Case Reports

Hyperimmunoglobulin-E syndrome

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ABSTRACT

Two Saudi girls aged 8 years and 5 years were seen over a period of 6 years and 5 years. Their clinical presentations consisted of recurrent bilateral otitis media, repeated episodes of tonsillitis and chest infection. Cultures from the ears grew on numerous occasions *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeroginosa, Proteus species* and *Providencia species*. The 8-year-old had a serum IgE level of 1431 iu/L, with normal levels of other immunoglobulin classes. The 5-year-old had an immunoglobulin E value of 1119 iu/L with normal values of other immunoglobulin classes. Both were human immuno-deficiency virus negative and no other causes for elevated immunoglobulin E were found. The mothers of both cases had elevated immunoglobulin E levels of 1216 iu/L and 1992 iu/L. Both fathers had normal IgE levels. A 13-year-old sibling of case one had a grossly elevated immunoglobulin E level of 2259 iu/L. She had diffuse lamellar icthyosis and recurrent episodes of chest infection and conjunctivitis. There was a good clinical response of patient one to monthly intravenous human immunoglobulin.

Keywords: Recurrent bacterial infections, hyperimmunoglobulin E.

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Two cases of recurrent bacterial infections in childhood are presented. They posed initial diagnostic difficulties in that no obvious cause was apparent. Further detailed investigations revealed hyperimmunoglobulin E as an etiological factor. Due to the inherited nature of this condition, a family pedigree study was undertaken for the 2 index codes. We also discussed a possible mode of inheritance and current and emerging therapy for this rare inherited condition.

Case Report. ***Patient one.*** An 8-year-old Saudi girl has been seen at Prince Sultan Hospital in Taif, Kingdom of Saudi Arabia (KSA) since 1993 when she was aged one year. She was a full term normal delivery, and was given a complete set of childhood immunizations. The parents are close relatives. She has 6 siblings, 3 brothers and 3 sisters, aged 25, 20, 13, 9, 7 and 5 years. Two of her siblings, aged 25 years and 20 years, had died from a road traffic accident and an unknown cause. Between 1993 and 1995, she was seen on 5 occasions with recurrent upper respiratory tract infections and was treated empirically with oral antibiotics. In March 1996, she developed purulent nasal discharge and purulent right otitis media. Four weeks later, a discharging left ear was noticed. Otoscopic examination showed bilateral, moderately sized, central tubo-tympanic perforations with negative Reservoir's sign. There were no physical findings suggestive of cholesteatoma formation. An ear, nose and throat consultant advised topical measures and systemic antibiotics, and frequent aural toilet. From August 1996 through to December 1996, she made 6 visits to the out-patient clinic with recurrent fever, cough with purulent sputum, inflamed tonsils and bilaterally discharging ears. Transient facial and perineal eczematous rashes were observed. In

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January 1997, another attack of chest infection and bilaterally discharging ears prompted the consideration of an immunodeficiency disorder. Measurement of serum immunoglobulin revealed an elevated serum immunoglobulin E level (IgE). Her serum IgE levels between January 1997 through to November 1999 ranged between 838 iu/L and 1431 iu/L (normal range 20-180 iu/L). She had an eosinophil count of 7% in November 1999 and repeated stool examination did not show ova, cyst or parasites. Other immunoglobulin classes were all within normal range. She was negative for human immuno-deficiency virus (HIV) 1 and 2. Throughout 1997, she had 2 suction clearances of both ears and received topical gentamicin and a course of oral co-amoxiclav followed by a course of oral cefuroxime. She had flies removed from both ears during this period. An x-ray and computerized tomographic (CT) scan of both mastoids were consistent with sclerosing mastoiditis and the CT scan did not reveal any cholesteatoma. Recurrent tonsillitis and discharging ears forced her to make 4 visits to the outpatient department in 1998. Bacteriological cultures from the ears showed *Staphylococcus aureus (Staph. aureus)* and *Streptococcus pneumoniae* to be dominant organisms, though *Proteus species* and *Providencia species* were seen on 4 occasions. Mycobacterium tuberculosis was not isolated. She had several sessions at the dentist for treatment of dental caries. Immunoglobulin therapy was instituted in March 1999, consisting of 5 grams of human immunoglobulin intravenously monthly. Prophylactic antibiotics were continued. Co-trimoxazole alternating with amoxycillin. By April 1999, the right ear was dry and the left ear showed only minimal discharge. In May 1999, both ears were dry. No further infective episodes occurred until a dental abscess occurred in August 1999; in addition bilateral otitis media and wheezy bronchitis were observed.

