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Autosomal Recessive Hyper-Ige Syndrome: Reported of Three Cases

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ABSTRACT

Hyper-IgE syndrome (Job syndrome, HIES) is a complex primary immune deficiency disease characterized by the triad of elevated serum IgE (>2000 IU/ml, approximately 75%), recurrent cutaneous abscesses of staphylococcal etiology, and recurrent sinopulmonary infections. Treatment of these syndromes has relied on prophylactic and therapeutic antimicrobials and aggressive skin care. We are reporting three cases with recurrent cutaneous and respiratory infections, marked elevated levels of serum IgE and high National Institutes of Health hyper-IgE syndrome scoring over the score 30.

Keywords: Hyper immunoglobulin E, Treatment, Prophylaxsis, Immunodeficiency, Sinusitis

Abbreviations: HIES: Hyper-IgE Syndrome; STAT3: Transcription 3; DOCK8: Dedicator of Cytokinese Protein 8; TYK2: Tyrosin Kinase 2; NIH-HIES: National Institute of Health - Hyperimmunoglobulin E Syndrome

INTRODUCTION

The HIES are rare primary immune deficiencies characterized by elevated serum IgE and recurrent skin and lung infections. There are two forms of HIHS: a dominant form caused by mutations in Signal transducer and activator of transcription 3 (STAT3) and a recessive form mainly result from mutations of dedicator of cytokinese protein 8 (DOCK8) and rare from Tyrosin kinase 2 (TYK2) mutations [1-4]. The dominant form is characterized by non-immunologic 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, neurologic complication and early-onset malignancy [5]. Complications of pulmonary infections are the most common causes of death and late diagnosis significantly worsens the respiratory function and reduces the chance for normal development of a child [6]. The condition is thought to be rare, although the exact prevalence is unknown; approximately 200 cases have been described in the literature [7].

CASE REPORTS

Case 1

A 10 year old girl born of a non-consanguineous marriage presented with severe eczema over face, retro-auricular area, trunk. Skin abscess were also associated. Paronychia of several fingers was present. Fever up to 38.5°C with stuffy nose and cough for one week. Plain chest film showed increased infiltrations over both low lung fields. History of allergic asthma which proved sensitized to dust mite, cat dander and dog dander. Recurrent upper respiratory infections and bronchopneumonia several times were also found. Physical examination showed decrease of bilateral breathing sound with fine moist rales. She has no facial dysmorphic features and/or history of bone fracture. Reveal of the laboratory evaluation findings showed increase of total IgE level (25100 IU/ml) and eosinophilia (WBC 10.99, Neu 69.8%, Lym 12.6%, Eso 8.3%, Baso 0.1%). Mycoplasm IgM concentration was 160x positive.

Diagnosis of autosomal recessive hyper-IgE syndrome was based on the National Institute of Health hyper-IgE syndrome scoring, the score is 42 points. After admission to the hospital, improvement of the clinical state of the respiratory tract was obtained as a result of continuous beta-lactase plus macrolide antibiotic treatment and nebulization with bronchodilator. The patient remains under care of hospital outpatient clinic and does not present with chest X-ray abnormalities at this time.

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Case 2

This 3 year old girl has been suffering from recurrent infections of otitis media, bronchitis and pneumonia in passed one year. Several upper respiratory infections were noted per year. Generalized pustular skin lesions associated with atopic-like dermatitis also persisted and staphylococcus aurous infection was proved by culture. Oral candidiasis was found. Doctor diagnosed allergy type asthma and food allergy were correlated with the patient's RAST test results, which showed positive to dust mite, cockroach, crab, shrimp, codfish, egg yolk, egg white, peanut, soybean and wheat. Moreover, high serum total IgE concentration up to 16100 IU/ml and eosinophilia (WBC 10.86, Neu 52.5%, Lym 29.2%, Mono 4.6%, Eos 13.4%, Baso 0.3%) were revealed. The patient did not show any skeletal and dental abnormalities but consanguineous marriage was found in history taking. According to the above clinical features and laboratory findings, type 2 hyper-IgE syndrome was diagnosed associated with National Institute of Health - Hyperimmunoglobulin E Syndrome (NIH-HIES) score 43 points. Treatment involves allergens avoidance and giving appropriate antibiotics, cefadroxil and cloxacillin, for *Staphylococcus aureus* infection. Also, intravenous immunoglobulins were used as adjunct therapy. This young girl's condition was being controlled and was followed at the outpatient clinic.

