Hyperimmunoglobulinemia E Syndrome
−A Case Report−

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The hyperimmunoglobulinemia E syndrome (HIE syndrome) is a rare autosomal dominant pri-
mary immunodeficiency disorder. It is characterized clinically by hyperimmunoglobulinemia E,
eosinophilia, chronic eczematoid dermatitis, recurrent bacterial infections particularly of the skin and
the respiratory tract, facial and skeletal abnormality features. We report a 22-year-old female who suf-
f ered from HIE syndrome since early childhood. Her serum IgE was extremely elevated to 22,000
IU/ml. In addition to displaying the major features of HIE syndrome, she also developed cold abscess-
es and hyperextensible joints. Bacterial cultures taken from the cold abscess and the neck pustules all
grew *Staphylococcus aureus*. Result of the skin biopsy showed spongiosis, superficial perivascular and
interstitial mixed infiltrate of lymphocytes, histiocytes and some eosinophils. After the skin condition
improved, we prescribed prophylactic antibiotics for her which greatly reduced the infections of the

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INTRODUCTION

The hyperimmunoglobulinemia E syndrome (HIE syndrome) is a rare autosomal dominant disorder with variable expression and incomplete penetrance. It is also named as Job's syndrome, hyper-IgE syndrome, Buckley syndrome and hyperimmunoglobulinemia E syndrome with recurrent infection by different authors. In 1966 Davis et al. first described two girls, and in 1972 Buckley et al. reported two boys with similar symptoms. Since then, over 150 cases have been described, mainly in children.

The HIE syndrome is an immunoregulatory disorder clinically characterized by hyperimmunoglobulinemia E, eosinophilia, recurrent bacterial infections and chronic eczematoid dermatitis that usually manifest in early life. The cutaneous findings include excoriated papules, pustules, furuncles, cellulitis. The most common bacterial pathogen in this disease is *Staphylococcus aureus*. These affected patients usually have histories of bone fracture, skeletal and dental abnormalities. We present a case of HIE syndrome and review the literature on this disorder.
CASE REPORT

A 22-year-old female student developed chronic, atopic-like dermatitis since early childhood. The patient had been hospitalized for many times due to exacerbation of dermatitis or infections. The recurrent infections include otitis, mucocutaneous candidiasis, furunculosis, cellulitis, skin abscess and pneumonia. When she was a child, she had retained primary teeth that needed dental extraction. She also has a history of radial bone fracture due to a minor trauma. The family history disclosed no dermatologic or allergic conditions. A physical examination showed coarse facial features, mild prognathism, a broad nasal bridge, a wide alar base and a wide fleshy tip of the nose. Hyperextensible joints of the girl were also noted (Fig. 1). There is no obvious scoliosis. Many variously sized erythematous papules, excoriated pustules and lichenoid plaques and nodules were present especially on the scalp, posterior auricular areas, neck, face, and buttocks (Fig. 2-3). Two fluctuant subcutaneous abscesses were found on the neck. They were neither hot nor tender and were not associated with systemic symptoms, fever or local redness. Pus was drained out, of which bacterial cultures taken from the cold abscesses and the neck pustules all grew Staphylococcus aureus. Blood cultures didn't grow any bacteria. Laboratory examinations showed a peripheral leukocyte count of 11300/µl. Peak eosinophil rate were as high as 15%. Serum IgE level was extremely elevated to 22,000 IU/ml. Serum IgG, IgM and IgA levels were within normal ranges. Specific IgE antibody to Staphylococcus aureus was positive. The nitroblue tetrazolium (NBT) test was normal. We also used the Pharmacia CAP system for the measurement of allergens. The result was that all of the 10 common food allergens and the 10 common air allergens were strongly positive (+++). Chest X-ray study revealed bronchiectasis and fibrosis of bilateral lower lung lobes due to previous recurrent infections. Dual-energy x-ray absorptionmetry of the lumbar spine showed normal bone mineral density. Skin biopsy taken form the neck skin revealed spongiosis, exocytosis, superficial perivascular and interstitial inflammatory cells infiltrations. The inflammatory cells were composed of lymphocytes, histiocytes and some eosinophils (Fig. 4). She was treated with local and systemic corticosteroids, emollients, antihistamines and antibiotics. After the skin condition improved, we prescribed prophylactic antibiotics for her which greatly reduced the infections of the skin and the respiratory tract.