On review in November 1999, both ears were dry and she was well. A family survey was carried out. The pedigree of the propositus and her family is shown in **Figure 1.** Their ages and IgE levels are also shown. Sibling E has grossly elevated IgE levels and the case notes showed recurrent upper respiratory tract infections and recurrent conjunctivitis. The skin showed diffuse lamellar icthyosis. None of the other siblings were affected. The mother, though having an elevated IgE level, was asymptomatic. The father had normal IgE value.

Patient 2. A 5-year-old Saudi girl first attended Prince Sultan Hospital in Taif, KSA in August 1995. She was a full term normal delivery and had her full complement of childhood vaccinations. She was noticed to have a generalized urticarial rash in August 1995, which subsided spontaneously. She had an upper respiratory tract infection in November of 1995, followed by bilateral otitis media treated with a course of co-amoxiclav. She had an episode of acute gastroenteritis in August 1997. Discharge from purulent bilateral otitis media in April 1999 grew *Pseudomonas aeruginosa* sensitive to ceftazidime. There were recurrent episodes of discharging ears until December 1999, in spite of topical measures and several courses of systemic antibiotics. *Pseudomonas aeruginosa* was again isolated from the ears in January 2000. Otoscopic examination revealed bilateral tubo-tympanic perforations. An x-ray of both mastoids showed sclerosing mastoiditis. She declined a CT scan to exclude a cholesteatoma. Her serum IgE level was elevated at 1119 iu/L. Other immunoglobulin classes were normal, as were her hemoglobin and white cell count. She was HIV negative. A stool examination revealed no ova, cysts or parasites. A series of monthly human immunoglobulin infusions was

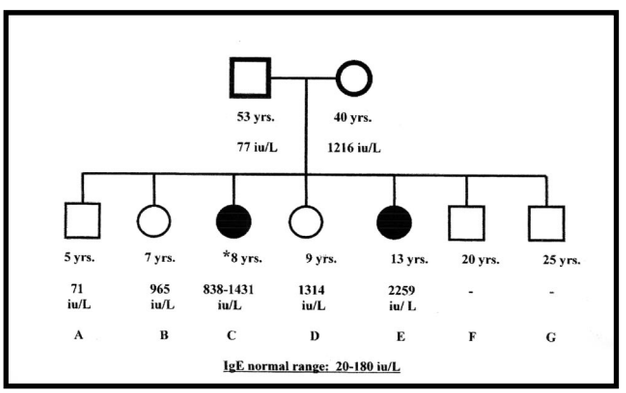

Figure 1 - Pedigree of the propositus and her family. The propositus is indicated by an asterisk. Solid symbols denote affected family members. Sibling E has generalized lamellar icthyosis. Ages and immunoglobulin E values are indicated. Circles, denote female family members, squares denote male family members. IgE = Immunoglobulin E.

