and willpower among the physicians, government, and health authorities. Severe financial hardship, illiteracy, social taboos, and unavailability of diagnostic tests and treatment modalities are other contributors. Financial barriers and government unwillingness are the most difficult to overcome.

Patients from Nepal and Bhutan were included. After CDIs, we observed 7 times increment in seeking doctor's help from patients and a 3-fold increase in immunological tests. Baseline public awareness increased from 2.1% to 7.1%

Only 1/5th of needful patients could procure intravenous immunoglobulin even after CDI. Genetic tests were still outsourced. While 123 patients were diagnosed with IEIs genetically, 353 patients with suspected IEI or immune dysregulation could not proceed ahead with any test. Hematopoietic stem cell transplantation (HSCT) could be expedited for 4 patients only.

Conclusions: In Nepal, 22% of the population live below poverty line. Logistic constraints coupled with a lack of awareness and willpower for IEIs among laity and pediatricians accounted for missed diagnoses and poor outcomes.

Pioneering New Avenues in Immunological Diagnostics for Severe Combined Immunodeficiency Using LySIM Technology

Henkie Isahwan Ahmad Mulyadi Lai[1,5], Adli Ali[1,2,3,4]

1 *Faculty of Health Science, Department of Medical Science and Technology, University College of MAIWP International, Kuala Lumpur, Malaysia*
2 *Research Center, Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, UKM Specialist Children's Hospital, Kuala Lumpur, Malaysia*
3 *Department of Pediatric, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, 56000, Malaysia*
4 *Institute of IR4.0, Universiti Kebangsaan Malaysia, Bangi, Malaysia*
5 *Infection and Immunology Health and Advanced Medicine Cluster, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia*

Background and aims: Accurate quantification of lymphocyte subsets is essential for understanding immune function and its involvement in various diseases. This is particularly important in primary immunodeficiency disorders (PIDs), such as Severe Combined Immunodeficiency (SCID), a life-threatening condition requiring prompt diagnosis. In Malaysia, the prevalence of PIDs, including SCID, emphasizes the need for affordable and accessible diagnostic methods. Current approaches often rely on expensive equipment and specialized expertise, limiting their utility in resource-constrained settings. To address these challenges, we developed LySIM, an innovative and cost-effective method for lymphocyte subset quantification using immunofluorescence microscopy.

Methods: Peripheral blood mononuclear cells (PBMCs) were collected from both healthy individuals and patients diagnosed with SCID. The cells were stained with fluorescence-conjugated antibodies targeting CD4+ T cells, CD8+ T cells, and B cells. Lymphocyte quantification was initially conducted using a hematology analyzer for baseline comparison and then analyzed using the LySIM method. This approach involved mounting stained samples on slides for examination with an immunofluorescence microscope.

Results: The LySIM method demonstrated high accuracy and reproducibility in lymphocyte subset quantification, successfully distinguishing SCID patients from healthy individuals. Compared to conventional methods, LySIM significantly reduced costs, making it a viable option for research and clinical applications, particularly in low-resource settings. The user-friendly interface of the custom software minimized the requirement for advanced technical expertise, further enhancing its accessibility. Importantly, LySIM's ability to differentiate lymphocyte subsets in SCID patients highlights its potential as a practical tool for diagnosing and monitoring primary immunodeficiency disorders.

Conclusions: LySIM represents a practical and affordable tool for lymphocyte subset quantification, particularly in diagnosing SCID and other PIDs. By utilizing basic equipment and custom software, LySIM addresses challenges in cost and accessibility, making it an impactful solution for improving diagnostics in resource-limited settings, including Malaysia, where PIDs remain a significant concern.Years of practice and specialty show as significant predictors on practices which play important role in implementation of expanded NBS in Malaysia.

Immune reconstitution post-haploidentical hematopoietic stem cell transplant (HSCT)

Ki Lam[1], Elaine Au[1], Pamela Lee[2], Ricky Ip[1], Helen Wong[1], Wilson Chan[2], Daniel Cheuk[2]

1 *Division of Immunology, Department of Pathology, Queen Mary Hospital*
2 *Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital*

Background and aims: Hematopoietic stem cell transplant (HSCT) is an important cure for many primary immunodeficiency diseases (PIDs) like severe combined immunodeficiency (SCID)1,2, oncological conditions like leukaemia, neuroblastoma, and haematological condition like thalassemia. Haploidentical HSCT from a mismatched family member provides an alternative option for patient lacking a human leucocyte antigen (HLA)-matched donor, but the main obstacles include delayed immune reconstitution. Lymphocyte subsets, serum immunoglobulins (Ig) and post-transplant chimerism were useful methods for monitoring post-HSCT immune reconstitution. Nevertheless, B and T cell subsets were less commonly used.

Methods: Twenty-two patients who underwent haploidentical HSCT in Hong Kong Children's Hospital from the period of January 2022 to August 2023, were recruited. Both donor baseline samples, as well as patient samples at various time points post-HSCT *(Figure 1)*, were checked for B and T cell subset, and compared to other clinical and laboratory parameters.

Results: The recruited patients (9.0± 4.4 years) had HSCT due to underlying immunological or haematological conditions *(Figure 1)*. Donor age (42.0± 11.4 years) was inversely correlated with their CD8+ naïve T cell numbers (R=0.738, p=0.003). 4 patients passed away before study completion.

At 1-month post-HSCT, most patients had very low (<100/uL) B (n=20; 90.9%) and CD4 or CD8 T (n=19; 86.4%) cells, whereas the oxidative burst activities of the 2 CGD patients normalized. With the naïve B and T cells improving over the months, 2 patients still failed to have their B, or B and T cell reconstituted at 6 months post-HSCT. At 1 year (n=18), the naïve B, naïve CD4 T and naïve CD8 T cells of the patients were 391.7± 264.6/uL, 356.2± 380.5/uL, and 223.8± 134.3/uL respectively, which were below age-matched reference range. Use of serotherapy, T cell depletion, GVHD prophylaxis, or donor age itself, did not impact significantly for immune cell reconstitution. Comparatively, chimerism remained at least 95% for all studied time points.

Conclusions: Immune reconstitution was still going on 1-year post-HSCT. Use of B and T cell subsets was useful formonitoring.

References:

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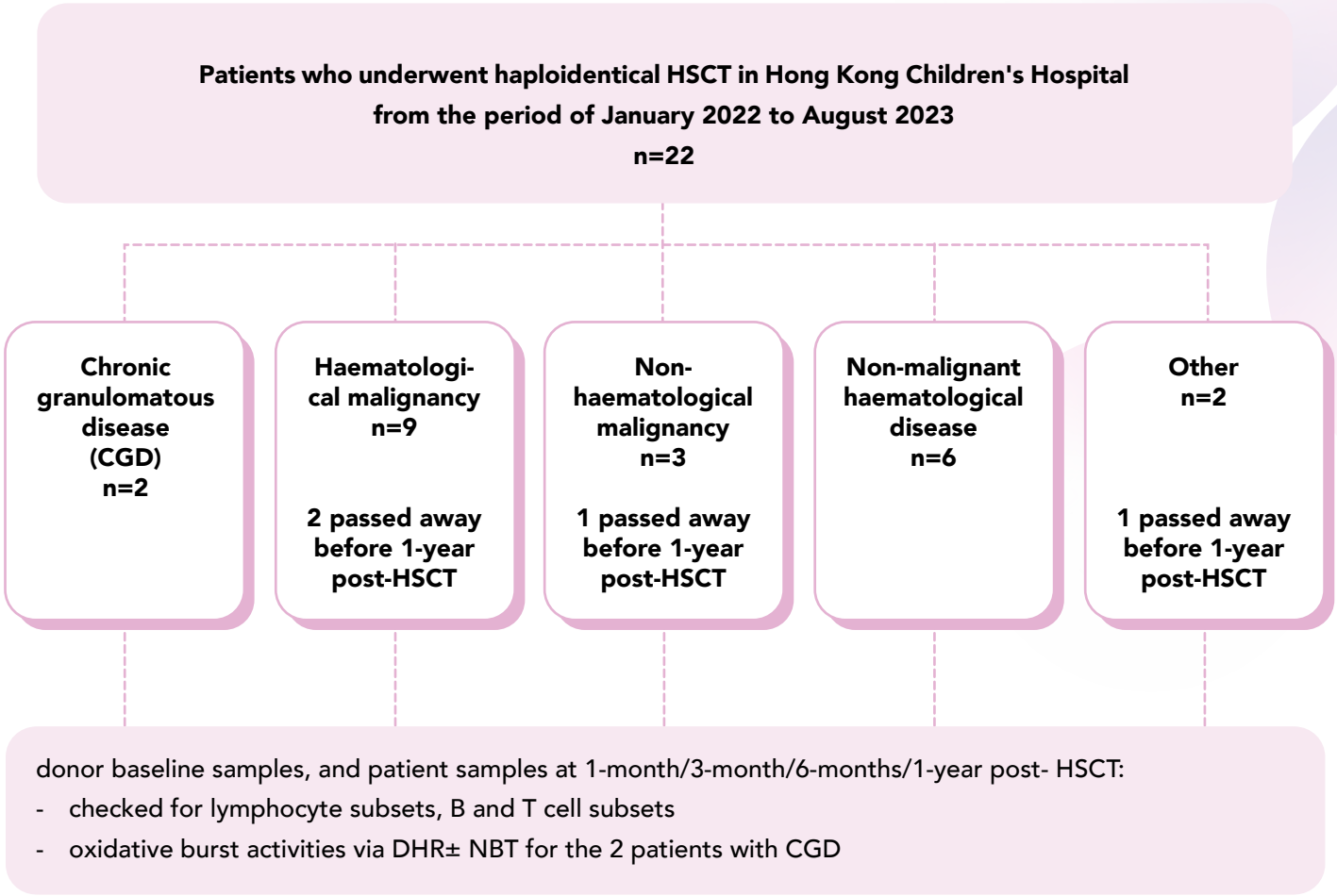
Figure 1.


Patients who underwent haploidentical HSCT in Hong Kong Children's Hospital from the period of January 2022 to August 2023
n=22
Chronic granulomatous disease (CGD) n=2
Haematological malignancy n=9
2 passed away before 1-year post-HSCT
Non-haematological malignancy n=3
1 passed away before 1-year post-HSCT
Non-malignant haematological disease n=6
Other n=2
1 passed away before 1-year post-HSCT
donor baseline samples, and patient samples at 1-month/3-month/6-months/1-year post- HSCT:
- checked for lymphocyte subsets, B and T cell subsets
- oxidative burst activities via DHR± NBT for the 2 patients with CGD

PID and Nocardia: An Ignored Association

Vaishnavi Iyengar, Akshaya Chougule, Vijaya Gowri, Prasad Taur, Mukesh Desai.

Department of Immunology, Bai Jerbai wadia hospital for children , Parel, Mumbai.

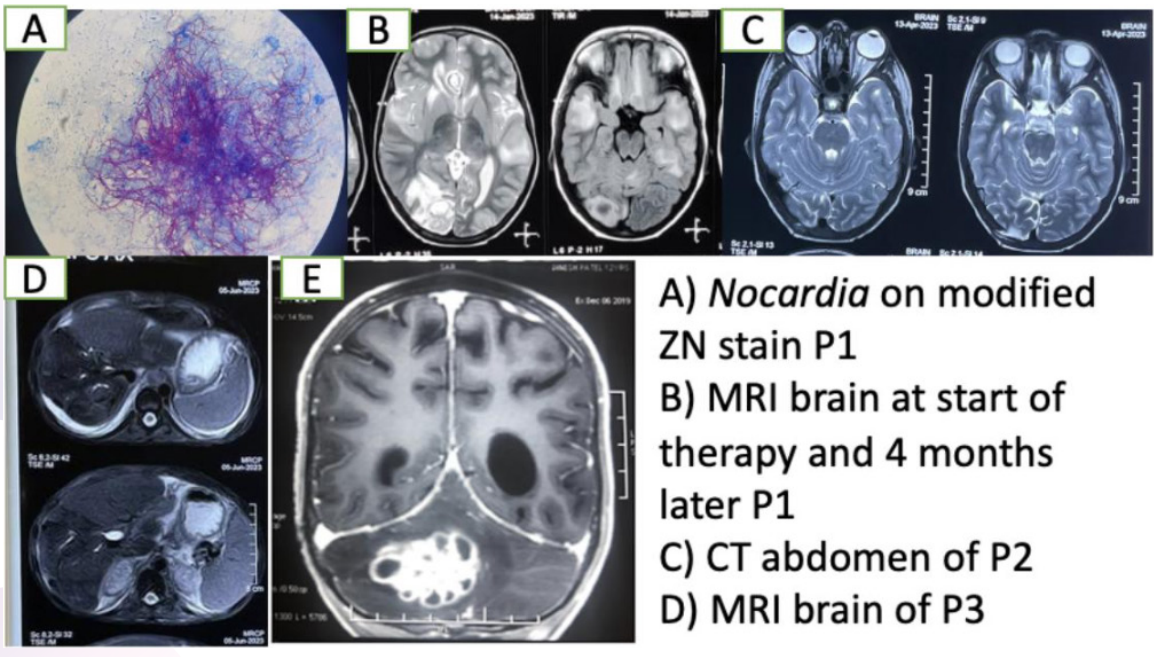
Background and aims: Nocardiosis is caused by the gram-positive bacterium Nocardia spp. The most common PID associated with nocardiosis is CGD. This case series highlights three cases of nocardiosis with a diagnosis of PID other than CGD.

Methods: Three patients with *Nocardia spp* isolated from different sites were included.

Results: P1, 9 year old male child, diagnosed case of IL12RB1 deficiency, presented with seizures. MRI brain showed multiple ring enhancing lesions. He was empirically treated with AKT and steroids for tuberculomas. Newer lesions on MRI brain prompted biopsy that showed acid fast filaments on modified-ZN stain. Culture grew *Nocardia spp*. P2, 10 year old male presented with cachexia, deep jaundice, abdominal distension with right pyopneumothorax and large splenic abscess. Splenic aspirate and pleural tap revealed presence of *Nocardia spp* on culture and *Nocardia cyriacigeorgica* on MALDI-TOF. In view of disseminated nocardiosis, NBT/DHR test was advised which was normal, WES revealed homozygous IL12RB1 pathogenic variant. P3, 9 year male with refractory atopic dermatitis since 3 months of age. He had eosinophilia (10,000 cells/cumm) and hyper IgE (2360 IU/ml). He was diagnosed with DOCK8 deficiency on NGS. While being evaluated for BMT he had focal seizure with ataxia, MRI brain revealed presence of cerebellar abscess. Biopsy revealed *Nocardia spp*.

Conclusions: Isolation of *Nocardia* at any age must prompt one to look for underlying PID other than CGD as well. Extensive and invasive tests along with radiological tests need to be undertaken in patients with PID to isolate and appropriately treat.

Figure 1



Clinical and Laboratory Profile in the Different Types of Primary Immune Deficiency Disorders (PIDs) in Children- A BSMMU perspective

Mohammad Imnul Islam, kamrul Laila, Hafiz Al-Mamun, Manik Kumar Talukder, Mohammed Mahbubul Islam, Chandan Kumar Roy, Mujammel Haque

Background: Recurrent infections, the hallmark of Primary immunodeficiency disorders (PIDs), present unique challenges in the context of Bangladesh's healthcare system. The wide spectrum of signs and symptoms, combined with the endemic nature of infectious diseases makes PID diagnosis particularly difficult in this region. This study aimed to assess the clinical presentations, different types, and laboratory evaluation of PIDs with the potential to significantly improve the diagnosis and management of these disorders in Bangladesh.

Methods: It was a cross-sectional study conducted in Paediatrics rheumatology division of the Department of Paediatrics and Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period of July 2022 to June 2024. One hundred forty three suspected cases of PIDs as per inclusion criteria were enrolled in the study. History, clinical examination and laboratory findings including complete blood count, serum immunoglobulin levels, and flow cytometric assessment were recorded in the predesigned data collection sheet.

Results: In this study, 69 (48.2%) cases were diagnosed with PIDs. Majority of cases were male (57%) and mean age of 63.65±57.01 months. The mean diagnostic delay was 40.21 months. Recurrent pneumonia was the most common (66%) presenting complains, and around 90% patients needed IV antibiotics to clear infections. Recurrent pneumonia, recurrent ear infections, persistent oral thrush, and need of IV antibiotics to clear infection were the important warning signs. Predominantly antibody deficiency was the most common type followed by immunodeficiency affecting cellular and humoral immunity (24.6%), combined immunodeficiency with associated syndromic features (12, 17.4%), and others.

Flow cytometry could effectively identify major forms of PIDs including X-linked agammaglobulinemia, severe combined immunodeficiency, chronic granulomatous disease etc.

Conclusions: PIDs are not uncommon in this region. Physician awareness is pivotal for timely diagnosis and to improve morbidity and mortality of this patient. Antibody deficiency disorders are the most prevalent types of PIDs in this study.

Infantile Monogenic Ibd: A Case Series

Vaishnavi Iyengar, Akshaya Chougule, Vijaya Gowri, Prasad Taur, Mukesh Desai.

Department of Immunology, Bai Jerbai wadia hospital for children , Parel, Mumbai.

Background and aims: Patients with a varied spectrum of rare genetic disorders can present with inflammatory bowel disease like phenotype.

Methods: Retrospective study of all children referred to us with infantile onset of chronic diarrhoea with a monogenic error.

Results: 12 children (6females:6males). All children had failure to thrive. The mean age of presentation was 3.5 months with an average delay in diagnosis of ~3 years. 6 were born of consanguineous unions. 7 children had enteropathy like presentation with chronic diarrhoea, 5 had enterocolitis like presentation with bloody diarrhoea and abdominal pain. Additional features included global developmental delay in 4, seizures in 1 among these 4, 5 had recurrent sinopulmonary infections. 3 had low birthweight, 3 children had facial dysmorphism. Hypothyroidism, IDDM and AIHA were also seen. Among the monogenic defects identified, 3 children had pathogenic variants in TTC37, 2 each with CARMIL2 and FERMT1 defect, 1 each with FOXP3defect, CD25deficiency, ARPC1B, Wiskott-Aldrich and LRBA defect. 2 children were initiated on sirolimus and 1 on abatacept. However, in majority the diarrhoea remained refractory to therapy. Currently 4 are alive, including all children with TTC37 who had self-limiting diarrhoea, 4 have died and 4 have lost to follow up.

Conclusions: Majority of children with monogenic IBD in this cohort had onset within 6 months of life. Extra-intestinal manifestations were common. There exist limited treatment options as majority remained refractory to therapy. HSCT can be performed for some of the defects hence early identification can be curative in some.

以免疫性血小板减少为初发表现的免疫失调型IEI患儿血小板特异性抗体分布差异

谷昊[1]、陈振萍[2]，吴润晖[3]，毛华伟[1]

1 首都医科大学附属北京儿童医院免疫科；
2 首都医科大学附属北京儿童医院液疾病研究室；
3 首都医科大学附属北京儿童医院血液病科

背景: 免疫出生错误（Inborn error of immunity，IEI）患儿相当一部分最初并不表现为感染，而是表现为免疫失调性疾病。受累血液系统的自身免疫表现以免疫性血小板减少为主。病初表现为免疫性血小板减少的免疫失调型IEI患儿在确诊前，大部分被诊断为持续性乃至慢性免疫性血小板减少症（Immune thrombocytopenia，ITP），并接受ITP的一线及二线治疗。伴免疫性血小板减少的免疫失调型IEI患儿与ITP患儿其血小板特异性抗体（抗-GPIIb/IIIa、抗-GPIb/IX及抗GPIa/IIa）的分布及抗体滴度尚无横断面比较及报道，本研究我们探索了以免疫性血小板减少为初发表现的免疫失调型IEI患儿与ITP患儿其血小板特异性抗体的分布差异。

方法: 该研究为单中心回顾性研究，入组收治于我院2016至2023年以免疫性血小板减少为初发表现并最终确诊为IEI的患儿。依据IEI患儿年龄、性别、血小板减少病程时间及出血严重程度分级匹配ITP患儿。所有患儿应用酶联免疫吸附法（PAKAUTO试剂盒）行血小板特异性抗体检测并分析组间特异性抗体分布差异。

结果 共计入组20例免疫失调型IEI患儿（4例ALPS-FAS、1例ALPS-FASLG、1例ALPS-CASP10、1例PRKCD 缺陷、2例CTLA4缺陷、3例LRBA缺陷、3例STAT3 GOF、3例IPEX、1例AIRE及1例UNC13D缺陷）。依据入组IEI患儿年龄、性别及出血严重程度分级匹配持续性及慢性ITP患儿共计44例。结果显示血小板特异性抗体抗-GPIIb/IIIa在免疫失调型IEI患儿与ITP患儿中分布无差异 ($\chi2 = 0.539$, $p = 0.463$)，ITP患儿其抗-GPIb/IX及抗GPIa/IIa分布多于免疫失调型IEI患儿($\chi2 = 14.87$, $p = 0.0001$; $\chi2 = 9.54$, $p = 0.002$)。

结论 以血小板减少为初发表现的免疫失调型IEI患儿与ITP患儿存在血小板特异性抗体分布差异，免疫失调型IEI患儿其血小板特异性抗体以抗-GPIIb/IIIa为主，持续性及慢性ITP抗-GPIb/IX及抗GPIa/IIa抗体分布多于免疫失调型IEI患儿，对于免疫性血小板减少病程超过半年的抗-GPIIb/IIIa阳性患儿应及时针对免疫失调型IEI开展诊断再评估。

Distribution of anti-glycoprotein autoantibodies between ITP and IEI (type IV)

		ITP	IEI (type IV)	χ^2	*P*
Anti-GPIIb/IIIa	Positive	36	14	0.539	0.463
	Negative	8	6		
Anti-GPIb/IX	Positive	33	4	14.87	**0.0001**
	Negative	11	16		
Anti-GPIa/IIa	Positive	24	2	9.54	**0.002**
	Negative	20	18		

Abbreviation: GP, glycoprotein.

Efficacy and Safety of First-Line Tocilizumab Therapy in Real-World Management of Systemic Juvenile Idiopathic Arthritis-Associated Macrophage Activation Syndrome (sJIA-MAS)

MaJing, MaoHuawei

Department of Immunology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045.

Background and aims: To assess the efficacy and safety of early tocilizumab use in treating systemic Juvenile Idiopathic Arthritis associated Macrophage activation syndrome (sJIA-MAS) and identify potential risk factors contributing to MAS recurrence during tocilizumab therapy.

Methods: This retrospective study reviews sJIA-MAS cases treated with tocilizumab from 2018 to 2024, collecting demographic, clinical, laboratory, and adverse event data to evaluate the safety and efficacy of treatment, as well as to identify risk factors associated with MAS recurrence. Statistical analyses used GraphPad Prism (v9.5.1), and R (v3.5.7, "survival" package), with tests for variable comparisons and Cox regression for survival analysis, at a significance level of $P < 0.05$.

Results: In this study, 29 children with sJIA-MAS received tocilizumab, administered at a median of 5 days after diagnosis, resulting in remission rates of 13.79%, 48.28%, and 82.76% at 2, 4, and 8 weeks, respectively. Eight patients experienced recurrence (6 MAS attacks, 2 sJIA flares), with a median time to recurrence of 4 days (IQR 3.8–7.3). Cox regression analysis identified significant risk factors for MAS recurrence, including higher Physician's Global Assessment (PhGA) scores (HR 2.64, 95% CI 1.13–6.19, P = 0.025) and meeting MAS diagnostic criteria (HR 11.53, 95% CI 1.18–112.48, P = 0.035) at tocilizumab initiation. The incidence of sJIA flares and MAS attacks was reduced during follow-up, with adverse events decreasing from 7.02 to 1.40 per patient-year.

Conclusions: Early addition of tocilizumab to treatment can help control disease and reduce steroid use, strong predictors of MAS recurrence include the Physician's Global Assessment score and the presence of MAS at tocilizumab initiation. Tocilizumab offers significant long-term protection against sJIA flares and MAS attacks.

Analysis of Variables Impacting Remission Probability in Patients Treated with Tocilizumab (TCZ)

Variables	Univariate Analysis					Multivariate Analysis				
	β	S.E	Z	P	HR (95% CI)	β	S.E	wZ	P	HR (95% CI)
MAS at TCZ										
	2.81	1.07	2.62	0.009	16.66 (2.03~136.92)	2.44	1.16	2.10	0.035	11.53 (1.18~112.48)
Serositis										
	2.23	0.73	3.05	0.002	9.33 (2.22~39.19)	-0.05	1.19	-0.04	0.969	0.96 (0.09~9.81)
PhGA	1.16	0.33	3.55	<.001	3.18 (1.68~6.01)	0.97	0.43	2.24	0.025	2.64 (1.13~6.19)

T.I.: Time Interval between Tocilizumab Administration and Diagnosis, HR: Hazard Ratio, CI: Confidence Interbal, PhGA: Physician Global Assesment

Good Syndrome: Not So Good After All

Vaishnavi Iyengar, Vijaya Gowri, Akshaya Chougule, Prasad Taur, Mukesh Desai.

Department of Immunology, Bai Jerbai wadia hospital for children , Parel, Mumbai.

Background: Good syndrome is a rare adult-onset immunodeficiency characterized by thymoma, immunodeficiency and autoimmunity. Here we present a case series of 6 cases diagnosed with Good syndrome.

Methods: 6 patients with Good syndrome were included and their clinical and laboratory data evaluated.

Results: The median age of diagnosis was 49 years. 4 males and 2 females were included. Two had Type AB thymoma, three had type B2 and in one the type was not available. In all except two, thymoma was the primary presentation while two patients had recurrent RTI and thymoma was detected while being investigated for it. Only one patient had myasthenia gravis. All patients had panhypogammaglobinemia with a median IgG of 500mg/dl (260-681mg/dl). 5/6 had recurrent RTI. Organisms detected in sputum included PCP, *pseudomonas, histoplasma, nocardia, & mycobacterium tuberculosis.* Two patients had severe COVID infection requiring remdesivir. 3/4 had B cell lymphopenia, 2/4 had reduced CD4 naïve and central memory cells and 1/4 had reversal of CD4/8 ratio. Two patients have been lost to follow up, 4 patients are on monthly IVIG and antibiotic/antifungal prophylaxis with significant reduction in RTI episodes. One has undergone radical thymectomy with persistent hypogammaglobinemia, in one it's unresectable due to encasement of aorta and two have been posted for thymectomy.

Conclusions: Patients with Good syndrome have diverse organisms including organisms usually found in phagocytic/innate immune defects. All patients had hypogammaglobinaemia including the patient without clinical RTI hence baseline IgG levels may not have prognostic value. Hypogammaglobinaemia may not improve even with thymectomy

Arrested maturation, reduced motility or abnormal function- study of patients with Neutrophil Defects from a center in Western India

Akshaya Chougule[1], Prasad Taur[1], Vaishnavi Iyengar[1], Vijaya Gowri[1], Manisha Madkaikar[2], Mukesh Desai[1]

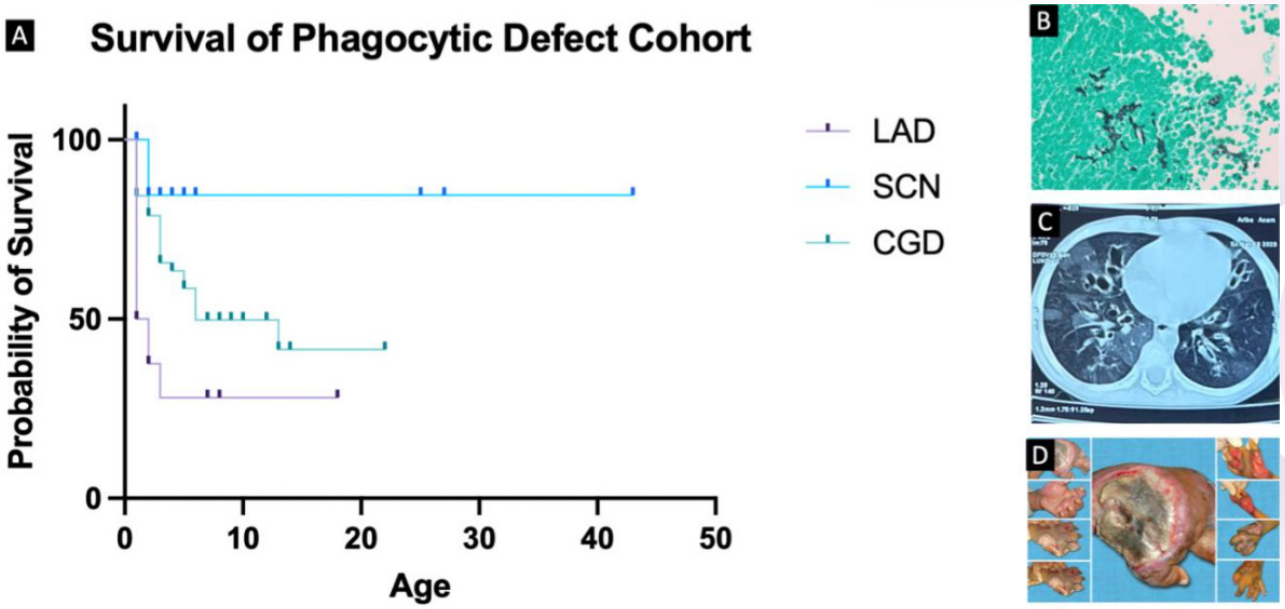
1 *Department of Immunology, B. J. Wadia Hospital for Children.*
2 *Department of Paediatric Immunology and leukocyte biology, ICMR NIIH.*

Background and aims: Phagocytic or neutrophil defects fall under class V, IUIS classification and are further grouped as IEI with neutropenia and functional defects. We present a retrospective analysis of patients with laboratory or genetically proven cases with neutrophil defects.

Methods: Clinical and laboratory findings were analysed retrospectively. 110 children were included, 71 had chronic granulomatous disease (CGD), 22 had leukocyte adhesion deficiency (LAD, 19/22- LAD-1 (Complete-15, partial-4), 3/22-LAD-3), 17 had severe congenital neutropenia (SCN).

Results: Median age of onset was 6months. Lungs were most common infection site, 73% had at least one pneumonia. Persistent pneumonia(39%) was more common with CGD. Recurrent pneumonia, pleural effusion/ empyema and bronchiectasis were noted. Subcutaneous abscesses were seen in all three groups. Deep-seated abscesses, osteomyelitis, septic arthritis were more common with CGD. CNS infections, including bacterial and tuberculous meningitis, tuberculoma and aspergilloma were more common with CGD. Omphalitis, neonatal sepsis were seen with SCN and LAD. BCG adenitis, BCGosis was seen in CGD only. Bacterial organisms isolated predominantly were Mycobacteria tuberculosis, Staphylococcus aureus, gram-negative organisms like Pseudomonas aeruginosa, klebsiella pneumonia. Uncommon organisms like Pasturella canis, Citrobacter freundi, Chromobacterium violaceum, non-typhi salmonella were seen with CGD. Fungal infections, including invasive aspergillus infections, were seen in all three groups. Immune dysregulation included pyoderma gangrenosum (LAD-1), HLH (CGD, LAD-3, SCN), recurrent oral ulcers (CGD, LAD-1, SCN). Mortality was higher and earlier for un-transplanted complete LAD-1, LAD-3 as compared to CGD, SCN. Initiation of Inj.GCSF reduced infections in patients with SCN. Longest duration on Inj.GCSF was 4.5years, dose range was 2.5mcg/kg/day to 12mcg/kg/day. None of the SCN patients developed MDS/ AML. G6PC3 responded to empagliflozin. 3/71 GCD and 3/19 LAD1 underwent successful HSCT.

Conclusions: Phagocytic defects have considerable morbidity and mortality, early diagnosis is essential. Patients with SCN on GCSF/ empagliflozin have better survival than un-transplanted CGD/ LAD.



A- Survival curve analysis showing early and higher mortality in patients with LAD1 and LAD3 as compared to CGD and SCN
B- Brain biopsy of P108 with CGD showing Aspergillus hyphae
C- HRCT chest of of P34 with cyclic neutropenia showing severe bronchiectasis
D- Picture of P43 with CGD with Basidiobolus infection of hand

B-lymphocyte abnormalities in patients with Chronic Granulomatous Disease

Vignesh Pandiarajan[1], Sanjib Mondal[1], Kaushal Sharma[1], Sumit Goel[1], Jhumki Das[1], Aditya Dod[1], Amit Rawat[1], Surjit Singh[1]

1 *Allergy Immunology Unit, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.*

Background and aims: The role of NADPH oxidase in phagocytes is known to an extent, but its role in other immunological cells like B lymphocytes is not largely explored. We aimed to investigate the biological significance of NOX in B-cells, the generation of regulatory B-cells and sustaining long-term memory.

