

# Hyper-IgE syndrome. A study involving 30 children from Makkah - Saudi Arabia.

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## Summary

The hyperimmunoglobulin E syndrome is a primary immunodeficiency state with elevated immunoglobulin E, eosinophilia, skin, skeletal and dental defects. The aim of this study was to determine the frequency of these abnormalities in children with Hyper IgE syndrome. This would enable in apprising clinicians of the importance of early recognition and management of this condition. This study was conducted at Alawi Tonsi Hospital, Makkah, Saudi-Arabia, from February 2001 to April 2004. We evaluated 30 human immunodeficiency virus-seronegative children from consanguineous -19- and non-consanguineous -11- families with hyperimmunoglobulin E syndrome. All the cases were new, aged 10 years or less and reported either directly to the dermatology outpatients or from other units of the same hospital. Their detailed histories were taken. Besides anthropometric measurements, physical and dental examinations were done and laboratory tests were performed. The classical findings of hyperimmunoglobulin E syndrome were put in evidence. 26 patients (86.66%) presented recurrent skin infections including bacterial, viral and fungal infections. 22 patients (73.33%) had respiratory tract infection with half of them suffering from bronchial asthma. 6 (20%) of the children had skeletal abnormalities such as scoliosis, repeated fractures and osteopenia. 16 (53.33%) children had dental abnormalities, while only 5 (16.66%) children had eye and 4 (13.33%) ear infections. Elevated serum immunoglobulin E levels were observed in 28 cases (93.33%), while hypereosinophilia was seen in 29 (96.66%) children. In conclusion, the hyperimmunoglobulin E syndrome is a multi-system immunodeficiency disorder involving cutaneous, skeletal, connective tissue, and dental abnormalities. This condition must be borne in mind when children with repeated skin and chest infections are encountered.

## Key words

Hyper-IgE syndrome, Job's syndrome, immunoglobulin E.

**H**yper IgE-syndrome also known as Job's syndrome was first described in 1966. It is a rare immunodeficiency disorder transmitted by an autosomal dominant inheritance pattern with variable expressivity. It is characterized by moderate to severe itchy atopic dermatitis, recurrent skin abscesses, chest infections leading in some cases to pneumatocele formation, defective granulocyte chemotaxis and extremely elevated levels of IgE in serum (2, 4, 6).

A study was done in Makkah to apprise clinicians of the importance of early recognition of

the disease and appropriate treatment. The latter is critical for a better outcome of this disease.

## Patients and methods

30 children diagnosed as Hyper-IgE syndrome, who were human immunodeficiency virus-seronegative, entered the study. They were analyzed prospectively for their epidemiological, clinical and serological features. All the patients belonged to Makkah region, were 10 years or less, and reported to the dermatology



Fig. 1



Fig. 2

Fig. 1, 2, 3, 4: In Fig. 1 you can see papular lesions and pustules of the scalp and face, with scaling and crusted blepharitis. In Fig. 2 you can see Herpes Simplex of the eyelid and nose. In Fig. 3 there is a little girl with erythrodermic eczema, scaling and impetiginization. In Fig. 4 there is a child with candidiasis of the perianal region and buttocks, associated to typical eczematous lesions of the right knee.



Fig. 3



Fig. 4

outpatients directly or referred from the pediatric, dental, chest and orthopedic units of our hospital.

These cases were then followed up for a period of 3 years at Alawi Tonsi Hospital Makkah, Saudi Arabia. The following epidemiological data were obtained: age at onset of first symptoms and age at diagnosis, area of referral, race, and sex. Detailed information of the clinical disease expression, including the skin, musculoskeletal, pulmonary, dental abnormalities were noted and recorded. These data were recorded at the time of presentation and at subsequent visits. Laboratory investigations included complete blood counts, erythrocyte sedimentation rate, serum IgE levels, using a radial immunodiffusion technique for IgE determination, and serology for HIV status and hepatitis. Skin biopsies, performed in three patients, revealed spongiosis and perivascular infiltrate with a predominance of eosinophils. In the other cases the clinical and laboratory findings were obvious, not requiring biopsies to establish diagnosis. The criteria for diagnosis especially versus atopic dermatitis were based on serum IgE levels at least 10 times greater than the upper limits of normal and history of recurrent skin, sinus and pulmonary infections. Laboratory investigations and clinical examinations of the relatives were also carried out.

