Tricho-Hepato-Enteric Syndromic Immunodeficiency

Amarilla B. Mandola MD[1,2,4], Shirly Frizinsky MD[1,2,4], Ido Somekh MD[1,2,5], Shachar Naor MD[3,4], and Raz Somech MD PhD[1,2,4,6]

[1]Department of Pediatrics A and [2]Pediatric Immunology Services, Safra Children's Hospital, Jeffrey Modell Foundation Center, Sheba Medical Center, Tel Hashomer, Israel
[3]Department of Pathology, Sheba Medical Center, Tel Hashomer, Israel
[4]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[5]Recanati School of Medicine, Reichman University, Herzliya, Israel
[6]Israel Association of Allergy and Clinical Immunology, Israel Medical Association, Ramat Gan, Israel

ABSTRACT **Background:** Syndromic inborn errors of immunity (IEIs) are a heterogeneous group of disorders characterized by immune dysfunction associated with congenital anomalies and multisystem involvement. Tricho-hepato-enteric syndrome (THES) is an ultra-rare autosomal recessive syndromic IEI caused by biallelic pathogenic variants in TTC37 or SKIV2L. Delayed recognition is common because of its broad clinical spectrum.

Objectives: To describe the clinical, immunologic, genetic, and histopathologic characteristics of two children with THES and to highlight a structured diagnostic approach for syndromic immunodeficiencies.

Methods: We retrospectively reviewed the clinical presentation, laboratory investigations, immune phenotyping, endoscopic and histopathologic findings, and molecular analyses of two unrelated children diagnosed with THES at a tertiary pediatric immunology center. Molecular confirmation was obtained by whole-exome sequencing.

Results: Both patients presented during early infancy with intractable diarrhea, severe failure to thrive, characteristic dysmorphic features, brittle woolly hair, and inflammatory enteropathy requiring prolonged nutritional support. Immunologic evaluation demonstrated immune dysregulation, including inverted CD4/CD8 ratios, abnormalities of humoral immunity, and impaired vaccine-specific antibody responses. Histopathology revealed chronic active colitis with crypt distortion, inflammatory infiltrates, and crypt abscesses, consistent with very-early-onset inflammatory bowel disease-like enteropathy. Whole-exome sequencing identified homozygous pathogenic variants in SKIV2L in one patient and TTC37 in the other, establishing the diagnosis. Management included nutritional support, immunoglobulin replacement, antimicrobial prophylaxis, and immunomodulatory therapy.

Conclusions: Recognition of syndromic phenotype combined with comprehensive immune evaluation and early genomic testing facilitates prompt diagnosis, multidisciplinary management, genetic counseling, and consideration of emerging targeted therapies.

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KEY WORDS: failure to thrive, inborn errors of immunity (IEI), RNA disorder, tricho-hepato-enteric syndrome (THES)

Syndromic immunodeficiencies are 83 distinct inborn errors of immunity (IEIs) characterized by immune dysfunction in the context of multisystem involvement. These disorders include characteristic, non-immunologic features in addition to immune dysfunction such as thrombocytopenia, DNA repair defects, thymic defects with or without dysmorphism, calcium channel defects, skeletal defects, syndromes associated with elevated IgE and/or atopic disease, defects of vitamin B12 and folate metabolism, anhidrotic ectodermal-dysplasia, neurodevelopmental abnormalities, growth impairment, and/or organ-specific defects.

The International Union of Immunological Societies (IUIS) 2024 criteria and the European Society for Immunodeficiencies (ESID) classify these disorders as syndromic IEI or immunodeficiencies with syndromic features. The organizations provide diagnostic criteria based on genetic, clinical, and immunologic findings [Figure 1]. IEIs with syndromic features are increasingly recognized due to improved genetic testing and awareness [1-4]. Classic examples include immunodeficiency with congenital thrombocytopenia such as Wiskott-Aldrich syndrome (eczema, thrombocytopenia, recurrent infections); DNA repair defects such as ataxia-telangiectasia (cerebellar ataxia, oculocutaneous telangiectasia, sinopulmonary infections, malignancy); and thymic defects such as DiGeorge syndrome (chromosomal microdeletion syndromes, 22q11.2 deletion, cardiac defects, hypocalcemia, abnormal facies, T-cell immunodeficiency) [1-5]. Other syndromic IEIs include hyper-IgE syndromes like Job-syndrome (skeletal and dental anomalies), Nijmegen breakage syndrome (microcephaly, growth retardation, cancer predisposition), and immuno-osseous dysplasias such as cartilage hair hypoplasia (CHH) [4-6]. Each of these conditions includes individual immunologic and distinct phenotypes. Diagnosis relies on recognition of syndromic features in addition to recurrent or severe infections, immune dysregulation, and laboratory evidence of immunodeficiency. Genetic evaluation relies primari-