Methods: The proportion of B-cell subsets was assessed in mutation-proven CGD [X-linked, AR and carrier CGD] (n=30). B-cell proliferation (BCR and TLR9 mediated) and generation of regulatory B-cell (TLR9 and CD40L mediated) were examined. Late autophagy markers (e.g. LC3 and Lyso-tracker Green) were assessed using flow-cytometry. Bulk RNAseq was done on Illumina HiSeqX in PBMCs obtained from patients with CGD.

Results: A significant reduction in total and activated memory B cells proportion was observed in CGD compared to controls. The degree of reduction in memory B cells directly correlated with residual NADPH oxidase activity. A rise in anti-pneumococcal antibody titres was not observed following polysaccharide vaccine administration in patients with CGD. A significantly higher proportion of CD5+ (CD19+CD27-IgD+) and CD5- (CD19+CD27-IgD+) naïve B-cells was seen in CGD compared to controls. Proliferation efficiency of B-cells was significantly reduced in TLR-mediated stimulation in CGD. B regulatory cells were reduced in XL-CGD group compared to control. Reduction of LC3 expression on whole lymphocytes and CD19+ B-cells in CGD was noted compared to controls after sirolimus treatment. Downregulation of B-cell survival factors (BAFF and APRIL) was observed in RNA sequencing data, which was subsequently validated by ELISA.

Conclusions: Results indicated biological significance of NADPH-oxidase in B-cell activation, proliferation, and generation of regulatory B-cells

TACI and BTK Gene Analysis in Predominantly Antibody Deficiency Disorders among the Primary Immunodeficiency Disorder Patients in Bangladesh

Tripty Chakrobortty[1*], Chandan Kumar Roy[2], Mohammad Imnul Islam[3], Ismet Niger[2], Kamrul Laila[3], Avizit Sarker[4], Nusrat Akhtar Juyee[5], Maidul Islam[2], Fahmida Hoque[6], Partho Protim Chakrobortty[7], S. M. Ali Ahmed[2] and Abu Naser Ibne Sattar[2]

1 *Department of Microbiology, Jashore Medical College, Jashore, Bangladesh*
2 *Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh*
3 *Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh*
4 *Department of Microbiology, Dhaka Medical College, Dhaka, Bangladesh*
5 *Department of Microbiology, Comilla Medical College, Cumilla, Bangladesh*
6 *Department of Microbiology, Jamalpur Medical College, Jamalpur, Bangladesh*
7 *Department of Orthopaedic Surgery, Magura 250 bedded general hospital, Magura, Bangladesh.*

Background and aims:
Common variable immune deficiency disorder (CVID) and X-linked agammaglobulinemia (XLA) are the most prevalent predominantly antibody deficiency disorders (PADs). Analysis of TACI/TNFRSF13B genes in CVID and BTK genes in XLA patients by exome sequencing can help to make specific diagnosis of these cases. The study aimed to find out the TACI and BTK genes mutations and its allelic variation with CVID and XLA patients.

Methods: This cross-sectional study was conducted on the clinically suspected PADs patient attended in the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh during September 2022 to August 2023. Serum immunoglobulin level, immunophenotyping by Flow-cytometry and PCR was conducted in the Department of Microbiology and Immunology, BSMMU and the genetic analysis of TACI and BTK gene were done by Sanger sequencing in DNA Solutions Limited, Dhaka, Bangladesh. Exome sequencing results were validated by the NCBI Genbank.

Results: Out of 35 clinically suspected PAD cases, 15 (42.86%) were diagnosed as PAD patients. Within this group, 7 (46.67%) were diagnosed with CVID, 7 (46.67%) with XLA, and 1 (6.66%) with agammaglobulinemia other than XLA. Analysis of the TACI gene revealed no pathogenic mutations in the CVID patients. Upon analyzing Exon 2 to 19 of the BTK gene, 7 pathogenic/likely pathogenic mutations were detected, consisting of 4 nonsense and 3 missense mutations. Among these, 3 were found to be novel mutations, including 2 missense and one nonsense mutation.y.

Conclusions: Analysis of TACI/TNFRSF13B gene in CVID patients revealed no pathogenic mutations. Mutations in BTK gene were heterogenous and the prevalent mutations are nonsense mutation found in XLA patients.

Transcriptome Analysis Reveals Immune Dysregulation in Neutrophils and Whole Blood in Patients with Common Variable Immunodeficiency

Rakesh Kumar[1], Manpreet Dhaliwal[1], Arunima Sharma[1], Khemraj Thakur[2], Sanchi Chawla[1], Vaishali Thakur[1], Saniya Sharma[1], Amit Rawat[1], Surjit Singh[1]

1 *Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh, India*
2 *Department of Microbiology, Panjab University, Chandigarh, India*

Background and aims: This study aims to identify immune dysregulation and differentially expressed genes (DEGs) in patients with Common Variable Immunodeficiency (CVID) compared to healthy controls.

Methods: A cohort of 3 CVID patients (age of onset: 10 years, 12 years, and 40 years) and matched healthy controls were recruited. Peripheral blood was collected from participants following informed consent. RNA sequencing was performed on neutrophils and whole blood cells. Raw sequencing data in Fastq format were processed using the HISAT2 pipeline. DEGs were analyzed and visualized using Volcano plots, Heatmaps, Gene Ontology (GO) bubble plots, and pathway analysis via R packages (ggplot2, pheatmap2, gprofiler2, and Pathview).

Results: Volcano plots revealed significant upregulation of ***PLPP2, NCBP2L, IGHGP, IGHV3,*** and ***ADCY6*** genes in whole blood cells, and ***CLEC4, LINC06291, DGCR6,*** and ***TB1D31*** genes in neutrophils in patients with CVID. Notable immune-related genes such as ***ALOX15***, involved in oxidative and inflammatory responses, and ***SIGLEC8***, expressed on eosinophils and neutrophils, were also upregulated.

Gene Set Enrichment Analysis of CVID whole blood and neutrophil transcriptomes identified several enriched pathways, including some upregulated pathways. These include response to external stimuli, negative regulation of immune responses, defense against viral infections, cytokine signaling, receptor binding, and regulation of cell differentiation. Pathview analysis revealed upregulation of ***p21***, suggesting enhanced cell cycle arrest, while pro-apoptotic genes ***(TRAIL, FAS, BAFF, LIGHT)*** were downregulated, indicating impaired apoptotic responses.

Conclusions: This transcriptome-based study suggests alterations in myeloid lineage and highlights significant perturbations in immune signaling pathways in patients with CVID. Notably, the upregulation of genes associated with apoptosis and cell cycle arrest, along with the downregulation of key immune modulators such as ***BAFF***, supports the hypothesis that defective immune regulation and impaired B cell differentiation contribute to the pathogenesis of CVID. These findings provide molecular insights into CVID, potentially guiding future therapeutic approaches.

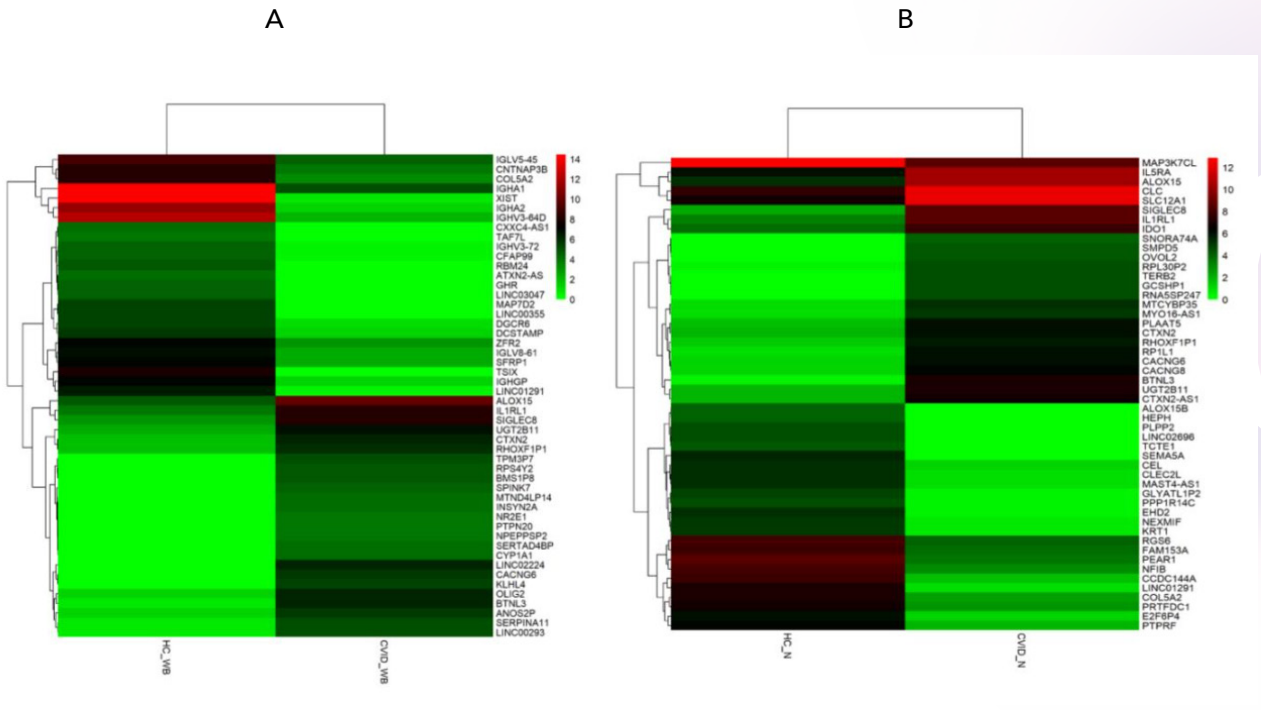


Figure 1: Heatmap showing the clustering of genes enriched in common variable immunodeficiency disease patients:

A.) Whole blood cells (CVID_WB) vs healthy controls (HC)

B.) Neutrophils (CVID_N) vs healthy controls (HC). The color intensity (green to red) corresponds to their normalized expression.

Bronchiectasis in Inborn Errors of Immunity

Akshaya Chougule, Vijaya Gowri, Vaishnavi Iyengar, Prasad Taur, Mukesh Desai

Department of Immunology, Bai Jerbai Wadia Hospital for Children, Mumbai

Background and aims: Bronchiectasis is caused by progressive injury of airway walls as a result of chronic/ repeated airway inflammation causing irreversible bronchodilation. Here we present a cohort of patients with IEI with bronchiectasis.

Methods: Clinical, laboratory information of 31 patients with genetic/ laboratory evidence of IEI were analyzed retrospectively.

Results: Male: female ratio-21:10. Median age at onset of symptoms was 1.5years, onset was earliest at 1month for P8 (ARPC1b deficiency) and latest at 12 years for P9, P22 (CVID). P9(CVID), P21(CVID), P26(XLA), P30(APDS2) had only one episode of documented pneumonia, whereas P29 had no document pneumonias, only hyperreactive airway disease. Rest of the cohort has had multiple pneumonias, with P5(STAT1 GOF) and P11(APDS1) having maximum number of documented pneumonias (seven). Ear infections were common, followed by CMC, meningitis, GIT, viral infections, sepsis. 19/31 had immune dysregulation (autoimmunity, HSP, allergies, oral ulcers, lymphoproliferation, EBV LPD). P23 (CVID) had B-ALL and P30 (APDS2) had hodgkins lymphoma. Organisms isolated were predominantly Pseudomonas aeruginosa, Streptococcus pneumoniae, MRSA, Mycobacterium tuberculosis. 4/31 had normal lymphocyte subsets, 6/31 had low B cells, 6/31 had isolated CD4 lymphopenia, 3/31 had low CD4 and B cells, 3/21 had low class switch and memory B cells, 3/31 had low T cells, 5/31 had panlymphopenia. 14/31 had panhypogammaglobulinemia, 6/31 had normal immunoglobulins, 3/31 had hyper IgM, 3/31 had hypergammaglobulinemia, 1/31 had low IgA, 1/31 had low IgA and IgM. Genetic diagnosis were STAT1 GOF(5/31), BTK(3/31), ARPC1b deficiency(2/31), DOCK8 (2/31), LRBA (2/31), PI3K(2/31), PI3KP1(1/31), TACI(1/31), TCF3(1/31), AICDA(1/31), CD40LG(1/31), ELANE (cyclic neutropenia)(1/31), P19(CVID) has heterozygous mutations in RAG1, RAG2. 5/31 did not have mutations but had laboratory evidence for CVID or XLA.

Conclusions: Apart from patients with B cells defects, patients with diseases of immune dysregulation (STAT1 GOF, LRBA deficiency and APDS) and those with combined immunodeficiencies (ARPC1b deficiency) can also have debilitating bronchiectasis.

Central nervous system involvement in X-linked lymphoproliferative syndrome type 1

Qian Zhao

National Clinical Research Center for Child Health and Disorders/Children's Hospital of Chongqing Medical University, Chongqing

Abstract:
Neurological involvement in X-linked lymphoproliferative syndrome type 1 (XLP1) presents with diverse clinical patterns and remains poorly understood. We analyzed 36 XLP1 patients with neurological symptoms, classifying them into four subgroups based on the timing of neurological involvement relative to hemophagocytic lymphohistiocytosis (HLH): pre-HLH, HLH-related, post-HLH, and non-HLH. Compared to non-neurological cases, patients with neurological symptoms exhibited later onset and diagnosis, lower EBV infection rates, and a higher incidence of lymphoma. Subgroup analysis revealed distinct clinical patterns, with pre-HLH cases showing early neurological symptoms, HLH-related cases experiencing acute crises, post-HLH cases displaying residual deficits, and non-HLH cases characterized by a chronic, slower disease course. Genetic analysis highlighted diverse SH2D1A mutations, and immunological findings demonstrated frequent dysgammaglobulinemia and altered lymphocyte subsets. Our findings underscore the necessity of early and timely diagnosis to address the heterogeneous and progressive nature of neurological involvement in XLP1, enabling more effective management strategie

Key words: X-linked lymphoproliferative syndrome type 1; Neurological symptom; hemophagocytic lymphohistiocytosis; inborn errors of immunity.

A De Novo NFKBIA Mutation Mimicking Features of SCID and Wiskott-Aldrich Syndrome: A Diagnostic Challenge

Khairoon Nisa Mohamed Nashrudin[1,2], Mohd Azri Zainal Abidin[1,2], Sithra Rengasamy[1,2], David Chun Ern Ng[3], Tan Yuong Chie[4], Intan Hakimah Ismail[1,2]

1 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor Malaysia*
2 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Serdang, Selangor Malaysia*
3 *Paediatric Infectious Disease Unit, Hospital Tuanku Jaafar, Seremban, Negeri Sembilan, Malaysia*
4 *Department of Paediatrics, Hospital Tuanku Ampuan Najihah, Kuala Pilah, Negeri Sembilan, Malaysia*

Introduction: NFKBIA mutations, associated with autosomal dominant ectodermal dysplasia with immunodeficiency (AD-EDA-ID), disrupt the NF-kB signaling pathway, leading to immune dysregulation and recurrent infections. These mutations present with severe immunodeficiency phenotype that often resembles severe combined immunodeficiency (SCID) or Wiskott-Aldrich syndrome (WAS). The clinical presentation of NFKBIA mutations can be challenging to distinguish from other immunodeficiencies, particularly in early stages, often resulting in delayed or misdiagnosis.

Case Presentation: A 1-year-old male infant presented at 3 months with infected eczema, oral candidiasis, and failure to thrive. At 4 months, he developed *Staphylococcus* aureus intramuscular abscess of the right thigh and central line bloodstream infection. By 6 months, he had recurrent viral pneumonias (RSV, rhinovirus, influenza A, bocavirus), disseminated ganciclovir resistant CMV, and chronic diarrhoea due to *Microsporidium* sp. On examination, he had generalised xerotic skin, severe growth faltering, hepatosplenomegaly, and an absent BCG scar. The hair appeared normal, and there was no tooth eruption.

Laboratory findings revealed persistent thrombocytopenia. Immunological profiles revealed elevated IgM, low IgA and IgG, low B cells, elevated total T cells, CD4 and CD8 T cells, normal naïve T cells, and reduced class-switched memory B cells. Despite intravenous immunoglobulin therapy, his CMV infection remained resistant to ganciclovir, cidofovir, and foscarnet, with an increased viral load of 675,600 copies and a liver biopsy confirming CMV-related transaminitis. He progressed to liver failure with coagulopathy and succumbed to intracranial bleeding. Genetic testing confirmed a de novo NFKBIA mutation.

Results: The patient's clinical presentation of recurrent infections, eczema, xerotic skin, and thrombocytopenia, strongly suggest a diagnosis of AD-EDA-ID, features closely resembling WAS. Immunological findings, including elevated T-cell and low B-cell counts, further complicated the diagnosis by resembling a SCID-like phenotype, underscoring the diagnostic challenges associated with this condition.

Conclusions: Early genetic testing is essential for accurate diagnosis and guiding appropriate management of this complex immunodeficiency.

Investigation	4 months	6 months	Normal Range
Complete blood count (x 10^9)			
Leukocytes	27.8	10.3	5.0-14.5
Neutrophils	8.3	3.7	1.5-8.5
Lymphocytes	9.6	6.0	2.0-8.0
Monocytes	1.0	0.6	0.4-2.0
Eosinophils	1.6	0.1	0.2-1.9
Basophils	0.2	0.03	0.0-0.1
Immunoglobulins (g/L)			
IgG	1.72	1.55	2.2-11.3
IgA	<0.26	<0.26	0.08-0.9
IgM	2.39	2.59	0.07-0.65
IgE (kU/L)	<2		
Lymphocyte subsets (x 10^6)			
T cells (CD3+)	7095 (93%)	13456 (94%)	1700-3600 (50-67%)
B cells (CD19+	226 (3%)	341 (2%)	500-1500 (19-31%)
CD4 (CD4+)	3476 (45%)	7857 (52%)	1700-2800 (38-50%)
CD8 (CD8+)	3664 (48%)	6144 (40%)	800-1200 (18-25%)
NK cells (CD16+/CD56+)	228 (3%)	313 (2 %)	300-700 (8-17%)
Naïve T cells and memory T cells (x 10^6)			Control
CD4+ CD45RA+	3006 (86.5%)		3596 (81%)
CD4+ CD45RO+	205 (5.9%		372 (8.4%)
CD8+ CD45RA+	3154 (86.1%)		1598 (70.8%)
CD8+ CD45RO+	304 (8.3%)		343 (15.2%)
B cell panel (x 10^6)			Control
CD19+ B cells	226 (2.9%)		5350 (29%)
Naïve B cells CD19+ IgD+ CD27-	215 (95.1%)		3152 (97%)
Transitional CD38+ IgM++	3.1 (1%)		32.5 (1%)
Total memory CD27+	11 (4.9%)		71.4 (2.2%)
Class-switched CD27+ IgM- IgD-	1.5 (0.7%		22.7(0.7%)
Non-switched CD27+ IgM+ IgD+	9.5 (4,2%)		48.7 (1.5%)
Plasmablasts CD38+ IgM-	0 (0%)		12.3 (17.2%)

Vitiligo, cytopenias and more: Autoimmunity Dominates in *RAG1* deficiency

Abarna Thangaraj[1], MD; Gayathri CV[1], MD; Pandiarajan Vignesh[1], DM; Amit Rawat[1], MD; Rakesh Kumar Pilania[1], DM

1 *Allergy immunology unit, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Introduction: Introduction: Hypomorphic variants of RAG deficiency have increased autoimmune manifestations compared to infectious complications. In this report, we are describing one patient with RAG deficiency who had predominant autoimmunity.

Case Presentation: A 2.5-year-old girl presented with recurrent oral thrush, acute febrile respiratory illness, and extensive vitiligo. She had previously undergone two exploratory laparotomies for subacute intestinal obstruction and experienced recurrent respiratory infections, petechiae, and onychomycosis. On examination, she showed fever, pallor, vitiligo (acral and scalp), hepatosplenomegaly, oral thrush, and bilateral bronchial breath sounds with crepitations. Investigations revealed anemia, thrombocytopenia, a positive direct Coombs test, elevated CRP, and bilateral fluffy infiltrates on chest X-ray **(Table 1)**. Computed tomography of the chest showed diffuse GGOs in bilateral lung fields. Infective workup revealed elevated CMV viral load, high BD glucan levels, and Pseudomonas aeruginosa in bronchoalveolar lavage. Differential diagnoses included primary immune dysregulatory disorders, autoimmune lymphoproliferative syndrome, APDS, and leaky SCID/RAG defects. Immunological studies showed hypergammaglobulinemia, reduced CD3+ T cells, decreased naïve T cells, and increased memory and senescent T cells. Double-negative T cells were also elevated **(Table 1)**. She was treated with ganciclovir, ceftazidime, amikacin, and liposomal amphotericin B for her infections. Autoimmune manifestations were managed with oral corticosteroids in tapering doses and high-dose intravenous immunoglobulin. Hematopoietic stem cell transplantation (HSCT) was planned as a definitive treatment. Whole exome sequencing revealed a compound heterozygous pathogenic variant in Exon 2 of RAG 1 (c.1421G>A).

Discussion:

Hypomorphic RAG mutations impair central and peripheral tolerance, leading to immune dysregulation. Leaky SCID presents with partially preserved T-cell counts and a reduced T-cell repertoire. CMV infection is often associated with γδ T-cell expansion and autoimmune cytopenias, as seen in this patient.

Conclusions: This case highlights the complex interplay of autoimmunity and immunodeficiency in hypomorphic RAG mutations, necessitating tailored diagnostic and therapeutic approaches.

Table 1: Laboratory Investigations of the Index Child

Parameter	Case	Reference value/ Control value
Hb (g/L)	65	115-145
TLC (× 10^9 /L)	6.2	5.0-14.5
Differential count	Polymorphs-32% Lymphocytes-47%	Polymorphs-25-57% Lymphocytes-35-65% Monocytes- 0-0.8% Eosinophils- 0-1%
LPlatelets (× 10^9 /L)	63	150-450
C-Reactive Protein (mg/L)	53	<6
Total bilirubin/ direct bilirubin (mg/dl)	1.47/0.56	
AST/ALT (U/L)	10/18	
Direct coombs test	Anti IgG: 4+ Anti C3d- Negative	
CMV Viral load	66000 copies/ml	
S. Galactomannan index	0.30	<0.5
β-D glucan (pg/mL)	>523	< 80
Blood culture	sterile	
Bronchoalveolar lavage culture	Pseudomonas aeruginosa	
IgA (mg/dl)	327	14-159
IgG (mg/dl)	1400	345-1236
IgM (mg/dl)	276	43-207
IgE (IU/ml)	9.93	0-230
IgG subclass profile (mg/dl)	IgG1: 1620 IgG2: 366 IgG3: 90 IgG4: 97	
CD3+ lymphocytes % (absolute counts × 10^9 /L)	22.59%(0.669)	53-75 % (1.4-3.7)
CD19+ lymphocytes % (absolute counts × 10^9 /L)	25.13 %(0.74)	16-35 % (0.39-1.4)
CD56+ % (absolute counts × 10^9 /L)	50.25% (1.4)	03-15 % (0.13-0.72)
CD4+ (out of CD3+ lymphocytes) % (absolute counts × 10^9 /L)	55.70 (0.43)	32-51(0.7-2.2)
CD8+ cells proportions (out of CD3+ lymphocytes) % (absolute counts × 10^9 /L)	29.19 (0.22)	14-30(0.49-1.3)
CD4/CD8 Ratio	1.9	0.9-2.9
CD45RA+ of CD3+lymphocytes % (absolute counts × 10^9 /L)	22.55 (0.17)	-
CD4+CD45RA+ cells of CD4+ lymphocytes % (absolute counts × 10^9 /L)	8.72 (0.038)	63-91(0.43-1.5)
CD8+CD45RA+ cells of CD8+ lymphocytes % (absolute counts × 10^9 /L)	40.75 (0.093)	71-98(0.38-1.1)
CD45RO+ of CD3+lymphocytes % (absolute counts × 10^9 /L)	66.01 (0.515)	09-31(0.33-1.0)

Parameter	Case	Reference value/ Control value
CD4+CD45RO+ cells of CD4+ lymphocytes % (absolute counts × 10^9 /L)	83.90 (0.36)	07-20(0.22-0.66)
CD8+CD45RO+ cells of CD8+ lymphocytes % (absolute counts × 10^9 /L)	41.77 (0.093)	02-12(0.09-0.440)
CD19+ CD27-IgD+ (Naïve B lymphocytes) %	77.42	75.2-86.7
CD19+27+IgD+ (Un-switched Memory B Cells) %	5.45	4.6-10.2
CD19+27+IgD- (Switched Memory B Cells) %	10.21	3.3-9.6
Test	**Patient**	**Age-matched control**
CD3+CD57+ %	21.31	1.41
CD3+CD4+CD57+ %	3.45	0.65
CD3+CD8+CD57+ %	63.71	4.05
CD4+ (TH lymphocytes)	8.16 % of Lymphocytes	38.69% of Lymphocytes
CD4+ CD127- CD25+	15.32 % Of CD4+ Cells	10.52% Of CD4+ Cells
Percentage of Gamma Delta T Lymphocytes (Gated on CD3 cells)	6.47%	5.08%
Percentage of Alpha Beta T Lymphocytes (Gated on CD3 cells)	76.89%	87.22%

A complex heterozygous mutation in RAG2 causes severe combined immunodeficiency: A case report

Wenyan Li, Kang Zhu, Shihong Chen, Yuhua Qu, Hua Jiang, Juan Zhou

Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

Introduction: Recombination-activating gene 2 (RAG2) mutations are a major cause of severe combined immunodeficiency (SCID), a rare but life-threatening condition characterized by profound defects in T and B lymphocyte development. RAG2, alongside RAG1, is essential for V(D)J recombination, a process critical for generating diverse antigen receptor repertoires in adaptive immunity. Mutations in RAG2 disrupt this process, leading to impaired immune responses. Early diagnosis and interventions, such as hematopoietic stem cell transplantation, are crucial for improving outcomes in patients with RAG2-SCID.

Case Presentation: A 11 month-old boy, born prematurely at 32+3 weeks with low birth weight, experienced repeated infection after birth for more than 10 months. He was diagnosed with severe pneumonia, cytomegalovirus infection, otitis media, immune thrombocytopenia and BCG infection-associated lymphadenitis. He has no rash or hepatosplenomegaly. Using whole-exome sequencing, a complex heterozygous mutation in RAG2 was discovered: a novel mutation c. 1320del [p.Lys440AsnfsTer4] in exon 2 of RAG2 from his father, and a reported mutation c. 1324G>A[p.Ala442Thr] in exon 2 of RAG2 from his mother. Immunoglobulin tests indicated reduced IgG and IgM levels, and transient elevated IgE. Lymphocyte test showed severe depletion of B cells, few T cells, and increased NK cells. T cells were mainly CD4+ effector memory T cells (CD4+CCR7-CD45RA-), CD4+ central memory T cells (CD4+CCR7+CD45RA+), and CD8+ terminally differentiated effector memory T cells (CD8+ CCR7-CD45RA+). TREC and KREC values below 1 copies/μl, which suggest SCID. Chimerism analysis (RQ-PCR) showed only 0.008% maternal cells, ruling out maternal engraftment. The patient has successfully undergone hematopoietic stem cell transplantation.

Discussion:
Whether he can diagnose with the Omenn syndrome. The cause of the patient's immune thrombocytopenia and cytomegalovirus infection.

Conclusions: We report a case of SCID caused by a compound heterozygous mutation in the RAG2, and a novel mutation was identified.

Successful HSCT Reverses Portal Hypertension and Hypercalcemia in Infant with Chronic Granulomatous Disease and Disseminated Fungal Infection After Vaginal Seeding

Loh Kent Mun[1], Dr Li Jiahui[1,2], Dr Rashida Farhad Vasanwala[1,3], Dr Michaela Seng Su-Fern[1,4], Dr Liew Woei Kang[1,5], Dr Chan Su-Wan Bianca[1,5]

1 *Department of Paediatric Medicine, KK Women's and Children's Hospital, Singapore*
2 *Department of Paediatric Subspecialties, Division of Infectious Diseases Service*
3 *Department of Paediatric Subspecialties, Division of Endocrinology Service*
4 *Department of Paediatric Subspecialties, Division of Haematology Oncology Service*
5 *Department of Paediatric Subspecialties, Division of Rhaematology and Immunology Service*

Introduction: Vaginal seeding was proposed as a way to restore the microbiome of infants born by caesarean section. However, its risk of introducing infection in newborns with underlying immunodeficiency is unknown. We present the first case of disseminated candidiasis after vaginal seeding in an infant with Chronic Granulomatous Disease and the challenges faced controlling the infection.

Case Presentation: A British-Taiwanese boy presented at 15 days-old with fever, hepatitis and a worsening maculopapular rash that was refractory to antibiotics. He had a family history of Chronic Granulomatous Disease (CGD) in an older brother and mother was confirmed carrier. The obstetrician was informed to avoid BCG vaccination at birth, but unexpectedly performed vaginal seeding for this neonate born by caesarean section. Blood cultures grew Candida and he was given intravenous amphotericin-B, but had recurrent fevers when switched to oral voriconazole until interferon-gamma was added. He developed symptomatic hypercalcemia presumably from excessive macrophage conversion of vitamin-D to active form in granulomas, which was only controlled with low-calcium formula milk.

He developed massive hepatosplenomegaly with transaminitis, and portal hypertension. At 7 months-old, he received TCR$\alpha\beta$/CD45RA-depleted haploidentical stem cell transplantation from his father, with conditioning chemotherapy Alemtuzumab 1mg/kg, Fludarabine 5mg/kg, Thiotepa 10mg/kg and Treosulfan 36mg/m2. Post-transplant, there was concern of silent graft rejection with failing blood counts and CD3-chimerism, which responded to CD3 donor lymphocyte infusions. Post-transplant evaluation showed resolution of hypercalcemia, transaminitis, and interestingly reversal of portal hypertension.

Discussion:

1. What's the appropriate timeframe to do screening and initiate prophylaxis in siblings of children with primary immunodeficiency?
2. What's the role of interferon gamma in controlling active infection in CGD?
3. Risk of new interventions like vaginal seeding triggering early manifestations in newborns with underlying primary immunodeficiency
4. Incidence and management of Portal hypertension in CGD.

Conclusions: Hypercalcemia is common in granulomatous inflammation but has not been reported in CGD. Interferon-gamma is used for prophylaxis in CGD but may exacerbate hypercalcemia. The early presentation of this infant with disseminated candidiasis highlights the danger of vaginal seeding in infants with underlying immunodeficiency and should be contraindicated in infants with positive family history. Successful HSCT can potentially reverse complications if carried out early.

Persistent herpetic infections in a patient with autosomal recessive Hyper-IgE syndrome.

Thi Thuy Quynh Bui, Thi Van Anh Nguyen, Ngoc Quynh Le Nguyen, Phúóng Anh Ha, Dinh Giang Nguyen

Department of Allergy, Immunology and Rheumatology - Vietnam National Children's Hospital

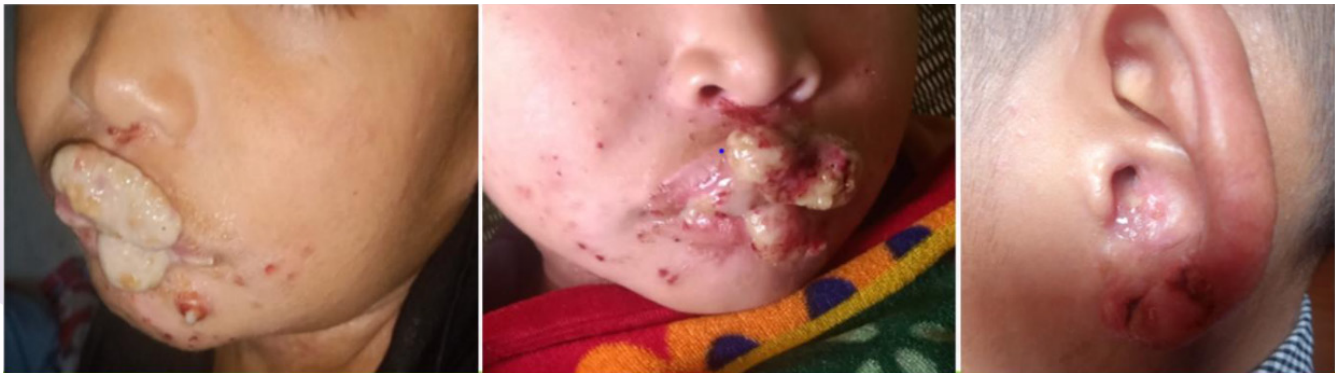
Introduction: Hyper IgE Syndrome (HIES) is a rare primary immunodeficiency disorder, characterized by eczema, recurrent skin abscesses, lung infections, eosinophilia, and elevated serum IgE levels. Two forms of HIES have been described: autosomal dominant (AD-HIES) and autosomal recessive (AR-HIES).