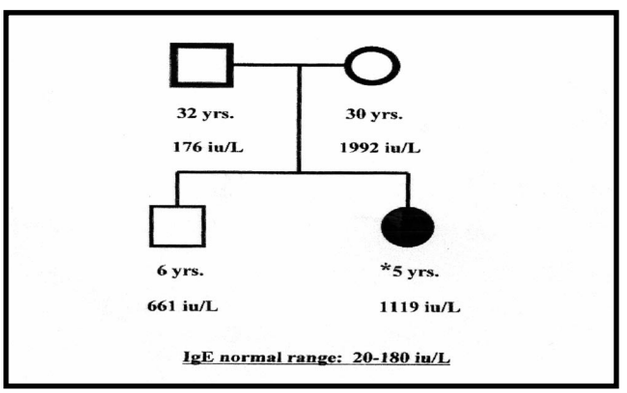

Figure 2 - Pedigree of the propositus and her family. Solid symbols denote affected members. The propositus is indicated by an asterisk. Circles, denote family female members, squares denote male family members. IgE = Immunoglobulin E.

planned but, after the first injection, she defaulted and has not been seen since.

The pedigree of the propositus and her family is shown in **Figure 2.** Their ages and IgE values are shown. Both parents and the other siblings were completely asymptomatic. The mother had a grossly elevated serum IgE level at 1992 iu/L (normal range 20-180 iu/L). The level of the other immunoglobulin types immunoglobulin G, immunoglobulin M, immunoglobulin A were normal. The other sibling had a moderately elevated serum IgE level at 661 iu/L, and was asymptomatic. The father's IgE level was within normal range.

Discussion. Hyperimmunoglobulin-E syndrome is a multi-system disorder, first described in May 1966 by Starkey Davis, Jane Schaller and Ralph Wedgwood.[1] They named it Job's syndrome, after the prophet Job who was said to be afflicted with sore boils from the sole of his foot up to his head. The multi-system nature of this disease has since been appreciated and in 1974, Job's syndrome was classified as one of the immunodeficiency diseases. It is an uncommon condition and just over 200 cases have been described worldwide.

Hyperimmunoglobulin-E syndrome is a multi-system disorder with immunological, skeletal, dental and facial manifestations, with variable expressivity of these features.[2] The clinical manifestations consist of severe, recurrent infections like skin abscesses and candidiasis, pneumatocoele-forming pneumonias and elevated serum IgE without any underlying defect in the immune system. Most cases of the hyperimmunoglobulin-E syndrome are sporadic. The genetic basis of hyperimmunoglobulin-E syndrome is unclear. Some reports suggest autosomal recessive inheritance.[3] A study of 30 patients with hyperimmunoglobulin-E syndrome and 70 of their relatives suggested single-locus autosomal dominant trail with variable expressivity.[2] Although originally described in red haired, white girls, it is now known to occur in all ethnic groups. The infections start in early childhood, usually before 3 months of age. The infections include recurrent cold abscesses, pneumonias, mucocutaneous candidiasis. Otitis externa, otitis media and mastoiditis, gingivitis and multiple caries also occur. Dental abscesses are not a common problem. Otitis media, with or without otitis externa, occurs in 7 out of 16 patients in the series of Donabedian and Gallin.[4] The cold abscesses are usually caused by penicillin-resistant *Staph. aureus*. *Hemophilus influenzae* and *Staph.aureus* cause most of the pneumonias in the hyperimmunoglobulin-E syndrome of severe repetitive infections and elevated serum IgE levels. The hyperimmunoglobulin-E syndrome is one of the immunodeficiencies and has all the potential for deep-seated and systemic infections, with common as well as unusual pathogens. The diagnosis of hyper-immunoglobulin-E syndrome thus has implications for long-term management, prognostication and genetic counseling. It is to be recognized that, with recurrent and frequent bacterial infections that are unexplained since an early age, immunodeficiency should come to mind and that one of the rare forms of immunodeficiency is the hyper-immunoglobulin-E syndrome.

In conclusion, repeated, unexplained bacterial infection should prompt the search for an underlying cause. The immunodeficiencies are one of the leading causes of such a clinical presentation. One of the rare causes of immunodeficiency is Job's syndrome. This syndrome, with its genetic basis of either autosomal recessive or single locus autosomal dominant trait, will be expected to be more prevalent in a highly inbred society like the KSA. A high index of suspicion of Job's syndrome in such settings is needed. It might transpire that Job's syndrome is more common in such societies than was hitherto believed.

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