

A young man with hyperimmunoglobulin-E syndrome and IgA and IgG deficiencies

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Summary

Hyperimmunoglobulin E syndrome (HIES) with recurrent infection is a rare primary immunodeficiency characterized by the clinical triad of recurrent staphylococcal abscesses, cyst-forming pneumonia and an elevated serum immunoglobulin (Ig)E level. We report an 18-year-old man with recurrent chest infections, skin infections and dermatitis. On examination, he had the characteristic facies of HIES: high arched palate, webbing between his thumb and index finger bilaterally, and extensive scarring from multiple staphylococcal skin abscesses. He had an elevated IgE level of 14 300 kU/L. IgA and IgG deficiencies were also identified, which are rare associations of this syndrome and complicated the patient's treatment. The coexistence of HIES, IgA and IgG deficiencies has, to our knowledge, not been reported previously in the literature.

Davis *et al.*¹ first described HIES (Job's syndrome), in two girls with frequent sinopulmonary infections, dermatitis and staphylococcal skin infections. Buckley *et al.*² subsequently described two boys with similar presentations and elevated IgE. We report an 18-year-old man with IgA and IgG deficiencies.

Report

An 18-year-old man with IgA and IgG deficiencies had been treated in infancy with immunoglobulin infusions from the ages of 1–5 years. His IgG deficiency resolved; however, his IgA deficiency remained. An eczematous rash involving his face, neck and trunk resolved at 15 years of age. As a child, he had had frequent admissions for bronchomalacia of his right upper lobe, pneumonia, sinusitis and otitis media. He also had numerous presentations with staphylococcal skin infec-

tions, including furuncles, carbuncles, axillary abscesses, cellulitis, impetigo, infected eczema and herpes stomatitis, and with candidal skin infection. He had sustained fractures of his left middle and ring fingers from minor trauma. His development was appropriate for his age, although he had experienced schooling difficulties as a result of his illness.

As children, his grandmother and mother had experienced 'boils' on their legs. His mother had had five miscarriages and died of heart failure secondary to cardiomyopathy in her 30s. His father had insulin-dependent diabetes. His mother and sister had been found to have low IgG4 levels.

On examination, the patient's occipitofrontal circumference was in the 98th centile. He had hypertelorism, inverse telecanthus, anteverted nostrils, broad forehead and neck, webbing between the thumb and first digits bilaterally, resulting in a fixed flexion deformity of his metacarpophalangeal joints, pectus excavatum, high arched palate, two areas of café-au-lait pigmentation, and extensive scarring from previous abscesses. There were multiple atrophic macules, double comedones, a nodular and inflammatory acneiform eruption, excoriations, and changes of pityriasis versicolor on his back (Figs 1–3).

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Figure 1 Characteristic facies with frontal bossing, deep-set eyes, broad nasal bridge and wide alar base to nose.



Figure 2 Webbing between thumb and first digits, resulting in a fixed flexion deformity of the metacarpophalangeal joints of both thumbs.

Investigations showed total IgE 14, 300 kU/L, eosinophilia $1.13 \times 10^9/L$ (normal range $0.04\text{--}0.4 \times 10^9$), undetectable IgA (0.85–5.13 g/L), complement $4 < 0.10$ g/L (0.18–0.37), IgG1 7.9 g/L (1.93–5.43), IgG2 1.10 g/L (1.24–5.49), IgG3 0.25 g/L (0.13–0.43) and IgG4 0.010 g/L (0.020–0.224), reduced neutrophil bactericidal activity 75% (normal $> 85\%$) and *Staphylococcus aureus* on multiple swabs of the abscesses.



Figure 3 Multiple atrophic macules, double comedones, a nodular and inflammatory acneiform eruption and excoriations on the back.

The patient was treated with topical antibiotics, and incision and drainage when required. He continued to develop abscesses requiring repeated antibiotics. Intravenous gammaglobulin was contraindicated because of the immunoglobulin deficiency. Isotretinoin was considered; however, the addition of prednisolone to prevent the initial exacerbation caused by isotretinoin would be contraindicated given his associated immunodeficiencies.