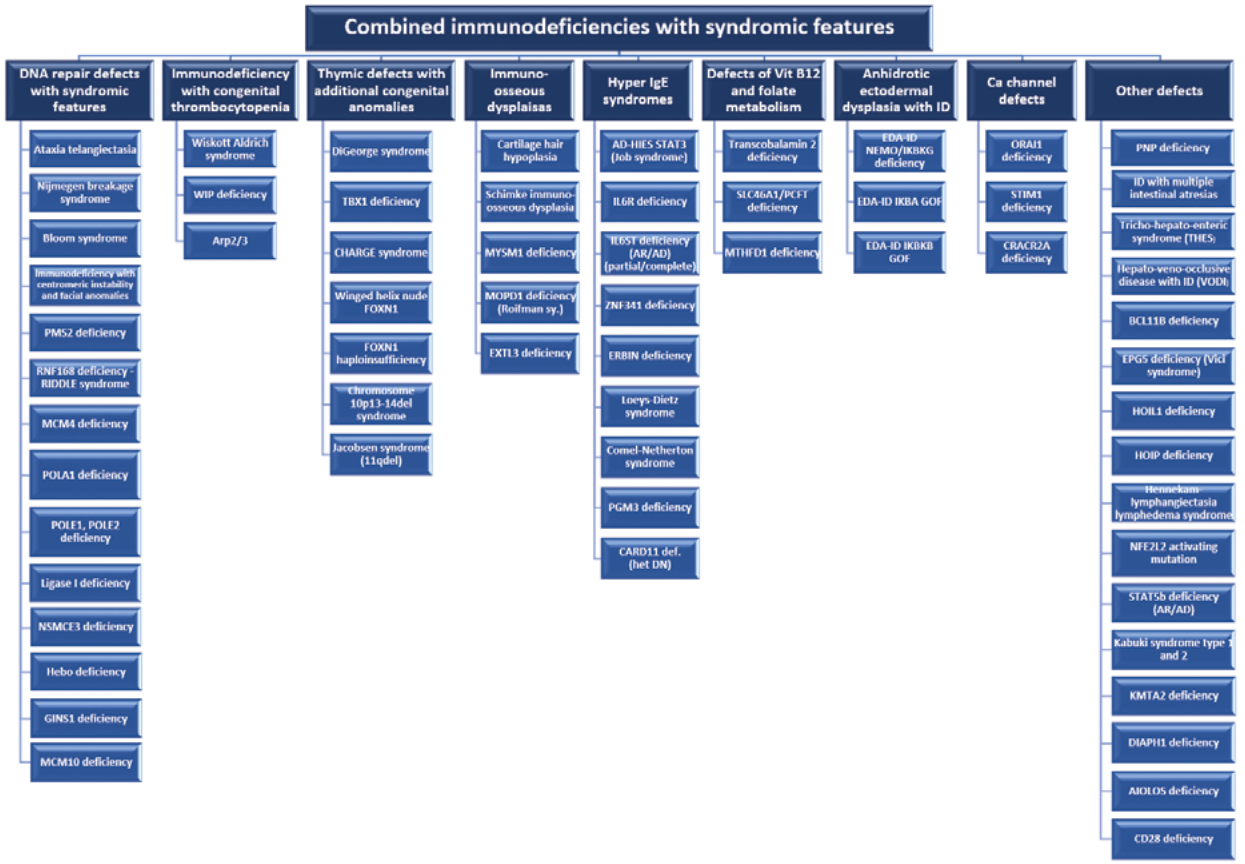
ly on targeted panels and whole-exome sequencing, with chromosomal microarray also serving as an important complementary diagnostic tool [7-9] [Figure 1].

