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A rare case of Autosomal Dominant Hyper IgE syndrome

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ABSTRACT

Inborn Errors of Immunity (IEI), once called Primary Immunodeficiency Disorders, are rare genetic conditions that weaken the immune system, making individuals prone to frequent infections, allergies, or even autoimmune problems. These conditions usually show up in childhood and vary widely in how they affect people.

One such condition is Hyper IgE Syndrome (HIES), a rare disorder known for high levels of IgE antibodies, recurring skin and lung infections, and eczema-like rashes. It can also involve bone, dental, and connective tissue abnormalities. There are two main types: the autosomal dominant form (AD-HIES), caused by mutations in the STAT3 gene, and the more severe autosomal recessive form (AR-HIES), often involving other genes like DOCK8.

We present a case of a 7-year-old girl with the dominant form of HIES, who had a long history of skin infections, dry skin and recurrent otitis. Genetic testing confirmed a mutation in the STAT3 gene. With supportive care and preventive treatment, her condition improved significantly.

This case highlights how important it is to recognize signs of IEI early. Thanks to modern genetic testing, many of these disorders can now be identified sooner, leading to better outcomes through targeted treatments and ongoing care.

Keywords: *Hyper IgE Syndrome (HIES), Primary Immunodeficiency, STAT3 Mutation, Autosomal Dominant HIES, Genetic Testing, Recurrent Infections*

1. INTRODUCTION

Inborn Errors of Immunity (IEI) are a group of genetically determined conditions that result from defects in the development or function of the immune system. These disorders manifest most commonly during childhood and can present with recurrent infections, immune dysregulation (such as autoimmunity or allergies), or increased susceptibility to malignancies.

The prevalence of IEI is estimated to be around 1 in 1,200 - 2,000 live births to 1 in 16,000 – 50,000, although this figure may vary depending on geographic and genetic factors [1,2] Due to increased awareness and the expansion of diagnostic

capabilities, particularly with the advent of next-generation sequencing (NGS) and whole-exome/genome sequencing, the number of recognized IEIs has dramatically increased in recent years. The International Union of Immunological Societies (IUIS) now classifies more than 500 distinct disorders under the IEI umbrella[3,4]

Hyper Ig E Syndrome (HIES), a rare primary immunodeficiency disorder with an estimated prevalence of <1 per million population, is characterized by markedly elevated serum Ig E levels, recurrent skin and lung infections, eczema-like dermatitis, and connective tissue and skeletal abnormalities. It was first described in 1966 by Davis et al.,[5] who reported two girls with "cold" abscesses (staphylococcal) and eczema-like skin lesions, coining it the “Job's Syndrome”. HIES affects multiple systems due to defects in immune regulation and tissue remodelling, and patients typically present in childhood. The condition is notable for its triad of features: eczema, recurrent skin/lung infections (often with Staphylococcus aureus), and significantly elevated serum Ig E levels (often >2,000 IU/mL). Autosomal Dominant Hyper Ig E Syndrome (AD-HIES) occurs as a result of STAT3 mutations and features non-immunological manifestations like characteristic facies, retained primary teeth, scoliosis, bone fractures, and vascular anomalies. Immune dysfunction in AD-HIES includes impaired Th17 cell development, leading to susceptibility to fungal and bacterial infections. The autosomal recessive Hyper Ig E Syndrome (AR-HIES) involves the DOCK8, TYK2, and many others and manifests more severe viral infections (e.g., molluscum contagiosum, HPV), neurologic manifestations, and increased cancer risk. Recessive condition also seems to lack connective tissue and skeletal abnormalities seen in AD-HIES. We report a case of AD-HIES in a young girl with multisystem involvement and a confirmed STAT3 mutation.

2. CASE PRESENTATION

A 7-year-old female, born of a non-consanguineous marriage, presented to the outpatient department with complaints of itchy eyes, watery ocular discharge, and blurring of vision. She also complained of recurrent otitis media with persistent ear discharge, frequent rhinorrhoea, multiple skin boils, and repeated hospital admissions for throat infections since early childhood. There was a history of episodic periorbital and labial swelling over the preceding two years. She underwent multitude of examinations and tests at multiple centres without a diagnosis before she attended our OPD.

At presentation, the child had no active infections. Perinatal history, developmental and family history were unremarkable. She was immunised up to age. She was noted to have below-average scholastic performance but maintained a cheerful demeanour.

On examination, she was vitally stable with normal anthropometric parameters for age and gender. Dysmorphic facial features included a low anterior hairline, synophrys, wide nasal bridge, and prominent ears with absent antihelices bilaterally. Dermatological findings included dry skin and healed scars from previous boils on the nose and extremities. Ocular examination revealed corneal opacities.

Laboratory investigations revealed leucocytosis with lymphocytic predominance and eosinophilia (PMN 41%, lymphocytes 44%, eosinophils 13%), with an absolute eosinophil count of 1036 cells/μL. Serum Ig E level was markedly elevated at 4560 IU/mL.

Ophthalmological evaluation revealed dry cornea and linear healed abrasions causing linear opacities and visual blurring. ENT examination confirmed chronic suppurative otitis media, requiring antibiotics. Dermatology consultation with expert was done. She was started on prophylactic antibiotics, emollients, topical agents, and antihistamines after dermatology consultation.

Genetic testing identified a heterozygous pathogenic mutation in the STAT3 gene, confirming the diagnosis of autosomal dominant Hyper-Ig E Syndrome. Dental evaluation was normal. Baseline chest radiography and echocardiography were within normal limits. She was closely followed and was re-admitted four months later for membranous tonsillitis, which was treated with intravenous antibiotics.

