HYPER IMMUNOGLOBULIN E IGE SYNDROME (HIES) WITH PARTIAL T LYMPHOCYTES DEFICIENCY

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ABSTRACT

The hyper immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by elevated serum IgE with recurrent skin and chest infections[1]. Hyper IgE syndrome exists in both dominant and recessive forms[2]. These two different forms have distinct presentations, courses and outcomes[1]. The autosomal dominant form is mainly due to mutation in STAT3 transcription factor which is associated with additional features of skeletal tissue, connective tissue, dental, vascular and pulmonary abnormalities[2]. The autosomal recessive form is associated with DOCK8 and Tyk2 mutations and absence of connective and skeletal muscle abnormalities but higher incidence of viral infections. Here, we present a two years old male child with skin rashes all over the body, off & on watery diarrhea and failure to gain weight. This patient was diagnosed as a case of coeliac disease at the age of one and half years at some local hospital with one-time assay showing increased anti-tissue transglutaminase antibody (anti TTG) antibodies. Patient was put on gluten free diet for six months but no symptomatic improvement was achieved. Small bowel biopsy showed mild duodenitis without villous atrophy. No organomegaly was detected on ultrasound abdomen. His skin rashes were treated with application of local steroids. Family history revealed that a nephew had undiagnosed diarrhea and skin rashes twenty years back. Blood complete picture, serum immunoglobulins and total IgE, lymphocyte subset analysis and repeat anti TTG antibodies were advised. On the basis of history, family history, examination and immunodeficiency work up final diagnosis of autosomal recessive hyper IgE syndrome (AR-HIES) with partial T lymphocyte deficiency was established.

Keywords: Coeliac disease, Hyper IgE syndrome, Lymphocyte subset analysis.

INTRODUCTION

The hyper immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by elevated serum IgE and recurrent skin and chest infections[1]. Hyper IgE syndrome exist in both dominant and recessive forms[2]. These two different forms have distinct presentations, courses and outcomes[1]. The autosomal dominant form is mainly due to mutation in STAT3 transcription factor which is characterized by immunologic abnormalities including eczematous rashes, skin abscesses, respiratory infections, elevated IgE levels, chronic mucocutaneous candidiasis and eosinophilia and non-immunologic features including skeletal tissue, connective tissue, dental, vascular and pulmonary abnormalities[1,2]. Patients with autosomal dominant hyper IgE syndrome also have increased susceptibility to fungal infections with more than 80% are affected with chronic mucocutaneous candidiasis[1]. The autosomal recessive form is mainly due to DOCK8 (Dedicator of cytokinesis 8) and Tyk2 (Tyrosine kinase 2) mutations and predominant clinical manifestations are severe eczema, recurrent skin and lung infections[1,2]. The patients with hyper IgE syndrome also have neutrophilic defect and eosinophilia secondary to the dysregulation of T and B cell function and very raised IgE. Diagnosis of hyper IgE syndrome is made with clinical history of eczema, recurrent skin and lung infections with IgE level >2000 IU/ml. These patients also have specific antibody deficiencies with poor/absent immunization responses. The principal goal of the management of HIES include prophylactic antibiotics, aggressive treatment of infections and good care of skin. Intravenous immunoglobulins (IVIG) should be used if antibody deficiency is present. INF

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Received: 13 Jun 2018; revised received: 20 Aug 2018; accepted: 28 Aug 2018

gamma has been used in severe infections with good outcome. Stem cell trans-plantation has been tried in some cases, with benefit[3].

