Hyper IgE syndrome

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ABSTRACT

Hyper IgE syndrome (HIES) is a rare disorder characterized by eczema, recurrent infections of the skin and lungs, typically with *Staphylococcus aureus*, *Candida albicans* and certain viruses, and elevated levels of serum IgE. Other clinical manifestations include characteristic facies (prominent forehead, broad nasal bridge and facial asymmetry), chronic eczematous dermatitis, retained primary dentition, recurrent pathological fractures, hyper-extensibility and scoliosis. The central nervous system (CNS) involvement in HIES has been rarely reported. Here we presented a case of HIES with rare associations of epilepsy in a young patient to raise awareness for this disorder.

Key words: Hyper IgE syndrome, epilepsy, eczema

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INTRODUCTION

Hyper IgE syndrome (HIES), first defined in 1966 by Davis,[1] is a multisystem disorder characterized by eczema, recurrent skin and pulmonary infections and markedly increased levels of serum IgE. Other clinical manifestations included characteristic facies (prominent forehead, broad nasal bridge and facial asymmetry), retained primary dentition, hyperextensibility and scoliosis. The majority of cases occur sporadically; however, two types of HIES, the autosomal dominant (AD-HIES) form and the autosomal recessive form (AR-HIES), have also been reported. Reports of the central nervous system (CNS) involvement are rare in both types of HIES. Here we present a patient with HIES who developed rare associations of epilepsy to raise awareness for this disorder.

CASE REPORT

An 18-year-old boy was referred to us because of widely disseminated erythematous plaque with scaling and lichenification since the age of one year. Growth retardation and mild psychomotor delay were observed during his development. At the six year of age, a history of intermittent epilepsy was recorded. The seizures consisted of loss of consciousness, deviation of eyes and head along with tonic posturing of arm or leg of either side or associated flushing. The seizures usually lasted for 10 minutes. The initial frequency was 5-6 times per year. He had been treated with sodium valproate. Improvement was noted after six years with frequency decreased to once per year. He was born healthy (weight = 3.59 kg, height = 49 cm) and followed the recommended schedule for vaccination. There was no history of asthma, epilepsy, trauma or atopic dermatitis among family members.

Physical examination revealed growth retardation for his age with height 150 cm and weight 40 kg. His facial abnormalities was obvious including a prominent forehead, a broad nasal bridge, deep set eyes, broad outer canthal distance [Figure 1a]. Chronic eczematous dermatitis including a diffuse erythematous with scaling and lichenification spread through his face, entire trunk and extremities [Figure 1b, d]. No obvious abscesses were noted on skin but seldom atrophic scars. Hyperextensible joints including scoliosis and talipes cavus [Figure 1c] were also seen. There was no abnormality of the hair or nails. Neurological examination showed limb muscle strength of grade V, normal muscular tension of upper limb, increasing active achilles tendon reflex of lower limb. The findings of the rest of the physical examination were unremarkable.

His laboratory work up included excessively elevated serum level of IgE 20800 IU/ml (normal range 0-100 IU/ml), IgA 441 mg/dl (normal range 69-382 mg/dl) and eosinophils 8.6%

with absolute eosinophils 0.8x10^9/L (normal range). Levels of IgM, IgG, and number of CD4$^+$ and CD8$^+$ T lymphocyte in serum were in normal range. The skin biopsy demonstrated mild epidermal hyperkeratosis with intermittent parakeratosis, exocytosis of neutrophils and intercellular edema. In the dermis, papillary edema, infiltration of lymphocytes and dilated capillaries in superficial dermis were prominent [Figure 2]. Maxillofacial X-ray showed primary dentition of the left maxillary first molar was retained [Figure 3] and X-ray of feet showed features of talipes cavus. EEG, CT of the brain, and chest X-ray was normal. Intelligence assessment showed decreased calculation ability.

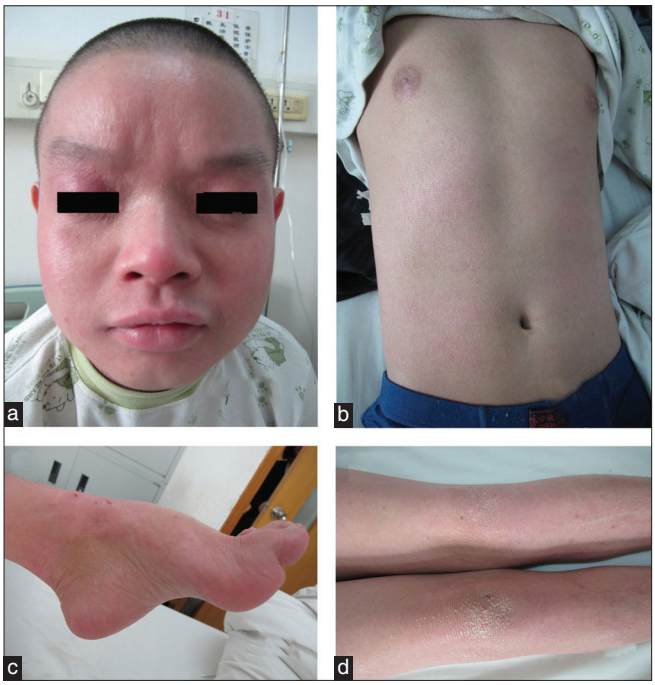

Figure 1: (a) Coarse facial features with a prominent forehead, a broad nasal bridge, broad outer canthal distance, (b, d) Diffuse erythematous plaque with scaling and lichenification, (c) Talipes cavus

