

## CASE REPORT

## AUTOSOMAL DOMINANT HYPER IGESYNDROME (JOB'S SYNDROME): A CASE REPORT OF TWO PATIENTS

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## ABSTRACT

Recently we came across two male patients with Hyper IgE type immune deficiency (HIES/Job's syndrome), a primary immune deficiency disorder characterized by abnormally raised serum levels of IgE and repeated childhood infections. In our hospital in pediatrics and nursery, acquired immunodeficiency secondary to severe malnutrition, prolonged steroid therapy, nephrotic syndrome, aplastic anemia, leishmaniasis, leukemias and other malignancies is more common as compared to inherited causes.

**Keywords:** Immunodeficiency, Job's syndrome, Hyper IgE syndrome.

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## INTRODUCTION

Autosomal dominant Hyper IgE syndrome (AD-HIES) occurs in all ethnic groups, males and females are affected equally<sup>1,2</sup>. Also known as Job's syndrome, it is a rare primary immune deficiency in children, characterized by a gradual rise in serum levels of IgE type antibodies after birth to more than 2000 IU/mL (normal range is 20 to 200 IU/mL)<sup>3,4</sup>. Associated signs may be an eczematous rash, recurring *staphylococcus aureus* skin and respiratory infections, pneumonias, pneumatoceles and a peculiar facies. Non immunological features are scoliosis, teeth anomalies e.g. retained primary teeth persisting till late childhood<sup>5</sup>.

The two types of HIES are: An autosomal dominant type (AD) or type 1 and an autosomal recessive (AR) or type 2 Hyper IgE Syndrome. Underlying cause is a mutation in a specific transcription factor. In type 1 HIES there's a STAT 3 deficiency as a result of the mutation. STAT 3 deficiency is not found in autosomal recessive HIES; However in some patients of AR type HIES a Tyk 2 deficiency might exist. Due to the many complications, children with HIES usually have a shorter over all life span though some may

survive up till their mid-adulthood. In some very rare occasions with meticulous management, survival may extend to the sixth decade of life. Usual age of death is between 20 to 30 years of age and usual cause is due to chest complications i.e. recurrent pneumonias<sup>6</sup>.

## CASE REPORT

Case 1: A 3 year old child was referred to us through a private set-up with bilateral enlargement of submandibular lymph nodes. Enlargement started around a week ago and gradually increased and became tender. At time of presentation submandibular nodes were a size 5 x 4 cm and child was in obvious discomfort. Upon palpation the lymph nodes were firm, erythematous and had started to point. Past history revealed identical swelling involving axillary lymph nodes a year back for which incision and drainage was done and pus was drained, but they had misplaced previous results of culture and sensitivity. About six months back child had a pustular swelling (skin abscess) over his cheek bone just lateral and inferior to the right eye. Upon incision and drainage it contained pus and a mild scar could be visualized. Presently child was afebrile. His growth charts fell on normal percentiles for height and weight for age and no other systemic anomalies were noted. Developmental assessment was normal. A differential diagnosis of chronic granulomatous disease, infectious

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mononucleosis and immunodeficiency was kept in mind. Blood samples were taken and he was sent home on analgesics and oral antibiotics and called back after a week. A week later he showed very little improvement. The blood reports revealed high White cell counts up to  $18,000 \times 10^9$  cells/L (normal upper limit is  $11,000 \times 10^9$  cells/L). Predominant cell type was neutrophils i.e. Up to 66.9%. Eosinophil counts were high up to  $1.11 \times 10^9$ /L. Red cells were normochromic normocytic. Platelet count was normal. ESR was raised up to 25 mm/hr. Brucella antibodies and Epstein-barr-virus antibodies were both negative. The child was sent for excisional biopsy of the submandibular nodes. Fine needle aspiration from the enlarged right and left submandibular lymph nodes showed sheets of neutrophils along with scattered macrophages, lymphocytes, immune blasts and plasma cells and gave a diagnosis of suppurative lymphadenitis with abscess formation. Immune globulins levels showed raised levels of IgE to more than 500 IU/L. Lymphocytes subsets and other immune globulins levels were normal. Report of the excisional biopsy of the affected lymph node showed only inflammatory changes and no caseation. Culture sensitivity of the drained pus from the submandibular inflamed lymph nodes yielded growth of gram positive cocci, methicillin resistant *staphylococcus aureus* (MRSA), sensitive to amikacin, sulfamethoxazole-trimethoprim, clindamycin, linezolid and fusicidic acid (fig-1).