Over the subsequent six months, her general condition improved with no further hospital admissions. Follow-up showed regression of corneal opacities, resolution of ocular discharge, and improved vision. She had two further episodes of ear discharge, both managed on an outpatient basis. A CT scan of the mastoid was performed, and she is planned for definitive surgical intervention. No new skin infections have occurred since.

Figure 1: Facial dysmorphism showing synophrys, wide nasal bridge, prominent ears with absent helices bilaterally

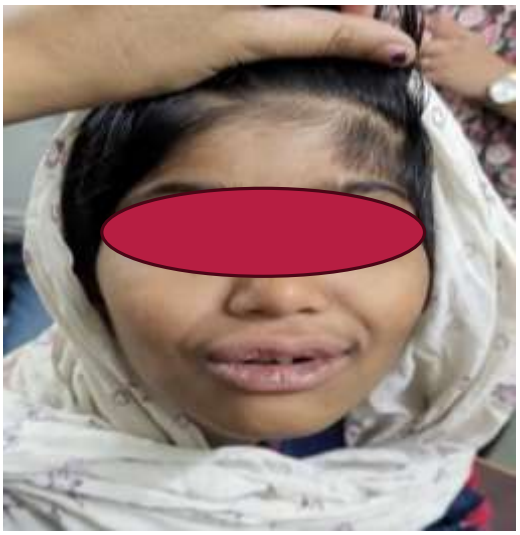

Figure 2: low anterior hair line and labial swelling

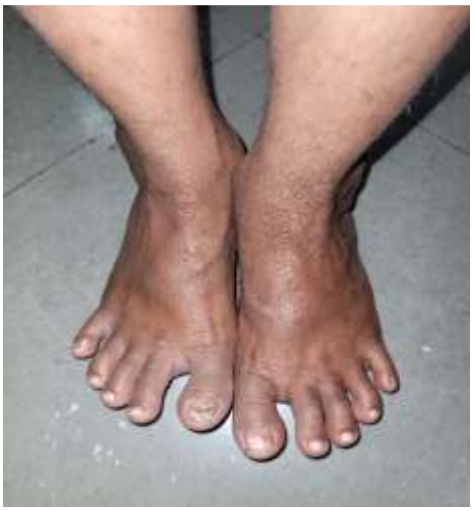

Figure 3: image showing feet revealing very dry skin, healed nail infection

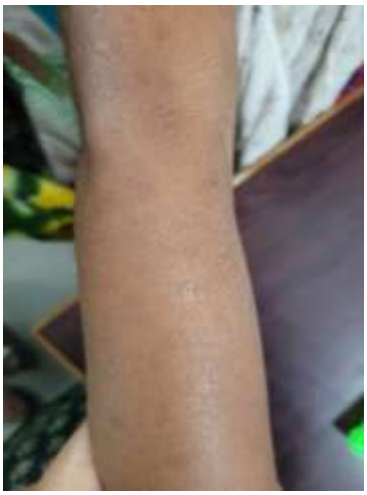

Figure 4: photo of cubital area showing dry skin, healed skin boils

Figure 4: healed skin boils scars evident on nose

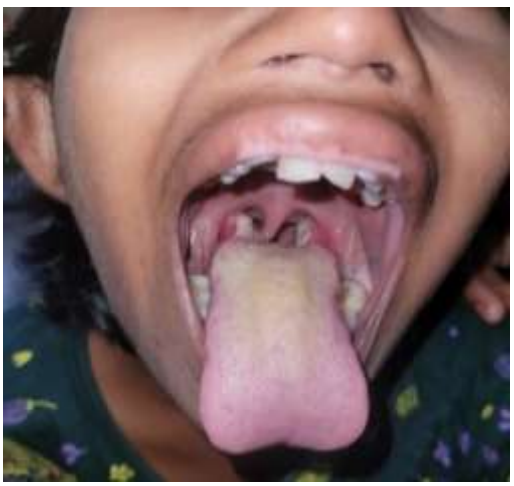

Figure 5: image taken during re admission after 4 months for acute membranous tonsillitis.

3. DISCUSSION

Hyper-IgE syndrome is a rare disorder with varied clinical manifestations. The autosomal dominant variant, caused by STAT3 mutations, leads to impaired Th17 cell differentiation, resulting in susceptibility to bacterial and fungal infections. Characteristic features include eczema, recurrent skin abscesses, pneumonia, and elevated serum Ig E. Dysmorphic facial features further support the diagnosis as in our case. Diagnosis is often clinical, supported by elevated Ig E levels, eosinophilia, and confirmed by genetic testing. Early recognition and diagnosis is vital, as prompt antimicrobial prophylaxis for infections and skin care can significantly improve outcomes, alleviate parental anxiety and help the family understand the condition better. Continued advancements in genomic medicine have expanded our understanding of HIES, revealing its heterogeneity and guiding individualized management approaches.

Newer disorders are continually being added to this classification as our understanding of immunogenetics deepens. Functional studies, high-throughput genetic testing, and the use of bioinformatics tools have enabled earlier and more accurate diagnosis in children, often even in the neonatal period. Early recognition is crucial, as it allows for timely interventions such as immunoglobulin replacement therapy, hematopoietic stem cell transplantation (especially in DOCK8 deficiency), or targeted biologic treatments, significantly improving outcomes and quality of life for affected children.

4. CONCLUSION

This case underscores the diverse clinical presentation of Hyper-IgE syndrome and the importance of considering primary immunodeficiencies in children with recurrent infections and dysmorphism. Multidisciplinary management and genetic confirmation can significantly improve patient outcomes.

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