Case Presentation: We present an 11-year-old boy with food allergies and recurrent skin and respiratory infections caused by Herpes simplex virus, Staphylococcus aureus, and Pneumocystis pneumonia since the age of 2. Laboratory studies revealed eosinophilia (21.7 G/L, 70.9%) and elevated serum IgE levels (13,595 IU/ml). Given his very high HIES score (42 points), we performed genetic analysis, which identified a pathogenic mutation in the DOCK8 gene, causing AR-HIES. Following treatment with prophylactic antibiotics (trimethoprim-sulfamethoxazole), the frequency of bacterial infections significantly decreased. However, herpes skin infections remain recurrent and persistent despite acyclovir prophylaxis.

Discussion: Could this patient have acyclovir-resistant HSV?

Potential treatment alternatives for this patient: foscarnet/cidofovir or subcutaneous pegylated interferon alfa-2b injections?

Conclusions: Patients with DOCK8 deficiency are susceptible to severe viral cutaneous infections, including Herpes simplex virus (HSV). Prophylactic acyclovir may not be sufficient for HSV suppression in these patients.



Case Report: Clinical Features of Leukocyte Adhesion Deficiency-1 with Compound Heterozygous Mutation

Alfonzo Miguel A. Alviar, MD; Jocelyne B. Aquino, MD; Ma. Lyn R. Benito, MD; Nancy N. Bermal, MD; Melissa M. Montoya, MD

San Juan De Dios Educational Foundation, Inc. – Hospital, Pasay City, Philippines

Introduction: One in one million people has Leukocyte Adhesion Deficiency-1, a rare autosomal recessive condition. Leukocyte recruitment to the infection site fails when the β2-integrin subunit on the leukocytes is absent or functions poorly.

Case Presentation: A 3 ½ month-old female was admitted in our institution due to recurrent skin infections. Born to a 26-yr old G3P2 (2012) of non- consanguineous marriage, without family history of immunodeficiency, or autoimmunity, she had omphalitis starting 2 weeks old requiring two hospitalizations with Intravenous antibiotics. Delayed cord separation at 4 weeks noted. At 3 months old, she was hospitalized twice, initially periclitoral and umbilical abscesses then perineal and perianal abscesses both requiring Intravenous antibiotics and surgical debridement without postoperative complications. Work-ups showed persistent leukocytosis, neutrophilia, anemia, elevated ESR and CRP. Cultures revealed S. *xylosus* (umbilical discharge), *C. freundi* (perineum), *E. coli* (Perianal Abscess), and *P. aeruginosa* (intraoperative rectal tissue).

Work-ups for phagocytic defect probably LAD-1 revealed normal Immunoglobulins, Anti-HBs and Flow cytometry. CD18 (β2-integrin subunit) however, is not available. Genetic analysis showed ITGβ2 (CD18) compound heterozygous mutation; mother heterozygous carrier exon 4 and father heterozygous carrier exon 7.

Episodes of mild infections after discharge (otitis media, pneumonitis and perianal infection) resolved with oral antibiotics. Currently doing well, without antimicrobial prophylaxis hence close surveillance done. Hematopoietic Stem Cell Transplant discussed.

Discussion: Delayed cord detachment, early onset of infections, frequent hospitalizations requiring surgical debridement, point to a severe disease. However, 95% of severe LAD-1 presents with ITGβ2 homozygous mutation and only less than 10% are heterozygous. Is it possible that her compound heterozygous mutation explains her stable course after an initially severe state? Future reports on LAD-1 might clarify this.

Conclusions: This is the first reported case locally of LAD-1 showing ITG β2 compound heterozygous mutation aims to increase awareness hence early referral to decrease morbidity and mortality.

Compound Heterozygous Mutations in LIG4 Gene in a Malay Boy with Severe Microcephaly and Cytopenia.

Nur Zulaika Madon[1,2], Che Syahida Silmi[1,2], Khairoon Nisa Mohamed Nashrudin[1,2], Mohd Azri Zainal Abidin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA.*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA.*

Introduction: LIG4 syndrome is a rare autosomal recessive disorder caused by biallelic pathogenic variants in the LIG4 gene, which encodes DNA ligase IV, an enzyme essential for DNA repair. It is characterized by microcephaly, unusual facial features, growth and developmental delay, immunodeficiency, pancytopenia, and pronounced radiosensitivity. Only a few cases have been reported worldwide, with a prevalence of less than 1 in 1000000.

Case Presentation: We report a 6-year-old Malay boy with early-onset atopic dermatitis, severe microcephaly, and recurrent infections since the age of 2 years, accompanied by anemia and thrombocytopenia. His cutaneous symptom was complicated with extensive viral warts, which were recalcitrant to multiple cryotherapies. Hematological evaluations were not suggestive of malignancy. His lymphocyte subset analysis revealed very low B cell numbers (0%), reduced T cell counts with decreased CD4 and CD8 subsets, and high NK cells. Additionally, he had low IgA levels. Genetic testing identified compound heterozygous mutations in the LIG4 gene.

Discussion: DNA ligase IV functions in the nonhomologous end-joining (NHEJ) pathway, a major mechanism involved in the repair of DNA double-strand breaks (DSBs). It is also involved in the process of class switch and V(D)J recombination during immune development. The diagnosis of LIG4 is typically initiated by clinical suspicion, mainly microcephaly, combined immunodeficiency with or without developmental delay, and supported by clinical laboratory features including marrow hypoplasia, lymphocytopenia with marked B lymphocytopenia, panhypogammaglobulinaemia or evidence of impaired isotype class-switching (e.g., raised IgM and absent or low IgA and IgG).

Conclusions: This case highlights the importance of considering LIG4 syndrome in the differential diagnosis of growth failure with developmental delay, marrow hypoplasia, and recurrent infection with lymphocytopenia. Early genetic diagnosis is crucial to prevent sequelae from the disease as bone marrow failure and immunodeficiencies can be progressive. Patients may benefit from more tailored therapeutic and curative strategies.

Immunological profiles of the patient

Investigation	Results	Normal Range
Complete blood count (x 10^9)		
Leukocytes	7.71	5.0-14.5
Neutrophils	3.47	1.5-8.5
Lymphocytes	3.20	2.0-8.0
Monocytes	0.86	0.4-2.0
Eosinophils	0.16	0.2-1.9
Basophils	0.02	0.0-0.1
Inflammatory markers		
CRP (mg/L)	13	< 5
Complement (g/L)		
C3	1.73	0.5-0.9
C4	0.84	0.1-0.4
Immunoglobulins (g/L)		
IgG	13.12	4.3-13.4
IgM	1.36	0.2-1.8
IgA	<0.02	0.19-2.2
IgE (kU/L)	<2.0	<100
Lymphocyte subsets (x 10^6)		
T cells (CD3+)	956	1800-3000
B cells (CD19+)	15	700-1300)
CD4 (CD4+)	269	1000-1800
CD8 (CD8+)	443	800-1500
NK cells (CD16+/CD56+)	3242	200-600
T cell Proliferation		
PHA (%)	3160	1730
Stimulation index (SI)	6560	7390
Autoimmune workup		
HLA B27 Typing Serology	Negative	

Fatal Co-Infections of Burkholderia pseudomallei and Aspergillus in A Boy with Chronic Granulomatous Disease

Syazwani Rahim[1], Che Syahida Silmi[1], Nura Hulwana[1], Farizza Hazlin Ramli[1], Khairoon Nisa Mohamed Nashrudin[1,2], Mohd Azri Zainal Abidin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA*

Introduction: Chronic granulomatous disease (CGD) is an inborn error of immunity characterised by recurrent life-threatening infections due to defective phagocytic burst activity. This leads to inability to effectively kill catalase-positive organisms, such as Burkholderia pseudomallei, the causative agent of melioidosis. Melioidosis is endemic in Southeast Asia, including Malaysia. The clinical presentation of melioidosis overlaps with other bacterial and fungal infections, posing significant diagnostic challenges. The gold standard for diagnosis is bacteriological culture.

Case Presentation: A 5-year-old Malay boy from Johor with X-linked CGD due to CYBB mutation, was initially treated for varicella pneumonitis complicated by secondary bacterial infection. Post-discharge, he continued to have persistent cough for one month. His CRP remained elevated (35-47 mg/L), and serial chest X-rays showed persistent bilateral lung consolidations. Bronchoalveolar lavage for fungal and TB infections was negative, while high-resolution CT showed signs of active infections with multiple nodular consolidations. He received treatment with multiple broad-spectrum antibiotics, but developed new respiratory symptoms during follow-up. Serum galactomannan from 3 months earlier was found to be elevated at 2.94 ng/mL, suggesting fungal infection. Antifungal therapy was initiated with partial improvement. However, on day 8 of hospitalisation, he developed spiking fevers (39-41°C) and rapidly deteriorated, progressing to septic shock and multiple organ dysfunctions, leading to death within 48 hours. Retrospective blood cultures revealed Burkholderia pseudomallei as the cause of death.

Discussion: This case highlights the increased susceptibility of CGD patients to melioidosis, particularly in endemic regions. Patient lived in Johor, which has many "FELDA" (Federal Land Development Authority) settlements with oil palm plantations. Additionally, this case emphasises the diagnostic challenges posed by the clinical overlaps between melioidosis and invasive aspergillosis

Conclusions: Clinicians should maintain high index of suspicion for melioidosis in at-risk populations, especially in endemic regions, to enable early diagnosis and prompt therapy, thereby reducing morbidity and mortality.

Chronic Infantile Neurologic, Cutaneous, and Articular Syndrome: A Case Report

Hye Jung Choi[1], Ji Young Lee[1], Jee Yeon Baek[1], Hyun-Soo Seo[1], Jong-Gyun Ahn[1,2], Ji-Man Kang[1,2]

1 *Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Republic of Korea*
2 *Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Republic of Korea*

Introduction: Chronic infantile neurologic, cutaneous, and articular syndrome (CINCA), the most severe phenotype of cryopyrin-associated periodic syndrome (CAPS), is a rare autoinflammatory disorder characterized by persistent rash, arthropathy, and neurologic symptoms. Early diagnosis is challenging due to non-specific presentations, but timely intervention can prevent complications.

Case Presentation: A 5-year-old boy presented with urticaria since birth, intermittent fever, and arthralgia. He exhibited short stature, elevated inflammatory markers (ESR 120 mm/h, CRP 78.3 mg/L), leukocytosis, and microcytic anemia. Imaging revealed arthritic changes in foot joints, and mild hearing loss was noted. A genetic test confirmed an NLRP3 mutation (c.1711G>A), diagnosing CINCA. Subcutaneous anakinra therapy rapidly reduced inflammatory markers, later switched to canakinumab for improved adherence. The patient showed sustained symptom relief without adverse effects.

Discussion: CINCA diagnosis requires a high index of suspicion, especially in infants with recurrent fever, rash, and systemic inflammation, where infections can obscure the clinical picture. Genetic testing for NLRP3 mutations is critical for confirming CAPS. Early use of IL-1 inhibitors like anakinra or canakinumab is essential to manage symptoms, improve quality of life, and prevent long-term complications.

Conclusions: The non-specific initial symptoms of CINCA highlight the importance of considering CAPS in differential diagnoses for persistent systemic inflammation. Prompt molecular diagnosis and targeted IL-1

blockade therapy can significantly improve clinical outcomes. Multidisciplinary approaches are vital for optimal management of these patients.

Cutaneous Ulceration Syndrome with Recurrent Organ Abscesses in A Child with TNFAIP3 mutation: Diagnostic and Management Challenges

Che Syahida Silmi Che Abdul Rahman[1,2], Nura Hulwana Bukhari[1,2], Syazwani Rahim[1,2], Khairoon Nisa Mohamed Nashrudin[1,2], Sangeetha Siniah[1,3], Mohd Azri Zainal Abidin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA.*
3 *Department of Paediatrics, Hospital Tuanku Azizah, Kuala Lumpur, MALAYSIA*

Introduction: Mutations in the TNFAIP3 gene, which encodes the A20 protein, lead to impaired regulation of the NF-κB signalling pathway, contributing to systemic inflammation and immune dysregulation. These mutations are associated with familial Behçet-like autoinflammatory syndrome, characterised by recurrent fever, vasculitis, mucosal ulcers, and cutaneous lesions.

Case Presentation: We report a 6-year-old girl with recurrent skin ulcerations and persistent liver and spleen abscesses, despite prolonged antibiotic treatments and multiple drainage procedures. Skin biopsy confirmed the lesion as pyoderma gangrenosum. Immunological evaluation revealed persistently low T-cell subsets and elevated serum IgE levels, with normal dihydrorhodamine (DHR) respiratory burst activity. Extensive infectious workup was negative, and autoimmune investigations yielded no significant findings. Genetic testing identified a heterozygous missense mutation in the TNFAIP3 gene, classified as a variant of uncertain significance, suggesting a probable familial Behçet-like syndrome. Her father also had the same mutation. Initial treatment with steroids and regular intravenous immunoglobulin (IVIG) led to significant clinical improvement, but symptoms recurred after discontinuing IVIG and steroids. Immunosuppressive therapy was subsequently initiated, resulting in gradual resolution of the abscesses.

Discussion: Loss-of-function mutations in the TNFAIP3 gene lead to A20 haploinsufficiency, which presents with varied phenotypes of autoinflammation and recurrent infections. The clinical course of TNFAIP3-related disorders is often challenging due to overlaps with other inflammatory and infectious conditions. The identification of a TNFAIP3 variant of uncertain significance underscores the complexity of interpreting genetic findings in rare autoinflammatory syndromes, though its presence supports its potential pathogenic role. While there is no definitive treatment for A20 haploinsufficiency, various therapeutic strategies can alleviate symptoms in the affected patients.

Conclusions: This case underscores the importance of integrating clinical, immunological, and genetic assessments in managing TNFAIP3-related syndromes. Early recognition and appropriate immunosuppressive therapy are crucial for reducing disease burden and preventing long-term complications.

Immunological profiles of the patient

Investigation	Results	Normal Range
Complete blood count (x 10^9)		
Leukocytes	19.2	5.0-14.5
Neutrophils	1.66	1.5-8.5
Lymphocytes	3.08	2.0-8.0
Monocytes	0.38	0.4-2.0
Eosinophils	0.57	0.2-1.9
Basophils	0.04	0.0-0.1
Inflammatory markers		
CRP (mg/L)	86	< 5
ESR (mm/Hr)	76	<10
Complement (g/L)		
C3	1.65	0.5-0.9
C4	0.15	0.1-0.4
Immunoglobulins (g/L)		
IgG	14.79	4.3-13.4
IgM	0.856	0.2-1.8
IgA	1.196	0.19-2.2
IgE (kU/L)	561	<100
Lymphocyte subsets (x 10^6)		
T cells (CD3+)	2786	1800-3000
B cells (CD19+)	1116	700-1300)
CD4 (CD4+)	1313	1000-1800
CD8 (CD8+)	1171	800-1500
NK cells (CD16+/CD56+)	277	200-600
Dihydrorhodamine (DHR)	Not consistent with chronic granulomatous disease	
Autoimmune workup		
ANA	Negative	
ANCA	Negative	

A Cyclic Neutropenia Patient with ELANE Mutation Accompanied by Hemophagocytic Lymphohistiocytosis

Lang Yu, Yulin Li, Wenhui Li, Yunfei An and Xiaodong Zhao.

Children's Hospital of Chongqing Medical University, Chongqing, China

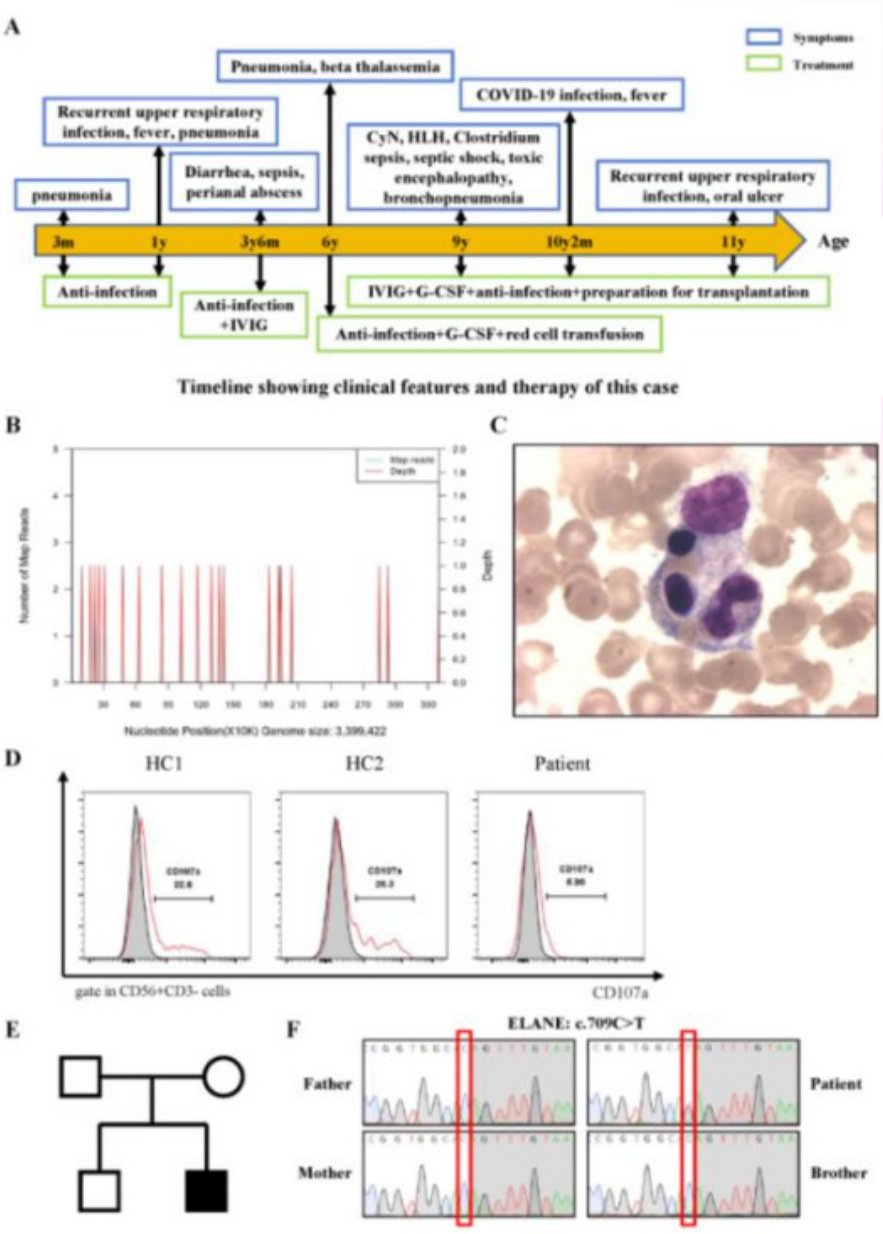
Introduction: Many inborn errors of immunity may accompany secondary hemophagocytic lymphohistiocytosis (HLH). A considerable proportion of HLH cases also stem from chronic granulomatosis (CGD) with phagocytic dysfunction. However, the development of secondary HLH in patients with severe congenital neutropenia (SCN) or cyclic neutropenia (CyN) has been less frequently reported.

Case Presentation: Herein, we present a case of a pediatric patient with CyN and recurrent fever (Fig A). Peripheral blood metagenomics (mNGS) testing revealed positive findings for Clostridium perfringens and HSV-1(Fig B). A diagnosis of HLH was established, as the patient met 7 out of 8 diagnostic criteria for HLH (Fig C). Notable observations included impaired NK cell degranulation function (CD107a) (Fig D). WES found a de novo variant, c.709C>T (p.Gln237Ter), in exon 5 of the patient's ELANE gene, established a genetic diagnosis for neutropenia(Fig E and F).

Discussion: While neutrophil dysfunction contributes significantly to secondary HLH cases, alterations in neutrophil counts are typically associated with congenital neutropenia, with only a few reported cases of HLH.

We presented a case of cyclic neutropenia in a patient harboring a heterozygous Q237X mutation in the ELANE gene, who developed secondary HLH following severe infections. In our patient, we observed a decrease in the absolute number of T cells and NK cells, with the proportions remaining within the normal range, as well as impaired degranulation function of NK cells (CD107a). It is currently unclear whether this impairment was related to CyN caused by ELANE mutations.

Conclusions: This was the first documented occurrence of secondary HLH in ELANE-related congenital neutropenia due to severe infections. Our findings contribute to broadening the phenotype associated with this disease and emphasize the importance of considering HLH diagnosis in patients with hemophagocytic manifestations of both SCN and CyN.


A
Symptoms
Treatment
Pneumonia, beta thalassemia
COVID-19 infection, fever
Recurrent upper respiratory infection, fever, pneumonia
CyN, HLH, Clostridium sepsis, septic shock, toxic encephalopathy, bronchopneumonia
Diarrhea, sepsis, perianal abscess
Recurrent upper respiratory infection, oral ulcer
pneumonia
3m
1y
3y6m
6y
9y
10y2m
11y
Age
Anti-infection
Anti-infection +IVIG
IVIG+G-CSF+anti-infection+preparation for transplantation
Anti-infection+G-CSF+red cell transfusion
Timeline showing clinical features and therapy of this case
B
Number of Map Reads
Depth
Nucleotide Position(X10K) Genome size: 3,399,422
C
D
HC1
HC2
Patient
gate in CD56+CD3- cells
CD107a
E
F
ELANE: c.709C>T
Father
Patient
Mother
Brother

Heterozygous Out-of-frame Frameshift Mutation in ELANE Without Evidence of Neutropenia

Yulin Li[1,2*], Lang Yu[1,2*], Yishi Zhang[1,2], Liwen Zhang[1,2], Xiaodong Zhao[1,2,3]

1 *National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China*
2 *Chongqing Key Laboratory of Child Rare Diseases in Infection and Immunity, Children's Hospital of Chongqing Medical University, Chongqing, China*
3 *Department of Rheumatology & Immunology, Children's Hospital of Chongqing Medical University, Chongqing, China*

Introduction: Mutations in the ELANE gene, which encodes neutrophil elastase, are known to cause cyclic neutropenia (CyN) and severe congenital neutropenia (SCN). Currently, targeting ELANE for insertion-deletion to trigger NMD may be a simple and universal method to treat SCN caused by ELANE mutations.

Case Presentation: Here, we present a patient with a heterozygous out-of-frame frameshift mutation in exon 4 of the ELANE gene. The patient underwent whole exome sequencing during hospitalization for acute parotitis and bronchitis, and found mutations in ELANE, c.581_588del AGGCCGGC (p.Q194Rfs*93), traceable to the father. Despite experiencing severe neutropenia and lymphocytopenia during the course of this severe infection, long-term follow-up after discharge showed the patient maintained normal absolute neutrophil counts. Both parents are healthy without a history of recurrent infections or neutropenia.

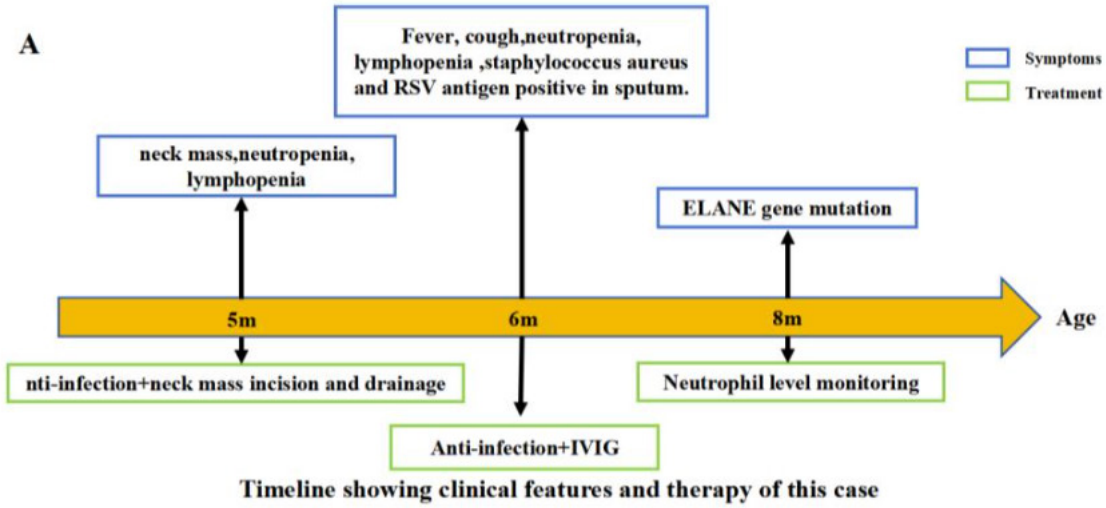
Discussion: A notable characteristic of ELANE gene mutations is their typically autosomal dominant nature, and the aberrant NE protein still leads to neutropenia.The majority of SCN-associated ELANE mutations is missense mutations.SCN-associated frameshift mutations are confined to exon 4 and 5. Only -1 frame insertion or deletion (indel) can generate PTCs, impacting protein function and causing neutrophil maturation arrest. Currently, there is insufficient evidence to diagnose our patient with congenital neutropenia. This could be attributed to the -2 frame indel in late exon 2 of the ELANE gene, which causes an extension of the C-terminal amino acid sequence and a shortened 3' untranslated region (UTR). Although mRNA levels remain unchanged, the reduction in protein production reflects inefficient translation, and prevents the generation of mutant proteins, thus supporting neutrophil maturation.

Conclusions: This case provides clinical evidence supporting the notion that late exon frameshift -2 frame indel insertions can inhibit mRNA translation efficiency and prevent the production of mutant proteins, thereby promoting neutrophil maturation. It also bolsters the ongoing development of gene therapy for ELANE-related diseases.

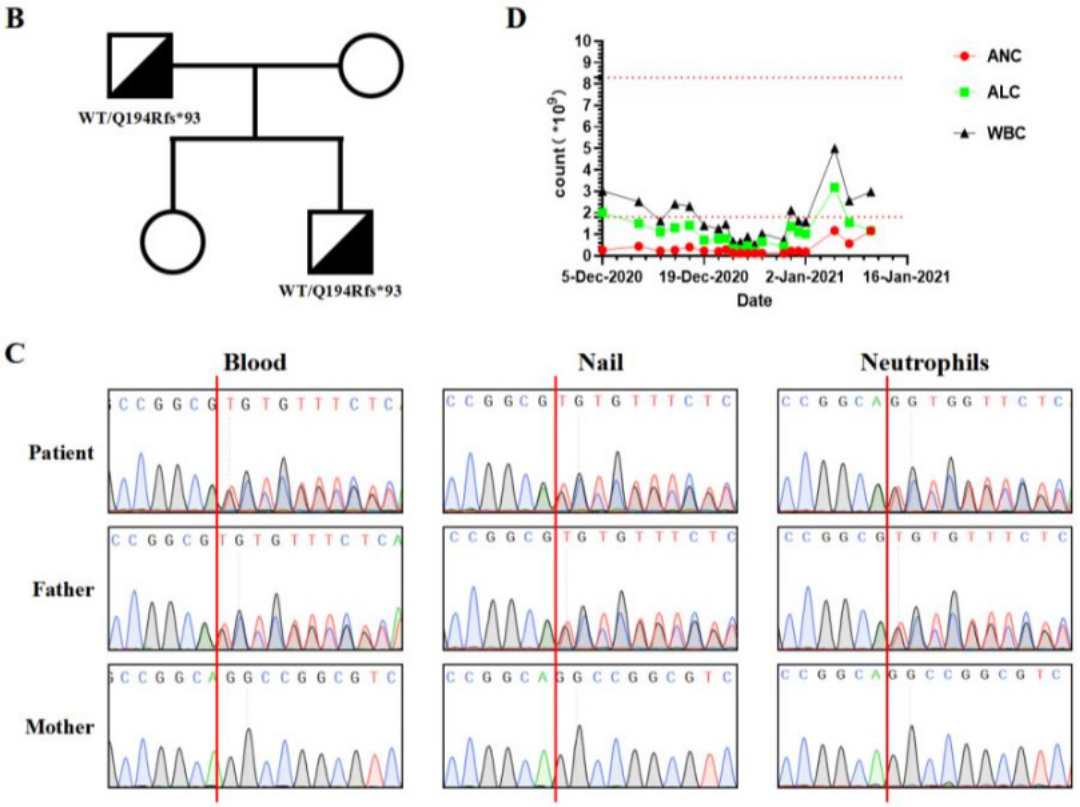
Figure legends

Figure 1. ELANE mutation and absolute neutrophil count (ANC) (A) Clinical course of the patient. (B) Family pedigree. ELANE Q194Rfs*93 mutation in patient and his father is indicated. (C) Sanger sequencing of the ELANE gene in patient and family members. Genomic DNA from blood, nails and neutrophils was used. (D) Absolute number of peripheral blood white blood cells (WBC), lymphocytes, and neutrophils during follow-up. Horizontal dashed lines indicate upper and lower reference values of ANC.

Figure 1



Timeline showing clinical features and therapy of this case



The first case of disseminated BCG infection in an IL-12R β1deficiency Korean boy

Yoonsun Yoon[1], Doo Ri Kim[2], Areum Shin[2],Yae-Jean Kim[2]

1 *Department of Pediatrics, Korea University Guro Hospital, Seoul, Korea*
2 *Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*

Introduction: Interleukin-12 receptor subunit beta-1 (IL-12R β1) deficiency is a common cause of Mendelian Susceptibility to Mycobacterial Diseases (MSMD). MSMD is a group of genetic disorders characterized by a defect in interferon γ (IFN γ)–mediated immunity, with a predisposition to infections caused by atypical and low virulent Mycobacteria and other intra-macrophagic organisms like Salmonella. About 200 cases have been reported in the world. However, there were no reports about IL12RB1 mutation in Korea.

Case Presentation: A six-month-old Korean boy was referred to the infectious disease physician due to persistent discharge from the excision site of a left axillary mass. In the culture, Methicillin-resistant Staphylococcus aureus was confirmed, and he was treated with antibiotics. However, another lesion on the left upper arm, involving triceps and teres major muscle and axilla, extending to skin and chest wall, appeared. We surgically removed the mass composed of suspected BCG lymphadenitis with abscess from the axilla and shoulder muscle. In the pathologic evaluation, chronic granulomatous inflammatory process was observed with many AFB-positive bacilli. *Mycobacterium bovis* was confirmed. There was no significant family history of immunodeficiency but genetic testing revealed autosomal recessive pathogenic homozygous variants in IL12RB1 Exon 9, c.637C>T (p.Arg213Trp). His parents had both one pair of IL12RB1 variants. He has been treated with isoniazid, rifampicin, and ethambutol for one year and lesions were resolved.

Discussion: The duration of anti-mycobacterial treatment for MSMD varies depending on the type of treatment and the patient's response. Interferon-gamma therapy with the anti-mycobacterial regimen and stem cell transplantation may be considered in MSMD patients.

Conclusions: Children presenting with disseminated infections with atypical mycobacteria and salmonella must be evaluated for MSMD.

Vasculitis as A Clue to IL12RB1 Deficiency in Mendelian Susceptibility to Mycobacterial Disease

Muhammad Shafiq Safwan[1], Noorzeehan Zakaria[1], Khairoon Nisa Mohamed Nashrudin[1,2], Mohd Azri Zainal Abidin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA.*

Introduction: Mendelian susceptibility to mycobacterial disease (MSMD) is a rare inborn error of immunity that predisposes individuals to weakly virulent mycobacteria and other intracellular pathogens. Although rheumatologic manifestations such as vasculitis are uncommon, it poses clinically significant complication.

Case Presentation: We report a 10-year-old girl with recurrent severe infections since neonatal period. Her medical history includes Salmonella meningitis, disseminated BCG disease, tuberculous lymphadenitis and recurrent arthralgia with purpuric rashes later diagnosed as leukocytoclastic vasculitis via skin biopsy. Immunological study showed low levels of CD4+, CD8+ and CD19+ lymphocytes, alongside elevated immunoglobulins (IgM, IgG, IgA). Autoimmune screening revealed low C3 and C4 and positive rheumatoid factor. Genetic testing identified pathogenic mutations in IL12RB1 associated with autosomal recessive MSMD. The patient had been treated with prolonged anti-tuberculosis therapy since the age of 3, along with multiple broad-spectrum antibiotics and prophylactic trimethoprim-sulfamethoxazole to prevent further infections.

Discussion: MSMD typically presents as mycobacterial lymphadenitis and salmonella infections. Leukocytoclastic vasculitis (LCV) although rare, is linked to IL12RB1 defects and impaired IL12/IL23 immunity. It is considered as a novel manifestation in MSMD patients and most of the reported cases had concurrent Salmonella infections as IL-12 pathway is involved during Salmonella infection. However, some cases lack detectable pathogens, suggesting subclinical infections or diagnostic limitations. Cutaneous vasculitis in MSMD often presents as palpable purpura and may respond to combined antibiotic and interferon-gamma therapy. BCG vaccination remains a key risk factor, as disseminated BCG disease frequently occurs in MSMD patients. This underscores the important of screening family history for abnormal vaccine response or atypical infections before BCG administration.

