Clinical Diagnosis of Autosomal Recessive Hyper-IgE Syndrome: Report of Three Cases

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Abstract
Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency disease characterized by the triad of elevated serum IgE (>2000IU/ml, approximately 75%), recurrent cutaneous abscesses of staphylococcal etiology, and recurrent sinopulmonary infections.

Keywords: Serum IgE; Sinopulmonary Diseases; Antibiotic Prophylaxis

Abbreviations: HIES: Hyper-IgE Syndrome; DOCK8: Dedicator of Cytokinesis 8; TYK2: Tyrosine Kinase 2; STAT3: Signal Transducer and Activator of Transcription 3; AR-HIES: Autosomal recessive hyper-IgE syndrome

Introduction
Hyper-IgE syndrome (HIES) is a rare primary immune deficiency characterized by elevated serum IgE and recurrent skin and lung infections. There are two forms of HIES: a dominant form caused by mutations in Signal transducer and activator of transcription 3 (STAT3), and a recessive form mainly resulting from mutations in Dedicator of cytokinesis 8 (DOCK8) gene and rarely in tyrosine kinase 2 (TYK2) gene [1]. The dominant form is characterized by non-immunological features including skeletal, connective tissue, and pulmonary abnormalities in addition to recurrent infections and eczema. In contrast, the recessive form lacks the somatic features and has marked viral infections, severe atopy, neurological complications and early-onset malignancy [2]. The condition is thought to be rare, although the exact prevalence is unknown; approximately 200 cases have been described in the literature [3].

Case Reports
Case 1
A 10-year-old girl born of a non-consanguineous marriage presented with severe eczema over her face, and trunk, with associated skin abscesses. Paronychia of several fingers was also noted. She had a fever of up to 38.5 °C with a stuffy nose and cough for one week. A plain chest film showed increased infiltrations over both lower lung fields. Recurrent upper respiratory infections and several episodes of bronchopneumonia were also noted. She had no facial dysmorphic features or a history of bone fracture. Laboratory examinations showed an increase in total IgE level (25100IU/ml) and eosinophilia (912). A diagnosis of autosomal recessive HIES was made based on a National Institutes of Health hyper-IgE syndrome (NIH-HIES) score of 42 and DOCK8 gene mutation.

Case 2
This 3-year-old girl had been suffering from recurrent infections of otitis media, bronchitis and pneumonia in the past one year. Generalized pustular skin lesions associated with atopic-like dermatitis also persisted, and Staphylococcus aurous infection was proven by culture. Oral candidiasis was also found. A diagnosis of allergy-type asthma and food allergy correlated with her RAST test results. Moreover, a high serum total IgE concentration of up to 16100IU/ml and eosinophilia (1455) were found. No skeletal or dental abnormalities were found; however a consanguineous marriage was noted. According to the above clinical features and laboratory findings, and DOKK8 deficiency was found in further investigation, type 2 HIES was diagnosed. Also, patient’s NIH-HIES score was 43.

Case 3
A 14-year-old boy born of non-consanguineous parentage and uneventful pregnancy was brought to our hospital on several occasions with fever, moderate to severe eczema with latensification and X-ray proven recurrent pneumonia. He had a history of allergic
rhinitis. No facial dysmorphism or a history of fracture was noted, however oral candidiasis was detected very early in life with paronychia of several fingers. On this presentation, the patient was suffering from mycoplasma pneumonia and herpes simplex skin infection. His serum IgE concentration was up to 7430IU/ml and eosinophilia was found (2122). Based on the above history, laboratory results, and a NIH-HIES score of 42 points, autosomal recessive HIES was highly suspected even DOCK8 gene mutation was not presence.

Discussion

Hyper-IgE syndrome is a rare disorder with multi-organ manifestations which was first described in 1966. Two genetic defects have been described: STAT3 mutations act in a dominant negative manner to cause autosomal dominant HIES, and DOCK8/TYK2 deficiency acts in a recessive manner to cause autosomal recessive HIES. Both forms commonly present with immunological dysfunction accompanied by high IgE (>2000IU/ml) concentration and eosinophilia. In 1999, Grimbacher et al 4 established a NIH clinical HIES scoring system, and a more recent scoring system with fewer but more pathognomonic clinical findings was proposed in 2010 [4]. A clinical diagnosis of HIES can be made with a NIH-HIES score of more than 40, with confirmation by molecular analysis. Autosomal recessive hyper-IgE syndrome (AR-HIES) was first described by Renner 5 and colleagues in patients from 6 consanguineous families that had features consistent with a diagnosis of HIES, including recurrent pneumonia and staphylococcal skin abscesses, eczema, viral infections such as chronic refractory molluscum contagiosum and herpes simplex, mucocutaneous candidiasis, elevated serum IgE and eosinophilia.

However, these patients did not have connective tissue and skeletal abnormalities as seen in autosomal dominant HIES [5]. Subsequently, mutations in the DOCK8/TYK2 genes were found to account for the patients with AR-HIES. DOCK8 deficiency impacts the long-term memory of B cells as well as of virus-specific CD8+ T cells [6,7], which may explain the susceptibility to bacterial and persistent viral infections. Both TYK2-HIES and DOCK8 are also prone to allergic rhinitis and food allergies, whereas this finding is atypical in autosomal dominant HIES [8]. Treatment remains supportive and has been less explored than in STAT3 deficiency. Prophylactic antimicrobials appear to help, and antivirals and antifungals should be given if needed [9].

Conflicts of interest

The authors declare no conflicts of interest that may be inherent in the submission. The Institutional Review Board (IRB) of the Hospitals approved the study and all the participants’ parents or guardians provided written informed consent.

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