

Tanaffos (2010) 9(1), 54-58

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Pulmonary Manifestations of Hyper IgE Syndrome: Case Series and Literature Review

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ABSTRACT

This study aimed to present four children suffering from recurrent pulmonary infections in the context of hyper IgE syndrome. All patients had recurrent pulmonary infections including pneumonia, bronchiectasis, pulmonary abscess and hydropneumothorax. Serum IgE level was greater than 2000 IU/ml in all cases.

Microbial cultures showed Staphylococcus aureus and Pseudomonas aeruginosa in two cases. All responded well to the wide spectrum intravenous antibiotics. Extra-pulmonary manifestations included purulent lymphadenitis as well as skin and brain abscesses.

Hyper IgE syndrome causes recurrent pulmonary and extra-pulmonary infections which respond fairly well to wide spectrum antibiotic therapy. (Tanaffos 2010; 9(1): 54-58)

Key words: Hyper IgE syndrome, Infection, Children

INTRODUCTION

Hyper - IgE (HIES) or Job syndrome is a rare primary immunodeficiency disease with a classic triad of abscesses, pneumonia, and elevated IgE level (1).

Patients with HIES are often afebrile despite serious pneumonia and dermal pathology, and they have cold abscesses (2). IgE level is usually higher than 10,000 IU/ml. Eosinophilia is usually above 700 cells/ml. IgE level is not correlated with either the level of eosinophilia or disease severity (1).

A typical presenting sign of HIES is a newborn rash (3). Most cases are sporadic. However, both autosomal dominant (AD-HIES, type1) and autosomal recessive (AR-HIES, type 2) forms have been reported (1,4)

Autosomal dominant HIES is a multisystem disease that, in addition to the classic triad of HIES, presents with distinct abnormalities of the connective tissue, skeleton and dentition along with coronary artery aneurysms (1,2,4)

Facial appearance (coarse texture of facial skin, asymmetric facial appearance, prominent forehead, deep-set eyes, broad nasal bridge and bulky nasal tip), fractures with minor trauma, retained primary

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Received: 13 April 2009

Accepted: 27 June 2009

teeth, scoliosis, and hyper extensibility of joints are observed among these patients. The other manifestations include parenchymal lung abnormalities (1,5)

Pneumonia in patients with AD-HIES is typically caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*. Recurrent pneumonias are complicated with bronchiectasis and pneumatoceles, probably because of the impaired remodeling of lung tissue. (2, 3)

Lung destruction is further exacerbated by super infection with *Pseudomonas aeruginosa*, *Aspergillus fumigatus*, and rarely, *Pneumocystis jirovecii*, *Mycobacterium intracellulare*, and Nocardia. (2)

The most common opportunistic infection in HIES is Mucocutaneous candidiasis (1).

Cryptococcosis, histoplasmosis, disseminated candidiasis, and post-vaccination necrotizing BCG infection have also been reported (2).

There is often history of recurrent staphylococcal abscesses involving the skin, joints and other sites in infancy (6).

More than 200 patients with hyper IgE syndrome have been reported. (7)

Recently, impaired signaling of the cytokines IL-6 and IL-10, along with the intact signaling of IL-12 and IFN γ was detected in patients with HIES. In a survey on possible abnormalities in the IL-6 specific signal cascade, heterozygous mutations in DNA-binding and Src homology 2 (SH2) domains of STAT3, were detected. All mutations were hypomorphic (missense mutations or in-frame deletions) and involved only 1 allele of STAT3, which suggests a dominant-negative effect (5). Most cases follow either an autosomal dominant pattern or are sporadic (1). A distinct recessive form of this syndrome has been described, in which the patients have autoimmunity, vasculitis and central

nervous system complications. These patients do not develop pneumatoceles, as seen in the autosomal dominant pattern. (4)

All patients demonstrate an exceptionally high serum IgE (>2000 Iu/ml) concentrations, elevated serum IgD concentration, and usually normal concentrations of IgG, IgA and IgM. (6)

The most effective therapy is long-term administration of therapeutic doses of a penicillinase-resistant anti-staphylococcal antibiotic, adding other medications as required for specific infections. IVIG should be administered to antibody-deficient patients and appropriate thoracic surgery should be provided for super infected pneumatoceles or those persisting beyond 6 months. (6)

Although hyper IgE syndrome is a rare condition, the recurrent infections should always raise a suspicion, requiring further evaluation for detecting the syndrome.

We present four cases of HIES with recurrent lung infection and pneumatoceles formation.

CASE SERIES

In this article, we have presented 4 girls with hyper IgE syndrome (HIES) who were admitted to the pediatric ward of Masih Daneshvari Hospital. Their mean age was 5.7 yrs. and age at the time of diagnosis of HIES was 1.6 years. Based on the growth chart, 50% of the cases were above the 50 percentile, while the remaining were below this level. Pneumonia was the clinical presentation in 3 cases and one presented with hydropneumothorax. Other manifestations included skin infections and brain abscess. It is notable that there was a past medical history of recurrent respiratory infections in all patients. In addition, purulent lymphadenitis and multiple cutaneous abscesses were observed in 1 and 3 cases, respectively (Table1).

Table 1. Clinical data of patients.