Conclusions: The presence of LCV in MSMD patients, especially when associated recurrent Salmonella infections, often indicates IL12RB1 deficiency. Awareness of this association is crucial for timely diagnosis and intervention. Pre-vaccination evaluation and multi-disciplinary care are vital in managing MSMD, improving patient outcomes and preventing complications.

Immunological profiles of the patient

Investigation	Results	Normal Range
Inflammatory markers		
CRP (mg/L)	12.9	< 5
ESR (mm/Hr)	24	<10
Autoimmune workup		
Direct Coombs	Negative	
ANA	Negative	
RF	Positive	
Complement (g/L)		
C3	0.37	0.5-0.9
C4	<0.01	0.1-0.4
Immunoglobulins (g/L)		
IgG	41.91	4.3-13.4
IgM	12.39	0.2-1.8
IgA	3.51	0.19-2.2
Lymphocyte subsets (x 10^6)		
T cells (CD3+)	676	1800-3000
B cells (CD19+)	417	700-1300)
CD4 (CD4+)	187	1000-1800
CD8 (CD8+)	438	800-1500
NK cells (CD16+/CD56+)	930	200-600
T cell Proliferation	**Patient**	**Control**
Unstimulated (SFU per million cells)	140	840
PHA stimulated (SFU per million cells)	8240	11210
Antibody responses to vaccine antigens	**Pre**	**Post**
Tetanus toxoid, IgG (mg/L)	8.61	181
Pneumococcal polysaccharide, IgG (U/ml)	0.215	7.048

Henoch-Schoenlein purpura (HSP) like lesions in IL12RB1 and IL12B defects- Our Experience from North India

Yamini Sharma, Jhumki Das, Ahmed Jamal, Pallavi Nadig, Saniya Sharma, Manpreet Dhaliwal, Vignesh Pandiarajan, Amit Rawat, Surjit Singh

Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and research, Chandigarh, India

Introduction: Mendelian susceptibility to mycobacterial disease (MSMD) is a rare group of human inborn error of immunity. Here we describe a cohort of children with underlying *IL12RB1/ IL12B* defects who had skin vasculitis resembling Henoch-Schoenlein purpura (HSP).

Case Presentation: Of the 21 patients with pathogenic homozygous *IL12RB1/IL12B* defects (19 *IL12RB1* and 2 *IL12B*), 4 of them (19%) (*IL12RB1-3; IL12B-1*) developed HSP-like lesions [Table 1]. All had maculopapular purpuric rash in lower limbs, predominantly in the anterior aspect of legs and posterior thighs resembling the rash of HSP. Two children had multiple recurrences of the skin lesions and were thought to have an underlying autoimmune/ autoinflammatory disease before a diagnosis of MSMD was made. All of them had associated bacterial infections along with rash that include *Salmonella* sp. and *Pandorea apista*. None had recurrence following treatment of underlying infections.

Discussion: The HSP-like vasculitic rash usually occurred in setting of underlying bacterial infections in these patients and treatment of underlying infections usually resulted in complete remission of vasculitic lesions. Presence of such vasculitis–like lesions suggest underlying immune dysregulation in *IL12RB1/ IL12B* defects. These skin lesions can also be considered as one of the potential clinical clues for underlying *IL12RB/IL12B* defects.

Conclusions: Our report shows that patients with *IL12RB1/IL12B* defects can present with cutaneous vasculitis resembling HSP. These lesions are usually associated with underlying bacterial infections, an important clinical clue for underlying *IL12RB/ IL12B* defects, and are likely to be much more common in developing countries as compared to West.

Table 1. Clinical, immunological, and molecular analysis of patients with IL12RB1/ IL12B defects and HSP-like skin lesions

Patient No.	Age at onset	Age at diagnosis of MSMD	Age of small vessel vasculitis	Associated infections	Past infections	Skin findings	Flow cytometry	Genetic diagnosis	Follow-up
1	8 months	3 years	3 years	*Salmonella typhi*	BCG adenitis	HSP-like rash, Leukocytoclastic Vasculitis in biopsy, DIF- negative	IL12RB1 expression in activated lymphocytes – 27.57% in case Vs 85.51% in control. pSTAT4 expression following IL 12 stimulation in lymphocytes- reduced	Homozygous pathogenic variant in exon 11 of *IL12RB1* c.1021+1_1022 (1189+1_1190-1) exonic deletion	On azithromycin prophylaxis, no recurrence of skin Vasculitis noted
2	1 year	10 years	10 years	*Pandorea apista*	Oral thrush, generalised lymphadenopathy, Paraspinal collections	HSP-like rash, Leukocytoclastic Vasculitis in biopsy, IF study: IgA deposits	IL12RB1 expression in activated lymphocytes- 1.32% in case Vs 47.44% in control pSTAT4 expression following IL 12 stimulation in lymphocytes- reduced	Homozygous pathogenic splice-site variant *IL12RB1* (NM_005535.3): c.1189+1del	On azithromycin prophylaxis, no recurrence of skin Vasculitis noted
3	1 month	10 years	10 years	*Salmonella typhi*	BCG adenitis Oral thrush, Tubercular osteomyelitis	HSP-like rash, Leukocytoclastic Vasculitis in biopsy, DIF- negative	IL12RB1 expression in activated lymphocytes – reduced	Homozygous Nonsense mutation in *IL12RB1*gene (c.962C>A, p.S321)	No recurrence of vasculitis lesion in follow-up; however, succumbed to a pulmonary infection later
4	2 years	4 years	3 years	Probable bacterial infection (responded to antimicrobials)	Cervical lymphadenopathy	HSP-like rash, recurrent, biopsy not done	IL12RB1 expression in activated lymphocytes Comparable to control	Homozygous Microdeletion 5q33.3 (g.158745703_ 158747541del) that included deletion of exons 5 and 6 of *IL12B gene*	On azithromycin prophylaxis, no recurrence of skin Vasculitis noted

Case Report of Tuberculous Lymphadenopathy in a Patient with Congenital Immune Deficiency

Nguyet Nguyen Nhu, Hieu Chu Chi, Hang Vu Thi, Lam Do Thi Tung

Introduction: Congenital immune deficiency (CID) is considered a "rare" disease that may affect up to 1% of the population. Patients with CID are prone to infection with a wide array of microbes, including Mycobacterium tuberculosis. If not detected and treated promptly, the disease can have serious or life-threatening consequences.

Case Presentation: A 17-year-old male, with a diagnosis of CID since the age of 8 years, was managed and treated regularly with IVIg every 4 weeks along with antibiotic prophylaxis for infection. The disease was stable with IgG levels in the serum maintained at about 600mg/dL. Two weeks before admission, the patient developed a persistent high fever with fatigue, poor appetite, weight loss, and no cough or sputum. The patient was admitted 1 week early. We quantified IgG in the patient's blood, and the result was below 200 mg/dL. We found that the IgG level decreased quickly despite the patient receiving IVIg sufficiently.

On the other hand, the inflammation markers increased with the discovery of multiple depressor mastoid and clavicular muscles on both sides. The histopathological result proved that there was evidence of tuberculosis bacteria in the pathological functional tissue. The patient was treated actively with IVIg combined with SCIg and tuberculosis treatment according to the regimen. Clinical symptoms improved after 2 weeks of hospitalization and tuberculosis was completely controlled with a 9-month treatment regimen.

Discussion: Tuberculosis infection causes a rapid decrease in serum IgG concentrations. IVIg rapidly increases serum IgG concentrations but does not maintain stable concentrations thereafter. Therefore, using SCIg helps maintain stable IgG concentrations, increasing the ability to control tuberculosis infection..

Conclusions: A combination of IVIG and SCIG should be considered in CID patients with tuberculosis infection to achieve stable IgG levels and good control of infection.

Genetic Analysis and Clinical Presentation of Autosomal Recessive Hyper-IgM Syndrome: A Case Study

Yijiu Gao, Xiongbin Chen,Han Yang, Dan Lu, Huawei Mao

Department of Immunology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045.

Introduction: Hyper-IgM syndrome is a primary immunodeficiency characterized by normal or elevated IgM levels and reduced or absent levels of IgG, IgA, and IgE. This condition increases susceptibility to infections, particularly those caused by encapsulated bacteria. It can be inherited in two ways: X-linked and autosomal recessive. While most cases are X-linked, the patient in this case has autosomal recessive inheritance.

Case Presentation: The patient, a 10-year-old boy, has been diagnosed with hyper-IgM syndrome for over six years. On the third day of his current hospitalization, tests revealed significantly reduced levels of IgA, IgG, and IgE, while IgM levels were elevated. The child had an insidious onset of illness, with a history of recurrent respiratory infections, otitis media, sinusitis, and bronchitis, and has recently had repeated fevers. Further genetic testing using next-generation sequencing identified one heterozygous deletion and one heterozygous mutation in the AICDA gene: a heterozygous deletion in exon 1, with the father being a carrier of the deletion and the mother showing no variation; a c.274C>T (p.Arg92Ter) mutation, with the father showing no variation at this site and the mother being a heterozygous carrier.

Discussion: The patient was found to have a heterozygous deletion in exon 1 of the AICDA gene. According to the ACMG guidelines, this variant is initially classified as likely pathogenic based on PM2_Supporting and PVS1 criteria. The PVS1 variant is a null variant (exon deletion), which may lead to loss of gene function, and there are no related reports of this variant in the literature database. The c.274C>T mutation (exon 3, NM_020661.4) results in an amino acid change p.Arg92Ter, which is a nonsense mutation. Based on the ACMG guidelines, this variant is initially classified as pathogenic with PVS1+PM2_Supporting+PM3, where the PVS1 variant is a null variant (nonsense mutation), and it is expected to trigger NMD, potentially leading to loss of gene function. Family segregation analysis confirmed that the father is a carrier of the deletion and the mother shows no variation.

Conclusions: When the AICDA gene is pathogenic due to heterozygous deletion, the newly discovered heterozygous deletion in exon 1 of the AICDA gene may contribute to hyper-IgM syndrome.

Mycoplasma pneumoniae arthritis in X-linked hypogammaglobulinemia (XLA)

DR NGUYEN DINH GIANG

DR NGUYEN THI VAN ANH

Introduction: X-linked hypogammaglobulinemia (XLA) is one of the most common congenital immunodeficiency diseases, characterized by recurrent pyogenic bacterial infections such as otitis media, pneumonia, cutaneous abscess, arthritis... due to too low IgG in the blood. Regarding genetics, XLA is an X-linked recessive genetic disease - Bruton Tyrosine kinase mutation (BTK). Common microbiological pathogens include P.aeruginosa, S.aureus, S.pneumonia, and less common atypical bacteria

Case Presentation: In this report, we present a compelling case study of an 11-year-old male patient suspected of having immunodeficiency due to pneumonia - otitis media recurring many times since the age of 1 year and knee arthritis for the past 3 months. B cell count was zero in two samples 2 weeks apart, along with low IgG/IgA/IgM. The child's ear discharge culture was positive for P.aeruginosa. We first looked for mutations in the BTK gene, a gene that plays a crucial role in the development and maturation of B cells. The results revealed that the patient's BTK gene lost two exons 8-9. Due to late detection of the disease, at the time of diagnosis, the child encountered severe infection (pneumonia – bronchiectasis, otitis media, myositis) and especially had arthritis. Mycoplasma pneumoniae was found positive in many organs, with a remarkably elevated CRP of 300mg/dl. The patient was treated with broad antibiotics, namely Meropenem and Levofloxacin, which mainly targeted Pseudomonas Aeruginosa and M. pneumoniae, respectively, along with IVIG periodically. His condition improved significantly after antibiotic therapy and three rounds of IVIG every 3 weeks.

Discussion: Though he witnessed improvement in knee pain, knee effusion tended to increase. In medical literature, M.pneumonie arthritis was found in three groups: 1-using immunosuppressants; 2-decreasing blood IgG level; 3-after organ or stem cell transplantation. Antibiotics were used for a long time and were less effective.

Conclusions: Therefore, we are considering using corticosteroids, which play a similar role in M. pneumonia, because the patient had LDH 800U/L and high level of blood IgG.

A case of X-linked thrombocytopenia and suspected IgA nephropathy – not as benign as we think

Hayley HN Ip[1], Sophie HY Lai[1], Qin Ying Lim[1], Matthew HL Lee[1], Koon-Wing Chan[2], Crystal K Lam[3], Elaine YL Au[3], Rever CH Li[4], Eugene YH Chan[5], Alison LT Ma[5], Terry TW Chow[5], Shau Yin Ha[5], Jaime S Rosa Duque[2], Yu Lung Lau[2]

1 *Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong*
2 *Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong*
3 *Department of Pathology, Queen Mary Hospital, Hong Kong*
4 *Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong*
5 *Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong, Hong Kong*

Introduction: X-linked thrombocytopenia (XLT), clinically is a milder form of Wiskott Aldrich syndrome (WAS). Despite known to have excellent survival rates, patients are at risk of severe disease related autoimmune and malignant complications, including IgA nephropathy.

Case Presentation: An 18 years-old Chinese boy, with no significant family history, presented at 9 months-old for petechiae. He had thrombocytopenia (19 x 109) and normal mean platelet volume (6.3fL). Bone marrow exam showed adequate megakaryocytes, consistent with peripheral causes of thrombocytopenia. He was treated as chronic ITP, unresponsive to IVIG with partial response to steroids. At 13 years-old, there was mildly raised serum creatinine (78umol/L) (Figure 1). He remained largely asymptomatic except for occasional skin bruising and mild eczema. At 17-years old, he presented with gum bleeding. There were elevated urine red blood cells (>250/uL), urine protein (>30mg/dL), serum creatinine (156umol/L) and urea (9.3mmol/L), normal IgA levels (254mg/dL) and low IgM levels (28mg/dL). Targeted WAS genetic testing showed c.559+5G>A mutation, a pathogenic variant for XLT. IgA nephropathy was suspected, however renal biopsy was not performed due to bleeding risks. He is now on amlodipine and supportive management for chronic kidney disease stage IIIB.

Discussion: This case highlights the diagnostic and management challenges of XLT. Microcytic thrombocytopenia may not always be present as classically described leading to easy misdiagnosis. Close monitoring of disease was difficult during the COVID pandemic, which unfortunately led to delayed diagnosis of IgA nephropathy. Renal biopsy poses significant bleeding risk and there is no clear consensus regarding the treatment of IgA nephropathy in XLT. Haemotopoietic stem cell transplant (HSCT) is an option, but deteriorating renal function rendered our patient a poor candidate.

Conclusions: Traditionally, XLT is regarded to have a "benign" disease course compared to WAS, however as illustrated by our case, patients are at risk of debilitating autoimmune complications during paediatric ages. This warrants vigilance in clinicians to enable early disease detection, close monitoring and multidisciplinary management is also recommended.

Figure 1. Serial blood parameters

Date	September 2017	August 2020	December 2023	October 2024
Patient's age (years)	10.9	13.7	17.2	18.0
Haemoglobin (g/dL)	12.6	10.7	8.6	10.2
Platelet (/L)	15×10^9	19×10^9	21×10^9	16×10^9
Mean platelet volume (fL)	7.1	6.8	6.0	8.3
White cell count (/L)	7.90×10^9	8.30×10^9	7.10×10^9	6.97×10^9
Sodium (mmol/L)	140	139	140	142
Potassium (mmol/L)	3.5	4.2	4.1	4.3
Adjusted Calcium (mmol/L)	2.36	2.43	2.26	2.34
Phosphate (mmol/L)	1.43	1.32	1.30	1.06
Urea (mmol/L)	2.5	5.7	9.3 ↑	11.8 ↑
Creatinine (umol/L)	48	78 ↑	156 ↑	169 ↑
eGFR (ml/min/1.73m2) based on Revised Bedside Schwartz Formula	95	63	36	33

Activated Phosphoinositide 3-kinase Delta Syndrome (Apds) Presenting as an Early Onset Malignancy

Farizza Hazlin Ramli[1], Siti Wardah Abdul Jabar[1], Muhammad Shafiq Safwan[1], Noorzeehan Zakaria[1], Khairoon Nisa Mohamed Nashrudin[1,2], Mohd Azri Zainal Abidin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, MALAYSIA*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, MALAYSIAg*

Introduction: Activated phosphoinositide 3-kinase delta syndrome (APDS) is a rare immunodeficiency caused by gain-of-function (GOF) mutations in PIK3CD (APDS1) or PIK3R1 (APDS2) genes. The syndrome manifests as immune dysregulation, leading to recurrent infections, autoimmunity, and lymphoproliferation. Its clinical heterogeneity and overlap with other conditions such as infections, immune dysregulation and malignancies make diagnosis and management challenging.

Case Presentation: We report an 11-year-old Malay girl with APDS, initially diagnosed with nodal marginal zone lymphoma at age three years old, presenting with left neck swelling and splenomegaly. Lymph node biopsy confirmed lymphoma with immunostaining revealing CD20-positive neoplastic cells. Despite her diagnosis, she required no chemotherapy due to an excellent prognosis. Her medical history included recurrent dysentery with bicytopenia from infancy, treated as Tuberculosis Colitis. Following that, she also has a history of Recurrent Warts, and Chronic Suppurative Otitis Media. By age nine years old, she exhibited digital clubbing and was diagnosed with Bronchiectasis via high-resolution computed tomography (HRCT). Immunological workup revealed low T and B-cells, elevated IgG and IgA, and reduced vaccine-specific antibody responses. Genetic testing confirmed a pathogenic PIK3CD mutation, consistent with APDS1. Treatment with mTOR inhibitor (Sirolimus) and Immunoglobulin Replacement Therapy reduced infections, resolved lymphadenopathy, and improved splenomegaly.

Discussion: This case highlights malignancy as a possible presenting feature of inborn errors of immunity (IEI). Diagnosis of APDS is often delayed due to overlapping features with common infections and malignancies. The need for advanced diagnostic tools and lack of awareness among healthcare providers further complicate timely diagnosis. APDS's diverse symptoms necessitate tertiary-level investigations, sometimes requiring international resources.

Conclusions: Accurate APDS diagnosis is vital but challenging due to its complex presentation. Timely identification enables personalized therapies, including immunomodulation, infection control, and reduced chemotherapy toxicity. Multidisciplinary involvement and heightened awareness are crucial to improving outcomes in APDS patients.

A Classic Case of Hyper IgE Syndrome

Tiara Nien Paramita, Endah Citraresmi

Allergy, Immunology, and Rheumatology Working Group, Harapan Kita National Women and Children Health Center

Introduction: Hyper-IgE syndrome (HIES) is a rare inherited immune disorder characterized by elevated serum IgE levels, recurrent infections, and various associated clinical symptoms. Early detection, prompt treatment of infections, and supportive care are essential for improving the prognosis of individuals affected by HIES.

Case Presentation: A three-month-old boy was admitted to the emergency room after experiencing shortness of breath for three weeks. Since he was two weeks old, his skin had been coarse and dry, accompanied by a generalized erythematous rash and an ulcer on his chest. At two months of age, he developed shortness of breath and a high fever. The ulcer had spread, affecting almost the entire chest wall and becoming suppurative.

There was no reported consanguinity within the family. Laboratory examinations revealed a significantly elevated eosinophil count of 2723 cells/μL. Upon admission, the patient was in septic shock, necessitating emergency debridement surgery. During the operation, necrotic empyema was discovered in both lungs. His serum IgE level was measured at 1174.7 IU/mL, which raised the suspicion of Hyper-IgE syndrome. This suspicion was further supported by a HIES scoring system, which assigned the patient a score of 47.

Management included appropriate antibiotics to treat severe lung and skin infections, along with skincare to address the abscess and severe eczema. The patient was discharged after 13 days in the hospital. Currently, at ten months old, he is developing healthily, and cotrimoxazole is administered routinely as antibiotic prophylaxis.

Discussion: This patient fulfills the classic triad of HIES symptoms: skin and pulmonary infections, eczematous dermatitis, and elevated total serum IgE levels. In settings with limited resources and without access to genetic testing, the HIES scoring system developed by the US National Institutes of Health can assist clinicians in suspecting HIES. Treatment focused on supportive care and antibiotic management of infections.

Conclusions: This case report highlights the critical importance of early diagnosis and effective management of infections in improving the prognosis for patients with Hyper-IgE syndrome.

Diagnostic Complexities, Hyper-IgE Syndrome Associated with a STAT3 Mutation: A Clinical case

Brenda Guendulain Velázquez, Estefanía Guendulain Velázquez

Mexican Social Security Institute

Introduction: Autosomal dominant hyper-IgE syndrome (AD-HIES) is caused by mutations in the STAT3 gene, characterized by elevated IgE levels, eczema, and multiple recurrent infections.

Case Presentation:

Background

32-year-old female, Mexican. Family history: brother with poliosis, mother with bronchial asthma.

Medical History

At 6 years old, she developed vitiligo, treated with phototherapy and melanin, with no response. She suffered tibia and fibula fractures at 7 and 9 years old, following minor trauma. At 8 years old, developed atopic dermatitis, treated topically with partial improvement. Between 6 and 14 years old, experienced six pneumonia episodes requiring hospitalization. At 17, presented herpes zoster keratoconjunctivitis and a corneal ulcer. At 30 years old, was diagnosed with gastroesophageal reflux disease, treatment; proton pump inhibitors.

Laboratory Findings:

2006-2007: IgE 3856 UI/ml, IgA 148.7 UI/ml, IgG 980 UI/ml, IgM 223.4 UI/ml.

Altered lymphocyte subpopulations.

Exome sequencing: mutation in the STAT3 gene, resulting in an amino acid change from cytosine to thymine at position 292 of the protein and an early stop codon (loss of function).

Diagnoses

Hyper-IgE syndrome: innate immune deficiency due to STAT3 mutation.

Gastroesophageal reflux disease.

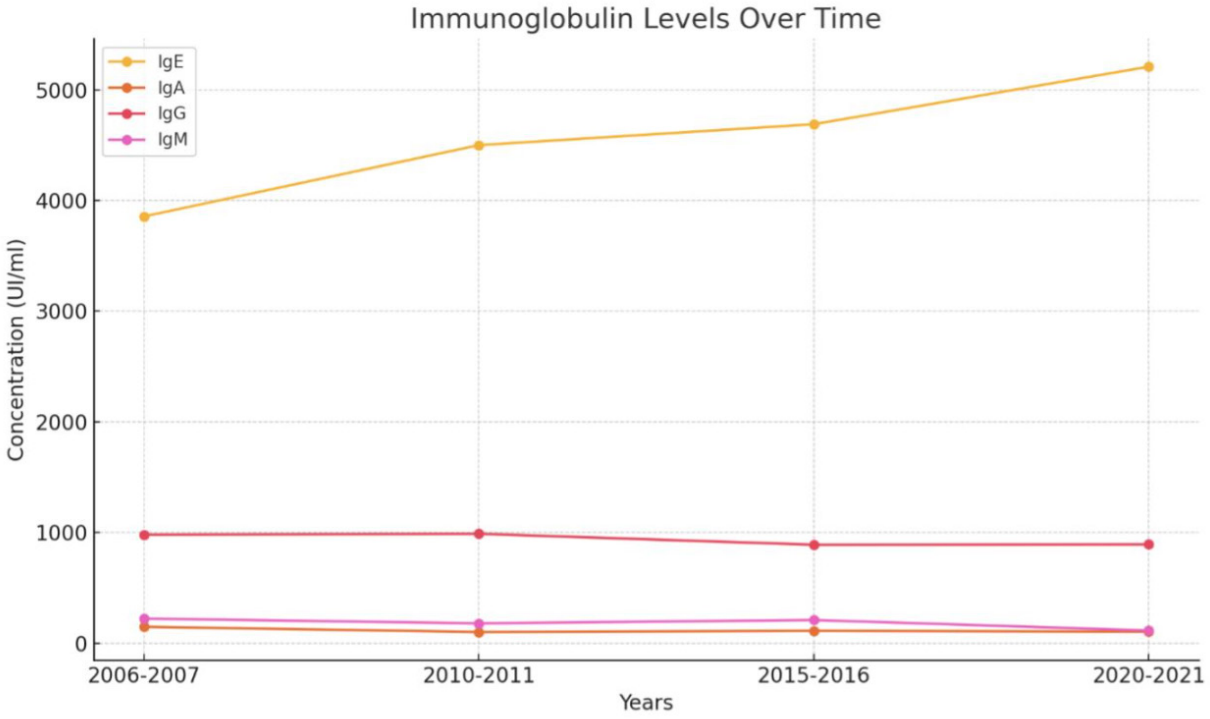
Atopic dermatitis.

Vitiligo.

Corneal leucoma due to herpes zoster infection.

Discussion: The STAT3 loss of function affects T cell differentiation and cytokine production, leading to recurrent infections from childhood and reactivation of viral infections. Treatment focuses on the prevention and management of infections, and in severe cases, hematopoietic stem cell transplantation may be considered, despite the complications involved.

Conclusions: AD-HIES presents a diagnostic challenge due to its complexity. Identifying elevated IgE levels, along with the use of standardized scores for AD-HIES, provides a structured approach that can facilitate the diagnosis of this condition. Early detection and appropriate management are essential to improve the patient's quality of life and prevent complications associated with the disease.


Immunoglobulin Levels Over Time
IgE
IgA
IgG
IgM
Concentration (UI/ml)
5000
4000
3000
2000
1000
0
2006-2007
2010-2011
2015-2016
2020-2021
Years

APSID POSTER

Day 2

Ataxia, Infections, Autoimmunity, Neoplasms- varied clinical manifestations of patients with Ataxia Telangiectasia from a center in Western India

Akshaya Chougule, Vaishnavi Iyengar, Vijaya Gowri, Prasad Taur, Mukesh Desai

Department of Immunology, Bai Jerbai Wadia Hospital for Children, Mumbai

Background and aims: Ataxia Telangiectasia (AT) is characterized by progressive cerebellar ataxia, variable immunodeficiency, malignancies and radiation sensitivity. We present clinical details of seven children with AT.

Methods: The clinical details and laboratory findings of seven children, with pathogenic/ likely pathogenic mutations in ATM gene and fulfilling the ESID criteria for AT, were analyzed retrospectively.

Results: Consanguinity was seen in 4/7; P3, P4 are brothers, P6 had two older sibling losses to AT. Male: female ratio-4:3. Median age at diagnosis-5years (Range- 1year to 8years). Onset of infections preceded onset of neurological manifestations in 4/7 (median age of onset of infections-1year, range- day6 of life to 5years). Infections included recurrent URTI (6/7), ear infections (3/7), mastoiditis (1/7), chronic sinusitis (1/7), UTI (2/7), sepsis 2/7. 4/7 had at least one pneumonia, 1/7 had recurrent pneumonias, 2/7 had persistent pneumonia, 1/7 had empyema. MRSA, Mycobacteria tuberculosis, CMV, Parvovirus B19 were isolated. Median age of documentation of ataxia was 3years (range-2years to 6years). P5 had global developmental delay with hypotonia, gross motor milestones affected more than social milestones. Others had normal social and mental milestones. Cutaneous manifestations included Café-au-lait spots(3/7), generalized hyperpigmentation(1/7), 4/7 had conjunctival telangiectasia. P5 had anterior mediastinal mass (T lymphoblastic lymphoma). P1 had autoimmune hemolytic anemia and autoimmune hypothyroidism. 7/7 had elevated AFP. All had T and B lymphopenia. P1 had low IgA, P5 and P7 had hyper IgM and 4/7 had normal immunoglobulin levels. 5/7 had diffuse cerebellar atrophy on MRI, in addition, P3 had left periventricular white matter lesion favoring low grade neoplasm, P1 had atypical PRES. 2/7 had normal MRI. All were started on IVIG and prophylaxis. P1 succumbed to pneumonia.

Conclusions: Patients with AT show variability in clinical features with respect to ataxia, infections and can present with varied manifestations ranging from immunodeficiency to malignancy and autoimmunity.

Clinical and genetic features of UNC13D deficiency with hypogammaglobulinemia

Linyan Xiong, Xi Yang

Children's Hospital of Chongqing Medical University

Background and aims: UNC13D deficiency is the predominant form of familial hemophagocytic lymphohistiocytosis (FHL) in Asia. Hypogammaglobulinemia is a rare phenotype in FHL3, as well as in sporadic HLH. Therefore we have summarized the clinical and genetic features of UNC13D deficiency with hypogammaglobulinemia.

Methods: We retrospectively analyzed the clinical features of two patients with UNC13D deficiency with hypogammaglobulinemia in our center, along with three patients previously reported. Then the findings were compared to sporadic HLH with hypogammaglobulinemia obtained from literature review.

Results: All patients presented with fever and hepatosplenomegaly. All patients experienced respiratory infections, while recurrent respiratory infections only occured in two patients. EBV infection and seizures were observed in 40% and 75% of the patients, respectively. Cytopenia, increased ferritin level, and decreased fibrinogen level were detected in all patients. All four non-transplanted patients died. Eight mutation sites were identified, with 25% located in exon 9 and 25% in exon 20. The majority (57%) of the mutated amino acids were situated in the region of interaction with RAB27α. In contrast to sporadic HLH with hypogammaglobulinemia, UNC13D deficiency with hypogammaglobulinemia was more likely to present with respiratory manifestations (100% vs. 44.5%), exhibited a higher frequency of neurological involvement (75% vs. 33.3%) and had a higher mortality rate (80% vs. 66.7%).

Conclusions: We provide the first conclusion of clinical manifestations, genetic characteristics, and treatment of UNC13D deficiency with hypogammaglobulinemia. Patients with this condition tend to be more critically ill and have a poorer prognosis. However, hematopoietic stem cell transplantation may improve immune dysregulation. Additionally, a larger sample of FHL3 is necessary to determine whether regular immunoglobulin supplementation can improve outcomes. It is also crucial to explore the mechanisms through which UNC13D deficiency leads to antibody deficiency.

A Clinico-Molecular Profile of Patients with X-Linked Chronic Granulomatous Disease: Our Experience At Chandigarh, North India

Abarna Thangaraj[1], Pandiarajan Vignesh[1], Ridhima Aggarwal[1], Prabal Barman[1], Taru Goyal[1], Madhubala Sharma[1], Jhumki Das[1], Manpreet Dhaliwal[1], Saniya Sharma[1], Rakesh Kumar Pilania[1], Ankur Kumar Jindal[1], Deepti Suri[1], Sheetal Sharma[2], Alka Khadwal[3], Surjit Singh[1], Amit Rawat[1]

1 *Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh*
2 *Department of Experimental Medicine and Biotechnology, PGIMER, Chandigarh*
3 *Department of Clinical Haematology and Medical Oncology, PGIMER, Chandigarh*

Background and aims: Reports of genotype-phenotype correlation in X-linked Chronic Granulomatous disease (XL-CGD), X-linked carriers of *CYBB* defect, and *G6PD*-deficient forms of CGD are scarce from developing countries.

Methods: Records of XL-CGD were reviewed for the period August 1993- December 2024. Diagnosis was based on nitroblue tetrazolium, dihydrorhodamine (DHR) assays, flow cytometry for gp91phox expression, and variant confirmation by Next-Generation or Sanger sequencing. Patients were categorized into null variants (DHR Stimulation index (SI) <2) and residual NADPH oxidase activity (DHR SI ≥2) and their clinical characteristics were compared.

Results: Of the 54 patients with XL-CGD, 49 had hemizygous pathogenic variants in *CYBB*, 3 were X-linked *CYBB* carriers with skewed lyonization, and 2 had *G6PD* defects. 35 patients were categorized in null variant group and 14 in residual NADPH oxidase group. Age at diagnosis (p=0.002), and median delay (p< 0.001) in diagnosis were high in residual NADPH oxidase group. Spearman correlation coefficient suggests that higher the DHR SI, older the age at diagnosis (p<0.001) and higher the delay in diagnosis (p<0.001). Residual NADPH oxidase group had increased rates of pneumonia (p=0.02) and lymphadenitis (p=0.03). Mortality was higher in null group (82.8%, p=0.001) compared to residual NADPH oxidase group (35.7%). Kaplan Meir analysis revealed better survival in residual NADPH oxidase group (p=0.0034). There were 44 *CYBB* variants (12 novel), predominantly missense variants in residual NADPH group. Three patients of skewed lyonization and 2 *G6PD* variants had severe manifestations, and 1 patient with *G6PD* defect succumbed to pulmonary complications. Five XL-CGD carriers were symptomatic, of which 1 patient had severe lupus-like manifestation.

Conclusions: XL-CGD patients with residual NADPH oxidase activity exhibit better survival with increased morbidity than null variants. G6PD-associated CGD-like manifestations and severe presentations in *CYBB* female carriers with skewed X-linked lyonization emphasize the need for its awareness and timely diagnosis.

