Case Report
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Is it hyper IgE syndrome or something else?

Abstract

Elevated IgE levels can be associated with a variety of causes. The diagnosis is most often made on a clinical basis taking into consideration a complete history and physical. In this case report we describe a patient with elevated IgE levels and our discovery upon further investigation after noticing some unique findings on his physical examination. The differential diagnosis of extremely elevated IgE levels is also discussed to help assist the clinician in the workup of a patient with elevated IgE levels.

Keywords: 18q-, eczema, atopic dermatitis, hyper IgE syndrome, elevated IgE level, genetic disease

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Case presentation

Chief complaint

Persistently elevated IgE level in a patient with atopic dermatitis.

History of present illness

Our patient is a 39 year old male who was referred to our clinic for evaluation of an extremely elevated IgE level. He had been followed by an outside allergist for severe atopic dermatitis, asthma and upon their evaluation was found to have extremely elevated levels of IgE, beyond the level expected in a patient with atopic dermatitis. He complained of nasal congestion, itching and sneezing. There was no history of recurrent staphylococcal skin or pulmonary infections. In addition, he did not have a history of viral diseases or prolonged illness.

Medical history

Review of our patient's history revealed that he had bilateral foot surgery as a child and hearing loss since the age of ten. He also has developmental delay and mental retardation.

Physical examination

Physical examination was notable for a diffuse eczematoid skin rash, complicated by excoriation and lichenification especially on his upper and lower extremities, face, and groin. In addition he had dysmorphic facial features, proximal thumbs, and single palmar creases. He did not have coarse facies, scoliosis or delayed shedding of the primary teeth.

Family history

He has a sister with historical cat allergy, but no other family members with atopy.

Laboratory and other diagnostic findings

The results of a CBC with differential showed an absolute eosinophil count of 2003 cells/ul, but were otherwise normal. Patient's IgE level was 32,161ku/L on our initial evaluation, but was as high as 90,000ku/L on another visit. Specific IgE testing was significantly positive for Bermuda grass, cat dander, dog dander, house dust, egg white, and egg yolk. Stool ova and parasites were negative in addition to specific IgE to anisakis and IgG to strongyloides. Levels of IgA were 284 mg/dl, IgG 1720mg/dl, IgM 63 mg/dl.

B cell subsets were also evaluated. Marginal zone B and class switch memory B cells are low. Transitional B cells and CD21 low are high. The other subsets were within the normal range.

What is the differential diagnosis of an elevated IgE level?

The differential diagnosis of elevated IgE level is extensive. In this discussion we will include those causes that can be associated with levels greater than 5000 IU/ml (Table 1).

Inflammatory Causes

Kimura disease

Kimura disease is a rare, benign inflammatory disease most frequently affecting Asian men in the third decade of life. Presenting symptoms include regional lymphadenopathy and adenitis of the face and neck. Laboratory studies reveal peripheral eosinophilia, and elevated total IgE levels reported in case reports as greater than 5,000 IU/ml.[1]

Churg-strauss syndrome

Churg-Strauss syndrome features extravascular granulomatosis, eosinophilic vasculitis of small and medium-sized vessels, severe peripheral eosinophilia, and elevated IgE levels usually up to 5,000 IU/ml.[2]

Allergic Causes

Atopic dermatitis

In atopic dermatitis, IgE levels may be elevated, even to more than 10,000 IU/mL. There is increased susceptibility to cutaneous infections, but more invasive infections should prompt an evaluation for immunodeficiency. Importantly, the IgE level in patients with atopic dermatitis has reactivity to a broad range of food and inhalant allergens.[3]

Primary immunodeficiency causes

Hyper-IgE syndrome: The prototypic example of a primary immunodeficiency disorder with an elevated total IgE level is the rare Hyper-IgE syndrome, also known as Job syndrome. Patients characteristically have recurrent abscesses, pneumonias or bronchiectasis. IgE levels range from 2,000 to greater than 50,000 IU/ml. Eczema, mucocutaneous candidiasis, retention of the primary teeth, coarse facial features, osteopenia, hyperextensible joints and increased risk of malignancy are also common.