Management is multidisciplinary and specifically designed to meet the needs of the specific syndrome. Therapy may include immunoglobulin replacement, antimicrobial prophylaxis, and in selected cases even hematopoietic stem cell transplantation. Novel targeted pharmacological therapies and gene therapy are emerging for select disorders [3,10]. Early recognition and diagnosis, as well as close follow-up are critical to optimize outcomes and prevent immune dysfunction associated complications [4,11].

In this article, we highlight the case of two patients with syndromic tricho-hepato-enteric syndrome (THES), an ultra-rare autosomal-recessive multisystem disorder.

THES was first described in 1982. It is characterized by infantile-onset intractable diarrhea, failure to thrive, distinctive woolly and fragile hair, facial dysmorphism, and hepatopathy, immune dysregulation, viral susceptibility, and chronic inflammation. Global prevalence is estimated at approximately 1 per 1,000,000 live births, but underdiagnosis is likely in consanguineous populations. The syndrome is caused by biallelic pathogenic variants in either tetratricopeptide repeat domain 37 (TTC37) or Ski2 like RNA helicase (SKIV2L), encoding core components of the cytosolic SKI RNA-exosome complex [12,13]. Case management emphasizes nutritional support, infection prevention, immunoglobulin replacement when needed, and emerging targeted therapy, such as Janus kinase (JAK) inhibition and potentially mammalian target of rapamycin (mTOR) blockade.

Figure 1. Combined immunodeficiencies with syndromic features. Data adapted from the 2024 update of IUIS phenotypic classification of human inborn errors of immunity [1]



PATIENTS AND METHODS

GENETIC EVALUATION

DNA was prepared from the patient PBMCs for a generation of whole-exome libraries using the SureSelect XT Human All Exon V5+UTR or V6+UTR kit (Agilent Technologies, USA). Barcoded libraries were sequenced on a NextSeq 500 platform (Illumina, USA) with an average coverage depth of 100×. Bioinformatics analysis and subsequent filtering identified rare sequence variants.

LYMPHOCYTE MARKERS

Cell surface marker expression of peripheral blood mononuclear cells (PBMCs) was analyzed by immunofluorescent staining with monoclonal antibodies and flow cytometry (Epics V; Coulter Electronics, Hialeah, FL).

QUANTIFICATION OF T-CELL RECEPTOR EXCISION CIRCLES

Signal joint T-cell receptor excision circle (TREC) copy numbers were determined by using quantitative real-time polymerase chain reaction (PCR) of genomic DNA (0.5 µg)

Table 1. Clinical and immunological features of our patients with THES

Clinical description			**Patient 1**	**Patient 2**		
Intractable diarrhea (onset)			Yes (D30)	Yes (D60)		
Small for gestational age			Yes	Yes		
Hair abnormalities			Yes	Yes		
Facial dysmorphism			Yes	Yes		
Liver disease			No	No		
Dermatological abnormalities			Contact dermatitis	Microsporium		
Cardiac abnormalities			No	No		
Skeletal abnormalities			No	CRMO		
Hemophagocytosis			No	No		
Immunological evaluation					**Age-matched normal range (< 5 years)**	**Age-matched normal range (> age 10 years)**
Absolute leukocyte count (cells/µl)			10120	7340	4500–13500	4500–11000
Absolute lymphocyte count (cells/µl)			2975	3200	1500–6800	1000–4800
Immune phenotyping	T cells	CD3 (cells/µl)	1636	2784	400–2500	780–3000
		CD4 (cells/µl)	684	1152	200–1700	500–2000
		CD8 (cells/µl)	1131	1600	200–1700	200-1200
		CD4:CD8	**0.61**	**0.72**	(1.5–2):1	(1.8–2.2):1
	NK	CD56 (cells/µl)	35%	8%	3–30%	3–30%
	B	CD19 (cells/µl)	268	288	100–800	64–820
TCR Vβ repertoire			normal	Normal		
TRECs (copies)			497	**122**	> 400	> 400
Serum total immunoglobulin		IgG (mg/dl)	**300**	1640	633–1280	639–1349
		IgA (mg/dl)	38	394	33–202	70–312
		IgM (mg/dl)	200	298	48–207	40–230
		IgE (U/ml)	0	NA	1.03–161	3–100
Specific IgG antibodies (hepatitis A/B)			**Negative**	**Negative**		
Cytokines			**Elevated IL18**, normal INF-G	NA		
Immunoglobulin replacement therapy			**Yes**	No		