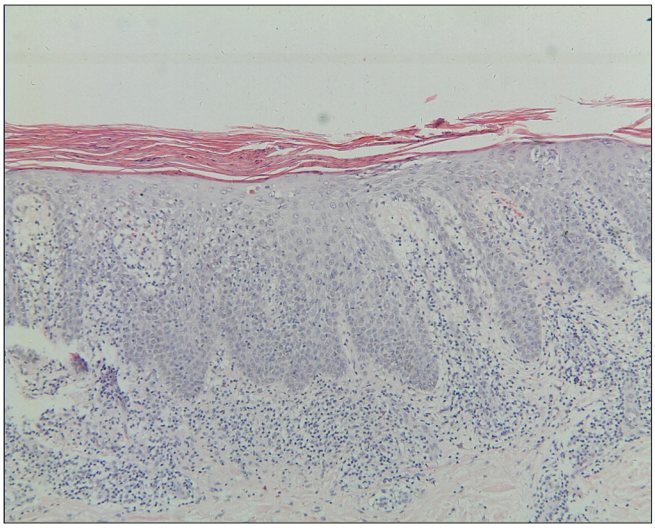

Figure 2: Nonspecific histological feature with mild epidermal hyperkeratosis, exocytosis of neutrophils, papillary edema, infiltration of lymphocytes and dilated capillaries (H and E, ×100)

Based on the typical clinical features, excessively increased IgE levels and the histopathology findings, the diagnosis of HIES was confirmed. Moreover, neurological complication was prominent in this case and other related neurological diseases were differentiated. The patient was treated with moisturizer for the rash and oral antihistamine. Improvement was noted at week three post-treatment and the treatment was well tolerated.

DISCUSSION

HIES is a multisystemic disorder characterized by eczema, recurrent pulmonary and skin infections and markedly increased levels of serum IgE. The majority of cases occur sporadically; however, two types of HIES have also been reported. AD-HIES, caused by mutations in STAT3 identified in 2007,[2] presents with skeletal, connective tissue, and pulmonary abnormalities by whereas, AR-HIES, caused by mutations in DOCK8, identified in 2009,[3] manifests as severe eczema, recurrent bacterial and viral skin infections.

Our patient had hyperextensible joints including talipes cavus. To date, hyperextensibility was present in about 70% in HIES,[4] including fingers, wrist, shoulders, hips, and knees. However, there were no reports of talipes cavus. Our patient also had decreased calculation ability, which has not been reported in HIES. Moreover, the patient developed the rare association of epilepsy. Reports of the central nervous system (CNS) involvement are rare. It were first described by Renner *et al.*[5] in 2004. They identified neurological symptoms in 7 of 13 patients. Among these patients, there were five patients who presented with neurological symptoms due to vascular anomalies such as stenosis and aneurysm formation, there were also three patients with an infectious cause underlying the neurologic disease (sepsis, cryptococcal meningitis, otitis). After studying cerebral MRI findings in a larger cohort of HIES patients, Freeman *et al*,[6] in 2007, claimed that the abnormalities frequently presented on brain MRI suggest

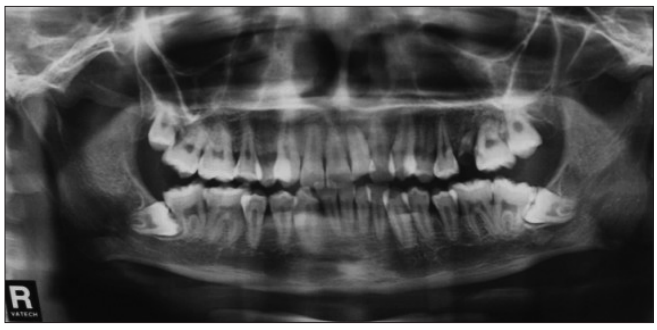

Figure 3: Maxillofacial X-ray showing retained primary dentition of the left maxillary first molar.

possible small vessel disease. There were also some reports which hold that an infectious cause, such as: tuberculosis brain abscess,[7] Coccidioides immitis meningitis,[8] Community acquired *Staphylococcus aureus* meningitis,[9] was a possible factor underlying the neurologic involvement in HIES. Although these associations were of unclear etiology, mostly related to infections and vessel diseases, it is important to consider these in HIES patients. As for our patient, he had no history of trauma or signs of infection and vasculitic abnormality in the central nervous system. He was affected by epilepsy without any overt CNS abnormality.

Our patient had no obvious history of recurrent infections, we speculate that the cause is associated with elevated total serum IgA, which have functional attributes, both direct and indirect, serving to defense by limiting invasion of infective agents such as bacteria and viruses at the vulnerable mucosal surfaces.[10] Another reason may be that the patient was not treated with steroids and other immunosuppressant drugs.

The coexistence of growth retardation, psychomotor delay, epilepsy and talipes cavus are rare and we suggest that this is the first such case in literature.

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