CASE REPORT

A two year old male infant, first baby of parents with consanguineous marriage, resident of Lahore, Punjab, visited immunology department at Armed Forces Institute of Pathology. without any improvement. Small bowel biopsy showed mild duodenitis but no villous atrophy was seen. A cousin of the patient had similar symptoms twenty years ago and died at the age of eleven years. The child was vaccinated according to the EPI schedule. Umbilical cord separation occurred on 5th day of postnatal life. On examination, the boy had stable vitals with no

Name: CNE M Adeeb Age: 2 yrs Date: 18.7.17

Parameter	Results	Reference Range Age Specific
1. WBC	6100/ul	4000-12000/ul
2. Lymphocyte Percentage	32%	35-65%
3. Lymphocyte Count	1952/ul	1340-3173
4. CD3+ cells	30%(586)	56-75%(1400-3700)
5. CD3+CD4+ cells	15%(293)	28-47%(700-2200)
6. CD3+CD8+ cells	12%(234)	16-30%(620-2000)
7. CD19+ cells	35%(683)	14-33%(370-1400)
8. CD16+56+ cells	31%(605)	4-17%(130-720)
9. CD4:CD8	1.2	1.0-2.5

Figure-1: Lymphocyte subset analysis.

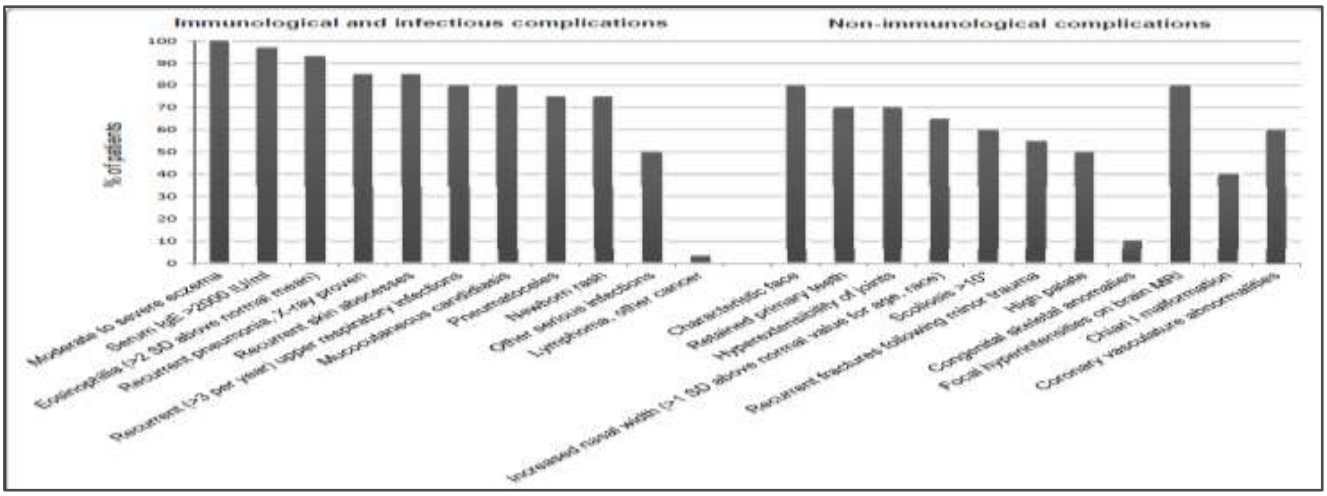

Figure-2: Complications associated with HIES.

The child was suffering from skin rashes all over the body for one year, episodic watery diarrhea and failure to gain weight. Parents visited a hospital in Lahore and got diagnosis of coeliac disease on the basis of increased anti-tissue transglutaminase-antibodies (anti-TTG) antibodies at the age of one and half year. Parents put the child on gluten free diet for six months pallor, cyanosis or mouth ulcers. BCG scar was absent. Skin rashes were present all over the body. Liver and spleen were not palpable. All maternal uncles were alive and healthy. The child was assessed for immunodeficiency. Blood complete picture showed Hb 9.6 g/dl, TLC 6.1+ 109/L and eosinophilia. Serum IgG level 17.3 g/l, IgM 1.22 g/l, IgA 2g/l g/l, serum total IgE levels