Bold indicates abnormal.

extracted from patients' PBMCs. The surface expression of individual T-cell receptor Vβ gene families was assessed using a set of 24 Vβ-specific fluorochrome-labeled monoclonal antibodies (Beckman Coulter, USA) and flow cytometry.

PATIENT 1

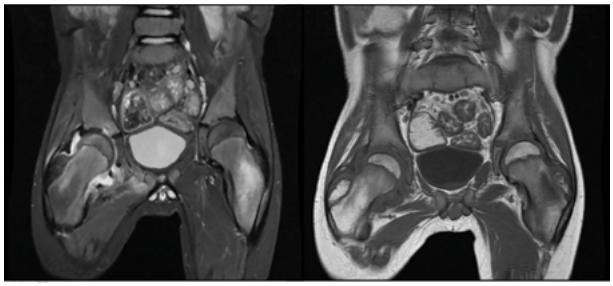
A 4-year-old male patient was admitted at age 1 years 3 months with cachexia, intractable diarrhea, and syndromic features [Figure 2A, 2B] following two previous pediatric intensive care unit admissions at another hospital. Born to first-degree consanguineous parents of Palestinian descent, born at term, and small for gestational age, his family history was remarkable for a deceased male sibling with intractable diarrhea at age 7 months and an older brother with diarrhea and failure to thrive. He started to experience diarrhea at age 1 month and was total parenteral nutrition (TPN) dependent. An upper endoscopy demonstrated a proximal esophageal ulcer and exudative changes in the distal esophagus. The gastric body showed diffuse erythema. A duodenoscopy revealed multiple lymphatic dilations in the second portion of the duodenum. A colonoscopy identified continuous erythema, erosions, and exudate from the rectum to 40 cm, beyond which the procedure could not be advanced.

Overall, the findings were consistent with severe inflammatory colitis with mucosal breakdown. Histopathology [Figure 3A] showed chronic active colitis with crypt architectural distortion, eosinophilic inflammatory infiltrates, and mucosal ulceration, suggesting monogenic inflammatory bowel disease (IBD)-like disease. Initial therapy for his enteropathy included systemic corticosteroids and sulfasalazine, with partial clinical response. Sirolimus was tried but discontinued due to lack of response. Peripheral blood immunophenotyping was remarkable for an inversed CD4/CD8 ratio (0.6), with otherwise normal T, B, and NK cell representation (35%), with normal T cell receptor excision circles (TRECs) and T cell repertoire (TCRV-ß). Immunoglobulin levels revealed hypogammaglobulinemia (IgG 300 mg/dl, IgA 38 mg/dl), elevated IgM (200 mg/dl), and normal protein and albumin levels at the time of evaluation. Cytokine assessment demonstrated inflammatory signature with markedly elevated IL-18 (641 pg/ml), normal IFN-γ, IL-10, and IL-12. He started regular immunoglobulin replacement therapy, per immunoglobulin replacement therapy guidelines, which he tolerated well. [Table 1]. Whole exome sequencing showed a homozygous pathogenic mutation in gene SKIV2L Chr6:31964262 G>A, c.1891G>A, p.Gly631Ser NM_006929.5 HG38, and previously reported pathogenic variant (PMID:27431780, PMID:27050310).