Case 3

A 14 year old boy born of non-consanguineous parentage and uneventful pregnancy was brought on several occasions with fever, moderate to severe eczema with lichenification and X-ray proven recurrent pneumonia. Upper respiratory infections more than 6 times per year were documented. History of allergic rhinitis and allergen-specified IgE of dust mite, candida, cat dander, dog dander and cockroach were positive. No facial dysmorphism or history of fracture was noted but oral candidiasis starts very early in life and paronychia of several fingers present. Currently, patient has suffered from mycoplasma pneumonia and herpes simplex skin infection, which treated at our outpatient clinic with macrolide antibiotic and oral acyclovir treatment for two weeks. Serum IgE concentration was determined up to 7430 IU/ml and eosinophilia was found (WBC 7.950, Neu 36%, Lym 30.3%, Mono 6.5%, Eos 26.7%, Bso 0.5%). Based on the above history and investigation and NIH-HIES equal to 42 points, autosomal recessive hyper-IgE syndrome is highly suspected.

DISCUSSION

Hyper-IgE syndrome is a rare disorder with multi-organ manifestations and it was first described in 1966. Now two genetic defects have been described: STAT3 mutations act in a dominant negative manner to cause of autosomal dominant HIES, and DOCK8/TYK2 deficiency act in a recessive manner to cause of autosomal recessive HIES. They commonly present with immunological dysfunction accompanied by high IgE>2000 IU/ml concentration and eosinophilia. A NIH clinical HIES scoring system was established by Grimbacter et al. in 1999 [8] and a more recent scoring system with fewer but more pathognomonic clinical findings was reported in 2010. A clinically diagnose HIES if the score of the patient is above 40 points, which is confirmed by molecular analysis [9].

Autosomal recessive hyper-IgE syndrome (AR-HIES) was first described by Renner et al. [10] and colleagues of 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, muco-cutaneous candidiasis, elevated serum IgE and eosinophilia. However, these patients did not have the connective tissue and skeletal abnormalities as in AD-HIES. Subsequently, mutations in DOCK8/TYK2 gene were found to account for the patients with AR-HIES. In B-cells, DOCK8 functions as an adaptor protein downstream of TLR9 and upstream of STAT3, driving B cell proliferation and immunoglobulin production [11]. DOCK8 deficiency impacts long-term memory of B cells as well as of virus-specific CD8+ T-cell1 [2,13], which might 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 AD-HIES [14,15].

Treatment remains supportive and less explored than STAT3 deficiency. Prophylactic antimicrobials likely help, antivirals and antifungals if needed [16].

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REFERENCES

1. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, et al. (2007) STAT3 mutations in hyper-IgE syndrome. N Engl J Med 18: 1608-1619.
2. Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, et al. (2009) Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med 361: 2046-2055.
3. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, et al. (2004) Autosomal recessive hyerimmunoglobulin E syndrome: A distinct disease entity. J Pediatr 114: 93-399.
4. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, et al. (2006) Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 25: 745-755.

5. Zhang Q, Su HC (2011) Hyperimmunoglobulin E syndromes in pediatrics. Curr Opin Pediatr 23: 653-658.

6. Jonczyk-Potoczna K, Szczawinska-Poptonyk A, Warzywoda M, Bręborowicz A, Pawlak B et al. (2012) Hyper-IgE syndrome (Job syndrome, HIES)-radiological images of pulmonary complications on the basis of three cases. Pol J Radiol 77: 69-72.

7. Yong PFK, Freeman AF, Engelhardt KR, Holland S, Puck JM, et al. (2012) An update on the hyper-IgE syndromes. Arthritis Res Ther 14: 228.

8. Grimbacter B, Schaffer AA, Holland SM, Davis J, Gallin JI, et al. (1999) Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Jum Hum Genet 65: 735-744.

9. Woellner C, Gertz EM, Schaffer AA, Lagos M, Perro M, et al. (2010) Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol 125: 424-432.

10. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, et al. (2004) Autosomal recessive hyperimmunoglobulin E syndrome: A distinct disease entity. J Pediatr 144: 93-99.

11. Jabara HH, McDonald DR, Janssen E, Massaad MJ, Ramesh NV, et al. (2012) DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. Nat Immunol 13: 612-620.

12. Randall KL, Chan SS, Ma CS, Fung I, Mei Y, et al. (2011) DOCK8 deficiency impairs CD8 T cell survival and function in humans and mice. J Exp Med 208: 2305-2320.

13. Randall KL, Lambe T, Goodnow CC, Cornall RJ et al. (2010) The essential role of DOCK8 in humoral immunity. Dis Markers 29: 141-150.

14. Robinson WS, Arnold SR, Michael CF, Vickery JD, Schoumacher RA, et al. (2011) Case report of a young child with disseminated histoplasmosis and review of hyper immunoglobulin E syndrome. Clin Mol Allerg 9: 14.

15. Zhang Q, Davis JC, Dove CG, Su HC (2010) Genetic, clinical and laboratory markers for DOCK8 immunodeficiency syndrome. Dis Markers 29: 131-139.

16. Freeman AF, Holland SM (2008) The hyper IgE syndromes. Immunol Allergy Clin North Am 28: 277-viii.