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Hyper-IgE syndromeN Rezaei¹, A Aghamohammadi²

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Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency disease, characterized by increased serum levels of IgE as well as eczema and recurrent cutaneous and pulmonary infections. It was first described as Job's syndrome in 1966, in patients who suffered from

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recurrent sinopulmonary infections and cold skin abscesses due to *Staphylococcus aureus*; however, the term was subsequently changed to "Hyper-IgE syndrome", when an elevated level of IgE was detected in the serum of affected patients. ^[1]

:: Genetic Defects

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Although autosomal dominant (AD-HIES, OMIM#147060) and autosomal recessive (AR-HIES, OMIM#243700) patterns of inheritance were described for HIES, underlying genetic defects of disease were not discovered for about four decades. Recent studies demonstrated that mutations in the signal transducer and activator of transcription 3 (*STAT3*, OMIM*102582) gene lead to AD-HIES, ^[2] whereas mutations in either the dedicator of cytokinesis 8 (*DOCK8*, OMIM*611432) gene ^[3] or the tyrosine kinase 2 (*TYK2*, OMIM*176941) ^[4] gene cause AR-HIES. There are still several patients with HIES phenotype in which the underlying genetic defect is unknown. Although the pathophysiology of the disease has not been completely understood, combined B- and T-cell immunodeficiency is reported in *DOCK8* deficiency, whilst impaired T-helper 17 function due to defective signal transduction for multiple cytokines could be the molecular basis of HIES phenotypes in *STAT3* deficiency and *TYK2* deficiency.

:: Clinical Manifestations

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AD-HIES. Hyper-IgE syndrome is a multi-system disorder with a wide range of clinical phenotypes, including connective tissue, skeletal, and vascular abnormalities. ^[5] The patients with classical form (*STAT3* deficiency) often present their first manifestations early in life. Patients' coarse facial appearance is distinctive with broad nasal bridge, deep-set eyes, prominent chin and forehead, cheilitis, and thickened skin. Osteoarticular abnormalities include short stature, osteoporosis, pathologic fractures, scoliosis, craniosynostosis, and hyperflexible joints. Eczema and delay in shedding of primary teeth are common findings in the affected children, whilst they usually suffer from recurrent bacterial infections, especially skin abscesses due to *Staphylococcus aureus*, and pneumonia with pneumatoceles formation. Malignancies (such as lymphoma and leukemia) and arterial malformations (such as coronary artery aneurysms) have been reported in some cases. ^{[1],[6]}

AR-HIES. Although connective tissue and skeletal abnormalities are not associated with AR-HIES, these patients experience eczema and recurrent cutaneous and pulmonary infections. ^[7] Severe viral infections such as *Molluscum contagiosum* and *Herpes simplex virus* infections have been frequently seen in *DOCK8* deficiency, whereas an increased susceptibility to intracellular bacteria such as *Mycobacteria* and *Salmonella* [More Details](#) as well as fungi and viruses has been reported in *TYK2* deficiency. Neurological symptoms, such as partial facial paralysis, hemiplegia and central nervous system hemorrhage have also been reported in a number of patients with AR-HIES. ^{[1],[6]}

:: Diagnosis

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The diagnosis of HIES is usually made based on characteristic clinical phenotypes associated with increased serum levels of IgE (typically >2000 IU/mL) and eosinophilia. Although the National Institute of Health scoring system (NIH-HIES) based on clinical and laboratory test criteria had been developed a decade ago, a very recent paper suggests diagnostic criteria of increased IgE (>1000 IU/mL) plus a weighted score of clinical features >30 (based on five features of recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic face and high palate) as possible diagnosis of AD-HIES. ^[8] However, considering recently identified genetic defects, a definite diagnosis can be made by mutation analysis. Consequently, prenatal diagnosis for pregnancies at increased risk is possible, but requires prior identification of the disease-causing mutation in the family.

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Although no curative treatment is available, prophylactic antibiotics and specific treatment based on organ involvement (e.g., surgical interventions for abscess drainage and conventional care for dermatitis) and systemic antibiotics in case of infections are suggested. Immunoglobulin replacement therapy and some other treatments such as IFN- γ , Histamine-2 antagonists, and cyclosporine have been tried, which seem to be useful in the management of patients with HIES. [\[1\]](#),[\[6\]](#)

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Prophylactic antibiotic therapy (e.g., trimethoprim-sulfamethoxazole) should be recommended in the HIES patients with recurrent sinopulmonary and cutaneous infections to prevent Staphylococcal infections. The coverage of gram-negative bacteria should also be considered in selecting prophylactic antibiotics, when patients are complicated with pneumatoceles or bronchiectasis. Antifungal prophylaxis (e.g., fluconazole) is also required because most patients are at increased risk for mucocutaneous candidiasis and invasive fungal infections. [\[1\]](#),[\[6\]](#)

:: Conclusion[Top](#)

HIES is a complex primary immunodeficiency disease with increased serum levels of IgE and distinct phenotypes: the classical form of the disease is characterized by coarse face and connective tissue, skeletal, and vascular abnormalities which is inherited in an AD-HIES (due to *STAT3* mutations). The patients with AR-HIES lack the connective tissue and skeletal manifestations, but there is an increased rate of severe viral infections (due to *DOCK8* mutations) and intracellular bacteria (due to *TYK2* mutations). Although mutations in *STAT3* account for most cases of AD-HIES and mutations in *DOCK8* were identified in some patients with AR-HIES, there are still several patients with unknown genetic defect. Indeed the exact pathophysiology of the disease has not clearly been understood. It is to be hoped that better understanding of underlying mechanisms will be achieved in the near future, in respect to recent progress in discoveries of genetic defects, which could lead to designing new therapeutic strategies for HIES.

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