DISCUSSION

In 1966, prior to the discovery of IgE, Davis et al. reported two girls who had a red hair, hyperextensible joints, chronic dermatitis, recurrent staphylococcal infections of the lung and cold cutaneous abscesses. He named this disease as Job's syndrome by the biblical character who had his whole body smitten with boils by Satan. In 1972, Buckley et al. reported 2 boys with similar symptoms and with coarse facies, recurrent lung and skin abscesses, low grade eosinophilia, and marked elevated concentration of serum IgE. Serum IgE concentrations of these two Job's syndrome girls were also later found to be markedly elevated. This shows that Job's syndrome and HIE syndrome are probably the same conditions. But some authors consider that the term Job's syndrome is a subtype of HIE. In addition to displaying the major features of HIE, patients of this subgroup develop cold abscess and also have red hair and hyperextensible joints.

HIE syndrome is rare and there are no published reports of its incidence. There is a familial tendency that follows an autosomal dominant pattern with variable penetrance. A genetic linkage to a region on chromosome 4q has been reported in several families. Buckley evaluated 40 patients and found familial occurrences were noted in 14/40 patients among 8 families. Since no obvious family history was found in our patient, the form of inheritance in this patient may be sporadic or incomplete penetrance.

The bacterial infections generally commence in infancy or early childhood involving...
the skin and sinopulmonary tract in the presence of elevated serum levels of IgE which are at least 10 times the normal level (> 2000 IU/mL). Infections of the skin and lung are more common, but the ears, eyes, oral mucosa, sinuses, joints, blood, and even viscera could also be involved. Skin infections include furunculosis, cold abscesses and cellulitis. A cold abscess is a large fluctuant mass that feels like a tumor or cyst. It is neither hot nor tender and is not associated with systemic symptoms, fever or other signs of local or generalized inflammation. The abscess is filled with pus that always grows *Staphylococcus aureus*. A peculiar tendency of the abscesses to localize about the scalp, face, and neck was observed. Pulmonary infections are also recurrent and severe. The most common bacteria involved are *Staphylococcus aureus* and *Haemophilus influenza*, although *Streptococcus pneumoniae* and enteric gram-negative rods are seen in some cases. Long-term complications include bronchiectasis, bronchopleural fistulae and pneumatoceles. The upper respiratory tract is also affected causing sinusitis, otitis media, otitis externa and mastoiditis. Fungal infections including oral moniliasis are common. The nails are often chronically infected and dystrophic secondary to *candida albicans* infection.

Distinctive facial characteristics of patients with HIE syndrome were pointed out by Grimbacher et al. They found that to be universal by the age of 16 years. Coarse facial features with prominent pores is a consistent feature in HIE syndrome. Patients usually have a prominent forehead, deep-set eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy. The mean nasal interalar distance in patients of HIE syndrome are above the 98th percentile. Other facial anomalies include midline facial defects and a high arched palate. It is common for patients to have retained primary teeth that require dental extraction. This manifests as two rows of teeth as the primary fail to shed.

Hyperextensible joints and scoliosis have been found among as many as 68% and 76% of patients. Osteopenia is also present in most patients with HIE syndrome. Long bone fractures occur to minor trauma and may be recurrent. Grimbacher et al. found that bone density was decreased in five of nine patients tested by densitometry. Fractures had occurred in two of those with reduced mineral density and three of those with normal bone density. Although the bone mineral density is also normal in our patient, she still suffered from a radial bone fracture in childhood. Peripheral blood monocytes from HIE syndrome patients have been found to resorb bone to a greater extent than normal monocytes and to release abnormally high levels of prostaglandin E2 (PGE2). The underlying cause of HIE syndrome is still unclear. The defective polymorphonuclear chemotaxis reported in some cases of the HIE syndrome was suggested to be the basis for infection susceptibility. But such chemotactic abnormalities were found to be highly variable and infrequent. Besides, the assay of neutrophil function by nitroblue tetrazolium (NBT) test is normal.

