Case Report

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Hyper-IgE Syndrome: Report of Three Cases and Review of Literature

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Abstract

The hyper-immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency disorder characterized by high serum levels of immunoglobulin E (IgE), recurrent skin and lung infections, chronic dermatitis and a variety of connective tissue and skeletal abnormalities. The bacteria that commonly infect these patients are Staphylococcus aureus and Haemophilus influenzae. These patients share some characteristic facial appearance and many oral manifestations. Therapy should include prolonged antibiotic therapy. We report the clinical picture of three patients that presented recurrent infections and different outcomes, and then we describe and compare with our patients the clinical, laboratory and therapeutic aspects of HIES.

Keywords: Hyperimmunoglobulin E syndrome; Job's syndrome; Primary immunodeficiency; Eosinophilia; Recurrent infections

Introduction

The hyper-immunoglobulin E syndrome (HIES) is a complex and rare primary immunodeficiency disorder characterized by recurrent skin and lung infections, dermatitis and elevated serum IgE concentrations [1-3]. Davis and colleagues described this disease first as "Job's syndrome" in two girls suffering from recurrent "cold" staphylococcal abscesses, pneumonia and neonatal-onset eczematoid rash [4]. In 1972, the syndrome was characterized further by Buckley et al. [5] who found extremely high serum IgE levels in the patients. Since that time, other manifestations of the disease were established, like skeletal, connective tissue, cardiac, and brain abnormalities [6-8].

Most cases are sporadic, but at the present time, two forms of HIES are recognized: a dominant form, caused by mutations in *STAT3* (Signal transducer and activator of transcription 3), and a recessive form for which a genetic cause is unclear [6, 9-11] although some cases are due to mutations in the gene *TYK2*. The dominant form (the classic HIES) is the commonest one, characterized by non-immunologic features including skeletal, connective tissue, and pulmonary abnormalities in addition to recurrent infections and eczema [3]. This type was the one presented by the first reports of the disorder [4, 5]. In contrast, the recessive form lacks the somatic features and has severe recurrent viral infections, extreme eosinophilia and devastating neurologic complications [9].

This article presents 3 patients suffering from HIES that were followed in our hospital at different times and with different outcomes; then, a description of the clinical, laboratory and therapeutic aspects of the disease will be made.

Case Report

Case 1

The first patient was a woman, born in 1975, without consanguineous parents, but 3 of her 4 siblings died in the first 2 years of life (cause of the deaths unknown). Since birth, she suffered from recurrent herpetic keratitis of the eye, motivating a corneal transplant at seven years old, that was rejected three years later. She also had a history of atopic eczema, recurrent mucocutaneous candidiasis, multiple *verrucae*, infected cutaneous ulcers and dental abscesses, one episode of intestinal infection with *Giardia lamblia*, and multiple hospitalizations from recurrent infected bronchiectasis. The infectious agents identified were *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *methicilin-resistant Staphylococcus aureus (MRSA)* and *Acinetobacter spp*. Her IgE values

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ranged from 2000 to 5000 UI/mL. She was hospitalized almost every month because of infected bronchiectasis and hemoptysis (pulmonary artery embolization was necessary). She had poor antibody response to polysaccharide antigens and started intravenous immunoglobulins (IVIg) in a dose of 0.4 g/kg/month. There was no change of the clinical picture. At 26 years old a spinocellular carcinoma in the vulva (T1N0M0) was diagnosed and she was submitted to surgery. She developed persistent respiratory insufficiency and died, at 27 years old, from one episode of infected bronchiectasis.

Case 2

The second patient was a woman born in 1976, with consanguineous grandparents (one healthy brother). She had a history of multiple infections of the eye, with three rejected corneal transplants. Recurrent respiratory infections were the rule in her life (the infectious agent identified was always *Staphylococcus aureus*) with structural and functional respiratory abnormalities. She also had recurrent infections of other organs (otitis, skin abscesses and purulent gingivitis). It was described, from the records, a rough skin and scoliosis. Her IgE values ranged from 900 to 1500 UI/mL. It was described an increased activation of lymphocyte B (increased expression of CD23). At 21 years old, she started IVIg in an irregular basis (0.4 g/kg), because of poor antibody response to polysaccharide antigens, and prophylaxis with trimethoprim/sulfamethoxazole because of persistent skin abscesses and respiratory infections. The quality of life was improved after this treatment, with decreased number of hospitalizations. At 28 years old she had an advanced non-Hodgkin lymphoma and started chemotherapy. She died two months later from sepsis.