HIES is a rare primary immunodeficiency characterized by recurrent staphylococcal abscesses, cyst-forming pneumonia and elevated IgE. The distribution of HIES is unaffected by race or gender. It is usually sporadic, although autosomal dominant and autosomal recessive inheritance has been described. Autosomal recessive HIES has specific features of severe viral infections and neurological complications. Linkage to a region on chromosome 4q has been shown.³

The underlying cause is unknown. Immunological abnormalities include impaired neutrophil chemotaxis and imbalance between T helper (Th)1 and Th2 cell cytokines. A predominance of the Th2 cytokines

interleukin (IL)-4 and IL-13 or a deficiency in the Th1 cytokines interferon (IFN)- γ and IL-12 results in elevated IgE synthesis.^{3,4} We hypothesize that in our patient a primary defect in T cells has resulted in reduced production of IgG2, IgG4 and IgA by B cells, loss of regulation of IgE production by plasma cells, and secretion of chemotactic inhibitors from mononuclear cells.

The reduction in IgG2 results in a reduced ability to protect against capsulated bacteria. Reduction in IgA results in susceptibility to respiratory tract infections. The inhibition of neutrophil chemotaxis contributes to recurrent infections.

A pruritic, lichenified dermatitis presents in the first weeks of life. The dermatitis, although similar to eczema, has an earlier onset and more prolonged course, is more severe and is resistant to conventional therapy. Skin biopsy reveals an eosinophilic infiltrate similar to eosinophilic pustular folliculitis.⁵

Skin infections commencing in infancy include furuncles, cold abscesses and cellulitis. Furuncles are common around the face, and are tender and warm to touch. Cold abscesses that lack signs of inflammation are pathognomic of HIES but not essential for diagnosis.⁵

Recurrent pneumonia is often complicated by bronchiectasis, bronchopleural fistulae and pneumatoceles requiring surgery. The upper respiratory tract is affected with sinusitis and ear infections. *Candida* infection is common; it is uncertain whether this is causally related or secondary to antibiotics.^{3,5}

The characteristic facie includes coarse skin, frontal bossing, large head circumference, deep-set eyes, broad nasal bridge, wide fleshy nasal tip, wide alar base to the nose, mild prognathism and a high arched palate.⁶ Patients commonly have retained primary teeth or two rows of teeth, as the primary fail to shed and require extraction. Fractures of the long bones and ribs from minor trauma, hyperextensibility of joints and scoliosis occur.⁶

Lymphoma has been associated with HIES. Patients need to be monitored for transformation. It is thought that polyclonal stimulation of B cells by viruses facilitates oncogenic transformation.⁴

Laboratory findings include an elevated IgE of > 2000 IU/mL. A normal adult level is pathological in infants. An IgE level 10-fold above the 95th percentile of the age norm is a more accurate guide. IgE levels are not related to disease severity.³

Typically, patients with HIES have normal levels of IgG and IgA.⁷ Mazzone *et al.*⁸ reported a woman with recurrent cystitis, eczema and stomatitis who had both HIES and IgA deficiency. Dreskin *et al.*⁹ reported

patients with decreased anti-*S. aureus* serum IgA correlating inversely with incidence of mucosal infections. No deficiency of total IgA was found. Although total IgG levels are within the normal range, patients may have a deficiency of IgG2.¹⁰

Most patients have eosinophilia. There is no correlation between eosinophilia and IgE levels or infections. Total white cell counts often fail to rise during infections.³

The mainstay of treatment is drainage of abscesses, prophylactic antibiotics and skin care. Several immunomodulatory agents have been trialled in single cases or small anecdotal series. Cimetidine, a histamine receptor-2 antagonist, reverses the neutrophil chemotactic defect *in vitro* and has resulted in clinical improvement. High-dose intravenous gammaglobulin and ciclosporin have been shown to decrease IgE and improve the dermatitis. Isotretinoin for 4 months in a 15-year-old boy with HIES resulted in no further abscesses over a 6-month follow-up period. Other agents reported to show clinical improvement are cromoglycate, IFN- γ and plasmapheresis.³

Bone marrow transplant has been attempted. The first was performed in a patient with B-cell lymphoma who was maintained on prednisone and ciclosporin. IgE fell and no infections characteristic of HIES occurred, but the patient died 6 months later from pneumonia. Another transplant, in a 7-year-old girl, resulted in clinical improvement but there was recurrence after discontinuation of immunosuppression.³

HIES is a rare primary immunodeficiency of unknown aetiology. To our knowledge, this is the first case in which the coexistence of both IgA and IgG deficiency has been described. Prophylactic skin care and antibiotics are the mainstays of treatment. Larger randomized controlled trials are required to evaluate the newer immunomodulatory therapies.

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