CASE REPORT

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Severe dermatitis in a 24-day-old baby with hyper-IgE syndrome

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ABSTRACT

Hyper-immunoglobulin E syndromes (HIES), also known as Job's syndrome, is a rare primary immunodeficiency disorder characterized by elevated serum IgE levels, recurrent cutaneous and sinopulmonary infections, and chronic eczematous dermatitis. The condition can manifest in two familial forms: autosomal dominant (AD-HIES) and autosomal recessive (AR-HIES), with most cases being sporadic. Herein we present the case of a patient with HIES associated with a mutation in the signal transducer and activator of transcription 3 (STAT3) gene. This case highlights the importance of recognizing the clinical manifestations of HIES in neonates. Early diagnosis through clinical evaluation and genetic testing is crucial for effective management and improving the quality of life for affected individuals.

Keywords: hyper-immunoglobulin E syndrome, HIES, Job's syndrome, primary immunodeficiency, STAT3 mutation, eosinophilia

INTRODUCTION

Job's syndrome, or hyper-immunoglobulin E syndrome (HIES), is a rare primary immunodeficiency disorder, occurring in approximately one in one million individuals [1]. Both males and females are equally predisposed to the disease. HIES is a multisystem disorder characterized by eczema, skin abscesses, recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, candidiasis, eosinophilia, and elevated serum IgE levels (>2000 IU/mL). Non-immunologic features of HIES include characteristic facial appearance, scoliosis, retained primary teeth, joint hyperextensibility, bone fractures following minimal trauma, and craniosynostosis.

HIES was first described in 1966 by Davis, Schaller, and Wedgwood [2]. While most instances occur sporadically, there have been reported cases of both autosomal recessive (AR) and autosomal dominant (AD) forms. AD-HIES, caused by heterozygous loss-of-function mutations with a dominant negative effect in the signal transducer and activator of transcription-3 (STAT3) gene, is the prototype of these disorders [3]. Based on the recent classification by the International Union of Immunological Societies (IUIS) for PID and Online Mendelian Inheritance in Man (OMIM), several other genes have been identified as causative or associated with HIES i.e. Zinc Finger Protein 341 (ZNF341)-LOF, Tyrosine kinase 2 (TYK2)-LOF, Serine Peptidase Inhibitor Kazal Type 5 (SPINK5)-LOF, Caspase recruitment domain-containing protein 11 (CARD11)-DN [1]. Additionally, several phenotypically distinct immunodeficiency disorders can mimic hyper IgE syndromes, adding to the diagnostic challenge.

STAT3 is a crucial component in the signal transduction pathways of various cytokines, including but not limited to IL-6, IL-10, IL-21, IL-22, and IL-23. It plays an essential role in diverse biological processes such as wound healing, angiogenesis, cancer development, and immune responses [4]. In 1999, the National Institute of Health (NIH) introduced a clinical scoring system for HIES that utilized 19 clin-

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ical and laboratory findings [5, 6]. A high total HIES score was strongly correlated with the presence of a STAT3 mutation [7]. AD-HIES was deemed highly probable with a score above 40, unlikely with a score below 20, and a score between 20 and 40 indicated an intermediate probability. Patients in the intermediate range might have AD-HIES and would require further monitoring to gather more data or could have another genetic form of HIES.