Case 3

The third case is a man, born in 1985, that at present is followed in our hospital. There is no known consanguinity in the family, but he has a cousin with the same disease. Since childhood, there has been a history of recurrent pneumonias (*Staphylococcus aureus*) and purulent otitis. At 20 years old he was hospitalized because of skin abscesses in the buttocks and dental abscesses, treated with antibiotics. Months later he had corneal ulcer of the eye (Staphylococcus aureus) and prolonged febrile syndrome, and it was the first time he had contact with our team. We documented some characteristic features like prominent forehead, facial asymmetry, a broad nasal bridge, prognathism and rough skin with prominent pores, scoliosis, lack of some teeth, eczematoid dermatitis, oral candidiasis and central depression on the tongue. He had no abnormalities in lung imaging and respiratory functional tests. No cause for the fever was encountered. He started topic treatment with antibiotics, and also systemic empiric antibiotics and antifungal (ciprofloxacin, flucloxacilin, itraconazole, trimethoprim/sulfamethoxazole, metronidazole and albendazole). The fever and the ulcer were treated, although he maintains a chronic diminished visual acuity. His IgE levels are between 8000 and 24700 UI/mL and eosinophilia is 2 - 4 times higher than the normal range. The levels of IgE and eosinophilia never were correlated with the clinical status of the patient. He had a low response to polysaccharide antigens. Since then, he has been with IVIg 0.4 g/kg/month, trimethoprim/sulfamethoxazole (960 mg twice a day) and vitamin C. Now he is 25 years old and no longer has new infections.

Discussion

Clinical manifestations of HIES

HIES usually presents very early in life. The clinical manifestations of the dominant form are resumed here.

Almost all patients suffer from recurrent staphylococcal infections, beginning in infancy and predominantly involving the skin and lungs [1, 2, 12]. A newborn pustular and eczematoid rashes are usually the first manifestations of the disease, typically affecting the face and scalp, with an eopsinophilic infiltrate and caused by *Staphylococcus aureus*. Boils are a classic finding [6]. Trouble areas may persist in intertriginous areas such as the axillae, the inguinal region, or under the breasts [3]. Recurrent pyogenic pneumonias are very common, starting in the childhood. They may present with fewer symptoms, leading to a subsequent delay in clinical presentation, contributing to advanced disease and significant tissue damage before identification and initiation of therapy [3].

In these patients, the degree of inflammatory symptoms is variable. The "cold" abscesses, without external signs of inflammation, initially described by Davis and colleagues [4], are common. *Staphylococcus aureus* is the bacterium most frequently isolated, but *Streptococcus pneumoniae*, *Haemophilus influenzae*, enteric Gram-negative bacteria, *Candida* and *Aspergillus* are also common. Pneumonia is frequently followed by pneumatocele or bronchiectasis, that are commonly superinfected by *Aspergillus fumigatus* and *Pseudomonas aeruginosa* [2, 13, 14]. The secondary infections are more indolent and difficult to clear. These long-term infections are more frequently associated with mortality than the acute pyogenic infections, causing rupture into large pulmonary vessels with life-threatening hemoptysis or fungal dissemination to the brain, for example [13]. Mucocutaneous candidiasis is the most common opportunistic infection. Several cases of *pneumocystosis*, *cryptococcosis* and *histoplasmosis* have also been reported [6, 13, 15-19].

The facial appearance is very characteristic: facial asymmetry, prominent forehead, deep-set eyes, a broad nasal bridge, mild prognathism, and rough appearance of the

facial skin with prominent pores [6, 20, 21]. Some individuals retain their primary teeth, because of the failure of those teeth to exfoliate. The secondary teeth can be present simultaneously when the secondary teeth emerge before primaries have fallen out. Other features are central depressions in the tongue and high arch of the palate [6, 22].