Patient	Age (years)	Gender	Growth chart	Manifestation	PMH *	Bacteriology	CT scan	Serum IgE	Treatment
1	4.8	female	>50th	right hydropneumothorax	recurrent respiratory infections, skin abscesses, suppurative lymphadenitis	empyema culture: <i>Pseudomonas aeruginosa</i>	RLL pneumatocele	7191 IU/ml	medical & surgical
2	4	female	>50th	pneumonia	recurrent respiratory infections	sputum culture: <i>Staphylococcus aureus</i>	alveolar bronchiectasis	400 IU/ml	medical
3	17	female	<5th	pneumonia & mass in brain	recurrent respiratory infections, skin abscesses	sputum culture: <i>Pseudomonas aeruginosa</i>	alveolar bronchiectasis and brain mass	3228 IU/ml	medical
4	7	female	<5th	pneumonia & skin abscesses	recurrent respiratory infections, skin abscesses	sputum culture: <i>Staph. aureus</i>	alveolar bronchiectasis	4848 IU/ml	medical

* Past medical history

Lung CT-scan demonstrated bronchiectasis and consolidation in 3 cases, while in the fourth patient pneumatoceles was observed. In one of the patients with bronchiectasis, two brain lesions were noted on brain CT scan (Figure 1-3). Immunological tests (including flowcytometry, nitro blue tetrazolium (NBT), immunoglobulin level except for IgE, isoagglutinins, and complements level) were normal in all cases. All had serum IgE levels greater than 2000IU/ml. The most common pathogens detected in the cultures were *Staphylococcus aureus* and *Pseudomonas aeruginosa*.



Figure 1. Hydropneumothorax in one patient.



Figure 2. Alveolar bronchiectasis in one patient.

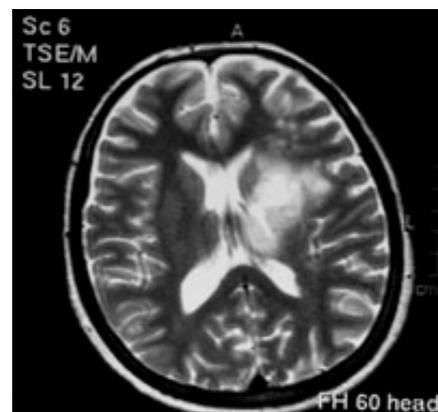


Figure 3. Brain abscess.

Therapeutic measures included administration of wide-spectrum antibiotics and chest physiotherapy for all cases. In one patient with empyema, surgery was also performed in addition to medical therapy. Finally, the patients were discharged with a prescription for antibacterial and antifungal agents as prophylaxis.

DISCUSSION

HIES is a rare multisystem primary immunodeficiency disorder that affects connective tissue, skeleton, dentition and skin. (1,8-10). This syndrome is inherited as a single locus autosomal dominant trait with variable expressivity (7). According to a study by Renner et al. (6), patients with the autosomal recessive form of disease lack skeletal symptoms and can develop autoimmune disease (5,11). Unfortunately, genetic study was not performed in our patients.

Paller AS demonstrated the characteristic clinical features of this syndrome consisting of severe pulmonary infections as recurrent pneumonia, which may complicate to staphylococcal abscesses, pneumatoceles and empyema. There is a high propensity for bronchiectasis. Allergic respiratory symptoms are usually absent (9). However, all of our patients had recurrent pneumonia and its related complications (abscess, and pneumatoceles). Three patients had bronchiectasis and the 4th one had pneumatoceles and empyema on CT-scan and HRCT. These findings are compatible with the manifestations of HIES (9,12).

Muhammed (10) and Paller AS (9) reported that dermatitis was present in more than 80% of the patients with HIES usually beginning in the age range of 2 months to 2 years. It resembles atopic dermatitis, but is accentuated in retroauricular and hairline areas in flexural involvement. The skin and soft tissue infections present as cellulitis, furunculosis, paronychia, suppurative adenitis and

deep soft tissue cold abscesses. Also, three of our cases had skin abscesses and dermatitis in their past medical history (9,12,13). However, the remaining one did not have any skin lesion.

Grimbacher et al. reported non-immunological symptoms consisting of, failure or delay of primary teeth eruption in 72% of patients, recurrent bone fractures in 5%, joint hyper-extensibility in 60% and scoliosis in 70%. However, no non-immunological symptom was detected in our patients (1).

Patients with HIES have a distinctive facial appearance that is independent of gender and race. However, all of our patients had normal appearance (7).

Grimbacher et al. found that IgE levels in HIES usually exceed 2000 IU/ml. However, IgE levels may decrease with age and fall to the normal range (1-90 IU/ml) in about 20% of the cases and do not correlate with disease severity. Therefore, when other features of HIES are present, normal IgE levels should not rule out the presence of HIES in older children. In three of our patients serum IgE levels were higher than 2000 IU/ml (4848, 7191, 3228 IU/ml) (1). The most common pathogens that affect HIES patients are *S. aureus*, *H. influenza* and *Candida albicans*. Our samples for culture were sputum and pleural fluid and the results were *S. aureus* and *Pseudomonas*. This finding was in accord with that of other published studies (7).

Treatment of HIES consists of long-term antibiotic therapy, respiratory physiotherapy and IVIG to antibody-deficient patients. Appropriate thoracic surgery is indicated for super-infected pneumatoceles or those persisting for more than 6 months. Thus, our patients were treated with wide spectrum antibiotics and respiratory physiotherapy in association with surgery (lobectomy and insertion of chest tube in one patient with empyema) (1,7,8).

In conclusion, we described 4 cases with clinical manifestations and characteristics compatible with

HIES. The above-mentioned patients are on antibiotic prophylaxis along with supportive treatment and are in good general condition. Further studies are recommended to determine the genetic etiology and immunological defects resulting in this syndrome.

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