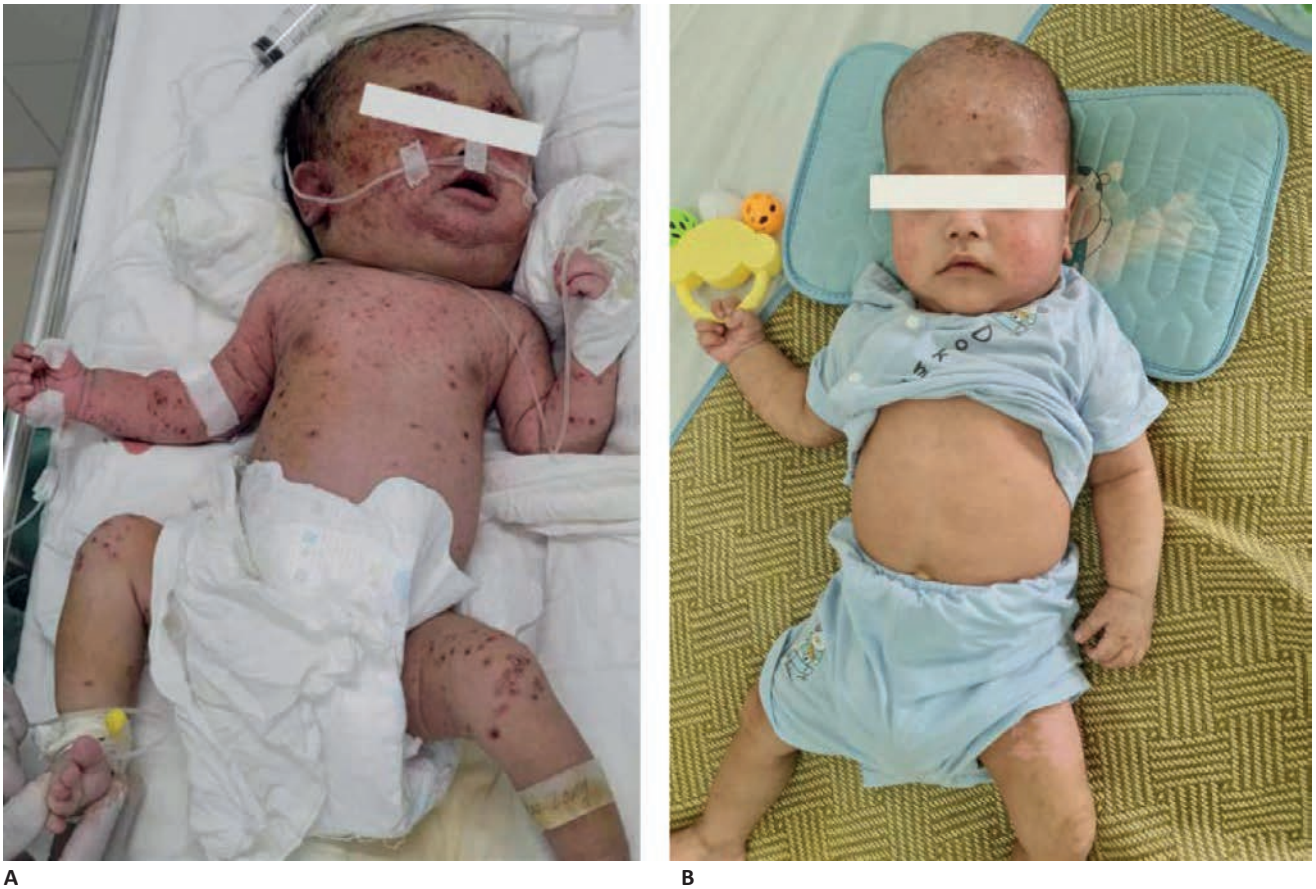
We herein report the first known case of HIES in a boy with STAT3 mutation from Central Vietnam treated at Hue Central Hospital. The diagnosis was confirmed through mutation analysis of the STAT3 gene, with the goal of improving HIES diagnosis and management through this report.

CASE PRESENTATION

A 24-day-old boy was admitted to the hospital due to vesicular rash. He was born full term without perinatal problems, weighing 3.4kg at birth. Nine days after birth, vesicular rash appeared on the face and then spread throughout the body. No treatment was administered at home. After three weeks, the vesicular rash spread over the entire body with accompanying fever, poor feeding, and swelling around the head, prompting admission to the district hospital. Pus culture revealed *Staphylococcus aureus*, blood culture was negative, and he was treated with Meropenem and Vancomycin for two days without clinical improvement, leading to transfer to Hue Central Hospital.

During physical examination, the infant appeared lethargic. Multiple 1–2 mm vesicles and pustules on an erythematous base were noted over chest, abdomen, back, and arms (Figure 1A). He had rapid breathing, mild respiratory distress, regular heart rhythm, palpable pulses, soft abdomen, and no distended anterior fontanelle. His family history was unremarkable.