were very high, 5956 IU/ml, compatible with hyper IgE syndrome. Surprisingly, lymphocyte subset analysis showed significantly reduced percentage and absolute number of total CD3+ T-lymphocytes. Absolute counts of CD4+ helper T lymphocytes and CD8+ cytotoxic T lymphocytes show marked depression proportionally (fig-1). Repeat anti TTG showed negative result. Negative anti TTG was further confirmed by endomysial antibodies which were also negative. On the basis of history, family history, examination and immunodeficiency workup, final diagnosis of autosomal recessive hyper IgE syndrome (AR-HIES) with partial T lymphocyte deficiency was established. Patient's parents were counseled and advised for prophylactic antibiotic and bone marrow transplantation.

DISCUSSION

The hyper immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by elevated serum IgE with recurrent skin and chest infections[1]. The pathophysiology of hyper IgE syndrome immunodeficiency has recently been linked to a disorder in the T helper 17 pathway and disruption of IL-17 and IL-233. These patients also have specific antibody deficiencies with poor/absent immunization responses[2]. Hyper IgE syndrome exists in both dominant and recessive forms[2]. These two different forms have distinct presentations, courses and outcomes[1].

A mutation in signal transducer and activator of transcription 3 (STAT3) is responsible for autosomal dominant hyper IgE syndrome, a rare and primary cellular complex disorder linked to mutation in the gene encoding for signal transduction STAT3[3]. STAT3 deficient hyper IgE patients are characterize by immunologic abnormalities including eczematous rashes, skin abscesses, respiratory infections, elevated IgE levels, chronic mucocutaneous candidiasis and eosinophilia[1,3]. Non-immunologic features include a characteristic face with thickened doughy skin, a broad nasal bridge, deep set eyes, a prominent forehead, cheeks and jaw, vascular, pulmonary and dental abnormalities[7]. Patients with AD-HIES also have increased susceptibility to fungal infections with more than 80% are affected with chronic mucocutaneous candidiasis[1,2] (fig-2).

The autosomal recessive form is mainly due to mutation in Tyk2 (Tyrosine kinase 2) and DOCK8 (Dedicator of cytokinesis 8). These patients are different from autosomal dominant hyper IgE syndrome as they do not have the skeletal tissue and connective tissue abnormalities but have increased neurological symptoms, features of autoimmunity and viral skin infections[1,2]. The patients with hyper IgE syndrome also have neutrophilic defect and eosinophilia secondary to the dysregulation of T and B cell function and very raised IgE. HIES is a very rare primary immunodeficiency and difficult to diagnose. Accurate diagnosis requires detailed history, family history, examination and elevated serum IgE levels more than 2000 IU/ml. Currently our patient is on prophylactic antibiotics and HLA matching is under process for bone marrow transplantation.

This case is a rare autosomal recessive hyper IgE syndrome with partial deficiency of T lymphocytes in which IgE levels were around 6000 IU/ml and total T lymphocyte (both CD4 and CD8) were significantly reduced (fig-1). The co-existence of hyper IgE syndrome with partial deficiency of T lymphocytes is probably the cause of episodic watery diarrhea which was misdiagnosed as coeliac disease. Few cases of hyper IgE syndrome have been reported in Pakistan but autosomal recessive hyper IgE syndrome with partial deficiency of T lymphocytes is being reported for the first time.

CONCLUSION

Lymphocyte subset analysis of all patients with hyper IgE syndrome must be advised to rule out the co-existence of cellular immunodeficiency. Our patient had skin rashes, watery diarrhea and failure to gain weight. Diarrhea raised the suspicion of coeliac disease and was treated with gluten free diet but no symptomatic

improvement was seen. After the diagnosis of hyper IgE syndrome with partial deficiency of T lymphocytes, patients must be treated as having cellular immunodeficiencies. No live vaccination should be given to new borns with strong sus-picion of hyper IgE syndrome and cellular immunodeficiencies. Importance of suspecting and diagnosing lies in the possibility of offering early prophylactic measures for possible infections and to plan early bone marrow transplantation.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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