Table 1: Demographics details, clinical features and infectious profile of null variants and patients with residual NADPH oxidase of X-linked CGD

Clinical features	XL CGD- Null variant (DHR SI<2) (n=35)	XL CGD- Residual NADPH activity (DHR SI >2) (n=14)	P value
Age at symptom onset	1.5 (IQR-0.6-5 months)	6 months (IQR-2.5-9.75 months)	p = 0.062
Age at diagnosis	9 (IQR-4 -24 months)	44 months (IQR-12.25-109 months)	p = 0.001
Delay in diagnosis	7 months (IQR1-12months)	36 months (IQR-9.97-81.5months)	P < 0.001
Number of admissions	3 (IQR-1-5)	5 (IQR-3.75-8.5)	P = 0.016
Pneumonia	30 (85.7%)	13 (92.85%)	P = 0.59
	65 episodes (8 patients had more than/ equal to 3 episodes)	47 episodes (8 patients had more than/ equal to 3 episodes)	P = 0.026
Lymphadenitis	16 (45.7%) with 32 episodes	11 (78.5%) with 19 episodes	P = 0.039
Abscess	15 (42.8%) with 33 episodes	7 (50%) with 17 episodes	P = 0.714
Liver abscess	2 (5.7%)	2 (14.2%)	-
Osteomyelitis	3 (8.5%)	1 (7.1%)	-
Hyperinflammatory complications	17(48.5%)	9 (64%)	p = 0.330
B558 Stain index	Median stain index -1.19 IQR- 1-1.3	Median stain index -3 IQR- 1.06-3.5	P =0.135
Mortality	29 (82.8%)	5 (35.7%)	P = 0.001
Follow up months	1 (IQR-0.55-22) Total – 473.5 patient months	22.5 (IQR-1-70) Total- 514 patient months	P = 0.006

A Novel CEBPE Variant Associated with Severe Infections and Profound Neutropenia

Anit Kaur[1], Aaqib Zaffar Banday[2] , Dharmagat Bhattarai[2] , Jhumki Das[2] , Kanika Arora[2] , Gurjit Kaur[2] , Vignesh Pandiarajan[2], Ankur Kumar Jindal[2], Deepti Suri[2], Jasmina Ahluwalia[2], Amit Rawat[2], Surjit Singh[2]

1 *Translational and Regenerative Medicine,*
2 *Allergy and Immunology Unit Advanced Pediatrics Centre,*
Post Graduate Institute of Medical Education and Research, Chandigarh

Background and aims: Specific granule deficiency (SGD) is a rare inborn error of immunity resulting from loss-of-function variants in *CEBPE* gene (encoding for transcription factor C/EBPε).

Methods: Light-scatter characteristics of granulocytes were examined on various automated hematology analyzers. Phagocyte immunophenotype, reactive oxygen species (ROS) generation, and Toll-like receptor (TLR) signaling were assessed using flow cytometry. Relative expression of genes encoding various granule proteins was studied using RT-PCR. Western blot analysis and luciferase reporter assay was performed to explore variant C/EBPε expression and function.

Results: Severe infections occurred in both siblings. Analysis of granulocyte light scatter plots revealed automated hematology analyzers can provide anomalously low neutrophil counts due to abnormal neutrophil morphology. Neutrophils displayed absence/marked reduction of CD15/CD16 expression and overexpression (in a subset) of CD14/CD64. Three distinct populations of phagocytes with different oxidase activities were observed. Impaired shedding of CD62-ligand was noted on stimulation with TLR-4, -2/6, and -7/8 agonists. We demonstrated the variant C/EBPε to be functionally deficient.

Conclusions: Homozygous c.655_665del variant in *CEBPE* causes SGD. Anomalous automated neutrophil counts may be reported in patients with SGD type I. Aberrant TLR-signaling might be an additional pathogenetic mechanism underlying immunodeficiency in SGD type I.

Clinical and Immunological Profile of patients with Mendelian Susceptibility to Mycobacterial Diseases: Our Experience from North-West India

Vignesh Pandiarajan[1], Jhumki Das[1], Kaushal Sharma[1], Abarna Thangaraj[1], Ridhima Aggarwal[1], Sathish Kumar Loganathan[1], Aditya Dod[1], Rakesh Pilania[1], Ankur Jindal[1], Manpreet Dhaliwal[1], Saniya Sharma[1], Deepti Suri[1], Amit Rawat[1], Surjit Singh[1]

1 *Allergy Immunology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*

Background and aims: Mendelian Susceptibility to Mycobacterial Diseases (MSMD) is caused by inborn errors of IFN-γ immunity that result in susceptibility to weakly virulent mycobacteria and salmonella. Reports of MSMD from Indian subcontinent are scarce. Our research aims to identify monogenic immune defects in IL-12/23/IFN-γ pathway in Indian patients with suspected MSMD and their functional characterization.

Methods: 69 patients who had either disseminated tuberculosis, disseminated BCGosis or intramacrophagic microbial infections were subjected to molecular evaluation using Next-generation Sequencing. Flow-cytometric evaluation and cytokine assessment for IFN-γ mediated immunity were performed to validate identified variants.

Results: 33 (47.8%) patients harbored pathogenic variants. Homozygous pathogenic variants in *IL12RB1, IFNGR1, IFNGR2, IL12B, ISG15, ZNFX1*, and *TBX21* genes were identified in 19, 5, 2, 2, 2, 1, and 1 patient, respectively. One had a pathogenic hemizygous variant in *IKBKG*. Most of them had evidence of local or disseminated BCG infections. Apart from mycobacteria, infections with *Salmonella* sp. (n=4) and *Pandorea apista* (n=2) were noted in patients with *IL12RB1* defects. Autoimmune hemolytic anemia, small vessel vasculitis, and features of Th2 skewing were observed in *IL12RB1* defects. Patients with partial dominant *IFNGR1* defects presented predominantly with multifocal bone involvement due to atypical mycobacterium. Protein expression of IL12Rβ1 and IFNγ R1 was decreased in all patients with homozygous IL12RB1 and IFNGR1 defects. Flow-cytometric assay revealed reduced phosphorylation of STAT4 and STAT1 in all patients with *IL12RB1* and *IFNGR1* defects, respectively. Significant reduction in cDC1 cells (p-value: ≤0.029) and cDC2 cells (p-value:0.001) and reduced Tfh, Th1, and Th17 lymphocytes were observed in IL12RB1 defect, compared to controls. None underwent hematopoietic stem cell transplantation.

Conclusions: We document the infective profile, natural course of the disease, and novel variants in a North Indian cohort of patients with MSMD. A decrease in dendritic cells (cDC1 and cDC2) was seen in *IL12RB1* defects.

Development of Thymic Output Assay Using Flow Cytometry

Noor Faralina Zainul Fadziruddin[1*], Intan Juliana Abd Hamid[1] and Zarina Thasneem Zainudeen[1*]

Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia, Bertam 13200, Kepala Batas, Penang, Malaysia

Background and aims: Thymic output refers to the production and release of naïve T cells from thymus into peripheral immune system. By maintaining T cell diversity of an individual, thymic output is critical during early of life and during immune system reconstitution such as immune suppression recovery. Defects in thymic output can lead to insufficient production of naïve T cells, disrupting the function of adaptive immunity. Thus, assessment of thymic output is vital for both suspected and confirmed inborn error of immunity (IEI) patients. Our aim is to develop and validate a flow cytometric based assay for thymic output, using naïve T cell markers, to improve the diagnosis of IEI patients in Malaysia.

Methods: Flow cytometric assay measuring specific T cell subsets markers, i.e. CCR7 and CD45RA, were used to determine the maturation status of T cells in different groups of IEI patients. Immunophenotyping reference ranges in healthy paediatric population was used to determine cut-off value for low naïve T cells. Blood was collected from four confirmed DiGeorge syndrome patients, two CVID patients and one CTLA-4 patient.

Results: Only three patients (one DiGeorge, one CVID and one CTLA-4 patient) presented with low percentage of naïve CD4+ and naïve CD8+. The naïve T cells (CCR7+CD45RA+) percentages were below the reference range cut-off point. Results were presented in Table 1.

Conclusions: Naïve T cells from both CD4+ and CD8+ subsets can serve as indicator markers for T cell production output of the thymus. This assay can be used as diagnostic test for IEI patients with defect in thymus output, thus acts as confirmatory test for genetic testing.

Keywords: inborn error of immunity, thymic output, T cell subsets, naïve T cells, flow cytometry

Table 1: Percentage of naïve T cells from patients as compared to reference range

Patient	Disease	Age (years)	Results naïve CD4+ (%)	Reference range naïve CD4+ (%)	Results naïve CD8+ (%)	Reference range naïve CD8+ (%)
P1	CTLA-4	18	9.72	31-57	17.5	18-61
P2	DiGeorge syndrome	2	72.4	54-80	45.4	34-73
P3	CVID	13	30.7	25-63	23.1	22-58
P4	DiGeorge syndrome	14	51.3	31-57	24.8	18-61
P5	CVID	2	50.7	54-80	28.8	34-73
P6	DiGeorge syndrome	2	53.5	54-80	26.1	34-73
P7	DiGeorge syndrome	9 month	83.4	54-80	69.5	34-73

Altered Immune Profiles Associated with Complicated Community-Acquired Pneumonia in Children

N. Nikitin[1,2], A. Moiseeva[1], A.Mukhina[1], E. Tolstova[3,4], M.Besedina[3,4], O. Zaytseva[3,4], D.Pershin[1], Y. Rodina[1], A.,Shcherbina[1]

1 *Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Department of Immunology, Moscow, Russia.*
2 *Center of Theoretical Problems of Physico-Chemical Pharmacology, Russian Academy of Science, Moscow, Russia*
3 *Federal State Budgetary Educational Institution of higher education « Russian University of Medicine» of the ministry of health of the Russian Federation, Moscow, Russia.*
4 *St. Vladimir Children's State Hospital, Moscow, Russia*

Background and aims: Community-acquired pneumonia (CAP) remains the largest cause of morbidity and mortality in children. Complicated community-acquired pneumonia (cCAP) is characterized by one or more of the following: parapneumonic effusion, empyema, necrotizing pneumonia and lung abscess. Though cCAP can be a symptom of primary immunodeficiency (PID), many patients have a stand-alone episode of cCAP, with no confirmed PID. We aimed to characterize cCAP pediatric cohort in whom PID has been excluded.

Methods: We analyzed a group of 27 patients (ages 2-17 years, median 5 years) with cCAP, necrotizing pneumonia was present in 44% (12/27).

PID was excluded based on immunoglobulin assessment, lymphocytes immunophenotyping and rhodamine test, performed at least 4 months after the resolution of pneumonia. Control group consisted of healthy 2-4 year old children (n=100) underwent in silico immunophenotype. Data analysis utilized decision tree classifiers and principal component analysis (PCA).

Results: Ten patients exhibited mild CD3+CD4+ lymphopenia (median: 986 cells/uL,min: 560 cells/uL, max: 2600). A majority displayed elevated relative counts of CD4+TEMRA (26/27) and CD4+CD279+ (15/27) and CD8+CD279+ T-cells (12/27). Humoral immunity showed mild B-cell lymphopenia (14/27) (median: 465 cells/uL, min: 120 cells/uL, max: 1710) with reduced proportion of IgD+IgM+CD27+ B-cells (11/27).

Decision tree analysis in most predominant 2-4 year age group (n=10) revealed association of decreased CD4+CD45RA+CD197- cells with necrotizing pneumonia (information gain (IG) 0,971) and decreased CD8+ CD45RA+CD197+ cells with viral etiology (IG=1,485). We also demonstrated decreased CD4+CD45RA-CD197+ cells in patients with cCAP compared to healthy controls (IG=0,344). PCA demonstrated distinct segregation of cCAP patients from healthy controls (Figure 1). CD4+ lymphopenia doesn't significantly reduce entropy at any decision tree.

Conclusions: Our findings suggest impaired T-cell differentiation in children recovering from cCAP. While no specific immune deficiency phenotype was identified, further investigation, including molecular-genetic analysis in more homogeneous groups, is warranted to elucidate risk factors for cCAP.

Estimation of Anticytokine Antibodies in Patients with Recurrent, Severe or Atypical Infections

Gayathri CV, Taru Goyal, Amit Rawat, Rakesh Kumar Pilania, Saniya Sharma, Vignesh Pandiarajan, Naveen Sankyan, Surjit Singh

Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and research, Chandigarh, India

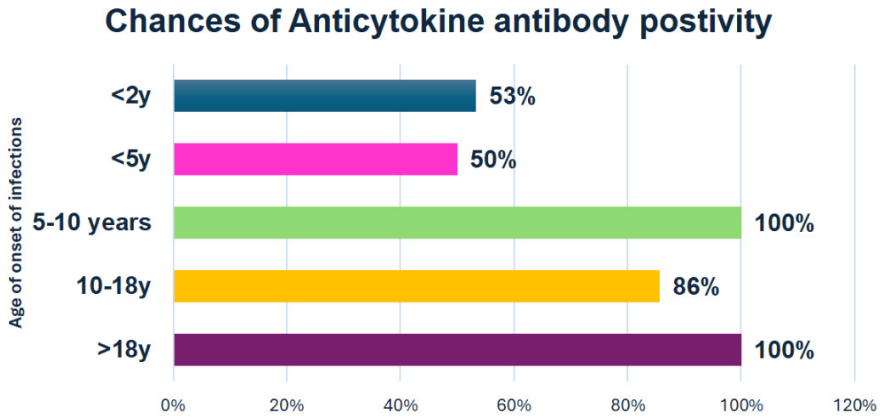
Background: Patients with anti-cytokine autoantibodies may present with a clinical profile similar to that of associated inherited illnesses because these antibodies inhibit the cytokine's biological action. Though a few genetic variants have been implicated, they are predominantly considered adult onset disease.

Objective: We aimed to identify and quantify anticytokine antibodies in symptomatic patients with recurrent/severe /disseminated infections and to study and analyze the clinical profile of patients with anti-cytokine antibodies in pediatric population in south east Asian country, India.

Methods: Patients with recurrent, atypical or severe infection attending the Out patient department or admitted in the wards of Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India were enrolled between July 2023 to Dec 2024.

Results: 11 female patients and 25 male patients were enrolled. All the patients were excluded of human immunodeficiency viral infection through serology. Median age at the time of collection of sample was 5 years (range 6months – 66 years).We classidied the patients into four groups as thos with intracellular fungal infections, Mycobacterial infection, Candida infection,Viral infections and those with Staphylococcal infections. Out of 13 patients with underlying Inborn error of Immunity, 6 had autoantibodies including *IL12RB1, RAG1, FOXN1, ZNFX1, STAT3DN* defect.

Conclusions: Anticytokine antibodies may be implicated in pathogenesis of diseases even in childhood. They may be implicated in the pathogenesis of infection even in those with underlying Inborn error of Immunity. A high index of suspicion may help in diagnosis, initiation of appropriate treatment including immunosuppression and targeted therapy, and prevention of infection in predisposed individual by appropriate use of vaccines, antimicrobial prophylaxis.



Immunogenicity Of A Fourth Dose of COVID-19 Vaccine In Individuals With Inborn Errors Of Immunity

Jeffery CH Chan[1], Daniel Leung[1], Chung Yuet[1], Jaime S Rosa Duque[1], Yu Lung Lau[1]

1 *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong*

Background and aims: Individuals with inborn errors of immunity (IEI) have higher risks of hospitalisation, case fatality rate, and chances of reinfection compared to healthy individuals after being infected with SARS-CoV-2. Evidence on humoral and cellular immunogenicity after a fourth dose of COVID-19 among individuals with IEI is limited.

Methods: Individuals aged 5 years or above and diagnosed with IEI who received at least four doses of the COVID-19 vaccine were recruited. Either BNT162b2 or CoronaVac was used as the fourth dose, which was given at least 90 days after the preceding dose. Humoral immunogenicity was evaluated using wild-type (WT) spike receptor-binding domain (S-RBD) IgG enzyme-linked immunosorbent assay (ELISA) and surrogate virus neutralisation test (sVNT) (GenScript Inc, Piscataway, NJ). Cellular immunogenicity was evaluated using intracellular cytokine staining on flow cytometry after stimulation with WT SARS-CoV-2 15-m23 peptide pool (Miltenyi Biotec, Bergisch Gladbach, Germany). In-house JN.1 ELISA and JN.1 SARS-CoV-2 15-m23 peptide pool (JPT Peptide Technologies, Berlin, Germany) were used for immunogenicity testing against JN.1 SARS-CoV-2.

Results: 20 participants (median age 17.0 years; 85% male) were included. 7, 4, 4, 3 and 2 participants had humoral, combined, phagocytic, dysregulation and innate defects, respectively. With a fourth dose of the COVID-19 vaccine, increase in geometric mean (GM) S-RBD IgG levels and sVNT levels were observed in both BNT162b2 and CoronaVac recipients, but the increase was not statistically significant (Figure 1). For T-cell responses, we observed an increase in the BNT162b2 group but not in the CoronaVac group after the fourth dose. Participants with humoral defect were found to have lower humoral and cellular immunogenicity compared to other participants. Significant increase in humoral response to JN.1 variant was observed in the BNT162b2 group.

Conclusions: A fourth dose of COVID-19 vaccine could provide additional protection for individuals with IEI.

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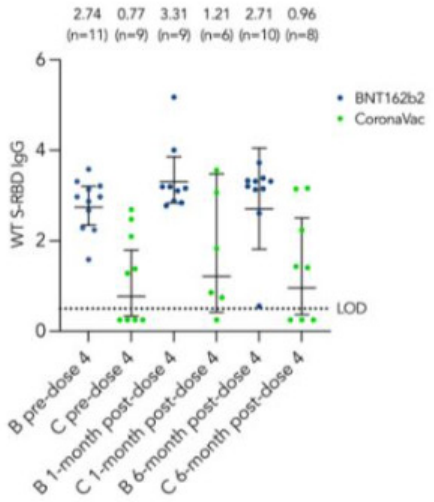

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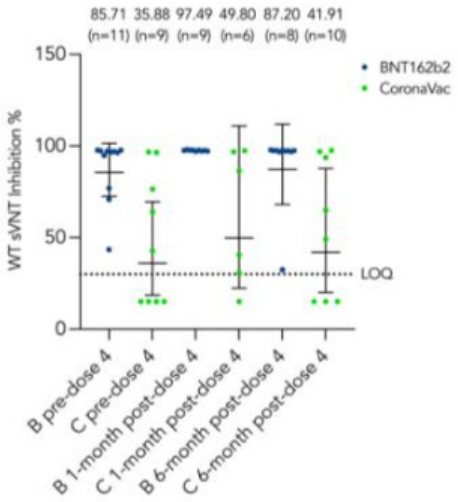

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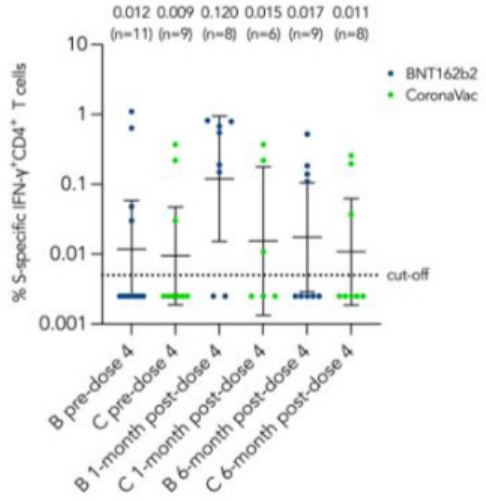

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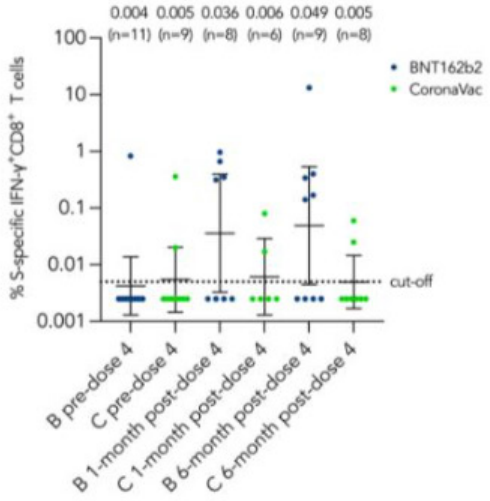

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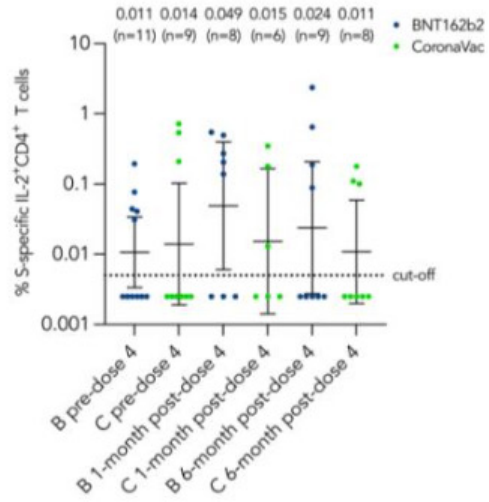

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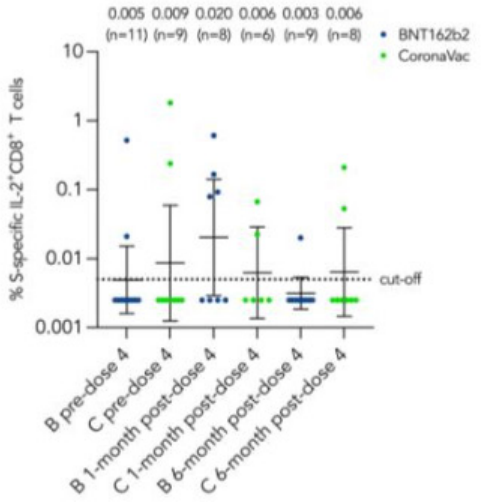


Novel compound heterozygous mutations in CARD11 underlie primary immunodeficiency with atopy

Dan Lu, Mengyue Deng, Zhou Shu, Xiongbin Chen, Huawei Mao

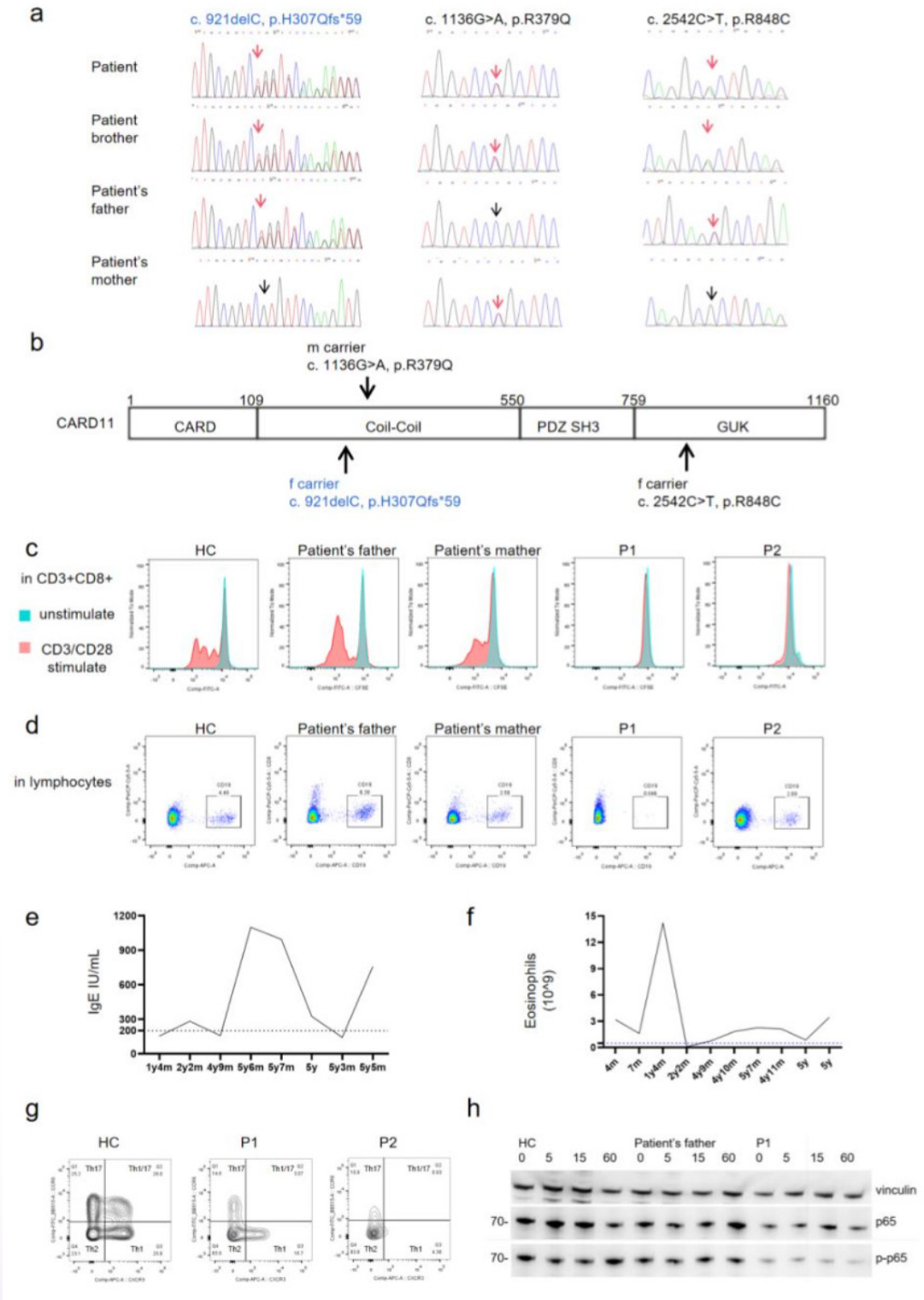
Department of Immunology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045.

Background and aims: Caspase recruitment domain (CARD) protein–B cell CLL/lymphoma 10 (BCL10)–MALT1 paracaspase (MALT1) [CBM] complexes is a critical signal transduction adapter that facilitates immune and inflammatory responses downstream of cell surface and intracellular receptors. Germline mutations that alter the function of the complex members, termed CBM-opathies, lead to a broad spectrum of clinical phenotypes, ranging from severe combined immunodeficiency to B-cell lymphocytosis. Previously, we identified a novel group of *CARD11* deficiencies causing primary immunodeficiency (PID) through clinical diagnosis, high-throughput sequencing, and functional biological experiments. Unlike previously reported cases, some children exhibit a new combination of immune deficiency and atopic dermatitis. Utilizing patient cells and tool cells with the same mutation, we delve into the biological and immune functional changes caused by the genetic mutation and its specific molecular mechanisms. Furthermore, we validate the efficacy of targeted drug therapy through the elucidation of the pathogenic mechanisms. This study is dedicated to elucidating the clinical spectrum and pathogenic mechanisms of *CARD11* deficiency to guide patient clinical management.

Methods: We performed whole-exome sequencing, followed by Sanger confirmation, assessment of the genetic variant effect on cell signaling, and evaluation of the resultant immune function.

Results: In the early clinical stage, two patients were found to exhibit severe atopic dermatitis and combined immunodeficiency. Whole-exome sequencing revealed that both children carried compound heterozygous mutations in the *CARD11* gene, specifically c.921delC, p.H307Qfs59 and c.1136G>A, p.R379Q. The mutation H307Qfs59 was inherited from the father, while R379Q was inherited from the mother. Flow cytometry revealed defects in B cells and impaired T lymphocyte proliferation in these patients. We also observed elevated serum IgE expression and a significant increase in eosinophils. Combined with the patients' symptoms of allergies and rashes, we hypothesize that there may be an imbalance in the Th1/Th2 axis, leading to an increase in IL-4-secreting Th2 cells. More importantly, after infection control, dupilumab targeted therapy completely alleviated their atopic dermatitis manifestations. This suggests that dupilumab, as an IL-4Rα blocker, diminishes the overproliferation effect of Th2 cells, alleviates allergic symptoms, and can be considered an important candidate drug for CARD11 deficiency associated with combined atopic dermatitis.

Conclusions: Compound heterozygous mutations in *CARD11* can lead to a combined phenotype of combined immunodeficiency and atopic responses: T and B cell functional defects caused by genetic mutations result in a phenotype of combined immunodeficiency; significant downregulation of the NF-κB and mTOR pathways, particularly the enhancement of Th2, caused by genetic mutations, leads to the development of atopic dermatitis.



A novel compound heterozygous mutations identified in CARD11. **a.** Sequence analysis of the patients and their parents. The heterozygous single base substitution (c.921delC, p.H307Qfs*39, c.1136G>A, p.R379Q) in *CARD11* are shown. **b.** The schematic diagram shows the location of mutations on the CARD11 protein. **c.** Proliferation in CD3+CD8+ population. **d.** Flow cytometry detection of the proportion of CD19+ B lymphocytes. **e-f.** IgE and eosinophil expression level quantification. g. Flow cytometry analysis of the proportion of regulatory T cells in healthy controls and patients. **h.** PBMCs stimulated with P/I for 15 minutes and immunoblotted for NF-kB pathway activation.

Immunoglobulin replacement or vaccination? Management of *IGLL1*-defects in a large paediatric cohort detected via newborn screening (NBS) using TREC/KREC testing

Aleksey Merkushov[1], Anna Mukhina[1], Andrey Marakhonov[2], Anastasia Bobreshova[2], Maria Ampleeva[2], Irina Efimova[2], Mariia Fadeeva[1], Ekaterina Malakhova[1], Dmitriy Pershin[1], Yulia Rodina[1], Irina Mersiyanova[1], Elena Raykina[1], Oxana Ryzhkova[2], Galina Novichkova[1], Sergey Voronin[2], Sergey Kutsev[2], Anna Shcherbina[1]

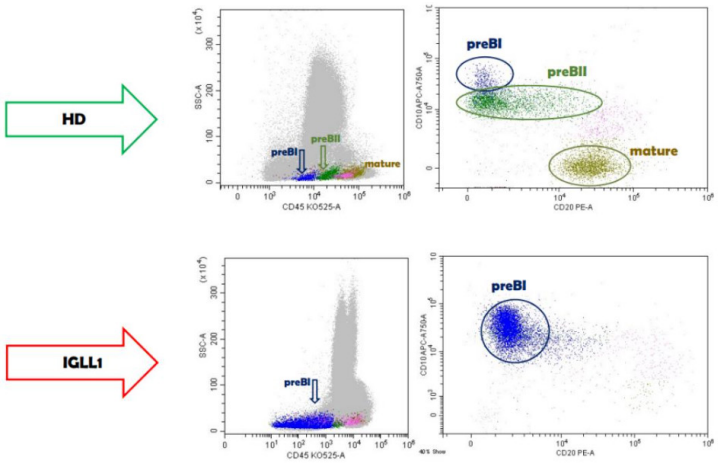
1 *Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation*
2 *Research Centre for Medical Genetics, Moscow, Russian Federation*

Background and aims: Before the era of NBS implementing KREC analysis *IGLL1* defects were considered to be a very rare form of agammaglobulinemia (AGG). We describe a cohort of children with *IGLL1* defects detected by NBS screening and the first results of their systemic vaccination.

Methods: Between 01.01.2022 and 01.07.2024 2,019,499 newborns underwent NBS with TREC/KREC detection in Russia. Flow cytometry and subsequent WES were performed in infants who had KREC below cut-off. *IGLL1* variants were verified by Sanger sequencing in patients, parents, and siblings, where possible. Follow-up included flow cytometry, serum Igg, and vaccinal antibodies measurements in vaccinated patients.

Results: 25 newborns with biallelic *IGLL1* variants were detected. Four novel alleles were identified, and three were previously described. Mean patients' follow-up was 9.5 (3-20) months. Four patients developed neonatal pneumonia and recovered without sequelae, the rest had no remarkable infectious history during the course of follow-up. Pre-B-I to Pre-B-II cells differentiation was blocked in 13/13 bone marrow samples. B-lymphocytes were low in all neonates: median 25 cell/μL (9-88) at screening, median 65 cell/μL (20-160) at 7 months, with increase to median 105 cell/μL (10-340) at 14 months (ANOVA test, p=0.0101). Median IgG level at 10-14 months was 3.3 g/l (n=8), IgM 0.38 g/l, IgA 0.29 g/l (n=15). Segregation analysis revealed 8 family members (mean age 37 (3-51) years): with homozygous variants in *IGLL1* with median 150 B-cells/μL. One of them had selective IgA deficiency, others – normal Ig levels. Eleven children diagnosed with NBS were vaccinated with DTaP-IPV/Hib. Adequate vaccinal IgG levels were found in 6/6 patients and 3/3 family members.

Conclusions: Based on NBS data *IGGL1* bi-allelic defects appear to occur more frequently than previously thought, mostly without features of severe infections. Approach to *IGLL1*-deficient patients' treatment, including safety of live vaccines administration, requires further investigation.



Development and validation of SYBR Green-based qPCR assay in *STAT3* mutation screening: a diagnostic accuracy study.

Anis Fatini Shamsul Bahrain, Intan Juliana Abd Hamid, Ilie Fadzilah Hashim and Zarina Thasneem Zainudeen

Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Advanced Medical and Dental Institute, University Sains Malaysia, Bertam 13200, Kepala Batas, Penang, Malaysia.