Blood analysis revealed a high C-reactive protein level of 128.3 mg/L (reference range: <5 mg/L) and significantly elevated eosinophil count of 4.08 k/μL (reference range: 0.05–0.5 k/μL). Immunological assessment showed elevated IgE level >2500 IU/mL, reference range: <130 IU/mL) and increased T cell count (CD3+) of 87.62% (reference range: 53-84%). He had both intrinsic and extrinsic coagulation disorders with a Prothrombin time of 17.1s, Prothrombin ratio of 49%, decreased APTT to 49.8s, reduced Fibrinogen of 0.77 g/L (reference range: 1.5-4.5 g/L), and decreased platelet count of 65 k/μL (reference range: 150-450 k/μL) (Table 1). Ultrasound results for the abdomen, heart, and arterial Doppler did not reveal any abnormalities. Chest X-ray showing infil-



A B

FIGURE 1. Patient's skin lesions before (A) and after treatment (B). (A) Multiple 1–2 mm vesicles and pustules on an erythematous base were noted over the chest, abdomen, back, and arms. (B) Improvement in the condition of the skin was noted

trate and brain MRI revealed scalp cellulitis with subgaleal collection (Figure 2). Additional pus culture from the skin grew multi-drug resistant Klebsiella pneumoniae and Acinetobacter baumannii, remaining sensitive only to Gentamicin and Trimethoprim-Sulfamethoxazole.

TABLE 1. Laboratory data

Laboratory data	Results
Complete blood cell count	
Hb (g/dL)	10.1
WBC (k/μL)	60.85
Segmented neutrophil (%)	6.7
Eosinophil count (k/μL)	4.08
Platelet (k/μL)	65
C-reactive protein (mg/dL)	128.3
AST/ALT (U/L)	172.2/135.3
Pro-BNP (pg/mL)	2670
D-dimer (ng/mL)	3817
Immunoglobulin level	
IgG (g/L)	<2.11
IgA (g/L)	<0
IgM (g/L)	<0.07
IgE (IU/mL)	
Lymphocyte subset	>2500
T3	87.62% (3.8 k/μL)
T4	67.66% (2.9 k/μL)
T8	15.32% (0.7 k/μL)
T4/T8 ratio	4.42
B (CD19)	7.69% (0.33 k/μL)
NK (CD16+CD56)	4.68% (0.20 k/μL)

During his hospitalization, Meropenem, Linezolid, Colistin, and Bactrim were used as systemic antimicrobial therapy. Topical Gentamicin, Gentamicin ointment, and Methylene Blue were used for local infection control. He had a poor antibody response to polysaccharide antigens and began treatment with intravenous immunoglobulins (IVIg) at a dose of 0.5 g/kg. Additionally, the patient was diagnosed with Disseminated Intravascular Coagulation (DIC) with a DIC Score of 7 points and received cold plasma and fresh frozen plasma transfusions.

Based on the above clinical features and supportive immunological findings, a diagnosis of HIES was made. Non immunological features of HIES, such as scoliosis, skeletal fractures, and vascular abnormalities were not identified. Following the application of a clinical scoring system (NIH-HIES) designed to screen individuals from known AD-HIES families, this patient scored 47 points (Table 2), suggesting a suspicion of HIES. The scoring system, initially developed by the NIH group to identify STAT3-HIES, and now commonly employed to assess sporadic cases, was utilized. In accordance with the guidelines established by Woellner et al.[7], whole-exome sequencing was conducted. Analysis of STAT3 sequencing unveiled a new, de novo, heterozygous c.1859C>G mutation. This mutation, classified as a nonsense variant (p.Thr620Ser), is likely to cause premature termination of the peptide in the DNA binding domain. Notably, both parents exhibited wild-type genotypes. Finally, we confirmed that the patient was diagnosed with AD-HIES.

