

PID123

Primary Immunodeficiency

HYPER IgE SYNDROME

In this article in our series on primary immunodeficiency, Dr Goodheart is referred a patient for whom she initially did not consider the diagnosis of an immune deficiency. The case shares one of the hallmarks of allergic conditions, that of elevated Immunoglobulin E (IgE), and may easily be mistaken for an atopic condition.

Fezeka, a six-year-old girl, lives with her aunt, who is trying her best to look after the girl's health problems since her mother died from cardiac problems. Fezeka has an older brother who was diagnosed with foetal alcohol syndrome (FAS). Fezeka's facial features are also suggestive of FAS.

Fezeka was breastfed during infancy and had all the routine childhood vaccinations. From approximately two years of age, she suffered from multiple respiratory infections, including pulmonary tuberculosis, which was treated successfully. At five years of age, she was diagnosed with chronic lung disease and pulmonary hypertension and it was also documented that she had developed bronchiectasis. Home-based oxygen care became necessary. Fezeka had also developed severe eczema and suffered from recurrent *Staphylococcus aureus* skin abscesses. She tested negative for HIV infection.

Dr Goodheart is consulted for a review of the causes of the chronic cough, recurrent pneumonia, severe eczema and skin abscesses. At this stage, she considers a number of possible diagnoses, which initially focus on atopic conditions such as atopic dermatitis and severe asthma.

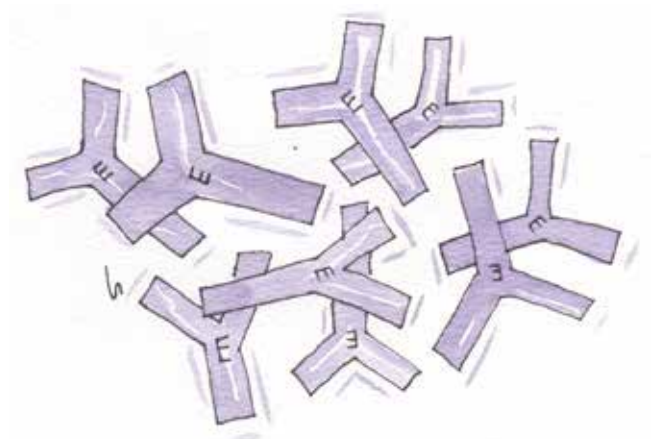
Initial laboratory tests reveal strongly elevated IgE levels ($>3\,000$ IU/ml) but no specific responses to known allergens. Her family history is also negative for atopy. Dr Goodheart is now alerted to the fact that Fezeka may not be suffering from an allergic condition. She requests further testing. Two subsequent sweat tests prove negative, excluding a diagnosis of cystic fibrosis. Sputum testing for tuberculosis is negative. A very basic screen for the immune deficit is ordered. The full blood count shows moderate white blood cell elevation, above normal neutrophil and lymphocyte numbers, and eosinophilia. Complement (C3 and C4) is within normal limits. Immunoglobulin levels (IgG, A, M) are elevated, possibly indicating frequent infections. Vaccine antibody results are in the protective range.

Dr Goodheart contacts her colleague, the paediatric immunology specialist, Dr Bala. She points out the severity of the respiratory infections, the documented presence of lung damage (bronchiectasis) in combination with very elevated



Fezeka has unusual facial features and severe eczema

IgE levels, the eosinophilia, and the skin abscesses despite the good care of the eczema. Dr Bala agrees that Hyper IgE Syndrome (HIES) and not allergy should be considered in the differential diagnosis.



Strongly elevated IgE levels were present in the serum

Dr Bala requests a clinical scoring test to be completed based on the features of the clinical phenotype of Hyper IgE Syndrome (see Table I). Fezeka scores above the cut-off of 40, which is suggestive of Hyper IgE Syndrome caused by a

mutation in the STAT3 gene.

Anatomical features that support the diagnosis include clubbing, pectus carinatum ('pigeon chest'), and a cathedral (high-arched) palate. Fezeka's coarse facial features, initially interpreted as part of foetal alcohol spectrum disorder, also fit the HIES physiognomy. However, there is no record of a newborn rash, though she is showing early signs of scoliosis. Her bone strength appears normal, although there is evidence of a forearm fracture that she suffered in a recent motor vehicle accident.

Dr Bala has blood samples extracted for DNA and referred to a genetic testing laboratory. This confirms the diagnosis of autosomal dominant (AD) STAT3 Hyper IgE syndrome. Fezeka is started on antibiotic prophylaxis in the form of daily azithromycin and her aunt is taught chest physiotherapy to be given at home. She can eventually stop her spironolactone given for pulmonary hypertension and requires oxygen only occasionally at night. Her skin is improving, too, with regular use of emollients.

TABLE I: HYPER IgE SYNDROME (HIES)

HIES is also known as 'Job Syndrome' after a character in the Old Testament of the Bible whom the Lord 'smote ... with sore boils from the sole of his foot until his crown'.

HIES not only affects the immune system, but also the skin and the respiratory system with pathological susceptibility to infections, the cardiovascular system, the skeleton and the central nervous system.

There are two better-known forms of HIES: an autosomal dominant (AD) and an autosomal recessive (AR) form. HIES (AD) is due to a mutation in STAT3, whereas HIES (AR) is due to mutations in Tyk2 or Dock 8. The clinical presentations differ slightly. For example, HIES (AR) presents with viral infections and neurological symptoms which do not fit the case described here.

Diagnosis of HIES

Elevated IgE levels of 2 000 IU/ml (or >10 times the norm for age) are the hallmark of HIES; however, high IgE levels are also observed in several other conditions, including allergies, infections and primary immunodeficiency disorders other than HIES. Note that patients younger than six months of age may have very low IgE levels and adult levels are reached only by five to seven years of age. There should be no evidence of T-cell or B-cell deficiency.

The diagnosis of HIES is facilitated by a clinical-scoring system devised by the National Institute of Health (NIH) (Grimbacher et al 1999). STAT3 deficiency is differentiated from atopic dermatitis by factors such as the presence of skin abscesses, pneumonia, pneumatocoles and anatomical abnormalities, in particular coarse facial features.

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