Background and aims: STAT3-Hyper-IgE Syndrome (STAT3-HIES) is a rare inborn error of immunity (IEI) characterised by elevated levels of serum IgE, recurrent bacterial infections on the skin, eczema and recurrent pneumonia and lung cysts. Due to the wide array of clinical manifestations, diagnosis is challenging and relies on genetic sequencing. The objective of this study was to develop a real-time quantitative PCR (qPCR) based assay for screening mutations in the *STAT3* gene using SYBR Green I. Sanger sequencing was used to validate the results and evaluate diagnostic accuracy.

Methods: *STAT3* gDNA sequence was retrieved from the NCBI database at RefSeq sequence NG_007370.1. Oligonucleotide primers were designed to encompass exons 2-23 based on the hotspot of reported mutations in the area. The panel was optimised for annealing temperature, efficiency and concentration of primers and DNA templates. Relative fold change was determined using the Pfaffl method. A one-way ANOVA was conducted followed by Dunnett's multiple comparison test to assess significant differences between patient samples and healthy controls. Sanger sequencing was used to further validate the sequences. Sensitivity, specificity, positive and negative predictive value were recorded.

Results: The *STAT3* gene panel captured mutations in 2 patients that were diagnosed with STAT3-HIES and had previously done genetic testing. Patient 1 (P1) possesses a partial deletion on exon 12 while patient 13 (P13) possesses a pathogenic heterozygous point mutation c.1934T>A. P1 and P13 returned statistically significant differences in relative fold change in primer pair STAT3 12 (0.55-fold) and STAT3 21 (0.76-fold) respectively. Diagnostic accuracy results are as follows; sensitivity=100%, specificity=82.6%, PPV= 0.46%, NPV=100%.

Conclusions: The STAT3 gene panel followed by validation on Sanger sequencing can be used as an alternative for STAT3-HIES screening during diagnosis. However, it might be limited in its capacity to capture point mutations due to SYBR Green's non-specific mode of action.

STAT3 loss of function in Hyper IgE syndrome: Molecular insight into bone dysregulation

Rashi[1], Abha Tiwari[1], Harshika Choudhary[1], Ankur Jindal[2], Amit Rawat[2], Surjit Singh[2], Biman Saikia[1*]

Departments of Immunopathology1 and Pediatrics2, Postgraduate Institute of Medical Education & Research, Chandigarh.

Background: Hyper IgE syndrome (HIES) is a rare disorder caused majorly by a mutation in the STAT3 gene. Up to 70% of patients experience skeletal and craniofacial abnormalities. Previous studies from our laboratory have shown that STAT3 plays a role in osteoclastogenesis (unpublished data). Recent studies using mouse models have demonstrated that STAT3 knockdown in osteoblasts (OB), but not osteoclasts (OC), leads to similar skeletal defects. Despite these findings, the role of STAT3 in mediating OB-OC crosstalk remains unclear.

Aim: **To decipher osteoblastic-osteoclastic dysregulation in STAT3-LOF-HIES patients by analysing differential gene expressions in OB-OC crosstalk.**

Methods: Four genetically confirmed HIES patients (NIH score ≥20, Th17 ≤0.5%, pSTAT3 <30%) and four healthy controls were recruited. To assess the STAT3-osteogenesis pathway, analysis of ALP activity, mineralization (Alizarin Red staining), and gene expression via RNA sequencing was done. Upregulated and downregulated genes were validated with RT-PCR.

Results: Flow cytometry analysis showed significantly reduced %pSTAT3 and %Th17 in patients ($p<0.05$). Clinical exome sequencing identified STAT3 mutations: DNA-binding domain (patients 1 and 3: p.Arg455Gln, p.Arg382Trp), coiled-coil domain (patient 2: p.Leu225Val), and linker domain (patient 4: p.Ile499Phe). Patient and control PBMC-derived MSCs were differentiated into osteoblasts. Osteogenic potential, measured by Alizarin Red staining and ALP activity, was significantly reduced in patients.

RNA sequencing analysis revealed 2,459 genes downregulated and 231 genes upregulated by more than 1.5-fold in patients compared to controls. Gene ontology analysis of significantly downregulated genes showed enrichment in biological processes involved in osteoblast differentiation that correlate with the skeletal abnormalities observed in patients. Key affected genes included **RUNX2, DLX5, STAT3**, and **COL2A1**, validated using RT-PCR and found to be significantly downregulated in patients compared to controls (p = 0.0286*).

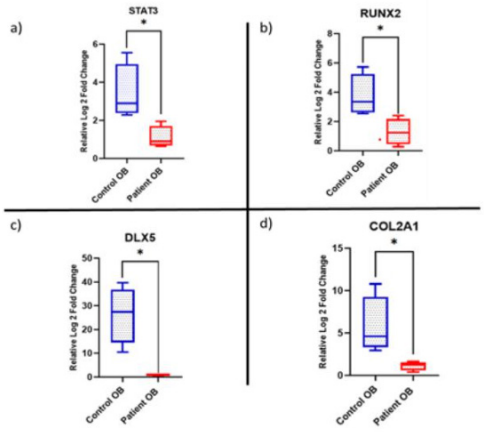


Figure: Relative Log2 Fold Change in mRNA Expression Levels: Analysis of mRNA expression levels of a) STAT3, b) RUNX2, c) DLX5, and d) COL2A1 in osteoblasts from healthy controls and HIES patients, assessed by qRT-PCR. Values are presented as median **with interquartile range. Significant downregulation of STAT3, RUNX2, DLX5, and COL2A1 was observed in HIES patients compared to controls ($p = 0.0286$*), $p < 0.001$, $p < 0.01$, $p < 0.05$.**

Conclusions: Our study showed significant downregulation of genes involved in STAT3-osteogenesis pathway in patients, reflected by reduced mRNA expression of RUNX2, DLX5, and Col2A1.

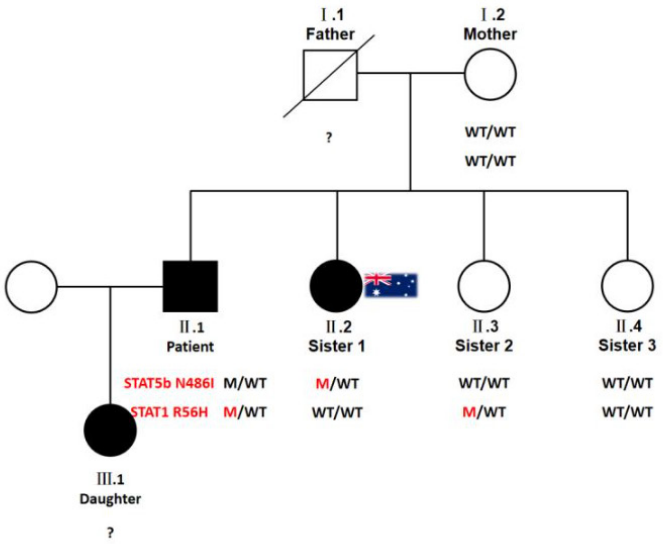
Determining the Digenic Effects of STAT1 and STAT5B Variants on Immune Function and Skin Disorders

YANG Zixuan, Yu Lung LAU, Jaime SOU DA ROSA DUQUE

The University of Hong Kong

Background and aims: Inborn errors of immunity (IEIs) comprise over 500 genetic types with diverse disease phenotypes. Mutations in the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, particularly in the STAT gene family, contribute to a significant number of IEIs. We have identified a family with two STAT mutations. The index patient has heterozygous mutations in both STAT1 (R56H) and STAT5B (N486I), and he has two sisters, each carrying either of the 2 STAT mutations, while another sister does not have these 2 mutations. These 3 siblings have different but overlapping disease phenotypes, including severe eczema, goitre with thyrotoxicosis, and susceptibility to herpes and enteroviral infections. This family provides a unique opportunity to study the impact of the two STAT mutations on disease phenotype singly and in combination.

We plan to employ luciferase reporter assays, Western blotting, and co-immunoprecipitation to assess the impact of these two STAT mutations on STAT protein expression and function. Furthermore, we shall examine the T lymphocyte differentiation and development in these 3 siblings to investigate the impact of these two STAT mutations singly and in combination. Lastly, we will develop 3 knock-in mouse models via CRISPR-Cas9 to further investigate the immunophenotypes and whether these mice manifest immunodysregulatory diseases.



Clinical phenotype:

Ⅰ.2 Mother:
- Goitre with thyrotoxicosis.

Ⅱ.1 Patient:
- Severe **eczema**, managed with dupilumab for over 5 years.
- Multiple documented food allergies.
- Chronic Cytomegalovirus (CMV) hepatitis, ongoing for 8 years.
- Persistent Hand-foot-mouth disease for 30 years.
- Recurrent episodes of zoster, totaling 5-6 occurrences in childhood.
- Severe loose stools, occasionally accompanied by blood.

Ⅱ.2 Sister 1:
- Moderate **eczema**, treated with dupilumab.

Ⅱ.3 Sister 2:
- Goitre with thyrotoxicosis.

Ⅱ.4 Sister 3:
- Small goitre; however, asymptomatic and without pharmacological intervention.

Ⅲ.1 Daughter:
- **Eczema**; topical steroids.

Methods:

1. **Patients and variant identification.**

   A male adult patient, diagnosed with Severe eczema since infancy, has been managed with dupilumab for over 5 years. He has multiple documented food allergies and a chronic Cytomegalovirus (CMV) hepatitis that has persisted for 8 years. Additionally, he has experienced persistent Hand-foot-mouth disease for 30 years and recurrent episodes of zoster, totaling 5-6 occurrences during his childhood. He also suffers from severe loose stools, occasionally accompanied by blood. After obtaining written informed consent from the patient and other family members, peripheral blood samples were collected. Currently, the patient is undergoing treatment with dupilumab and is being followed up regularly.

2. Functional validation experiments

To verify the pathogenicity of mutations in STAT1 and STAT5B within this family, initial basic functional validation is essential. Firstly, we will conduct protein level analysis and luciferase reporter assay to preliminarily ascertain whether these mutations result in a decrease or increase in the expression levels of STAT1 or STAT5B proteins. Building upon this foundation, we aim to explore the potential interplay between mutations in STAT1 and STAT5B by employing co-immunolocalization analysis to determine if an interaction exists between the two proteins. Furthermore, given that the STAT family functions as transcription factors, we will investigate whether these mutations impact the proteins' DNA binding ability by performing an Electrophoretic Mobility Shift (EMS) assay for analysis.

2.1 Luciferase report assay

293FT cells will be transiently co-transfected with a 6X-STAT-synthetic luciferase reporter plasmid and STAT1 or STAT5B variants. The transfected cells will be incubated overnight and then stimulated with IFN-γ (for STAT1) or IL-4 (for STAT5B) at a concentration of 100 ng/ml for 24 hours. Following this, cell lysates will be collected and analyzed for luciferase activities.

2.2 Western immunoblot and co-immunoprecipitation analysis.

Transfect 293FT cells using TransIT at a 1:1 ratio with either the wild-type (WT) or mutant plasmid. The transfected cells will be stimulated with IFN-γ (for STAT1) or IL-4 (for STAT5B) at a concentration of 100 ng/ml for 24 hours. Western blot analysis will be conducted to assess the levels of GAPDH, total STAT1 protein, STAT5B protein, phosphoSTAT1 (Y701), and phosphoSTAT5 (Y699). For co-immunoprecipitation analysis, tagged Flag-STAT1 and Myc-STAT5B variants will be pulled down from whole-cell lysate using anti-Myc magnetic beads. Western blots will be processed with the appropriate primary and secondary antibodies.

2.3 Electrophoretic mobility shift assay

A duplex DNA probe will be incubated with 2 μg (for standard EMSA) or 3 μg (for supershift assays) of protein extracts (as described above) at room temperature for 20 minutes, protected from light. The mixture will then be subjected to size fractionation on a native 5% acrylamide gel in standard tris-borate -EDTA buffer. Bands will be visualized by scanning the gel on a Li-Cor Odyssey CLx (Li-Cor Biotechnology, Lincoln, NE). For supershift EMSA, anti-FLAG antibody or anti-Myc antibody will be included in the reaction mix and incubated at room temperature for an additional 10 minutes prior to size fractionation of the DNA-protein-antibody complexes.

3. Flow cytometry

Based on the clinical manifestations observed in family members and a comprehensive literature review, we hypothesize that the combined mutations in various members of the STAT family may impact the differentiation and development of T lymphocytes in vivo. To validate this hypothesis, we aim to investigate the effects of STAT1 and STAT5B mutations, as well as their interactions, on T cell differentiation and development. To achieve this, we will obtain peripheral blood mononuclear cells from patients and utilize flow cytometry to analyze the specific subpopulations of T cells. Our focus will be on Th1, Th2, and Treg cells, which are defined as follows: Th1 cells are characterized by CD3+, CD4+, and IFN-γ+; Th2 cells are characterized by CD3+, CD4+, and IL-4+; and Treg cells are characterized by CD3+, CD4+, CD25+, and FoxP3+.

4. Animal model

We will generate knock-in mouse models using CRISPR-Cas9 technology to harbor STAT1 (R56H) and STAT5B (N486I) mutations identified in patients. The following experiments will be conducted

4.1 T Cell Surface Staining

Single-cell suspensions from peripheral blood, spleen, and lymph nodes of 6–8-week-old knock-in and wildtype mice will be prepared. Flow cytometry will detect lymphocyte subsets, including CD3 T cells, CD19 B cells, NK1.1+ NK cells, CD3+CD4+ T cells, and CD3+CD8+ T cells. Naive and memory T cells will be labeled by CD44 and CD62L. Thymocytes will be analyzed for CD4, CD8 double-negative, double -positive, and single-positive populations to assess thymocyte development.

4.2 T Cell Differentiation

The differentiation of Th1, Th2, Th17, and Treg cells will be examined in knock-in mice. Single-cell suspensions from spleen and lymph nodes will be stimulated to differentiate into respective T cell subsets. Flow cytometry will determine the proportions of each subset using specific markers and intracellular cytokine staining.

4.3 T Cell Activation, Proliferation, and Apoptosis

Single-cell suspensions from knock-in mice will be prepared and stimulated to assess T cell activation and proliferation via CFSE staining. Apoptosis will be detected using Annexin V-PI staining and activated Caspase 3 expression. T cell functionality will be evaluated by cytokine expression levels (e.g., IL-2, IFN-γ) using ELISA or flow cytometry.

4.4 Cytokine Secretion

Cytokine secretion by CD4+ T cells from knock-in mice will be assessed. Single-cell suspensions will be-stimulated, and supernatants will be collected to measure levels of cytokines such as IFN-γ, IL-4, IL-17, and IL-10 using ELISA or multiplex cytokine assays.

Results: After conducting whole-exome sequencing on all members of the family, two mutations were identified: STAT5b: NM_012448:exon12:c.A1457T:p.N486I and STAT1: NM_007315:c.167G>A, CGT>CAT:p.R56H. Notably, the mutation site of STAT5B is located in the DNA binding domain, while the mutation site of STAT1 resides in the N-terminal domain.

To determine whether the IL-2 or IL-4-induced phosphorylated STAT5B N4861 regulated gene transcription, an in vitro luciferase reporter assay system was employed. A mild decrease in luciferase activity was observed upon IL-2 or IL-4 treatment in cells transfected with the vector compared to WT.

Western Blot experiment was conducted to investigate the impact of the STAT5B N486I mutation on STAT5b protein expression and phosphorylation levels. The results indicated that, compared to the wild type, the phosphorylated STAT5B expression level was significantly reduced in the 293FT cell line transfected with the STAT5B plasmid containing the N486I mutation site. This finding aligns with the results obtained from the Luciferase reporter assay experiment. Based on these observations, we can tentatively conclude that this mutation leads to a loss of function in STAT5B.

Previous studies have demonstrated that CD25 and FOXP3 are important genes downstream of the STAT5B pathway. These two genes also serve as crucial markers for Treg (regulatory T cells). Therefore, we hypothesize that the N486I mutation in STAT5b, which leads to a loss of function, may also affect the quantity and functionality of downstream Treg cells. To test this hypothesis, we obtained PBMCs from patients and cultured them for a week. After one week, we measured the number of functional regulatory T cells marked by CD3+CD4+CD25+FOXP3+ using flow cytometry. The results revealed that after a week of cell culture with IL-2 and CD3/CD28 stimulation, the number of functional regulatory T cells in patients carrying the STAT5B mutation was significantly lower than that in healthy controls.

Conclusions: This study indicates that the N486I mutation in STAT5B leads to its loss of function and may further affect the number and function of downstream Treg cells. These results provide important clues for understanding the pathogenesis of STAT5B related diseases and developing potential treatment strategies

Immunophenotype of *IKZF1* haplodeficiency patient presenting as systemic lupus erythematosus

Zheng Qi*; Tan Yejun; Qian Yanjie; Lu Meiping

Department of Rheumatology, Immunology and Allergy, Children's Hospital, Zhejiang University School of Medicine; National Clinical Research Center for Child Health, Hangzhou, China

Background and aims: Analysis of the immunophenotype of a case with IKZF1 haplodeficiency, who presented as systemic lupus of erythematosus (SLE). To explore the possible mechanism of IKZF1 in the pathogenesis of monogenic lupus.

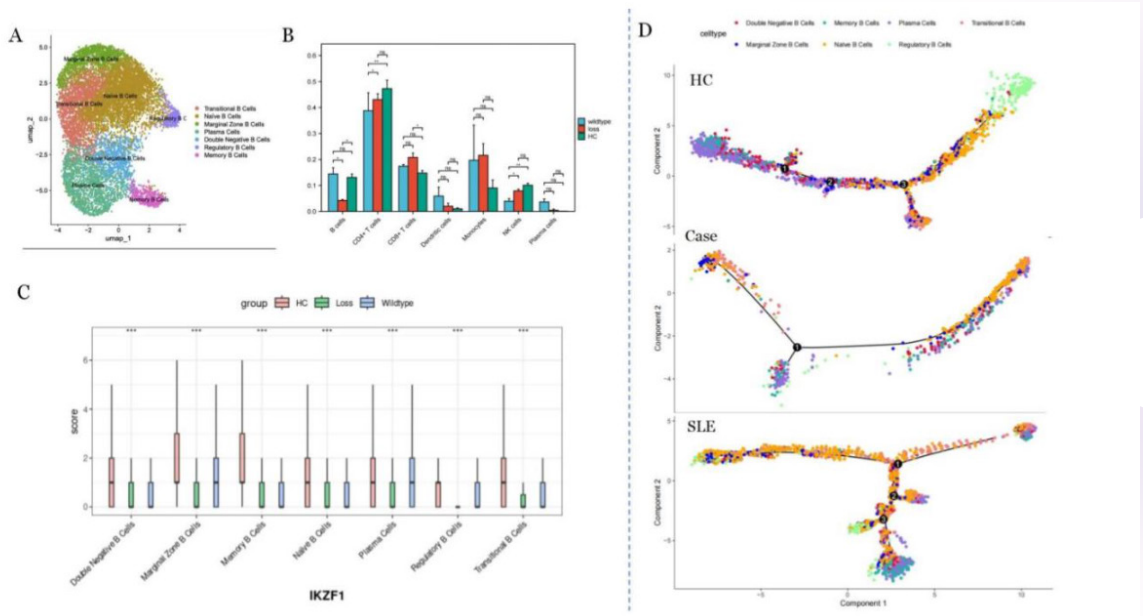
Methods: A female patient presenting with recurrent thrombocytopenia and haematuria was hospitalized. Immune work-up displayed she had positive ANA(1:100), positive dsDNA, and a decrease in complement C3 and C4. Her manifestations meet the criteria of SLE (2019 EULAR) and whole exome sequencing (WES) was performed at the same time due the low level of IgG (<3.5g/L). Gene result showed that she had *IKZF1* haplodeficiency *(De novo)*. We analyzed the transcriptomes of single PBMCs from the *IKZF1* haplodeficiency case, comparison with 3 cSLE and 4 matched healthy controls

Results: The number of B cells decreased significantly with increased CD4+ T lymphocytes in the patient of *IKZF1* haplodeficiency. Differential transcription of *IKZF1* was observed in different immune cells. The most significant are regulatory B cells, which barely transcript *IKZF1*.

Pseudotime analysis on PBMCs displayed that the cell trajectory was more sparse, with a simpler differentiation path and only one bifurcation point in *IKZF1* haplodeficiency case. In the early stages, the predominant cell types were Naïve B Cells, Double Negative B Cells, Memory B Cells, Transitional B Cells, and Marginal Zone B Cells. In the later stages, Plasma Cells and Regulatory B Cells became more prominent, and there was a noticeable increase in Naïve B Cells. IKZF1 expression showed a slight increase in the mid-stage, with minor fluctuations, and significantly rose in the later stages.

In the SLE group, the differentiation trajectory was more complex, with a fuller cell distribution and three bifurcation points. In the early stages, Naïve B Cells and Regulatory B Cells were the dominant populations, while in the later stages, Plasma Cells, Regulatory B Cells, and Double Negative B Cells became more prominent, with an increased presence of Naïve B Cells.

Conclusions: This study lays the groundwork for resolving the origin of the transcriptional signatures of *IKZF1* associated SLE and point towards specific cell subpopulations as potential therapeutic targets.



A. Immune cell composition
B. Significantly decreased B cell number in IKZF1 haplodeficiency
C. IKZF1 differentially expressed in different immune cells, among which regulatory B cellsare the most affected.
D. B cell developmental trajectory of IKZF1 haplodeficiency.

RasGRP1 mutation cause lupus-like autoimmune features.

Wenlu Xing, Yulu Li, Dan Lu, Mengyue Deng, Mengyang Yang, Xiongbin Chen, and Huawei Mao

Department of Immunology, Beijing Children's Hospital of Capital Medical University, National Center for Children's Health of China, Beijing, China

Background and aims: RasGRP1 (RAS Guanyl Releasing Protein1) gene functions as a diacylglycerol (DAG)-regulated nucleotide exchange factor specifically activating Ras through the exchange of bound GDP for GTP. Besides, RasGRP1 actives ERK/MAP kinase cascade and regulates T-cells and B-cells development and differentiation. In previous studies, it has been confirmed that RasGRP1 has an impact on the TCR (T cell receptor) signaling pathway. In addition, we found that patients exhibited manifestations of autoimmunity such as lymph node enlargement. Therefore, we explored the mechanism of autoimmunity in RasGRP1 mutation mice model.

Methods:

Mice: Construct RasGRP1 mice model through gene mutation and housed in the animal facility of the Institute of Genetics and Developmental Biology, Chinese Academy of Sciences.

Antinuclear antibody and double-stranded DNA testing: detect ANA (antinuclear antibodies) through ELISA and HEP-2, detect ds-DNA (double-stranded DNA) through ELISA.

Urine protein testing.

Tissue immune complexes deposition detection.

Results: Compared with WT (wild-type) mice, the concentrations of ANA (antinuclear antibodies), ds-DNA (double-stranded DNA) and urine protein in RasGRP1 mice were significantly increased. Under a fluorescence microscope, the deposition of immune complexes in RasGRP1 mice was significantly higher than that in WT mice.

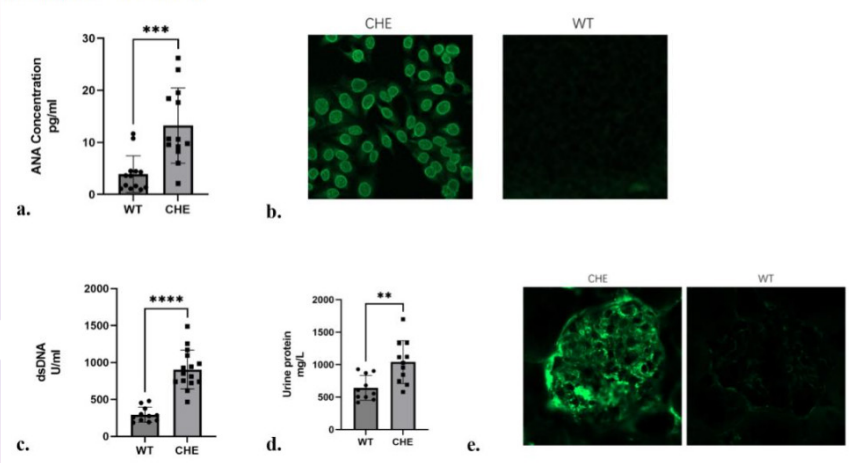


Figure1.

a. Detection of ANA (antinuclear antibodies) concentration by ELISA,

b. Detection of ANA (antinuclear antibodies) by HEP-2 cells,

c. Detection of ds-DNA (double-stranded DNA),

d. Detection of urine protein,

e. Kidney immune complexes deposition

Conclusions: Through the detection of relevant indicators, we preliminarily believe that RasGRP1 mutation mice exhibit lupus-like autoimmune features.

Understanding the molecular and immune mechanisms underlying deficiency of adenosine deaminase type 2 (DADA2) using RNA sequencing

Saniya Sharma, Arjun Ram, Madhubala Sharma, Jhumki Das, Gurjit Kaur, Rakesh Pilania, Ankur Jindal, Vignesh P, Manpreet Dhaliwal, Jayakanthan Kabeer Doss*, Deepti Suri, Amit Rawat, Surjit Singh

Pediatric Allergy Immunology Unit & Pediatric Biochemistry Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Background: DADA2 is a monogenic autoinflammatory disorder presenting as vasculitis, cytopenia, immunodeficiency, lymphoproliferation, and/or marrow failure, caused by *ADA2* mutations. Increased M1 macrophages and TNF signaling pathway are associated with pathogenesis. While substantial research has shed light on pathophysiology of DADA2, many knowledge gaps still persist. Our study aimed to investigate molecular and immune mechanisms underlying DADA2 using *RNA sequencing*.

Methods: Of 9 patients enrolled, mRNA sequencing (2x150 bp) was performed using 2.5 ml blood sample in 3 patients and 2 age-matched controls (1 control was replicated) on NovaSeq S4 NGS platform (Illumina).

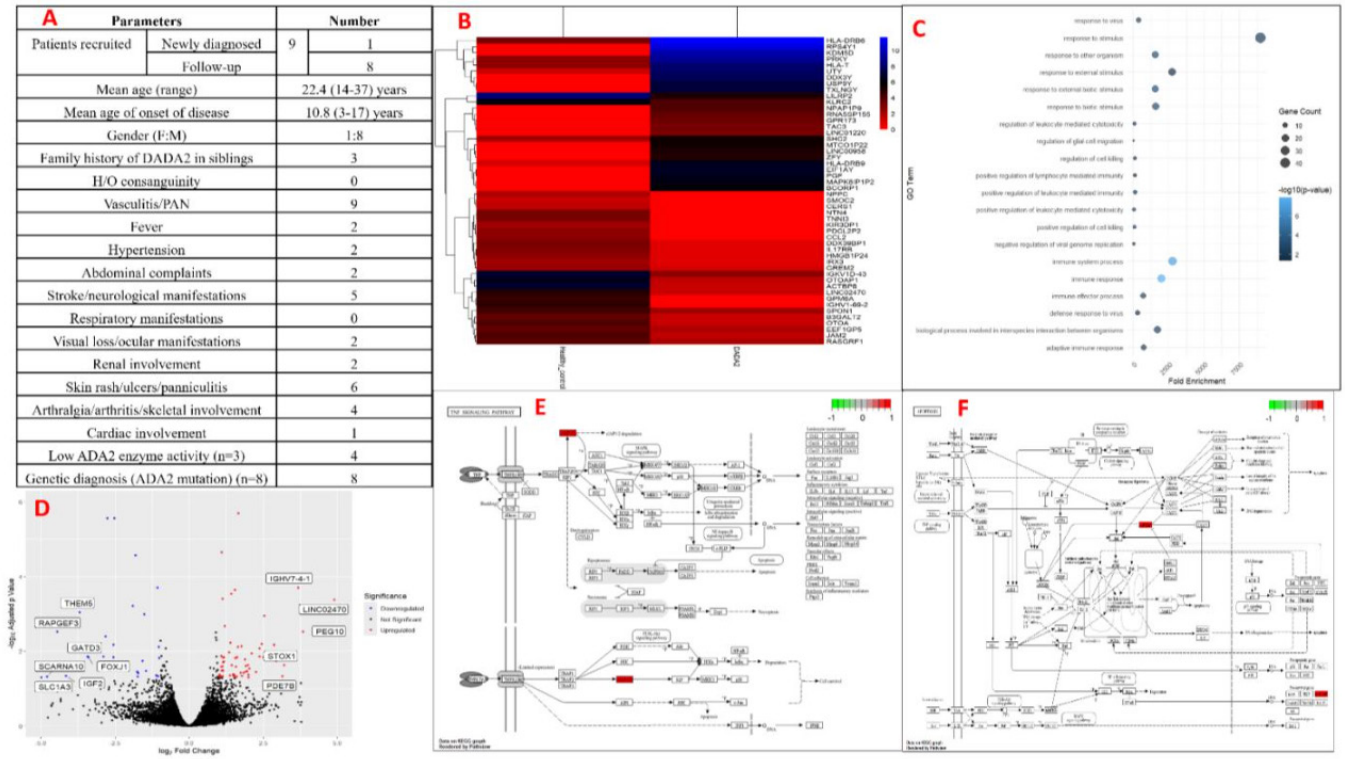
Gene expression count matrix obtained from the STAR (v2.7.3a) aligner tool was analyzed with DESEq2 package of R to identify the differential expressed genes (DEGs) in DADA2 disease. Data visualization of significant DEGs were represented using Volcano plot, Heatmap, Bubble plot (Gene ontology) and immunological pathways using pathview (v1.44.0) packages of R.

Type I interferon signature (IS) was performed by real Time-PCR. IL-18 and IL-1β serum levels were estimated by ELISA.

Results: Cut-off value of -1.0 & 1.0 log2 fold change (log2FC) with <= 0.05 p-adjusted values were used and 103 significant DEGs were detected of which 66 were up-regulated and 37 were down-regulated. Gene sets enriched were involved in immune responses including viral response, lymphocyte cytotoxicity, adaptive immunity, response to external stimuli and apoptosis regulation. Pathway analysis showed that upregulated genes play significant role in apoptosis and TNF signaling pathways. Type I IS was elevated in 1 patient. Mean IL-18 levels and IL-1β were elevated in patients than controls.

Conclusions: RNA sequencing reveals that DEGs upregulated are involved primarily in immune response pathways, particularly TNF signaling and apoptosis regulatory pathways in vasculitic phenotype of DADA2. Similar studies in other clinical phenotypes are needed to understand complex pathogenesis of this multifaceted disease.

A Parameters		Number
Patients recruited	Newly diagnosed	9 / 1
	Follow-up	8
Mean age (range)		22.4 (14-37) years
Mean age of onset of disease		10.8 (3-17) years
Gender (F:M)		1:8
Family history of DADA2 in siblings		3
H/O consanguinity		0
Vasculitis/PAN		9
Fever		2
Hypertension		2
Abdominal complaints		2
Stroke/neurological manifestations		5
Respiratory manifestations		0
Visual loss/ocular manifestations		2
Renal involvement		2
Skin rash/ulcers/panniculitis		6
Arthralgia/arthritis/skeletal involvement		4
Cardiac involvement		1
Low ADA2 enzyme activity (n=3)		4
Genetic diagnosis (ADA2 mutation) (n=8)		8



Bidirectional Causal Relationships Between Intestinal Microbiota and Juvenile Idiopathic Arthritis: Insights from Mendelian Randomization

Xiaolin Xu[1,2,4†], Xueting Mao[2,3†], Zhou Shu[4], Hongting Nie[2], Xiaoling Wang[2],and Changshan Sun[1*]

1 *School of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang, 110016, China*
2 *Department of Pharmacy, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China*
3 *Department of Clinical Pharmacology, College of Pharmaceutical Sciences, Capital Medical University, Beijing 100069, China*
4 *Department of Immunology, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China*
† *These authors have contributed equally to this work and share the first authorship*

Background: Juvenile idiopathic arthritis (JIA) is the most prevalent chronic rheumatic disease in pediatric populations, significantly decreasing their quality of life. Recently, intestinal microbiota has attracted significant attention as a potential etiological factor for JIA. This study aimed to investigate the causal association of intestinal microbiota with the risk of JIA through Mendelian randomization (MR) analysis method, to provide a basis for developing potential therapeutic interventions.

Methods: Summary statistics for gut bacteria were derived from a genome-wide association study (GWAS) meta -collection, which comprised 18,340 16S fecal microbiome genome sequencing data samples from 24 cohorts across Europe, Africa, Asia, the Middle East, and Hispanic populations. GWAS summary for the outcome comprised 4,520 JIA samples from the UK and 9,965 healthy control individuals. The primary analysis was performed using the Inverse Variance Weighted (IVW) method. Specifically, results of the IVW fixed effect model and the cML-MA method which accounted for pleiotropy at related levels, served as the benchmark. Supplementary validation was conducted using several other methods, including the IVW-multiple random effect (MRE), Weighted-median, Weighted mode, Simple mode, MR-Egger, MR-RAPS, and MR-PRESSO.