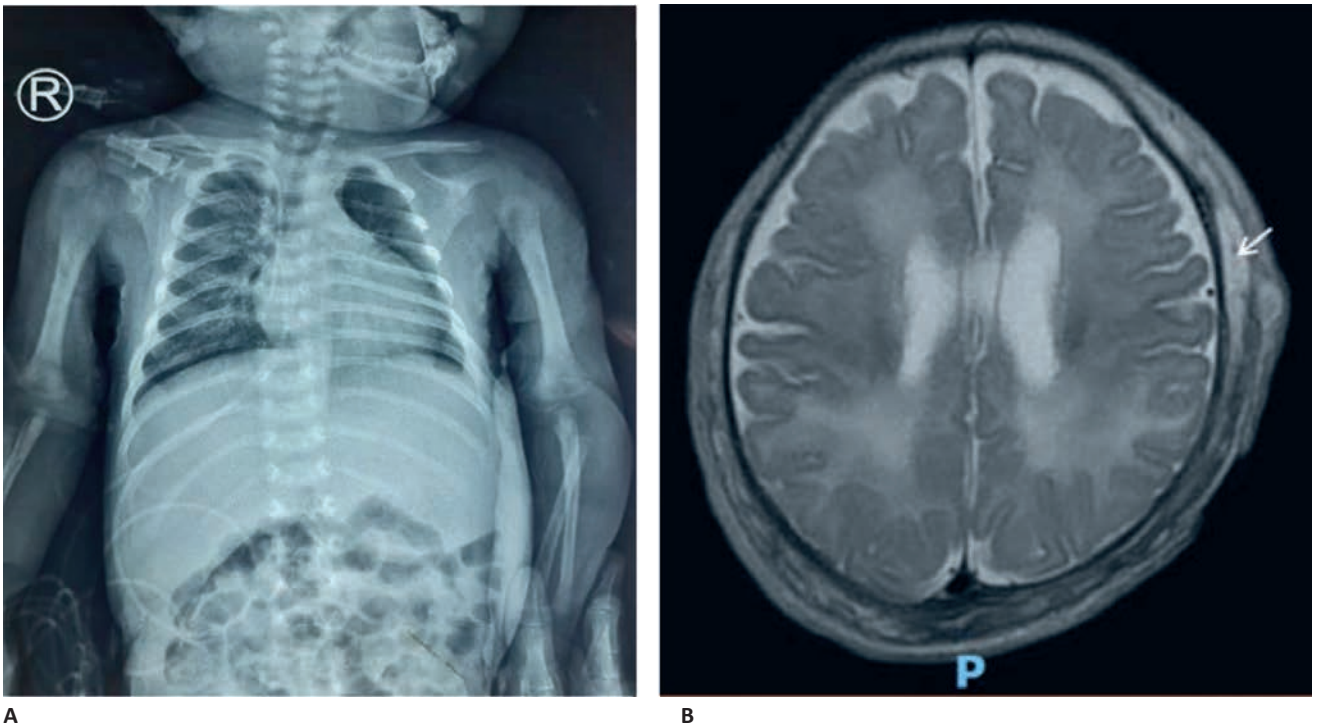


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FIGURE 2. (A) Chest X-ray at the time of admission (B) The MRI images of the brain showed inflammation of the scalp with associated subgaleal fluid collection (the arrow)

TABLE 2. Scoring system with clinical and laboratory tests for individuals in kindreds with HIES

Clinical Findings	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/ml)	<200	200-500			501-1,000				1,001-2,000	>2,000*
Skin abscesses	None		1–2		3–4				>4*	
Pneumonia (episodes over lifetime)	None*		1		2		3		>3	
Parenchymal lung anomalies	Absent*						Bronchi-ectasis		Pneumato-cele	
Retained primary teeth	None*	1	2		3				>3	
Scoliosis, maximum curvature	<10° *		10-14°		15°–20°				>20°	
Fractures with minor trauma	None*				1-2				>2	
Highest eosinophil count (cells/µl)	<700			700-800			>800*			
Characteristic face	Absent*		Mildly present			Present				
Midline anomaly	Absent*					Present				
Newborn rash	Absent				Present*					
Eczema (worst stage)	Absent	Mild	Moderate		Severe*					
Upper respiratory infections per year	1-2*	3	4-6		>6					
Candidiasis	None*	Oral	Finger-nails		Systemic					
Other serious infections	None				Severe*					
Fatal infection	Absent				Present*					
Hyperextensibility	Absent*				Present					
Lymphoma	Absent*				Present					
Increased nasal width	<1 SD*	1–2 SD		>2 SD						
High palate	Absent*		Present							
Young-age correction	>5 years			2–5 years		1-2 years		≤1 year*		