Figure 2. Clinical features of our patients with THES

[A] Patient 1 on admission at age 17 months presenting with facial dysmorphism (broad forehead, hypertelorism, broad nasal bridge, low sitting ears), brittle wooly hair, and severe cachexia

[C] The MRI examination with T1 and T2 series shows an increased amount of fluid in the right hip joint, which enhances following contrast injection, consistent with synovitis; bone marrow edema is demonstrated in the right ischium, at the base of the right superior pubic ramus, near the acetabulum, with bone marrow edema also seen in the femoral head and neck as well in the left femoral neck and in the region of the greater trochanter; the most probable diagnosis is bilateral chronic recurrent multifocal osteomyelitis



PATIENT 2

A 16-year-old male patient presented to our hospital initially at age 10 years with the clinical picture of IBD. Born to first-degree consanguineous parents of Palestinian descent, born at term, and intrauterine growth restriction (IUGR). He has two sisters, both of whom present with failure to thrive and diarrhea, and a healthy brother. He started to experience diarrhea at age 2 months, requiring combined enteral and parenteral nutritional support. Despite treatment, the patient demonstrated ongoing disease activity, reflected by

persistently elevated fecal calprotectin levels (453 to 1000 µg/g). Nutritional management included exclusive and supplemental enteral nutrition with extensively hydrolyzed formula, in addition to mesalamine therapy and intermittent TPN during periods of severe flare or malabsorption.

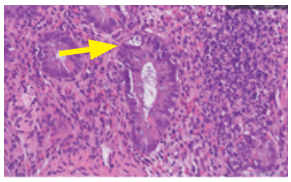
An upper endoscopy demonstrated a solitary ulcer in the gastric fundus accompanied by diffuse butterfly-pattern erythema, consistent with active mucosal inflammation. The duodenum exhibited a characteristic pavement-stone appearance reflecting prominent mucosal nodularity and lymphangiectasia. A lower endoscopy revealed pronounced inflammatory changes in the rectum, including mucosal edema, ulcerations, and excess mucus, compatible with active proctitis. More proximally, the colon showed patchy involvement characterized by scattered ulcers and interspersed segments of normal mucosa. The ascending colon, cecum, and terminal ileum appeared endoscopically normal; however, evaluation was partially limited by suboptimal bowel preparation. Collectively, these findings indicate multi-segment gastrointestinal involvement with fundic ulceration, duodenal lymphatic prominence, and patchy distal colonic ulcerative disease. The pathology results from a biopsy of the colon mucosa showed chronic colitis with crypt distortion and basal plasmacytosis as well as crypt abscess [Figure 3F, 3C].

The patient's growth remained markedly impaired throughout childhood and adolescence. At 10 years of age, the patient weighed 18 kg. By 16 years of age, his weight increased only to 26 kg, despite nutritional optimization. At age 10 years, he was diagnosed with chronic recurrent multifocal osteomyelitis (CRMO); hip joint arthritis and sacroiliitis, necessitating immunosuppressive therapy [Figure 2C], including systemic corticosteroids, anti-TNF-α adalimumab and adjunctive immunomodulation using methotrexate. Laboratory evaluation demonstrated anemia, but otherwise he exhibited a normal blood cell count.

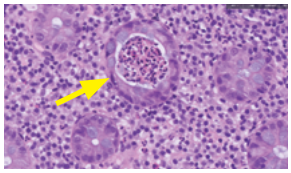
Lymphocyte immunophenotyping was remarkable for an inversed CD4/CD8 ratio (0.72), normal T-, B-, and NK cell numbers. Immunoglobulin levels were elevated (IgG 1640 mg/dl, IgA 394 mg/dl, IgM 298 mg/dl), suggestive of chronic inflammation. ANA testing was negative [Table 1]. TREC levels were low (122 copies/µL; normal > 400 copies/µL). Serologic testing demonstrated lack of protective antibodies (hepatitis A and hepatitis B), suggesting selective antibody deficiency. Prophylactic trimethoprim-sulfamethoxazole was maintained. Whole exome sequencing showed a homozygous pathogenic mutation in gene TTC37 Chr5:94852859 c.2282T>C, p.Leu761Pro NM_014639.3 PMID: 25335910 [13].