Results: In the positive MR analysis, a potential causal relationship was found between Rikenellaceae id.967 and elevated risk of JIA within the family-level intestinal microbiota. Conversely, Family XI id.1936 was associated with a reduced risk of JIA. At the genus level, *Ruminococcus2* (id.11374), *Rikenellaceae RC9* gut group (id.11191), *Olsenella* (id.11822), and *Lachnospiraceae* UCG001 (id.11321) were associated with increased risk of JIA. Conversely, *Eubacterium rectale* group (id.14374), *Enterorhabdus* (id.820), *Dorea* (id.1997), and *Catenibacterium* (id.2153) were associated with a reduced risk of JIA. At the species level, *Ruminococcaceae bacterium* D16, Ru*minococcus torques, and Ruminococcus* bromii were correlated with an elevated risk of JIA, whereas *Sutterella wadsworthensis* was linked to a reduced risk of JIA. However, in the reverse MR analysis, only *Eisenbergiella* id.11304 and *Eubacterium hallii* group id.11338 were associated with the risk of developing JIA.

结论: This study investigated the bidirectional causal relationship between intestinal microflora and the risk of JIA. The finding are expected to improve our understanding of the specific mechanisms by which intestinal flora influence JIA. Furthermore, we reveal valuable insights to guide future development of prediction, diagnostic, and therapeutic strategies for JIA.

关键词: Juvenile idiopathic arthritis, Intestinal microbiota, Mendelian randomization

Efficacy and Safety of Bisphosphonates in Pediatric Glucocorticoid-Induced Osteoporosis: A Meta-Analysis and Pharmacovigilance Study

Xiaolin Xu[a,b,†], Luquan Wang[b,c,†], Yan Lia, Changqing Yangc, Dong Meib, Peng Guob, and Huawei Mao[a,d,e*]

a *Department of Immunity, Beijing Children's Hospital, National Center for Children's Health, Capital Medical University, Beijing, China*
b *Department of Pharmacy, Beijing Children's Hospital, National Center for Children's Health, Capital Medical University, Beijing, China*
c *School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China.*
d *Ministry of Education Key Laboratory of Major Diseases in Children*
e *Department of Nephrology and Rheumatology, Children's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Hospital of Beijing Children's Hospital, Xinjiang, China*

Background and aims: The prevalence of glucocorticoids (GCs) administration in pediatric populations has resulted in numerous adverse reactions, notably osteoporosis. Given its role in managing glucocorticoid-induced osteoporosis, the efficacy and safety of bisphosphonates hold considerable importance. This study conducted a meta-analysis by systematically reviewing and incorporating relevant literature on the efficacy and safety of bisphosphonates in the management of osteoporosis or bone infarction induced by GCs therapy in pediatric populations. Additionally, the analysis of potential adverse reactions was augmented by utilizing real-world data from the FAERS database. The primary objective of this study is to offer insights and guidance for the treatment of glucocorticoid induced osteoporosis in pediatric patients.

Methods: A meta-analysis was performed on existing literature to assess the efficacy and safety of bisphosphonates for managing glucocorticoid-induced osteoporosis. Additionally, a retrospective pharmacovigilance study was carried out to investigate adverse reactions and medication variations in pediatric patients with glucocorticoid-induced osteoporosis, using data from the FDA Adverse Event Reporting System (FAERS) database between Q1 2004 to Q4 2023.

Results: The meta-analysis incorporated a total of 14 articles encompassing 572 patients. The findings of this study indicate that bisphosphonate therapy is more effective in enhancing bone mineral density (BMD) and BMD Z-scores in children compared to the control group, albeit with a heightened risk of adverse reactions. Furthermore, there was no significant disparity observed between the impact of bisphosphonate treatment and control groups on fracture outcomes. Subsequently, in the ensuing Pharmacovigilance investigation, 668 instances of adverse reactions associated with bisphosphonates are analyzed. The findings indicated that the most prevalent adverse reactions, as evidenced by the highest number of positive signals were various examinations, musculoskeletal and connective tissue diseases, injuries, poisoning and operational complications, as well as systemic diseases and reactions at the administration site.

Conclusions: This study conducted a comprehensive analysis of the efficacy and safety of bisphosphonates in the treatment of osteoporosis or bone infarction caused by GCs use in pediatric patients, laying the groundwork for future research. Nevertheless, the constraints of retrospective studies highlight the need for additional investigation through prospective studies.

Clinical Features and Novel Pathogenic Variants of Patients With Behçet's Disease Like Trisomy 8

Xingru Ding[1], Xiao Han[1], Kangkang Yang[1], Yaoyao Shangguan[1], Yiwei Dong[1], Xiaohua Ye[1*], Wenjie Zheng[*]

1 *Department of Pediatric Rheumatology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China.*

Background and aims: Chromosomal abnormalities, such as Trisomy 8 (T8), and genetic mutations may contribute to the unique clinical phenotype of Behçet's Disease (BD). This study aims to characterize the clinical and genetic features of patients presenting with BD-like symptoms associated with T8 (T8-BD).

Methods: We analyzed a cohort of 8 patients with T8-BD and associated genetic variants, including 1 newly identified case from our center and 7 previously reported in the literature. Genetic sequencing and karyotyping analyses were conducted, with Sanger sequencing used to confirm variants. We assessed clinical phenotypes, genetic backgrounds, treatments, and clinical outcomes.

Results: Most patients were female (87.5%) and of East Asian descent (87.5%). The cohort consisted of pediatric and elderly patients, and comorbidities were prevalent (87.5%), including autoimmune lymphoproliferative syndrome (ALPS), myelodysplastic syndrome (MDS), atypical familial Mediterranean fever (FMF), primary myelofibrosis (PM), polycythemia vera (PV), and Townes-Brocks syndrome (TBS). Common clinical manifestations included oral aphthosis (100%), intestinal lesions (100%), fever (85.7%), decreased hemoglobin levels (85.7%), and elevated C-reactive protein (CRP) levels (85.7%). Genetic variants were identified in NRAS, JAK2, MEFV, PTPN11, and SALL1, comprising 5 missense variants and 1 nonsense mutation, with the de novo NRAS mutation newly reported in a pediatric patient. Treatment included glucocorticoids (GC) combined with disease-modifying anti-rheumatic drugs (DMARDs) in 33.3% of cases, DMARDs alone in 16.7%, and a combination of GC, DMARDs, and biologics in 50%, with most achieving remission, except for one fatal outcome.

Conclusions: Patients with T8-BD and genetic mutations exhibit distinct clinical features. Greater clinical awareness of autoinflammatory syndromes, combined with genetic and chromosomal analysis, is recommended in patients with BD-like symptoms who do not fully meet BD diagnostic criteria, especially those presenting with oral ulcers and systemic inflammation. This approach may enhance diagnostic precision and inform tailored treatment strategies.

Table 1: Clinical information of eight T8-BD patients combined with genetic mutations.

Patient	P1	P2	P3	P4	P5	P6	P7	P8
Mutation	NRAS G12A	JAK2 V617F	JAK2 V617F	MEFV E148Q	MEFV E148Q	PTPN11 E76A	PTPN11 G503E	SALL1 Nonsense
Nation	China	Japan	Japan	Japan	Japan	Japan	China	England
Gender	Female	Female	Female	male	Female	Female	Female	Female
Age (years)								
First visit	0.5	50	61	78	53	4	NA	14
BD diagnosis	10.5	53	68	78	54	4	5	14
T8 diagnosis	10.5	53	61	78	54	4	5	14
Variant identification	1.5	50	61	*78*	54	4	5	14
BD classification criteria								
JPN	BD suspected	Incomplete type	BD suspected	Incomplete type	BD suspected	Incomplete type	Incomplete type	Incomplete type
CHN	Incomplete type	Incomplete type	✗	✗	✗	Incomplete type	Incomplete type	Incomplete type
ICBD	/	✓	✗	✗	✗	/	/	/
PEDBD	✗	/	/	/	/	✗	✗	✓
ISG	✗	✗	✗	✗	✗	✓	✗	✗
Comorbidity	ALPS	Primary myelofibrosi	Polycythemia vena , trisomy 9	MDS, atypical FMF	MDS, atypical FMF	MDS	None	Townes-Brocks syndrome
Clinical features								
Oral aphthosis	✓	✓	NA	NA	✓	✓	✓	✓
Genital ulceration	✗	✗	✗	NA	NA	NA	✓	✓
Skin involvement	✗	✗	NA	✓	NA	✓	✗	NA
Ocular lesions	✗	✓	✗	NA	NA	✗	NA	NA
Neurological signs	✓	NA	NA	NA	NA	✗	NA	NA
Vascular signs	✗	NA	✓	✗	NA	✗	NA	✓
Pathergy test	NA	NA	NA	NA	✓	✓	NA	NA
Gastrointestinal lesions	Multiple ulcers in ileum, ascending colon, and transverse colon with atypical IBD manifestation	Multiple ulcers in the terminal ileum	Multiple ulcers in the ileocecal region	Erythema, erosions, and mild oedematous mucosa in the caecum and ascending colon	Multiple oval ulcers in the colon, terminal ileum, duodenum, and jejunum	Multiple round ulcerations in the transverse and ascending colon without cobblestone appearance	Intestinal ulcers	NA
Fever	✓	✓	✗	✓	✓	✓	✓	NA

Patient	P1	P2	P3	P4	P5	P6	P7	P8
Arthralgia	✓	NA	NA	✓	NA	NA	NA	NA
Hepato-splenomegaly	✓	✓	NA	NA	NA	NA	✓	NA
Laboratory tests								
Hb (g/dL)	9.00	6.80	10.50	9.70	9.10	11.30	NA	Normal
WBC (× 10^9/L)	25.89	15.43	20.56	6.70	1.49	10.02	18.00	Normal
IgG (mg/dl	1930.00	NA	NA	NA	NA	Normal	1980.00	NA
ESR (mm/h)	38.00	NA	NA	NA	NA	NA	54.00	NA
CRP (mg/dl)	12.95	NA	2.68	8.25	2.16	0.56	4.00	115.00
Medical regimen								
Hormone	Prednisolon	Prednisolon	Prednisolon	Prednisolon	Prednisolone, hydrocortisone	NA	NA	✗
DMARDs	Mycopheno-late mofetil, sirolimus, thalidomide	Ruxolitinib, azathioprine, antibiotic drugs, azacitidine	Aspirin, hydroxyurea, cilostazol	Colchicine	Colchicine, antibiotic drugs, γ globulin, azacitidine, benzydamine hydrochloride	NA	NA	Benzydamine hydrochloride, chlorhexidine digluconate
Biologics	Adalimumab	Infliximab	✗	Canakinumab	✗	NA	NA	✗
Clinical outcome	Remission	Remission	Remission	Death	Remission	Remission	NA	Remission
Reference	This paper	[50]	[51]	[52]	[45]	[53]	[38]	[54]

BD, Behçet's Disease; T8, trisomy 8; ALPS, autoimmune lymphoproliferative syndrome; MDS, myelodysplastic syndrome; FMF, Familial Mediterranean fever; IBD, inflammatory bowel disease; Hb, hemoglobin; WBC, white blood cell; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate; DMARDs, disease-modifying anti-rheumatic drugs.

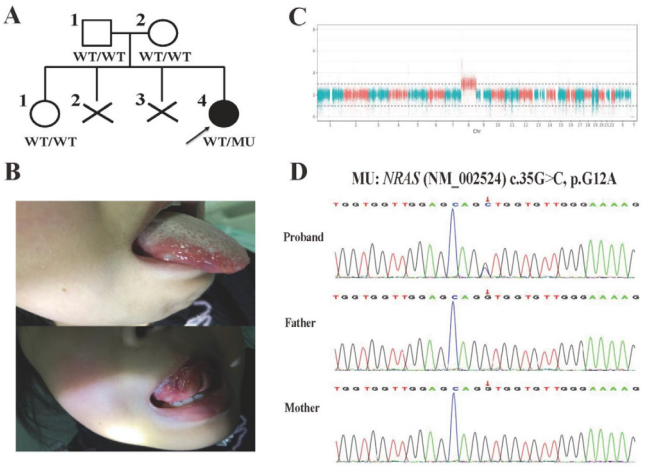


Figure 1. Clinical and genetic features of the reported case (P1) in this study.

(A) Pedigree of the affected family. Males and females were represented by squares and circles, respectively. The filled symbol denoted affected patients, and the arrow indicated the proband. WT, wild-type; MU, mutant.

(B) Oral aphthosis identified in P1. Multiple ulcers can be found on the lateral borders and the underside of the tongue.

(C) Results of chromosome abnormality detection in P1. Chromosome number map showed the haploid duplication of chromosome 8.

(D) DNA sequencing profiles of P1 and her parents. The parents' normal sequences are shown in the upper panel, while the DNA sequence of P1 is shown in the lower panel.

Severe phenotype of Wiskott-Aldrich syndrome due to C-terminal variant in *WAS*

Ryosuke Wakatsuki[1], Ryohei Watanabe[1], Dan Tomomasa[1], Madoka Nishimura[1], Satoshi Miyamoto[1], Akihiro Hoshino[2], Takahiro Kamiya[3], Takeshi Isoda[1], Michiko Kajiwara[4], Masatoshi Takagi[1], Hirokazu Kanegane[2]

1 *Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo, Japan*
2 *Department of Child Health and Development, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo, Japan*
3 *Clinical Research Center, Institute of Science Tokyo Hospital, Tokyo, Japan*
4 *Center for Transfusion Medicine and Cell Therapy, Institute of Science Tokyo Hospital, Tokyo, Japan.*

Introduction: Wiskott-Aldrich syndrome (WAS) is an X-linked inborn error of immunity with a broad clinical spectrum ranging from thrombocytopenia alone to combined immunodeficiency and autoimmune disease. Allogeneic hematopoietic cell transplantation is the only curative treatment. However, severe cases presenting with massive hepatosplenomegaly and daily platelet transfusion dependence are rare. Here we describe a case of severe WAS with intracranial hemorrhage despite daily platelet transfusions.

Case Presentation: The proband was a six-day-old male infant who presented with abdominal distention due to massive hepatosplenomegaly, and was associated with pancytopenia which was dependent on transfusion every two days. He was transferred to our hospital at 39 days of age due to low TREC levels on newborn screening and suspicion of severe combined immunodeficiency. Extensive genetic testing revealed a novel nonsense variant (c.1426A>T, p.Lys476*) at the C-terminus of the WAS gene. The patient had severe thrombocytopenia and platelet transfusion failure and was managed with platelet transfusions with a standard of >20,000/mL.

However, he was complicated by acute subdural hematoma with seizures. The patient underwent cord blood transplantation (CBT) at 4 months of age. The patient developed multiple episodes of sepsis and hemophagocytic lymphohistiocytosis requiring temporary intensive care unit management, but he achieved neutrophil engraftment 31 days after CBT. Platelet transfusion was discontinued 90 days after CBT. The patient was discharged without acute GVHD on day 108 post-CBT. His maternal cousin also had WAS and died of intracranial hemorrhage in utero.

Results: A similar severe case of WAS that presented with massive hepatosplenomegaly and was refractory to transfusion has been reported previously (PMID: 35777621). Interestingly, this patient was found to have a similar C-terminal variant in WAS.

Conclusions: These findings suggest the possibility of a variant-specific clinical picture of WAS.

Recurrent perianal ulceration in siblings with CD40LG mutation: case report

Intan Juliana Abd Hamid[1], Fazila Arifin[2], Pazlida Pauzi[2], Noorzaitun Ariffin[2], Zarina Thasneem Zainudeen[1], Fahisham Taib[3]

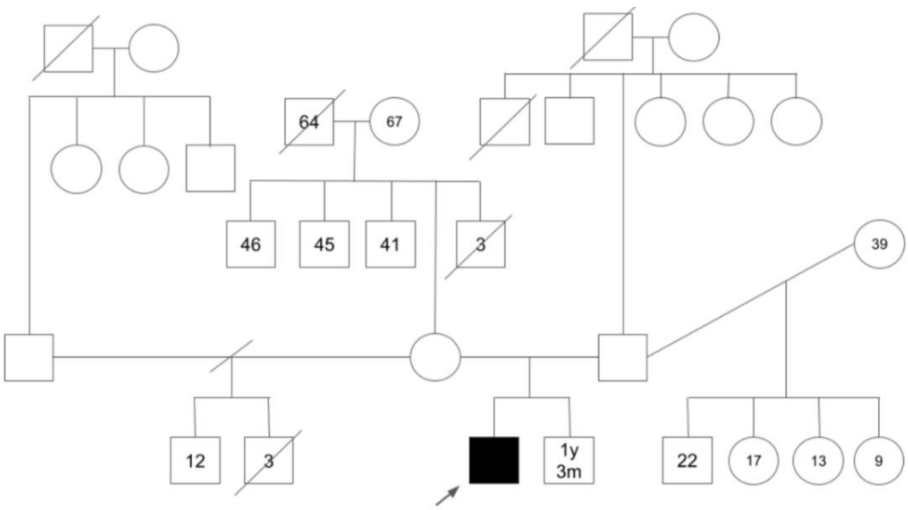
1 *Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Institut Perubatan dan Pergigian Termaju, Universiti Sains Malaysia, Bertam, Pulau Pinang, Malaysia*
2 *Paediatric Department, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia*
3 *Paediatric Department, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia*

Introduction: CD40LG defect affects the interaction between T cells and B cells, resulting in defective class-switch recombination and impaired production of IgG, IgA, and IgE with normal or elevated levels of IgM.

Case Presentation: We report cases of 2 male siblings who presented with recurrent peri-anal abscess and pneumonias. Child 1, aged 3 years, had recurrent Pseudomonas aeruginosa perianal abscess requiring multiple incision and drainage procedures and failure to thrive. Child 2 presented at the age of 1 year old with recurrent pneumonia requiring intravenous antibiotic treatment. Their mother had history of severe perineal abscess with prolonged hospitalization in 2018. She also mentioned another son from previous marriage who had invasive Pneumococcal infection, recurrent abscesses and died at the age of 3 years 9-month due to septicaemic shock secondary to bacterial laryngopharyngitis. Initial investigations in both siblings showed lymphopenia, hypogammaglobulinemia and borderline DHR test. Whole exome sequencing test revealed hemizygous mutation in CD40LG NM_000074.3:c.415C>T (NP_000065.1:p.Gln139Ter) in both siblings. They received intravenous immunoglobulin replacement therapy and currently awaiting parent's decision for allogeneic hematopoietic stem cell transplantation.

Discussion: The clinical findings of recurrent peri-anal abscesses, pneumonia, failure to thrive, and laboratory findings of lymphopenia and hypogammaglobulinemia pointed towards an underlying immunodeficiency. The CD40LG defect predisposes patients to severe, recurrent bacterial infections, particularly with encapsulated organisms such as *Pseudomonas aeruginosa*. In this case, the mother's history of severe perineal abscess and the death of a half-sibling with similar presentations strongly suggested an inherited pattern of immunodeficiency.

Conclusions: This case illustrates the clinical and genetic spectrum of CD40 Ligand defect and emphasizes the importance of a detailed family history, prompt genetic testing, and timely initiation of supportive therapies in optimizing patient outcomes.



T-cell Deficiency In a Wolf-Hirschhorn Syndrome Baby, Presenting With HSV Encephalitis

Florence CHOI[1], Kai Ning CHEONG[1], Claudia Tin Yan SHEK[2], Clara Yan Shi CHEUNG[2], Jaime SR DUQUE[1,3,4], Yu Lung LAU[1,3,4]

1 *Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong*
2 *Department of Paediatrics and Adolescent Medicine, Kwong Wah Hospital, Hong Kong*
3 *Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong*
4 *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong.*

Introduction: Wolf-Hirschhorn Syndrome is a genetic disorder due to partial deletion of chromosome 4p16.3. It is characterized by facial abnormalities, cardiac malformations, failure to thrive and developmental delay. Immunodeficiency is also one of the features, but is often overlooked and has only been reported in a few cases.

Case Presentation: We report an 8-month-old baby with genetically confirmed Wolf-Hirschhorn Syndrome, who presented with status epilepticus, requiring intubation and multiple anti-epileptics. Lumbar puncture revealed high opening pressure of 44cmH2O and cerebrospinal fluid (CSF) PCR confirmed Herpes Simplex Virus (HSV) 1 encephalitis. She was managed with a 3-week course of intravenous Acyclovir and was started on oral Valacyclovir as prophylaxis. She had recurrent history of infections during her neonatal period, which required

intensive care, hence prompted further immunological workup. Her serial lymphocyte subsets showed persistently low T cells with a rapid downward trend over a course of three months, borderline low B cells and normal NK cells. Her immunoglobulin pattern was in low normal range.

Discussion: Immunodeficiency is one of the least reported features of Wolf-Hirschhorn Syndrome. There have been few case reports highlighting a variety of associated immunodeficiencies, including common variable immunodeficiency (CVID). In a baby with such a severe presentation of HSV encephalitis, the finding of HSV in CSF may indicate a perinatal latent HSV infection, which may require long-term prophylaxis, especially in the context of T-cell deficiency.

Conclusions: A thorough baseline immunological evaluation is essential in Wolf-Hirschhorn Syndrome as it can be associated with a wide range of immunodeficiencies. Long-term monitoring is also necessary to consider the need for anti-microbial prophylaxis or intravenous immunoglobulin.

The first case of MHC class II deficiency treated with unrelated mismatched cord blood transplantation in Vietnam

Phuong Anh Ha,, Le Nguyen-Ngoc-Quynh, Anh Nguyen-Thi-Van

Vietnam National Children's Hospital

Introduction: MHC class II deficiency is a rare primary immunodeficiency disorder (CID) inherited in an autosomal recessive manner. The disease's immunologic hallmark is the absence of both constitutive and inducible expression of MHC class II molecules across all cell types. The only potential cure for this condition is allogeneic stem cell transplantation.

Case Presentation: We report the case of a fourteen-month-old boy who presented with persistent diarrhea and intermittent hypertransaminasemia. Laboratory investigations showed low CD4+ T cell counts, inversion of the CD4/CD8 ratio, and hypogammaglobulinemia. Flow cytometry revealed the absence or limited expression of HLA-DR on B cells and monocytes. Genetic analysis identified two variants in the CIITA gene: c.922C>T (p.Arg308Ter) and c.2889-1G>T. The patient was started on prophylactic antibiotics and regular intravenous immunoglobulin replacement therapy. He subsequently received a mismatched unrelated cord blood transplant following a conditioning regimen that included anti-thymocyte globulin, busulfan, fludarabine, and cyclophosphamide. Unfortunately, the patient died of veno-occlusive disease (VOD) and septic shock on day 16 post-transplant.

Conclusions: A review of the literature indicates that cord blood may serve as an alternative source of stem cells for children with MHC class II deficiency who lack a suitable donor. Close evaluation and management of infections in transplant patients are essential for improving outcomes.

A Heavy Heart: Delayed Diagnosis of X-linked Agammaglobulinaemia with Porcelain Aorta

Mohd Azri Zainal Abidin[1,2], Shahleni Paramasivam[2], Nura Hulwana Bukhari[1,2], Che Syahida Silmi Che Abdul Rahman[1,2], Syazwani Rahim[1,2], Khairoon Nisa Mohamed Nashrudin[1,2], Intan Hakimah Ismail[1,2]

1 *Advanced Medical Research in Allergy and Clinical Immunology (AMRAC), Clinical Immunology Unit, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, MALAYSIA*
2 *Clinical Immunology Unit, Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, MALAYSIA.*
3 *Rheumatology Unit, Department of Medicine, Hospital Putrajaya, Putrjaya, Ministry of Health Malaysia, MALAYSIA*

Introduction: X-linked agammaglobulinaemia (XLA) is a rare genetic immune disorder characterised by recurrent infections and severely low antibody levels due to the absence of functional B cells. Early recognition is essential to prevent serious complications. We present a case of a rare vascular complication, porcelain aorta, in a patient with a delayed diagnosis of XLA.

Case Presentation: A 24-year-old man with a history of recurrent respiratory infections since early childhood, persistent arthritis since adolescence, and a significant family history of immune disorders was referred for evaluation. His maternal cousins had been diagnosed with XLA, and his brother passed away from likely immune-related complications, suggesting a genetic preposition. The patient's condition went undiagnosed until he developed severe lung infections in adulthood, which led to vascular imaging revealing extensive aortic calcification, diagnosed as porcelain aorta with aneurysmal dilatation. Flow cytometry revealed the complete absence of B cells and critically low immunoglobulin levels, confirming the diagnosis of XLA.

Discussion: This case highlights the preventable nature of delayed diagnosis, which can lead to rare and life -threatening complications like porcelain aorta. Chronic infections and undiagnosed inflammation likely contributed to development of vascular changes observed. The family history of immune disorders underscores the importance of recognising familial patterns in early diagnosis. Prompt intervention with immunoglobulin therapy and vigilant surveillance could have potentially prevented the vascular complications in this patient.

Conclusions: Timely diagnosis of XLA is critical to prevent severe complications and improve quality of life. This case highlights the importance of family screening in individuals with recurrent infections and a family history of immune disorders. It's a responsibility shared by all to identify potential cases early and initiate treatment, as early treatment with immunoglobulin replacement and surveillance for immune dysregulation can significantly reduce the burden of illness and prevent complications like porcelain aorta.

Immunological profiles of the patient

Investigation	Results	Normal Range
Inflammatory markers		
CRP (mg/L)	64	< 5
ESR (mm/Hr)	7	<10
Autoimmune workup		
ANA	Negative	
Immunoglobulins (g/L)		
IgG	<0.16	4.3-13.4
IgM	<0.020	0.2-1.8
IgA	<0.101	0.19-2.2
IgE (kU/L)	N/A	<100
Antibody responses to vaccine antigens		
Tetanus toxoid, IgG	Pending results	
Pneumococcal polysaccharide, IgG	Pending results	

Differential Responses to Sirolimus and Leniolisib in an APDS Patient: Clinical and Transcriptomic Insights

Jaime S Rosa Duque[1], Xinxin Chen[1], Issan Yee San Tam[1], Yu Lung Lau[1]

1 *Dept. of Paediatrics and Adolescent Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China.*

Introduction: Activated PI3Kδ Syndrome (APDS) is a rare primary immunodeficiency caused by heterozygous gain-of-function mutations in the PIK3CD gene, leading to hyperactivation of the PI3K-AKT-mTOR signaling pathway. This results in immune dysregulation, including lymphoproliferation, recurrent infections, autoimmunity, and hypogammaglobulinemia. Here, we describe a patient with a PIK3CD mutation (NM_005026, c.3061G>A) who presented with severe clinical manifestations and was treated with sirolimus followed by leniolisib. We further explore the molecular mechanisms underlying the differential treatment responses using transcriptomic analysis.

Case Presentation: The patient, a child with a heterozygous *PIK3CD* mutation, presented with hemolytic anemia, generalized lymphadenopathy, hepatosplenomegaly, recurrent EBV, CMV, and HSV infections, C. *difficile* colitis, and bronchiectasis. Immunophenotyping revealed T and NK cell lymphopenia, low naïve T cells, high transitional B cells, low switched memory B cells, and elevated IgG and IgM. Initial treatment with sirolimus was effective in reducing lymphadenopathy and controlling infections; however, after 8 years, the patient experienced progressive lymphadenopathy and frequent infections. Transitioning to leniolisib resulted in significant clinical improvement, including increased naïve T and switched memory B cells, normalization of IgM, reduced transitional B cells, weight gain, reduced lymphadenopathy, fewer infections, and improved academic performance.

Bulk RNA sequencing was performed on five blood samples collected during different treatment stages, with healthy controls as the comparator. GSEA showed upregulation of immunoglobulin production, B cell activation pathways, and cell-mediated immunity during sirolimus treatment and washout. These pathways were progressively downregulated following leniolisib treatment, normalizing after 17 weeks. Genes involved in B cell activation and PI3K/AKT signaling *(PTEN, GAB2, ERBB2, PIK3C2B, BTN2A2, BANK1, MKRN2)* were significantly downregulated with leniolisib.

Discussion: This case highlights the differential effects of sirolimus and leniolisib in APDS. Sirolimus, an mTORC1 inhibitor, initially controlled lymphoproliferation and infections but lost efficacy over time, possibly due to incomplete targeting of the underlying PI3Kδ hyperactivation. In contrast, leniolisib, a selective PI3Kδ inhibitor, directly addressed the root cause of APDS. Transcriptomic analysis demonstrated that leniolisib effectively normalized immune dysregulation, including pathways related to B cell activation, immunoglobulin production, and the PI3K-AKT-mTOR signaling cascade. These findings underscore the importance of targeted therapy in APDS and provide insights into the molecular mechanisms of disease and treatment response.

Conclusions: Leniolisib demonstrated superior efficacy compared to sirolimus in this APDS patient, leading to clinical and immunologic improvement and restoration of immune homeostasis. Bulk RNA sequencing revealed that leniolisib downregulated key immune pathways dysregulated in APDS, highlighting its potential as a targeted therapeutic option. This case emphasizes the need for precision medicine approaches in managing rare immunodeficiencies like APDS.

BCGitis and atypical salmonella Infection in four patients with mendelian susceptibility to mycobacterial disease: case reports

Jing Yin, Xiaoxue Liu, Chongwei Li

Department of Rheumatology & Immunology, Tianjin Children's Hospital, Tianjin, China

Introduction: Mendelian susceptibility to mycobacterial disease (MSMD) is a rare group of congenital conditions characterized by selective susceptibility to poorly virulent intracellular bacteria, such as the Bacille Calmette-Guérin (BCG), the live attenuated vaccine form of Mycobacterium bovis, non-tuberculous environmental mycobacteria, and Selmonella. Local or disseminated BCG infection is usually the primary manifestation. Salmonellosis is more common in patients with IL-12Rβ1 deficiency.

Case Presentation: Case Presentation: Here we present four patients with MSMD from three different families with IL-12Rβ1 or TYK2 mutations. They all suffered from BCG disease .The first patient(P1) was IL-12Rβ1 deficiency who had recurrent hypereosinophilia and complicated with eosinophilic hyperplastic lymphoid granuloma, a chronic inflammatory disease and surprisingly responded well to TMP-SMX treatment. P2 presented with Salmonella cervical lymphadenitis . P3 and P4 were twins and BCG disease was the only manifestion. All patients responded well to prolonged anti-infectious therapy.

Discussion: Sufficient anti-infective and prophylactic treatments in MSMD are crucial. Additionally, some patients develop autoimmune or inflammatory diseases that are closely associated with the infection.

Conclusions: MSMD has unique clinical features and is susceptible to poorly virulent intracellular bacteria. The clinical manifestations and response to treatment for the four patients aided in the early identification and treatment options for MSMD.

First Case of STAT3 Mutation-Associated Hyper-IgE Syndrome in an Infant from Central Vietnam: Diagnosis and Management

Kiem Hao Tran[1], Thinh Tran Cong Quoc[1], Chi Nguyen Thi Diem[1], Son Bui Binh Bao[1,2], Phu Nguyen Manh[1], Chi Phan Thi Bich[1], Quan Ho Dang[1], Tho Nguyen Huu[1], Linh Hoang Mai[1], Trinh Nguyen Thi Thao[1], Nom Nguyen[1], Loc Pham Kieu[1], Huu Son Nguyen[1]

1 *Pediatric Center, Hue Central Hospital, Hue City, Vietnam*
2 *Pediatric Department, University of Medicine and Pharmacy, Hue University, Hue City, Vietnam*

Introduction: Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency characterized by significantly elevated IgE levels (>2000 IU/mL), eczema, and recurrent infections. This case report presents the first documented instance of STAT3 mutation-associated HIES in an infant from Central Vietnam, offering key insights into its diagnosis and management.

Case Presentation: A 24-day-old male infant was admitted with generalized vesicular rashes and systemic symptoms. Born at full term without complications, the infant developed a facial rash nine days after birth, which progressively spread. Initial treatment for *Staphylococcus aureus* at a district hospital was ineffective, prompting referral to a specialized center. On admission, the infant exhibited widespread vesiculopustular lesions, deep ulcerations, fever, lethargy, and poor feeding. Laboratory tests revealed elevated IgE (>2500 IU/mL) and low IgG (<2.11 g/L). The infant was treated with Meropenem and Linezolid, adjusted based on antibiotic susceptibility, which identified *Acinetobacter baumannii* and *Klebsiella pneumoniae*. The NIH scoring system indicated a high probability of AD-HIES with a score of 43. Genetic testing confirmed a heterozygous de novo mutation in the STAT3 gene (c.1859C>G, p.Thr620Ser). After nearly 50 days in the NICU and six skin grafts for extensive deep ulcerative lesions, the patient was discharged after four months.