*shows the case of the patient

After nearly 4 months of intensive treatment with antibiotics, antifungal prophylaxis, and skin grafts, the patient was discharged with no fever or signs of infection, and a marked improvement in skin lesions (Figure 1B).

DISCUSSION

The normal range for total serum IgE in adults is usually stated as below 100-140 IU/mL, though it can differ based on age and ethnicity [5,7]. An extreme increase in IgE levels, reaching ten times the upper normal limit, is used to define the typical HIES. Hyper-IgE syndrome (HIES) was first identified by Davis et al. in 1966 in two girls who had recurrent cold staphylococcal abscesses, pneumonia, and neonatal-onset eczema [2]. At that time, the significance of elevated serum IgE levels was not understood since the discovery of IgE had not yet occurred. The syndrome was later characterized by Buckley et al., who observed the correlation between recurrent staphylococcal abscesses and chronic eczema with remarkably high serum IgE concentrations [8].

Autosomal dominant Hyper IgE syndrome (AD-HIES) is a rare primary immunodeficiency characterized by eczema, recurrent skin and lung infections, elevated serum IgE, and various connective tissue, skeletal, and vascular abnormalities [5].

HIES is a rare genetically mediated primary immunodeficiency disorder with multisystem involvement. The most commonly observed immunological abnormalities include eczematoid rashes, skin abscesses, respiratory infections, significant elevation in serum IgE levels, mucocutaneous candidiasis, and eosinophilia. The rash typically appears within a few weeks after birth and may even be present at

birth. It commonly manifests as a pustular or eczematoid eruption on the face and scalp [9]. The rash may either improve or evolve into an eczematoid rash, which is frequently exacerbated by Staphylococcus aureus infection. Recurrent S. aureus boils typically begin in early childhood. In AD-HIES, the lungs are the next most frequent site of infection, typically affected by Staphylococcus, Streptococcus pneumoniae, or Haemophilus influenzae [4]. The interplay between pulmonary infections and impaired connective tissue remodeling can result in the formation of pulmonary structural abnormalities, including pneumatoceles and bronchiectasis, creating an environment conducive to colonization by various pathogens such as Pseudomonas aeruginosa, nontuberculous mycobacteria, and Aspergillus fumigatus. The latter complication is a significant contributor to morbidity and mortality [10]. Mucocutaneous candidiasis presents as nail, vaginal, and oral diseases. A distinctive facial appearance typically emerges during childhood and adolescence, marked by facial asymmetry, a broad fleshy nose, and porous skin. Common accompanying features include minimal trauma fractures, osteopenia, hyperextensibility, scoliosis, and degenerative joint disease [5]. It's crucial to note that these features may develop gradually over time and could be absent in early life, presenting a diagnostic challenge.

Laboratory findings in HIES are primarily characterized by eosinophilia and elevated serum IgE levels. IgE levels typically peak at over 2000 IU/mL (because of impaired IL-10 and IL-21 signaling) but may decrease over time and even normalize in adulthood [5, 10]. Despite IgE normalization, clinical symptoms of HIES may persist. HIES patients have normal or decreased serum IgM, IgG and IgA levels [10].