One of the most recent documented features are arterial aneurysms, which can be coronary and extra-coronary. We must recognize in the adult patients the high risk of myocardial infarction as the result of an aneurysm [8]. Brain abnormalities, like T2-weighted hypersensities seen on brain MRI are also present, but gross neurologic abnormalities are not detected in the majority of patients with these findings [1, 7, 8]. Ophthalmologic pathologies such as extensive xanthelasma, giant calazia and undefined tumors of the eyelid have been reported [23-25].

Osteoporosis is common [10, 14], and other skeletal abnormalities include scoliosis, minimal trauma fractures, hyperextensibility, and degenerative joint disease [3, 6, 26, 27].

An increased risk of malignancy is associated with this disorder, contributing to the high mortality. Several malignancies have been reported, including Hodgkin and non-Hodgkin lymphomas, leukemia, and cancers of the vulva, liver and lung [23, 28-31].

Laboratory investigations

Serum IgE concentrations are extremely high in patients with HIES (> 2000 IU/ml) sometimes even at the time of birth. The molecular mechanism of hyper-IgE-emia remains unclear [3, 14]. The IgE levels are not static: they usually are undetectable in cord blood and rise to the adult range slowly over the years, and can diminish again. Substantial fluctuation has been documented over time without any obvious change in clinical presentation [6]. HIES patients have normal or decreased serum IgM, IgG and IgA levels, but most have defects of various types in the antigen-specific antibody response to immunization. IgG subclass deficiencies have been reported in some patients [1].

Eosinophilia is the other consistent laboratory finding [3]. There is no correlation between eosinophilia and IgE levels or eosinophilia and infectious complications of HIES [2]. Total white blood cell counts are normal but they often fail to elevate appropriately during acute infection [2, 3].

An impaired chemotaxis of neutrophils or monocytes has been described, a defect that explains the "cold abscesses" presented by the patients [32].

There is a lack of other pathognomic laboratory signs [3].

Autosomal recessive HIES

Patients with the recessive form have no skeletal and connective tissue abnormalities. They have recurrent or severe infections by *Staphylocuccus aureus*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Cryptococcus*, chronic refractory *Molluscum contagiosum* infections, recurrent aphtoid herpes simplex infections. They are also susceptible to intracellular bacteria (mycobacteria, *Salmonella*). The neurological symptoms are more severe, from partial facial paralysis to hemiplegia. The levels of serum IgE are more elevated than the dominant form. Eosinophilia is also more severe [2, 9].

Therapy of hyper-IgE syndromes

There is no cure for HIES yet. The consensus favors long-term prophylactic therapy of *Staphylococcus aureus* skin and lung infection with an anti-staphylococcal antibiotic such as trimethoprim/sulfamethoxazole [2]. The efficacy of antifungal prophylaxis remains unproven [3]. If possible, the etiologic agent should guide treatment of pneumonia; bronchoscopy may be helpful [3]. Because patients feel well and are unware of how severely ill they are, we need to have a low threshold for investigating slight changes [2, 3].

IFN-gama had inconsistent effects on IgE levels [33]. Intravenous immunoglobulin may decrease the number of infections for some patients [34-36].

Conclusion

In the past five years, there was a significant improvement of the diagnosis of the HIES syndromes. These primary immunodeficiency disorders are rare and usually first manifest during childhood. Patients usually die prematurely due to pulmonary infections; early diagnosis and treatment can be lifesaving and can lead to a significant reduction in morbidity. To best diagnose and treat, we should be familiarized with the clinical and laboratorial aspects of the disease. Besides the infections, we should not forget the risk of malignancy that is associated with HIES. The long-term prophylactic therapy with trimethoprim/sulfamethoxazole is mandatory. We hope that developmental, biochemical, and molecular studies should help us to understand the pathogenesis of the disease and lead to new therapies for patients with HIES.

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