Case 2: A 7 years old male child with weight of 11 kg, height 91 cm and mid upper arm circumference 10.5 cm (all falling below the 5th centile of growth charts), was admitted in Ayub Teaching Hospital through OPD. He was unwell since infancy with a history of recurrent chest infections, chronic eczema, progressive weight loss, chronic boils and spine deformity that developed and worsened over the past 6 years. He had multiple admissions for same complaints and had undergone extensive investigations. He had coarse facial features, irregular dentation, dry itchy skin, a broad nose, and deep-set eyes with prominent forehead, clubbing, scoliosis, rachitic

rosary, protuberant abdomen and tinea capitis. Auscultation of chest revealed bilateral crepitations. Workup for celiac disease and primary immunodeficiency was done. X-rays of long bones showed osteopenia and a delayed bone age. Serum levels of IgE were more than 10,000 IU/mL, while other immune globulins were in



Figure-1(A, B, C): Bilateral Submandibular lymph node swelling gradually increasing in size.



Figure-2 (D, E, F): Extreme wasting, delayed bone age and malformed teeth.

normal range (fig-2). A final diagnosis of Job's syndrome was made in both.

## DISCUSSION

Skin lesions in Job's syndrome include *staphylococcus* skin infections and eczema like rash. *Staphylococcal* skin infections present as deep abscesses in contrast to the more superficial lesions and absence of skin abscesses in atopic dermatitis. A recent study reported that in almost 81% of HIES cases skin eruptions were present in newborns, average age of onset being early neonatal<sup>7,8</sup>. In one rare case psoriasis like lesion was found<sup>9,10</sup>. Systemic complications are mostly due to infections with streptococcus, pseudomonas and candida albicans. Opportunistic infections like pneumocystitis carinii can also occur. In non-immunological features, retained primary teeth, scoliosis, joint hyper extensibility, high palate and osteoporosis may be present. Apical facies with a broad nose, deep-set eyes, prominent forehead, and generalized coarsening of the facial features with age is found. Recurrent otitis media can lead to scarring of tympanic membrane.

Autosomal recessive is the more severe form of the disease with worse outcome. It has higher susceptibility to recurrent viral infections e.g. Molluscum contagiosum infection, warts and herpes simplex infections. Patients with TYK 2 mutations have an increased risk for mycobacterium infections. Impaction of a permanent tooth, presence of double rows of teeth and malocclusion may occur<sup>11</sup>. There may be sinusitis, otitis media, respiratory tract infections and pneumatocoele formation<sup>9</sup>. Skeletal findings include Scoliosis greater than 10 degrees is observed in 60% cases. Hyperextensibility of at least one joint is present in 70%. Diagnosis is difficult at an early age unless high suspicion is present. Average age of diagnosis is about 11.5 years. Early diagnosis and better management improves life span. In AD type offspring of diagnosed patients can be diagnosed early and started on therapy. HIES patients are at increased risk of developing Hodgkin and non-Hodgkin lymphoma.

Genetic testing confirms diagnosis. Supporting evidence are raised levels of serum IgE and in some patients eosinophilia. Impairment of TH 17 cells function can be used as a screening test in suspected cases. Treatment is supportive and prophylactic e.g. good skin care with bleach baths. Use of symptomatic and prophylactic antibiotics decreases incidence of abscesses<sup>8</sup>. Immunoglobulin replacements can be used to decrease infections and modify levels of IgE with some success. Proper counseling, preventive measures for skin care to prevent skin infections and regular follow-ups are backbone of long term management.

## RECOMMENDATION

Though rare but HIES is an important inherited cause of immunodeficiency in children and should be considered in differential diagnosis in children who present with repeated childhood skin and chest infections.

## CONFLICTS OF INTEREST

There was no conflict of interest to be declared by any authors.

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