In 2007, the molecular cause of HIES was identified as autosomal dominant mutations in the STAT3 gene, leading to loss of function [3]. The majority of cases of AD-HIES are attributed to dominant negative mutations in STAT3 [4]. STAT3, a critical mediator in cytokine signaling, is pivotal for various interleukins, including IL-6, IL-10, IL-11, and IL-21. IL-6, an inflammatory cytokine, triggers STAT3 activation, influencing Th17 cell differentiation, which produces IL-17 crucial for combating bacterial and fungal pathogens. IL-10, on the other hand, known for its anti-inflammatory effects, also relies on STAT3 for regulation, contributing to immune balance. IL-11, another cytokine, is regulated by STAT3 and influences processes like primary teeth shedding and skull development. Furthermore, IL-21, whose signaling is modulated by STAT3, promotes B-cell differentiation and suppresses IgE production, impacting immune responses. Beyond immunity, STAT3's involvement in IL-11 signaling influences non-immune processes like primary teeth exfoliation and skull sutures' ossification [10]. Dysfunction in the STAT3 signaling pathway hinders the liver's response to IL-6, resulting in a reduced production of acute phase proteins like C-reactive protein (CRP) [1]. HIES with mutations in STAT3 is inherited as an autosomal dominant trait. Consequently, STAT3-mutated HIES patients carry a 50% risk of passing the disease to each of their offspring. Therefore, a positive family history increases the likelihood of having HIES [3].

The NIH scoring system has been modified and validated to help identify and diagnose this autosomal dominant condition [7]. However, it has limited applicability to other primary immunodeficiency (PID) conditions that also show extreme IgE elevation and susceptibility to infections and other T-cell development defects. These disorders include complete DiGeorge syndrome, Omenn syndrome, Wiskott-Aldrich syndrome, and immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) [10, 11]. It is necessary to exclude these disorders to diagnose HIES. The NIH score also depends on the appearance of sufficient immunological, infectious, and anatomical features. Unfortunately, this characteristic may not become evident until irreversible damage has already occurred.

In this patient, the typical symptoms of HIES, such as bone and primary teeth abnormalities, and characteristic facial features, were not apparent. However, severe skin infections were present, with skin pus cultures testing positive for Staphylococcus aureus at the initial hospital. Consequently, his condition could be mistaken for severe infantile eczema or bacterial skin infection. The occurrence of multidrug resistant Klebsiella pneumoniae and Acinetobacter baumannii infections raised concern, as infections with antibiotic-resistant strains are a significant worry in patients with an immune deficiency. The clinical and laboratory findings in our patient prompted us to concentrate on the gene set associated with AD-HIES. Following a genetic analysis, we identified a novel mutation in the STAT3 gene. In line with the patient's phenotype, no mutations were detected in other genes such as DOCK8, ZNF431, TYK2, PGM3, CARD11, and SPINK5. The mutation c.1859C>G in the STAT3 gene of this patient is an established pathogenic mutation [7]. This patient obtained a score of 47 on the HIES NIH scoring system, and all of his symptoms, laboratory tests, and genetic results confirmed a diagnosis of HIES. [10]. Additionally, his CRP level was elevated, along with a pulmonary infection, which is uncommon in patients with AD-HIES.

There is no definite treatment for HIES. The cornerstone of therapy involves proactive and meticulous skin care, along with prophylactic administra-

tion of anti-staphylococcal and antifungal agents [10]. Trimethoprim/sulfamethoxazole is often used as an antibacterial agent against S. aureus due to its relatively low likelihood of developing resistance, even with prolonged use. Additionally, penicillinase-resistant penicillin antibiotic flucloxacillin and macrolide azithromycin may be administered. Prophylactic administration of antifungal agents such as itraconazole, voriconazole, and posaconazole, which are effective against Aspergillus, is also recommended. Immunoglobulin replacement therapy is recommended for children with this disease due to their deficiency in producing specific antibodies [1]. Hematopoietic stem cell transplantation (HSCT) is curative in patients with DOCK8 deficiency but is less effective or controversial for those with AD-HIES attributed to STAT3 mutations [10]. The use of HSCT in AD-HIES remains a subject of debate, and additional research is required to elucidate its effectiveness and potential risks.

CONCLUSION

In conclusion, HIES poses diagnostic and treatment challenges due to its rarity. Thorough history-taking, physical examination, and serum IgE level assessment are pivotal in diagnosis. Mutational analysis aids in confirmation. Our report documents the first case of a child diagnosed with HIES due to a STAT3 mutation in Hue Central Hospital and the Central region of Vietnam. This underscores the need to broaden our understanding of this condition for improved patient care.

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