IgE synthesis is normally enhanced by T-helper2 (Th2) cytokines IL-4 and IL-13 and repressed by T-helper1 (Th1) cytokines interferon-γ (IFN-γ) and IL-12. The two responses act in opposition to each other. Defective in vitro production of IFN-γ and tumor necrosis factor-alpha (TNF-α) by circulating T Cells from patients with the HIE syndrome was demonstrated by Del Prete G. Wellington G et al. found that the lymphocytes of patients with HIE syndrome have an impaired response to IL-12, resulting in decreased IFN-γ. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. An aberrant Th2 immunoregulatory response of Th2 cytokines in the HIE syndrome was described by Sergio Romagnani. However, it has been difficult to prove that patients with HIE syndrome produce excessive IL-4, because IL-4 cannot be measured in body fluids as a result of its short half-life. Shirafuji Y et al. suggested the hypothesis that Th1/Th2 imbalance is involved in HIE syndrome. Nevertheless, abnormal IgE regulation does not explain
the infection-susceptibility of these patients, because high levels of IgE are found in many patients with atopic dermatitis who have no susceptibility to abscess formation.

Although the skin rash of HIE syndrome looks like atopic dermatitis, Hochreutener et al. emphasized the importance of clinical differentiation of the HIE syndrome from atopic dermatitis because the treatment and prognosis are different. The initial eruption of HIE is primarily a papulopustular eruption distributed on the scalp, face, neck, axillae, and diaper area. The rash is typically pruritic, often lichenified. The main clinical guidelines for the diagnosis of HIE syndrome apart from laboratory evaluation are Staphylococcal lung infections with an onset in infancy and recurrent pyodermatous eruption often associated with ulceration and/or lymph-node abscesses. The pruritus may be secondary to histamine release of intradermal mast cell triggered by the elevation of available IgE. The most consistent findings presented in skin biopsy of children and infants are eosinophilic spongiform dermatitis. Other histopathological findings include eosinophilic folliculitis, superficial and deep perivascular dermatitis with abundant eosinophils.

In addition to atopic dermatitis, the differential diagnosis of HIE syndrome includes DiGeorge syndrome, Wiskott-Aldrich syndrome and chronic granulomatous disease. They all have the susceptibility of skin infections. DiGeorge syndrome is a developmental defect of derivatives of the third and fourth pharyngeal pouches, almost always associated with agenesis or hypoplasia of the thymus and parathyroid gland, characteristic facies with downsloping palpebral fissures and ocular and nasal anomalies. Wiskott-Aldrich syndrome is inherited as an X-linked recessive genetic trait, the disorder is usually fully expressed in males only. The immune system of patients with Wiskott-Aldrich syndrome is characterized by partial defects in T lymphocyte and B lymphocyte systems (combined immunodeficiency). Thrombocytopenia is a constant finding of it. Chronic granulomatous disease is inherited by two forms, X-linked recessive and autosomal recessive. It is characterized by dysfunctional neutrophils resulting in chronic and recurrent pyogenic and fungal infections of the skin and GI tract and the formation of granulomas and abscesses. In contrast to HIE syndrome, the NBT dye test is abnormal.

Prophylactic antibiotics, skin care and prompt treatment of the infections are the mainstay of the treatment of HIE syndrome. Surgical intervention may be required for the incision and drainage of abscesses. Treatments by cimetidine, levamisole, isotretinoin, INF-α, INF-γ high dose intravenous γ-globulin (IVIG), and cyclosporin A have been proposed, but clinical benefits have not been unequivocally established. Based on the observation that INF-γ inhibits IgE synthesis, King et al. firstly administered recombinant human INF-γ to patients with HIE syndrome. We highlight the nowadays generally accepted need to employ long-term anti-staphylococcal antibiotic treatment combined with INF-γ to correct the underlying immune defect in this disorder.

In conclusion, HIE syndrome is a multisystem disorder that affects the skin, the skeleton, connective tissues, and the immune system. It manifests since infancy or early childhood. However, in most cases the diagnosis is not established until late childhood or even adulthood. Early diagnosis of the disease and prescription of prophylactic antibiotics is mandatory to prevent infections.

REFERENCES
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