A Two Homozygous Mutations in DOCK8 Gene in Saudi Infant with Hyper IgE Syndrome.

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ABSTRACT

Hyper IgE syndrome (HIES) is a form of primary immunodeficiency associated with eczema, sinopulmonary infections, and elevated serum IgE. The majority of cases are sporadic but autosomal dominant and recessive forms are identified. We report a one year old Saudi girl with a two homozygous mutations in DOCK8 Gene.

الملخص: تعتبر متلازمة فرط الأجسام المناعية (إي) نوع من أمراض نقص جهاز المناعة الأولي والتي يصاحبها التهاب الجلد التأتبي والتهابات الجيوب الأنفية والرئتين مع ارتفاع في مستوى الأجسام المناعية (إي) (IgE) في الدم. أغلبية الحالات المصابة ناتجة عن طفرات فردية ولكن هناك حالات ناتجة عن اضطرابات صبغية جسدية سائدة ومتنحية. هنا نعرض حالة طفلة سعودية لديها متلازمة فرط الأجسام المناعية (إي) وتحمل طفرة وراثية نادرة لم يسبق وصفها من قبل في مورثة الصفات المسماة (DOCK8).

Introduction

Hyper Immunoglobulin E Syndrome (HIES) is a rare immune deficiency disease due to mutations in the signal transducer and activator of transcription-3 (STAT3) (chromosome 17, MIM=147060), Dedicator of Cytokinesis 8 (Dock-8) (chromosome 9, MIM=243700) and Tyrosine Kinase-2 (TYk2) (chromosome 19, MIM= 611521) genes. The incidence of the syndrome is about 1/10000 to 1/200000.[1] It is characterized by recurrent skin and chest infections, atopic dermatitis and elevated serum IgE concentrations. [2-3] Autosomal dominant form is more common than autosomal recesive.[4] HIES symptoms that usually appear in the infancy are characterized by eczema, recurrent infections like skin abscess, sinusitis, otitis media, and pneumonia. The diagnosis of HIES is based on symptoms determining of mutation. Treatment of this syndrome include prophylactic antibiotics ,management of infections, and skin care measures. Hematopoietic cell transplantation (HCT) is the last and definitive therapeutic method. [5] Here, we describe a 1 year old Saudi female infant with hyper IgE syndrome. The patient was shown to have two homozygous mutations in DOCK8 gene that not reported before.

CASE REPORT

We report the case of one year old girl infant who was born for consanguineous

parents with no family history of immunodeficiency. She was admitted to our hospital at age of one year because of fever, cough, and shortness of breathing. The patient had generalized scaly erythematous skin rash which involve the whole body include the scalp. She had recurrent chest infections and atopic dermatitis.

The physical examinations revealed well looking ,mildly dehydrated, tachypnic and febrile child. She had generalized erythematous maculpopular skin rash with scaly apperance. Chest examination was showed decreased air entry bilaterally with expiratory wheezes. There were no lymphadenopathy, hepatomegaly or splenomegaly. Overall, the other parts of the exam were unremarkable.

The initial CBC was showing the following results: WBC count of 25.1×109/L, of which the neutrophil count was 12×109/L, lymphocyte count was 6.6×109/L, and eosinophil count was 5.6×109/L. Hemoglobin count was 12.2 g/dl and the platelet count was 1053×109/L. Lymphocyte marker revealed an absolute lymphocyte count of 4.48×109/L absolute CD3+ 2.17 ×109/L (48%), absolute CD4+ 1.54 ×109/L (34 %), absolute CD8+ 0.63×109/L (14 %), absolute CD19+ 1.61 ×١٠٩/L (٪٣٥), and absolute CD+١٦/CD+٥٦ ١٠٩×٠,٦٣/L (١٤ ٪). IgG, IgM, and IgA were normal with very high serum IgE levels > 5000 Ku/L.