Discussion: Diagnosing HIES can be challenging due to its overlap with other immunodeficiencies. In this case, he exhibited extremely elevated IgE and eosinophil levels, surpassing typical thresholds, along with low IgG levels. Early manifestations, including severe skin infections and systemic symptoms like fever and altered consciousness, initially resembled neonatal eczema or sepsis. Genetic testing confirmed the STAT3 mutation, finalizing the diagnosis of AD-HIES.

Conclusions: This case underscores the importance of clinical evaluation and genetic testing in diagnosing rare immunodeficiencies. It also highlights the challenges in managing HIES in resource-limited settings and the need for early detection to improve patient outcomes

Figure 1. Patient's Skin Lesions at Admission
Multiple vesicles and pustules, 1-2 mm in size, were observed on an erythematous base across the chest, abdomen, back, and arms, along with extensive deep ulcerative lesions on the back and head.

STAT3 基因功能获得性突变所致免疫失调性疾病一例

张博慧，刘思娴，刘奉琴*

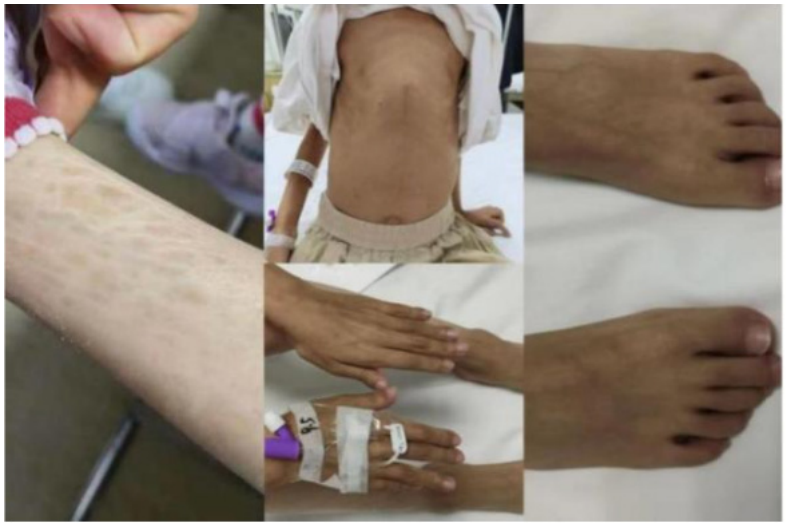
山东第一医科大学附属省立医院小儿呼吸科，济南 250021

前言： 目的 对STAT3基因突变所致免疫失调性疾病的发病机制、临床及实验室检查特点和治疗选择进行归纳总结。方法 对2024年9月就诊于山东第一医科大学附属省立医院小儿呼吸科的1例STAT3基因功能获得性突变所致免疫失调性疾病患儿临床特征、辅助检查、基因测序结果和治疗过程进行分析总结。

病例介绍： 患儿，女，7岁8月，因“反复皮疹7年余，反复血小板减少4年半，反复发热1月余”入院，患儿自生后全身反复干性湿疹，生长发育落后，查体肝脾和淋巴结肿大，杵状指（趾）。自幼多次血常规示贫血和血小板减少：血红蛋白（88-139）g/L，血小板（4-174）×109/L；入院影像示双肺弥漫性间质性病变，细胞免疫功能：CD4+%：18.1%，CD8+%：57.42%，CD4+/CD8+：0.32；血清Ig：IgA：127.6mg/dL，IgM：114.4mg/dL，IgG：768mg/dL，IgE：＜17.5IU/ml；骨髓常规：巨核系增生明显活跃伴产板障碍；全外显子基因检查示STAT3：c.519T>G(P.T716M) 突变，诊断为STAT3基因获得性突变致免疫失调性疾病。患儿接受激素及JAK抑制剂治疗后病情有所好转。

讨论： 此类患儿常有反复感染，实验室检查可见免疫学异常，还可有肝脾、淋巴结肿大、自身免疫性血液病、身材矮小、甲状腺功能减退症等表现

结论： 对于反复呼吸道感染伴多系统损害患儿，要考虑到IEI，早诊断、合理治疗可改善患儿生活质量和预后。



The imbroglio of immune thrombocytopenia in a challenging case of chronic granulomatous disease

Aaqib Zaffar Banday[1], Aneek Farooq[1], Altaf Hussain Kambay[1], Syed Tariq Ahmad Bukhari[1]

1 *Government Medical College, Srinagar, Kashmir, India*

Introduction: Immune thrombocytopenia (ITP) is a rare occurrence in chronic granulomatous disease (CGD). Various therapeutic options including ciclosporin, romiplastim, intravenous immunoglobulin (IVIG), and rituximab have been employed successfully previously (individual case descriptions). Herein, we describe a child with CGD and ITP who responded poorly to most of the above-mentioned therapies.

Case Presentation: A ten-month-old boy, born to consanguineous parents, presented to us with growth failure and bleeding diathesis (epistaxis, gum bleeding, petechial skin rash, and blood in stools). His previous medical history was very significant and is summarized in **Figure 1**. At presentation, we noted thrombocytopenia (platelets: 28×109/L [normal 150–400×109/L] with large/giant platelets on peripheral smear, previously normal platelet counts), hypergammaglobulinemia, and megakaryocyte hyperplasia on bone marrow examination. Autosomal recessive CGD (pathogenic NCF2 gene variants) with ITP (and other organ-system autoimmunity) was diagnosed. Subsequent therapies with high-dose IVIG, steroids, romiplostim, and rituximab also did not result in the resolution of thrombocytopenia. Post-rituximab, he developed hypogammaglobulinemia requiring IVIG replacement therapy. Finally, he developed severe Klebsiella pneumoniae infection and succumbed to his illness **(Figure 1)**.

Discussion: Our case highlights numerous challenges during the management of ITP in a challenging case of CGD with multiorgan immunity. From a socioeconomic perspective, the family lacked healthcare insurance and the patient's father was the sole breadwinner. Most of the testing and therapeutics were arranged through philanthropic and hospital support. We couldn't employ cyclosporine A and/or sirolimus (for management of ITP) or get to transplant due to logistic/financial constraints and severe disease course. The patient's disease course transitioned from hyper- to hypo-gammaglobulinemia post-rituximab. All these factors resulted in severe caregiver burnout with an adverse impact on family/other siblings (health, education, etc.)

Conclusions: In resource-limited regions, therapy of ITP in CGD requires careful consideration of various socioeconomic factors. Sirolimus or ciclosporin may be employed preferentially before rituximab in such settings.

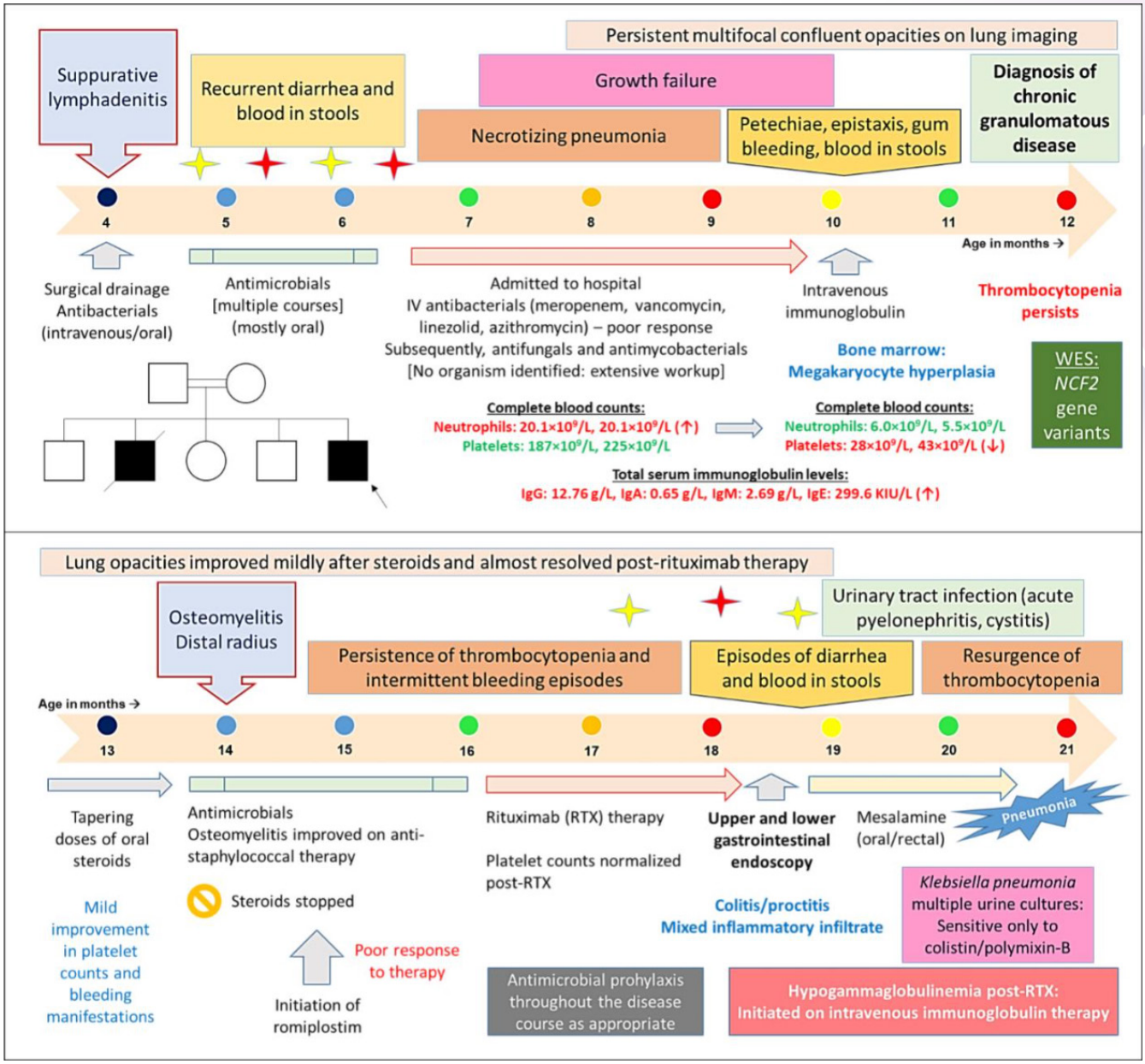


Figure 1: Disease course in our patient with CGD

A Case Study of a Baby Girl with Chronic Granulomatous Disease Due to NCF1 Mutation: Treatment Outcome with Pioglitazone

Tran Thi Thanh Tam MD, MSc, Phan Nguyen Lien Anh MD, PhD

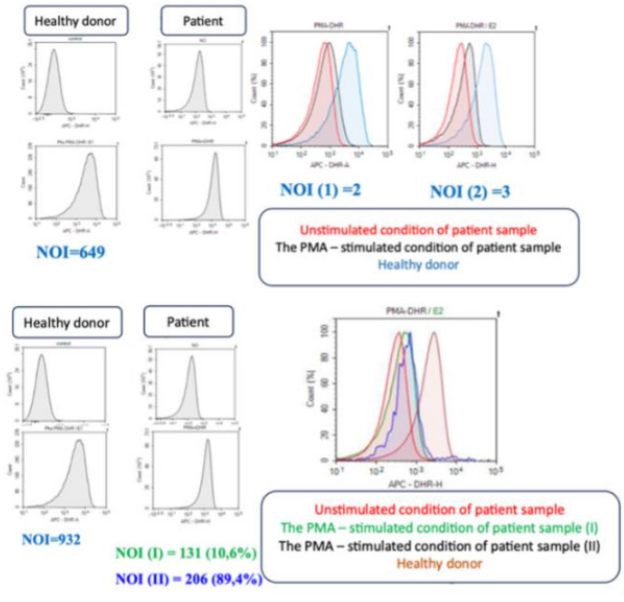
Children's Hospital No.1, Ho Chi Minh City, Vietnam

Introduction: This research outlines the clinical manifestations, laboratory findings, and treatment of a 4-year-old girl diagnosed with homozygous NCF1 mutation

Case Presentation: The patient is the second child in a non-consanguineous family, with one healthy brother. She did not experience any complications following BCG vaccination at birth. The girl has been hospitalized multiple times due to severe necrotizing pneumonia, lymphadenitis, and sepsis, requiring broad-spectrum antibiotic treatment. At six months of age, she began antituberculosis therapy, which resulted in a partial response. Prophylactic treatment with fluconazole was planned once she stopped all other treatments. A CT scan revealed poly-necrotizing pneumonia on the right side, while complete blood count (CBC) and immunoglobulin levels (IgG, IgA, IgM) were within normal ranges. B cell, T cell, NK cell counts, and T-cell receptor excision circles (TRECs) were also normal for her age. Chronic granulomatous disease (CGD) was diagnosed through a dihydrorhodamine (DHR) test, which showed an absent right shift upon stimulation with phorbol myristate acetate (PMA); however, whole exome sequencing (WES) did not reveal any pathogenic mutations. PCR-restriction fragment length polymorphism (RFLP) analysis confirmed a homozygous mutation in the NCF1 gene, with the analysis conducted at the Faculty of Medicine, Chulalongkorn University. We initiated treatment with pioglitazone at a dose of 3 mg/kg/day. Pioglitazone is a peroxisome proliferator-activated receptor gamma agonist that is approved for the treatment of type 2 diabetes and has been reported to induce mitochondrial reactive oxygen species (ROS) production in mouse models with X-CGD. After two months of treatment, we observed an increase in DHR fluorescence in two granulocyte populations upon PMA stimulation. The patient demonstrated significant improvement in her clinical condition and responded well to the initial antibiotics, resulting in shorter hospitalization times.

Discussion: What other techniques can be utilized to identify mutations in the NCF1 gene when RFLP identifies a mutation? What has been the experience with pioglitazone treatment in CGD—should it be used for long-term or short-term management during infections, or for prophylaxis?

Conclusions: Pioglitazone was effective in treating our patients with CGD and in outlining its role in the therapeutic options for these individuals.



DHR results when started and day +61 use pioglitazone for patient.

Ecthyma gangrenosum in a previously healthy boy disclosing an underlying cyclic neutropenia

Xiaoqi Wu, Xiaoxue Liu, Xiaojie Li, Yang Cao, Jijun Ma, Chongwei Li*

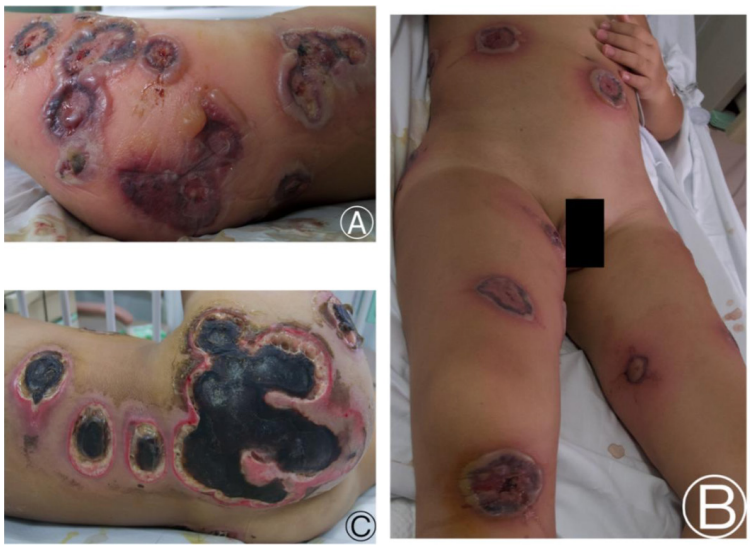
Department of Rheumatology & Clinical Immunology ,Tianjin Children's Hospital, Tianjin, China

Introduction: Ecthyma gangrenosum (EG) is pathognomonic of pseudomonas aeruginosa septicemia and usually seen in immunocompromised patients, particularly those with malignancy, neutropenia, or primary immunodeficiency.

Case Presentation: A 9-year-old boy with no significant medical history presented with a 4-day history of painful skin lesions and fever after skin being cut by a seashell while swimming two days before the onset of symptoms. Physical examination revealed extensive hemorrhagic necrosis surrounded by pustules over the gluteal areas, lower limbs, and abdominal wall (Panel A, B). Laboratory tests were WBC 35.14×10^9/L with 81% neutrophils, CRP 211.6 mg/L, and PCT 14.43 ng/ml. Both blood and blister fluid *grew pseudomonas aeruginosa* and a diagnosis of EG was made. Meropenem and IVIG were administered, leading to resolution of fever and retraction of skin ulcers. On Day 10, thick eschar crusted with well circumscribed red margins at all the original sites (Panel C). He underwent a series of operations of debridement and skin grafting. Neutropenia (ANC $0.66\text{-}1.35\times10^9$/L) along with fever was noted from Day 27 to 33 between operations. Genetic testing identified a pathogenic *ELANE* gene mutation (c.659G>A), disclosing the underlying cyclic neutropenia (CyN). The boy was discharged after two-month hospitalization without functional disabilities. His mother declined granulocyte-colony stimulating factor treatment. He was being followed up and remained uneventful.

Discussion: CyN is a rare autosomal dominant hematological disorder caused by mutations in *ELANE* gene. Patients often have an ANC$<0.2\times10^9$/L for three to five days at approximately three-week intervals with fever. Infections are common during neutropenic periods, most of which are mild, but life-threatening infections can occur. It was reasonable that the beginning of EG fell in the neutropenic period which had ended by admission.

Conclusions: EG should be quickly recognized for timely empiric antibiotics treatment. A comprehensive evaluation for underlying conditions, like CyN, is also needed.



Complex Inflammatory Bowel Disease in a Child with Leukocyte Adhesion Deficiency Type 1: A Case Report

Phan Nguyen Lien Anh

Children's Hospital 1, Ho Chi Minh City, Vietnam

Introduction: Leukocyte adhesion deficiency type 1 (LAD1) is a rare autosomal recessive immunodeficiency caused by mutations in the ITGB2 gene, leading to defective neutrophil migration. LAD1 presents with recurrent bacterial infections, poor wound healing, and severe inflammatory disorders, including early-onset inflammatory bowel disease (IBD). This case highlights the diagnostic and therapeutic challenges in managing IBD associated with LAD1.

Case Presentation: A 5-year-old girl presented with a history of neonatal umbilical infection, followed by necrotizing enterocolitis poorly responsive to treatment. She subsequently developed recurrent gingivitis, periodontitis, cellulitis, and refractory bowel inflammation. Family history revealed an older sister who died at 4 months from prolonged enteritis. Immunological evaluation showed reduced CD18 expression on neutrophils, and WES confirmed homozygous LAD1 mutation.

Over time, the patient experienced worsening bowel symptoms, unresponsive to antibiotics, with elevated fecal calprotectin and MRI findings of diffuse bowel wall thickening. Endoscopic biopsy confirmed Crohn's disease-like histopathology. Despite dietary changes and anti-inflammatory treatments, disease progression led to small bowel perforation, requiring emergency surgery and stoma creation. Postoperative complications included severe wound infection, non-healing stoma, and septic shock, resulting in death. The patient was counseled for hematopoietic stem cell transplantation (HSCT), but no HLA-compatible donor was identified.

Discussion: This case underscores the dual role of ITGB2 mutations in LAD1 and early-onset monogenic IBD. Management is particularly challenging due to overlapping immunodeficiency and inflammation. HSCT is the definitive treatment for LAD1 but requires timely access to a suitable donor.

Conclusions: Early recognition of LAD1 and its association with monogenic IBD is crucial for timely interventions. In cases with severe manifestations, expedited HSCT should be pursued to reduce mortality risk. This case highlights the importance of family history and genetic testing in diagnosing rare syndromes.

Eleven Cases of Autoinflammatory Recurrent Fevers

ShuLan, WuXiaolin, LiXiaohui, GongYi, LiuDonglei, ZhuSongbai, GuiLin, ZhengRonghao

Division of Immunology, Rheumatology and Nephrology, Pediatric department, HuBei Maternal and Children's Hospital

Introduction: Eight cases of PFAPA syndrome and three cases of FMF are illustrated to arouse the awareness and deepen the understanding of these diseases.

Case Presentation: There were 6 boys and 2 girls of PFAPA syndrome. Their ages at onset were all below 5 years with the exception of one boy whose onset age was 9-year-old. All the patients had periodic fever followed by an asymptomatic intercurrent period, with the self-limiting episodes of febrile illness lasting 2 to 5 days. Exudative pharyngitis was presented in 8 cases. Single-dose corticosteroid administration was adopted as the main treatment.

The 3 cases of FMF included two boys and a girl. They were typically characterized by recurrent episodes of fever. The two boys represented with extra symptoms of transient arthralgia and erysipelas-like erythema. The onset ages of the two boys were 6 months and 13-year-old respectively. For the younger boy, compound heterozygous mutations of MEFV were found respectively from his father and mother. Treatment of colchicine controlled his flares well. However, the older boy refused to take any medicine but he also did well in the follow-ups. There was a MEFV variant in this boy, and his father had a pair of homozygous alle without any symptom. The girl was suspected as PFAPA at first, since she manifested with pharyngitis, but intermittent steroid therapy was proven poor response. We found a MEFV variant in this girl too, and her mother had a pair of homozygous alle without any symptom. Thalidomide was used and she did well since then.

Discussion: Before the diagnosis of PFAPA or FMF, all the patients had received multiple courses of antimicrobials, which are actually unnecessary.

Conclusions: it is crucial to enhance the recognition of autoinflammatory recurrent fevers, which will reduce undesirable antimicrobial use in such children.

IL12RB1 with ALPS-like phenotype

Vaishnavi V Iyengar[1], Akshaya Chougule[1], Prasad Taur[1], Vijaya Gowri[1] , Mukesh Desai[1]

1 *Department of Immunology, Bai Jerbai Wadia Hospital for Children, Parel.*

Introduction: IL12RB1 is one of the mendelian susceptibility disorders. Here we present a child with homozygous IL12RB1 deficiency presenting with lymphoproliferation and autoimmune cytopenia.

Case Presentation: A 5-year-old male born of consanguineous marriage presented with persistent cervical lymphadenopathy, hepatosplenomegaly and fever. He had a previous sibling death with suspected disseminated tuberculosis. He was treated with antitubercular therapy in past for left axillary lymphadenopathy at 6 months of age. At 1.5 years fever with cervical lymphadenopathy was treated with ATT. From 2 years of age, he additionally developed recurrent lower limb palpable purpura rash responding to short courses of steroids. Skin biopsy revealed leucocytoclastic vasculitis. In view of past history with possible BCG adenitis and a sibling death with disseminated Tb, MSMD was suspected clinically and exome sequencing was undertaken. It showed a homozygous IL12RB1 defect. Current investigation also revealed normocytic normochromic Coombs positive anemia with Hb 7g/dl. In view of persistent lymphoproliferation with AIHA ALPS-like illness was considered. Literature suggested patients with IL12RB1 defect can have apoptosis error similar to ALPS. DNT estimation 2% with normal CD4 and CD8 ratio. He was started on 2mg/m2 of sirolimus with levels 10ng/ml. This normalized hemoglobin with DCT turning negative and reduction in lymph node sizes with disappearance of the palpable spleen.

Conclusions: IL12RB1 may lead to different clinical phenotypes, including ALPS-like disease and Mendelian susceptibility to mycobacterial diseases. Knowledge of the genetic defect underlying an ALPS-like phenotype helps to decide choice of treatment options.

ADA1 缺陷：单基因狼疮的新遗传基因

张松

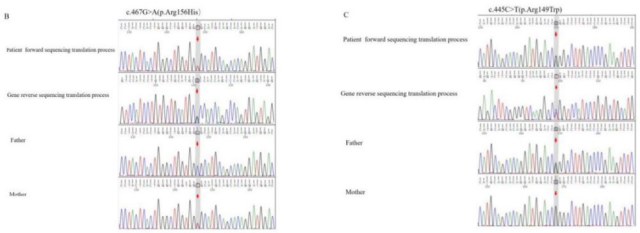
广州医科大学附属广州市妇女儿童医疗中心

前言： 青少年系统性红斑狼疮 (JSLE) 被认为是一种多基因疾病。严重形式的系统性红斑狼疮可能是由单个基因的改变引起的（因此称为单基因系统性红斑狼疮），并且通常在儿童期表现出来。广泛而言，这些改变影响补体系统、细胞外和细胞内核酸传感和处理、RAS 信号传导和代谢途径。我们报告了一名患有与 JSLE 相关的新型有害 ADA1 突变的患者，该患者对血浆和红细胞替代疗法表现出有效的反应

病例介绍： 该患者是一名健康父母所生的女孩，自2.5岁起7个多月以来反复出现低血红蛋白和血小板。 6 个月大时，她频繁出现呼吸道感染，2.5 年后，败血症和肺部感染反复发作。三岁时，她双下肢反复出现皮疹，发热时更为明显，退烧后逐渐消退。三系血细胞系均明显下降，主要是血红蛋白浓度为 20 g/L，血小板浓度为 20 × 10^9/L。尽管通过感染控制和治疗，显示轻微改善，骨髓活检显示活跃增生伴巨核细胞减少。六岁时，她在过去三个月开始出现发烧、呼吸困难和咳嗽的症状。胸部CT提示肺炎，白细胞2.3×10^9/L，血红蛋白75g/L，血小板45×10^9/L减少。 CRP为24.7毫克/升，并且间歇性出现棕色尿液。血胆红素轻度升高。体格检查显示神志清楚、贫血、呼吸急促、双肺广泛湿罗音。心脏或腹部未见明显异常，但全身散在陈旧性皮疹。 免疫学检测显示：IgG 16.60 g/L，IgA 3.08 g/L，IgM 1.89 g/L，C3 0.68 g/L，C4 0.13 g/L，IgE 1280.00 IU/ml。炎症标志物显示ESR 49.0 mm/h，CRP 49.27 mg/L，FER 8759.90 ng/mL。自身抗体：ANA 1:1280，具有同质和核膜模式、核周 ANCA 阳性、抗组蛋白抗体阳性、dsDNA 阳性、抗 nRNP 抗体 +/- 、抗 Sm +/- 和抗核小体抗体阳性。Coombs test 测试直接4+，间接3+。呼吸道病原体呈阴性。孩子父母身体健康。全外显子组测序揭示了 ADA 基因变异：chr20:43254221 NM_000022.4:c.467G>A (p.Arg156His)（母亲）（图 1B）和 chr20:43254243 NM_000022.4:c.445C>T (p.Arg-149Trp) （父亲）（图1C）。诊断为： 1.系统性红斑狼疮； 2. 免疫缺陷（ADA杂合突变）； 3.重症肺炎。舒巴坦头孢哌酮、复方磺胺甲恶唑、伊曲康唑治疗感染未见好转，尽管给予甲泼尼龙10mg/kg治疗，患者仍出现咳嗽和呼吸困难，血细胞计数减少。贫血和血小板减少持续存在，肺炎和呼吸困难仍然明显，肺部仍存在广泛的固定啰音。随后，治疗改为口服泼尼松 20 mg，并静脉注射血浆和新鲜红细胞，每周约 3 次，持续约两周。这导致呼吸困难得到改善，红细胞和血小板逐渐恢复到正常水平，肺部啰音消失。治疗近1个月后，复查血红蛋白119g/L，血小板115×10^9/L，随访6个月未见感染。

讨论： 该患者的常规治疗不足以平衡感染控制和免疫抑制。改用血浆和红细胞替代疗法可显着改善呼吸困难和肺炎，血红蛋白和血小板接近正常化，抗核抗体结果呈阴性。腺苷脱氨酶 (ADA) 的遗传缺陷可导致严重的联合免疫缺陷 (SCID) 亚型称为 ADA-SCID 。应监测患者的 ADA-SCID、与 ADA 缺乏相关的特定非感染性呼吸系统、神经系统和生化并发症。所有患者最初都应接受酶替代疗法（ERT）。目前的免疫抑制剂治疗效果有限；因此，使用血浆和红细胞替代疗法是一种有效的替代疗法

结论： ADA1缺陷引起的SLE,使用血浆和红细胞替代疗法是一种有效的替代疗法



Effective Treatment of Intractable Diarrhea and Alopecia in Two Cytotoxic T lymphocyte Antigen-4 Haploinsufficiency patients with Abatacept therapy

Doo Ri Kim[1], Yeon Ju Lee[2], Areum Shin[1], Eun Seop Seo[3], Kyung Yeon Han[4], Se Jin Im[5], Eun-Suk Kang[6], Woong-Yang Park[7,8], Yae-Jean Kim[1,9]

1 *Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
2 *Department of Health Sciences and Technology, Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University, Seoul, South Korea.*
3 *Department of Digital Health, Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University, Seoul, South Korea.*
4 *Samsung Genome Institute, Samsung Medical Center, Seoul, South Korea.*
5 *Department of Immunology, Graduate School of Basic Medical Science, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea.*
6 *Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
7 *Samsung Genome Institute, Samsung Medical Center, Seoul, South Korea.*
8 *Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, South Korea.*
9 *Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Seoul, Korea*

Germline heterozygous mutations in cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) disrupt regulatory T cell function, causing immune dysregulation with incomplete penetrance. CTLA-4 haploinsufficiency manifests as a diverse range of symptoms, including organ-specific autoimmune diseases, lymphoproliferation, hypogammaglobulinemia, recurrent infections, and malignancies. We report two CTLA-4 haploinsufficiency cases presenting intractable diarrhea and alopecia, both successfully treated with abatacept therapy.

A 39-year-old patient was diagnosed with histiocytosis at 3 months and treated with splenectomy. At 10 years, she was diagnosed with ulcerative colitis and managed with long-term steroids. Later, she was diagnosed with common variable immunodeficiency (CVID) at 14 years and started regular intravenous immunoglobulin (IVIG) replacement. At 32 years, she was finally diagnosed with CTLA-4 haploinsufficiency (c.406C>T, p.Pro136Ser) by whole exome sequencing. At age 33, abatacept, a CTLA-4-Ig was started. Abatacept therapy significantly improved gastrointestinal symptoms, allowing steroid tapering and discontinuation within nine months. The patient has remained

diarrhea-free on abatacept for over five years. Notably, liver cirrhosis, diagnosed prior to abatacept, improved significantly, with stiffness index decreasing from 18.4 kPa to 10.3 kPa.

Patient 2, a younger sister of patient 1, was diagnosed with CVID at age 14 and had been receiving IVIG replacement. At 25, she was diagnosed with early gastric cancer, without Helicobacter pylori infection. At age 28, CTLA-4 haploinsufficiency was confirmed. At age 31, she was diagnosed with type 2 diabetes and initially treated with oral medication but eventually she began insulin injections at 33. By the end of age 33, she developed alopecia areata, which worsened gradually. Given the association between alopecia and autoimmunity in CTLA-4 haploinsufficiency, she was started on abatacept therapy at age 34. Two months after starting treatment, hair loss decreased and by six months, her alopecia fully resolved.

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Pediatric case of immune-mediated necrotizing myopathy associated with anti-HMGCR antibodies: multi-target therapy and long-term follow-up

Yurong Piao, Yan Li, Tongxin Han, Huawei Mao

Department of Immunity, Beijing Children's Hospital, National Center for Children's Health, Capital Medical University, Beijing, China

Introduction: Immune-mediated necrotizing myopathy (IMNM) is a subgroup of idiopathic inflammatory myopathy associated with positive anti-HMGCR or anti-SRP antibodies. It is characterized by markedly elevated creatine kinase (CK) levels and myocyte necrosis pathology with little or no inflammatory cell infiltration. Pediatric case is rare. Long disease duration and high risk of relapses are the main concerns. In this study, we report a pediatric case of HMGCR antibody-positive IMNM to investigate an effective therapeutic strategy.

Case Presentation: A 6-year-old girl presented with 11 months of muscle weakness and CK level of 9100 IU/L at her first visit. Gowers' sign was positive. Electromyography showed myogenic damage, and anti-HMGCR antibody was positive. Muscle pathology showed multiple muscle fibers with atrophy, necrosis and regeneration, MHC-I expression on myofiber membrane and cytoplasm, and C5b-9 staining of necrotic muscle fibers. Diagnosis of IMNM was made. As primary treatment, intravenous immunoglobulin (IVIG 2g/kg) was administered for six months with methylprednisolone pulse therapy for three times. Oral prednisolone was started at 2 mg/kg/d. Cyclosporine, tofacitinib, and thalidomide were also administered. After 6 months, the patient was in remission. Her symptom was well controlled with normal CK level. At 1 year, CK level showed fluctuation. Using methylphenidate to replace cyclosporine, her current condition was stable with normal CK at 2 years of follow-up.

Discussion: Based on retrospective case series, treatment for IMNM includes glucocorticosteroid, IVIG, immunosuppressants, biologics such as rituximab, abatacept, complement C5 inhibitors, and FcRn blockers. IVIG helps to control the disease. The remission rate is only about 50%. Case reports indicate that despite the use of 2.4 immunosuppressants, disease remission was not achieved. Our case responded to IVIG, immunosuppressants and tofacitinib treatment and achieved long-term remission.

Conclusions: Pediatric IMNM patients may benefit from multi-targeted therapy approaches including IVIG plus immunosuppressants in combination with tofacitinib.

Tolerance to Balance...
...Creativity from Diversity