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Case Report

Hyper-IgE syndrome: case reports

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ABSTRACT

Hyper-IgE syndromes (HIES) are rare primary immunodeficiency disorders characterised by markedly elevated serum immunoglobulin E (IgE) levels, recurrent cutaneous and respiratory infections, and variable multisystem involvement. They arise from mutations in genes central to immune signalling pathways, most notably STAT3 in autosomal dominant HIES (AD-HIES) and DOCK8 in autosomal recessive HIES (AR-HIES). The first case, an 11-month-old boy with recurrent staphylococcal skin infections, sepsis, eosinophilia and an IgE level of 9,867 IU/ml, was found on whole-exome sequencing to have a heterozygous STAT3 mutation, confirming AD-HIES. The second case, a 2-year-old boy with severe atopic dermatitis, recurrent wheezing, repeated pneumonias and an IgE level exceeding 100,000 IU/ml, was diagnosed with AR-HIES due to a homozygous DOCK8 mutation. These cases highlight the distinct clinical patterns of the two forms: AD-HIES commonly presents with non-immunologic features such as skeletal and dental anomalies, whereas AR-HIES is associated with severe viral infections, profound IgE elevation and higher mortality. Early recognition through clinical suspicion and genetic confirmation is essential, as management requires multidisciplinary care, prophylactic antimicrobial strategies and, in severe DOCK8 deficiency, consideration of haematopoietic stem-cell transplantation.

Keywords: Hyper IgE, Children, Infections

INTRODUCTION

Hyper-IgE syndromes (HIES), historically referred to as "Job's syndrome", are a rare, heterogeneous group of primary immunodeficiencies characterised by markedly elevated serum immunoglobulin E (IgE) levels and recurrent infections. These disorders arise from inherited mutations that impair key immunological signalling pathways, most notably the signal transducer and activator of transcription (STAT) family.[1,2] The most widely studied subtype is autosomal dominant HIES (AD-HIES), caused by heterozygous pathogenic variants in the STAT3 gene on chromosome 17.[3] In addition, autosomal recessive variants (AR-HIES) are associated with mutations in genes such as DOCK8, ZNF341, IL6ST, IL6R and others.[1,4] The overall prevalence of HIES is estimated at less than one case per 1,000,000 individuals.[5] The term HIES was introduced in 1972 to denote the marked elevation of IgE as a defining feature.[5] Clinically, HIES is characterised by a triad of recurrent cutaneous infections, recurrent sinopulmonary infections and significantly raised IgE levels.[6] Additional features may include eosinophilia, typical facial dysmorphism, skeletal anomalies (such as scoliosis or pathological fractures) and delayed shedding of primary teeth.[1,7]

CASE REPORTS

Case 1

Autosomal dominant HIES (STAT3 mutation)

An 11-month-old male infant, the firstborn of a non-consanguineous marriage, was referred with recurrent

skin infections-begun in the neonatal period-manifesting as eczema and pyoderma. The child experienced a severe episode of sepsis with septic shock at nine months of age, followed by multiple episodes of eye and ear infections. Culture of pus revealed heavy growth of *Staphylococcus aureus*, and skin abscess culture yielded methicillin-resistant *S. aureus* (MRSA). On clinical examination: weight was 7.6 kg (grade I undernutrition); height 69 cm (grade I stunting); weight-for-height corresponded also to grade I wasting. Notable findings included coarse facial features, oral thrush, absent tonsils, absence of BCG scar, seborrhoea with scalp crusting, multiple abscesses, healing pyoderma and intertrigo lesions over the toes. A chest radiograph at ten months revealed an absent thymic shadow. Laboratory investigations showed eosinophilia and a markedly elevated IgE level of 9,867 IU/ml. In view of the clinical suspicion of HIES, whole-exome sequencing (WES) was performed, which revealed a pathogenic heterozygous variant in the STAT3 gene, confirming the diagnosis of AD-HIES. The child commenced prophylactic co-trimoxazole and has had no further severe pneumonias to date.

Figure 1:

Case 2

Autosomal recessive HIES (DOCK8 mutation)

A 2-year-old boy presented with severe atopic dermatitis complicated by secondary infection. Skin lesions had begun in the neonatal period. He also had a history of recurrent wheezing from age seven months onward, requiring frequent nebulisations and multiple admissions to the intensive-care unit for pneumonia. On examination, he exhibited extensive erythematous papules and plaques over the face, trunk and limbs; marked failure to thrive, with both weight (10 kg) and height (82 cm) are both below the 3rd percentile for age. Laboratory testing revealed eosinophilia (24%) and a profoundly elevated serum IgE (>100,000 IU/ml). Genetic testing confirmed a pathogenic homozygous mutation in the DOCK8 gene, consistent with AR-HIES.