The patient's Blastogenesis showed marked depression in lymphocytes response to phytohemagglutinin (RR 37%), and concanavalin A (RR 45%),normal response to pokeweed mitogen (%RR 87%) and mild depression in lymphocytes response to pooled allogeneic cells (RR 66).The sequence analysis of DOCK8 gene has identified the following mutations :

D N A Change:	**Mutation 1:** Homozygous mutation for c.4346 C>T From Variant one (ENST00000453981) **Mutation 2:** Homozygous mutation for c.4626+5 G>A From Variant one (ENST00000453981)
Protein Change:	**Mutation 1:** S1449L **Mutation 2:** Splice Site Mutation at position5 after the end of exon 45.
Predicted affect on gene/gene function	**Mutation 1:** A change from a conserved hydrophilic polar (S: Serine) To hydrophobic nonpolar (L: Leucine). Expected to be not a pathogenic change as predicted by PolyPhen-2. **Mutation 2:** Conserved Splice Site Mutation. The effect of the splice site mutation has not been determined. However, no DOCK8 protein was detected by western blot. The absence of the DOCK8 expression is significant and is expected to lead to be pathogenic of HIgE.

these changes have not been reported previously. The patient has been treated with broad spectrum antibiotics and intravenous hydration. She has been improved clinically and discharged on prophylactic antibiotics.

She had a full match donor (her sister). She has been referred to higher medical center for bone marrow transplantation that has been done successfully there. She has a good health status after the transplant with regular medical follow up.

DISCUSSION

Hyper IgE syndrome (HIES), first defined in 1966 by Davis[6].HIES is a multisystemic disorder characterized by eczema, recurrent pulmonary and skin infections and markedly increased levels of serum IgE.Most of the cases occur sporadically. Autosomal dominant form is caused by mutations in STAT3 identified in 2007,[7]presents with skeletal, connective tissue, and pulmonary manifestations by whereas, Autosomal recessive form is caused by mutations in DOCK8, identified in 2009, presents with severe dermatitis, and recurrent skin infections. [8]

The differential diagnosis of Hyper IgE syndrome (HIES) include other immunodeficiency diseases that associated with elevated IgE levels such as Wiscott-Aldrich syndrome, Omenn syndrome, atypical complete DiGeorge syndrome, Netherton syndrome and immune dysregulation, polyendocrinopathy and enteropathy X-linked (IPEX) syndrome. [9]

To diagnose classical Autosomal dominant-HIES a scoring system has been proposed.[10] In the presence of significantly high IgE level combined with lung or cutaneous infections. it may be relevant to perform genetic testing for STAT3 mutations. In certain cases of autosomal recessive-HIES, examining for DOCK8 or Tyk2 mutations may be considered.[11,12]

In Saudi Arabia, there were several cases of Hyper IgE syndrome (HIES) reported to have mutations in DOCK8 gene. This is the first report in the literature showing a two homozygous mutations that have not been descried before. In DNA, first mutation for c. 4346 C>T and Second one for c. 4626+5 G>A. Protein changes in first mutation is S1449L and in other one is splice site mutation at position 5 after the end of exon 45. Effect of the first mutation on gene function tend to be not a pathogenic as predicted by polyPhen-2 but in second mutation, there was NO DOCK8 protein detected by western blot that expected to result in Hyper IgE syndrome (HIES).

Our patient is presented with diffuse scaly erythematous skin rash,recurrent chest infections, and eczema since age of one year. The white blood cell count was elevated with eosinophilia and the IgE level was very high. Blastogenesis showed marked depression in lymphocytes response to phytohemagglutinin and concanavalin A, and mild depression to pooled allogeneic cells.

CONCLUSION

Hyper IgE syndrome (HIES) is a rare primary immunodeficiency . many gene mutations have been discovered recently. The identification of STAT3, DOCK8, and TYK2 mutations has a major role in the diagnosis and treatment for affected

individuals. Early diagnosis of Hyper IgE syndrome (HIES) is very important to initiate appropriate management. After all, Genetic counseling should be considered for family future planning.

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