Figure 3

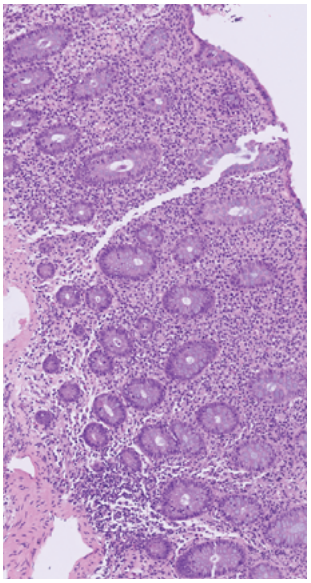
[A] Patient 1: Cecum biopsy (H&Ex40, Philips), numerous eosinophils in the lamina propria and the crypt apoptotic bodies (arrow); giemsa staining was negative for mast cells



[C] Patient 2: Descending colon biopsy (H&EX40 Philips), colon mucosa showing a crypt abscess (activity)



[B] Patient 2: Descending colon biopsy (H&EX10 Philips), colon mucosa showing chronic colitis with crypt distortion and basal plasmacytosis



ETHICS

Informed consent was obtained. This study conforms to the Declaration of Helsinki and all local ethical requirements. Information on presentation, complications, laboratory parameters, management, and outcomes were compiled both prospectively and retrospectively using parent interview and medical note review.

RESULTS

Both patients presented during early infancy with a characteristic syndromic phenotype comprising intractable diarrhea, severe failure to thrive, growth impairment, distinctive dysmorphic features, brittle woolly hair, and multisystem involvement, raising suspicion for a syndromic inborn error of immunity. Comprehensive immunologic evaluation demonstrated immune dysregulation in both patients, including inverted CD4/CD8 ratios, abnormalities of humoral immunity, impaired vaccine-specific antibody responses, and evidence of T-cell dysfunction. Patient 1 exhibited hypogammaglobulinemia with elevated IL-18 levels, whereas Patient 2 had hypergammaglobulinemia, reduced T-cell re-

ceptor excision circles, and selective antibody deficiency, accompanied by chronic recurrent multifocal osteomyelitis, arthritis, and sacroiliitis. Endoscopic and histopathologic evaluation demonstrated chronic inflammatory enteropathy with crypt architectural distortion, inflammatory infiltrates, crypt abscesses, and mucosal ulceration, consistent with monogenic inflammatory bowel disease-like disease. Whole-exome sequencing identified homozygous pathogenic variants in *SKIV2L* and *TTC37*, confirming the diagnosis of tricho-hepato-enteric syndrome.

DISCUSSION

THES results from biallelic pathogenic variants in either TTC37 or SKIV2L genes and is considered one of the mono-allelic diseases underlying early onset IBD and immunodeficiency. TTC37 is responsible for coding the KIC3 subunit of the SKI complex and is reported in most cases of THES, which is responsible for a broader phenotype spectrum. SKIV2L codes a SKI2-like RNA helicase with a more severe phenotype and interferon type I signature. Defective SKI complex function leads to abnormal cytosolic RNA degradation, accumulation of immunogenic RNA species, activation of RNA sensors, type I interferon upregulation, mTORC1 activation, epithelial stress, and immune dysregulation.

Murine models of rapamycin showed reversible mTORC1 activation; however, the response in humans was variable [14].

Clinical presentation is usually evident during early infancy and includes reports of IUGR as well as woolly, brittle hair, trichorrhexis nodosa, facial dysmorphism, and severe watery diarrhea and malabsorption, leading to failure to thrive and dependence on parenteral nutrition. Additional clinical features include hepatomegaly, elevated transaminases, and fibrosis and cirrhosis of the liver. The gastrointestinal and hepatic disease is highly penetrant, with universal need for specialized nutrition in infancy and frequent long-term intestinal inflammation [12,14-16]. Immune phenotypes include low serum IgG and vaccine-specific antibody deficiency, resulting in recurrent, mainly sino-pulmonary infections [17]. Frequent severe viral enterocolitis (rota/norovirus) reflects combined immunodeficiency and mucosal vulnerability. Elevated SKIV2L as well as rare hemophagocytic markers have been reported. On histopathology of small intestinal biopsies, there is a mixed pattern of villous injury; however, no pathognomonic features such as villous atrophy, crypt hyperplasia, apoptotic bodies, lamina propria infiltration with lymphocytes and plasma cells, goblet cell depletion, occasional crypt abscesses and epithelial apoptosis, nonspecific active colitis, villous blunting have been noted [17,18].