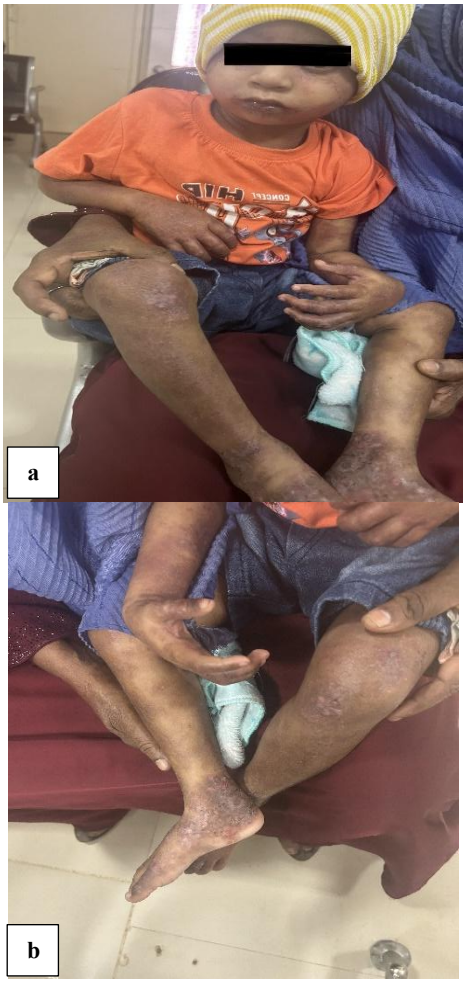

Figure 2 (a and b):

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
***DOCK8* (+)** (ENST00000432829.7)	Exon 20	c.2440G>T **(p.Ala814Ser)**	Homozygous	Hyper-IgE syndrome 2, autosomal recessive, with recurrent infections (OMIM#243700)	Autosomal recessive	Uncertain Significance **(PM2,PP3)**

Figure 3:

DISCUSSION

HIES represents a broad spectrum of genetically determined immunodeficiencies that, although sharing certain core features, display divergent immunologic and non-immunologic phenotypes.[8] In both dominant and recessive forms, recurrent staphylococcal skin abscesses, recurrent respiratory infections and high IgE levels are common, reported in around 75% of patients.[9] Yet, the differentiation between AD-HIES (STAT3 mutation) and AR-HIES (DOCK8 or related gene mutation) is important; given differences in clinical features, complications and prognosis.

In AD-HIES due to STAT3 mutation, patients often present with immunologic and non-immunologic features: characteristic facial dysmorphism (broad nasal bridge, prominent forehead, deep-set eyes), skeletal/connective-tissue anomalies (scoliosis, minor-trauma fractures, joint hyper-extensibility) and dental abnormalities (retained primary teeth).[1,10] By contrast, AR-HIES (for example due to DOCK8 mutation) typically lacks the classical non-immunologic features but is associated with pronounced susceptibility to viral skin infections (e.g., herpes simplex, molluscum contagiosum), more severe infections, central nervous system involvement and higher mortality.[4,8,11]

Moreover, gastrointestinal manifestations are increasingly recognised in STAT3-HIES: a study of 70 subjects found that 60 % had GI symptoms (e.g., GERD, dysphagia, colonic complications) and 65% had esophageal eosinophilic infiltration on histology.[13] These observations suggest that the STAT3 pathway might underlie a novel mechanism of GI dysmotility and eosinophilic inflammation beyond classical immunodeficiency.

An organised diagnostic algorithm is essential for suspected HIES.

Key elements include the following.

Elevated serum IgE, typically >2,000 IU/ml, and in AR-HIES may exceed 100,000 IU/ml.[1,6] Complete blood count shows eosinophilia.[1] Lymphocyte subset studies in AD-HIES often shows profoundly reduced Th17 cells; AR-HIES may show T-cell lymphopenia and reduced memory B-cells.[8,12] Chest radiography may reveal pneumatoceles or absent thymic shadow. Definitive genetic testing to identify pathogenic variants in STAT3, DOCK8 or other genes.[1] Dental and skeletal exam (for retained teeth, fractures) and echocardiography to exclude vascular complications.[4]

Management of HIES requires a multidisciplinary, preventive and supportive strategy. Early and aggressive treatment of bacterial and fungal infections, particularly staphylococcal skin abscesses and sinopulmonary infection is essential. Long-term prophylactic antibiotics (such as co-trimoxazole) are commonly used to reduce recurrent infections, and may be supplemented by antifungal therapy when indicated.[1] Because pulmonary complications (e.g., bronchiectasis, pneumatoceles) are frequent, ongoing pulmonary surveillance and intervention are important to preserve lung function. Nutritional support is crucial in children with failure to thrive or growth delay. Non-immunologic complications, such as skeletal abnormalities, dental retention, scoliosis, may require collaboration with orthopaedics or dental specialists. Genetic counselling is vital for families to understand inheritance patterns and recurrence risks. In severe cases of AR-HIES (DOCK8 deficiency), haematopoietic stem-cell transplantation (HSCT) is considered the only curative option and has been associated with improved survival.[8,11]

Emerging therapeutic options include the use of monoclonal antibodies targeting IgE (omalizumab) has reported improvement in respiratory symptoms and lung function.[14] In research settings, experimental approaches aimed at stabilising STAT3 protein function have shown potential: small-molecule modulators of chaperone proteins increased STAT3 stability and downstream IL-17 production in vitro.[13]

CONCLUSION

Hyper-IgE syndromes are rare but clinically significant primary immunodeficiency disorders defined by elevated IgE levels, recurrent infections and variable systemic manifestations. Distinguishing between autosomal dominant (STAT3) and autosomal recessive (DOCK8 and related) forms is clinically important, as the genetic basis, non-immunologic features, infection risks and management strategies differ substantially. Early recognition, prompted by clinical suspicion, supported by laboratory and imaging findings, and confirmed by genetic testing, enables timely intervention, infection prevention and tailored therapy. Long-term care mandates a comprehensive approach involving infection control, pulmonary and nutritional monitoring, multidisciplinary support for non-immune complications and family education. As our understanding of the molecular mechanisms improves, future targeted treatments may further enhance outcomes for affected individuals.

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