## Results

*Coarse facies.* 11/30 children had coarse “facies” with prominent brow and deep-set eyes.

*Skin infections.* 26/30 (86.66%) patients had some skin lesions during the three-year follow-up period. Out of total 26 patients with skin infections 16 (61.53%) had bacterial infections such as papulopustular eruptions or abscesses on the scalp, face and body. The most frequently isolated pathogen in the skin abscesses was *Staphylococcus aureus*. 7/26 (26.92%) patients had fungal infections. Particularly, four had candida infection, one being muco-cutaneous in nature, while other three had dermatophyte infections of the groin. 3/26 (11.53%) patients had viral infections. Particularly, 2 patients had herpes simplex infection, while 1 had molluscum contagiosum.

*Pulmonary problems.* 22/30 (73.33%) children had chest infections, 10 had mild to severe bronchial asthma, while 5 suffered from pneumatocele.

*Skeletal abnormalities.* 6/30 (20%) children had different skeletal abnormalities such as scoliosis of the spine, repeated fractures and osteopenia.

*Dental abnormalities.* 16/30 (53.33%) children had dental abnormalities such as lack of eruption of permanent teeth, retained teeth and delayed shedding of deciduous teeth.

*Eye and ear problems.* 5/30 (16.66%) patients had eye complications like conjunctivitis, keratitis and one of these had corneal ulceration. 4/30 patients (13.33%) had ear complications. 3 patients had otitis externa, while the fourth one had otitis media with perforation of the ear-drum (Table 1).

*IgE and eosinophils.* 28/30 children had increased immunoglobulin E levels while the

**Table 1: Details regarding the clinical manifestations of HyperIgE syndrome.**

Age (years)	Skin infect. (bacterial)	Skin infect. (fungal)	Skin infect. (viral)	Chest disorders	Skeletal defects	Dental defects	Eye infect.	Ear infect.
0-5	6	3	1	8	0	3	2	1
6-10	10	4	2	14	6	13	3	3
Total	16	7	3	22	6	16	5	4

**Table 2: Details of IgE levels and eosinophilia in thirty patients.**

AGE	IMMUNOGLOBULIN E LEVELS		EOSINOPHILIA	
	3,000-10,000 IU/ml	> 10,000 IU/ml	10-20%	>20%
0-5 years	4	8	7	5
6-10 years	7	9	11	6

levels of other classes of immunoglobulins were normal. 11 children had IgE levels ranging between 3,000-10,000 IU/ml, while 17 had IgE levels more than 10,000 IU/ml. In 2/30 children IgE levels were normal, respectively 112 and 150 IU/ml (normal values 0.3-215 IU/ml). 29/30 children had persistent peripheral eosinophilia. 18 were in the range of 10-20% while 11 had more than 20% eosinophils (Table 2).

*Relatives.* Of the 13 relatives of the affected children who were willing to undergo clinical examination and laboratory studies, 3 siblings were fully affected, 8 were unaffected and 2 had mild dental involvement and immunological abnormalities. Although quite a number of the patients relatives had clinical manifestations but were not willing to undergo clinical examination and laboratory investigations. 19 patients were from consanguineous families, but did not present different clinical features as compared with the 11 patients from non consanguineous parents. 13/30 patients had an atopic family history.

### Discussion

The IgE levels significantly vary in different individuals and populations. Waorani Indians of Eastern Equador have the highest blood levels of immunoglobulin E that have been reported in a human population so far (7).

Hyper IgE syndrome also known as Job's syndrome is a rare genetic disease, characterized by frequent skin and chest infections, bone abnormalities, dental defects and markedly elevated levels immunoglobulin E (IgE). No speci-

fic race is affected, it occurs in diverse ethnic backgrounds and is usually seen in infancy, although the diagnosis is often missed until childhood or even adulthood. Most of the cases involved in this study had the classical triad of hyper IgE syndrome, i.e. recurrent skin infections/abscesses, pneumonia, and elevated IgE levels. Similar clinical findings with high levels of immunoglobulin IgE causing recurrent pyogenic infections, chronic dermatitis and osteopenia have been reported in the past (3, 5, 8). Most of the cases observed in this study gave history of repeated exacerbations of dermatitis and multiple skin abscesses with no seasonal variations. In some cases there was severe exfoliation of the skin. (Fig. 3). In many cases the parents reported that their children had suffered with repeated episodes of skin and chest infections since infancy. Data obtained from the parents revealed that in some cases both the parents, while in others a single parent either mother or father were atopic in their childhood. Thirteen out of thirty had other relatives with atopic history.