Electron microscopy may reveal abnormal enterocyte microvilli distribution, abnormal localization of brush-border transporters and tight junction disruption. The mechanistic basis of diarrhea is the RNA-exosome dysfunction. Although diarrhea often improves with age, enteropathy may evolve to enterocolitis, resembling very early onset IBD (VEO-IBD) due to chronic inflammation, chronic malabsorption, and recurrent gastro-intestinal infections. An early need for parenteral nutrition is nearly universal. However, gradual intestinal adaptation occurs, with variable weaning success, of up to 50% of patients, with need for parenteral nutrition up to age 12 years. Extremely prolonged parental nutrition and failure to transition to enteral feeding are predictors of poor prognosis [14,17].

Both of our patients presented typical immunologic, gastrointestinal, and syndromic features of THES. The diagnostic evaluation of syndromic immunodeficiencies requires a structured approach that integrates clinical pattern recognition, immune phenotyping, and molecular testing, in accordance with IUIS and ESID recommendations. The guiding principle is early recognition based on the coexistence of immune dysfunction and systemic developmental or organ-specific features, followed by systematic laboratory and genetic investigation.

PATTERN RECOGNITION AND PHENOTYPE-BASED CLASSIFICATION

Initial assessments should begin with careful documentation of extra-immune manifestations, including dysmorphic features, congenital anomalies, growth restriction, enteropathy, hair/skin abnormalities, neurologic involvement, and hepatobiliary disease, as well as recurrent or severe infections, persistent inflammation, autoimmune cytopenia, or poor vaccine responses. When these features coexist, the disorder should be mapped to the appropriate IUIS classification table (e.g., combined immunodeficiencies with associated or syndromic features) [Table 1]. This classification supports phenotype-driven differential diagnosis, narrowing the gene list and preventing diagnostic delays. Importantly, some syndromic phenotypes evolve over time; thus, clinicians must remain alert to partial or evolving presentations, particularly in early infancy.

BASELINE IMMUNOLOGIC ASSESSMENT

A standardized immune workup is recommended for all suspected cases and includes complete blood count with differential, flow cytometry for lymphocyte subsets (T, B,

NK, and memory-B cell analysis), serum immunoglobulin levels (IgG, IgA, IgM, IgE), vaccine-specific antibody titers (e.g., tetanus, pneumococcus, Hib), basic inflammatory markers (CRP/ESR), and liver/renal function tests.

EARLY GENETIC EVALUATION

Because of the broad phenotypic spectrum and overlapping clinical features, early molecular testing is crucial. Current ESID and IUIS guidance supports whole-exome sequencing or whole-genome sequencing, preferably with a dedicated IEE gene panel and trio analysis (child + parents) when possible. Chromosomal microarray should be considered when appropriate. Early genetic testing is important because clinical features may be subtle, incomplete, or age-dependent (e.g., enteropathy preceding immunologic abnormalities). Phenotypic overlap can obscure initial diagnosis, and rapid identification allows timely intervention, organ surveillance, and family counseling (e.g., prenatal genetic diagnosis).

CONCLUSIONS

Clinicians should consider a syndromic IEI whenever features of immune deficiency, such as recurrent infections, chronic inflammation, or autoimmunity, coexist with extra-immune manifestations including gastrointestinal disease, liver dysfunction, hair or skin abnormalities, dysmorphic features, or growth failure. The IUIS classification provides a structured framework to narrow the differences and guide evaluation, while the ESID diagnostic criteria emphasize systematic immune phenotyping and rigorous clinical documentation. In syndromic IEIs, genomic testing should be pursued early rather than reserved as a final step. Many patients present in infancy with incomplete phenotypes, and delayed diagnosis can lead to irreversible complications. Interpretation of genomic findings must occur in a clinical context, ideally in collaboration with immunology, genetics, gastroenterology, hepatology, and other specialty teams. Because clinical manifestations in these disorders are dynamic and often evolve with age, close multidisciplinary longitudinal monitoring is required to recognize emerging immune or extra-immune complications so that therapy can be adjusted as needed and personalized treatment can be initiated to improve survival and quality of life.

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Correspondence

Dr. A.B. Mandola
Dept. of Pediatrics A, Safra Children's Hospital, Jeffrey Modell Foundation Center, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone/Fax: (972-3) 530-3477
Email: amarilla.mandola@sheba.health.gov.il

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