In most cases, initially, the children developed features of eczema at typical sites, few of them developed lichenification of these sites due to severe pruritus/scratching and later on developed moderate to severe recurrent bouts of skin infections. Only 4 cases at the time of presentation had mild clinical manifestations, although their investigations revealed significantly raised IgE levels.

11 children involved in this study had coarse facial appearance with prominent brow and deep-set eyes. Some had papulopustular lesions all over the body especially on the scalp, face

and scales on the eyelids as shown in Fig. 1. These bouts of infections had no seasonal variation and were present to some degree at all the times. As already reported (5) recurrent small and large skin abscesses were also observed during bouts of exacerbation.

Most cases of fungal infections were candida infections mostly in the axilla, groin and buttocks, while some patients had dermatophyte infection of the same regions. Fig. 4 shows a child with candidal infection involving the anal cleft and buttocks with typical atopic lesions behind one knee. Most of these children had these infections probably due to the immunocompromised status, however most of them responded dramatically to local anti-fungal ointments.

A few children had various viral infections such as herpes simplex involving nose and lips (Fig. 2).

In many cases there was history of cough, fever and breathlessness due to chest infections, while few of them were admitted in the hospital for pneumonias. The high number of respiratory tract infections observed in this study are similar to those reported in the past (2, 4, 6, 7).

There was considerable variation in the IgE and eosinophil levels in the children involved in this study. Serum IgE levels fluctuated between 3,000 IU/ml and 34,500 IU/ml, except for two children aged more than 5 years, who had normal IgE levels. After appropriate treatment, the IgE levels decreased, with a drop varying from 10-40% of the initial values. As already reported (5) eosinophil counts were increased in all patients but one, sometimes with values as high as 30%.

There were two cases with supracondylar fracture of the right humerus with limitation of extension of the elbow following the fracture, while three children had a history of fracture of ribs. Two children had scoliosis of the spine, which is also quite a common feature in most teenaged patients. Multiple fractures of the long bones, ribs or pelvis are common in this disorder (3, 5).

Dental abnormalities such as lack of eruption of permanent teeth, retained teeth and delayed shedding of deciduous teeth were found in some

cases. Retention of teeth and prolonged exfoliation of deciduous teeth caused by the lack of root resorption was another interesting finding. This previously unrecognized feature was found to occur among as many as 60% of patients with Hyper-IgE syndrome. Most of them need extraction of the retained deciduous teeth (5).

Some children had repeated attacks of conjunctivitis with purulent discharge resulting in dry scabs along the eyelid margins.

Some children suffered from recurrent attacks of uni- or bilateral ear infections. Cultures taken from the ear were positive for *Staphylococcus aureus*, *Streptococcus pneumoniae* and on one occasion for *Pseudomonas aeruginosa*.

The diagnosis of Hyper-IgE syndrome is usually made between 12-24 months after the onset of initial papulopustular eruption. It is important to recognize this disease early in order to start an appropriate treatment, which is critical for the optimum outcome of the disease (3). There is no definitive therapy for this condition and the aim of the treatment is to control the infection. Several regimes have been tried and one of them is life long administration of therapeutic doses of penicillinase-resistant penicillin with the addition of other antibiotics or anti fungal agents as required for specific infections. Anti-viral drugs and intravenous gamma globulin may be given when required. The response to monthly intravenous human immunoglobulin has been reported to be good (1, 9).

In conclusion, this study underlines that Hyper-IgE syndrome is not only an immunodeficiency but also a multi-system disorder that affects the skeleton, connective tissue and immune system. This syndrome must be therefore borne in mind whenever children with repeated skin and chest infections are encountered. A complete medical evaluation for diagnosis and management of this condition must be performed as early as possible.

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