Table 1 Summary table of diseases with IgE Levels >5000 IU/ml

Disease	IgE Level	Phenotype	Other Features
Kimura Disease	can be > than 5,000 IU/ml	Regional lymphadenopathy, adenitis	Asian men in the third decade Peripheral eosinophilia
Churg-Strauss syndrome	Up to 5,000 IU/ml	Extravascular granulomatosis, eosinophilic vasculitis (small and medium vessels)	Severe peripheral eosinophilia
Atopic Dermatitis	Can be > than 10,000 IU/ml	Eczematous skin	Reactivity to broad range of food and inhalant allergens
Hyper IgE syndrome	2,000-50,000 IU/ml	Recurrent abscesses, pneumonias or bronchiectasis	Eczema, mucocutaneous candidiasis, retention of primary teeth, coarse facial features, osteopenia, hyperextensible joints
Wiskott-Aldrich Syndrome	Up to 5,000 IU/ml	Microcytic thrombocytopenia, eczema, recurrent infections	X-linked, defect in WASp, elevated IgA and low IgM levels with impaired specific antibody responses
Netherton Syndrome	100- >than 10,000 IU/ml	Bamboo hair, ichtyhosis, atopy, immunodeficiency, recurrent infections	Eosinophilia, depressed IgG levels
Omenn Syndrome	Up to 45,000 IU/ml	Exudative erythroderma with desquamation, lymphadenopathy and hepatosplenomegaly. Severe respiratory tract infections with intractable diarrhea and FTT.	RAG1, RAG2 or ARTEMIS gene mutation. Eosinophilia and hypogammaglobulinemia
Nezeloff Syndrome	5-7000 IU/ml	Atopic dermatitis, recurrent infections, pondostatural retardation, oral or cutaneous candidiasis, diarrhea	Cutaneous anergy to skin prick tests and absent lymphocyte response to mitogens

Patients with HIES may also have immediate skin reactions to a number of inhalant and food allergens, they can also often demonstrate specific IgE and immediate skin test reactions to Staphylococcal aureus (although this can also be seen in patients with atopic dermatitis) and Candida albicans, as well as to other bacterial and fungal antigens.

Wiskott-Aldrich syndrome: It is a rare, X-linked syndrome due to mutations in the Wiskott-Aldrich syndrome protein (WASp), a regulator of actin polymerization and cytoskeletal reorganization. The triad consists of microcytic thrombocytopenia, eczema and recurrent infections. Infections include complicated otitis media, pneumonia, sinusitis, meningitis and sepsis. Dysregulated immunity may lead to vasculitis, inflammatory bowel disease and lymphoproliferative malignancies. Laboratory studies frequently reveal elevated IgE up to 5,000 IU/ml and elevated IgA levels. IgM levels are often low. Specific antibody responses to polysaccharides, protein antigens and isohemaglutinins are impaired.

Netherton syndrome: It is a rare autosomal recessive disease caused by mutations in SPINK5, a serine protease inhibitor. Features include trichorrhexis invaginata (bamboo hair), ichthyosis, atopy, immunodeficiency, eosinophilia and elevated IgE levels ranging from 100 to greater than 10,000 IU/ml. Recurrent or severe skin, respiratory tract, and systemic infections occur and may be related to depressed IgG levels. The characteristic bamboo hair and skin manifestations help distinguish this syndrome from HIES.

Omenn syndrome: It is caused by hypomorphic mutations in RAG1, RAG2 or ARTEMIS genes resulting in an oligoclonal T-cell population skewed toward autoreactivity. Similar to graft vs host disease, generalized exudative erythroderma with desquamation, lymphadenopathy and hepatosplenomegaly are seen along with severe respiratory tract infections, intractable diarrhea and failure to thrive (FTT). Laboratory studies demonstrate eosinophilia, hypogammaglobulinemia and elevated IgE levels up to 45,000 IU/ml.[4]

Nezel of syndrome: It is also known as cellular immunodeficiency with Ig, or combined immunodeficiency with a predominant T-cell defect is clinically less severe than Omenn syndrome. It is characterized by a form of atopic dermatitis, concentration of IgE that maybe be extremely elevated (5-7000IU/ml) and normal or increased serum levels of other Ig classes. There is cutaneous anergy to skin prick tests and a reduced or absent in vitro lymphocyte response to mitogens. From infancy patients present recurrent or chronic pulmonary infections, pondostatural retardation, oral or cutaneous candidiasis, chronic diarrhea, recurrent cutaneous and urinary tract infections, Gram negative bacterial sepsis and a particularly severe form of chicken pox.[5]

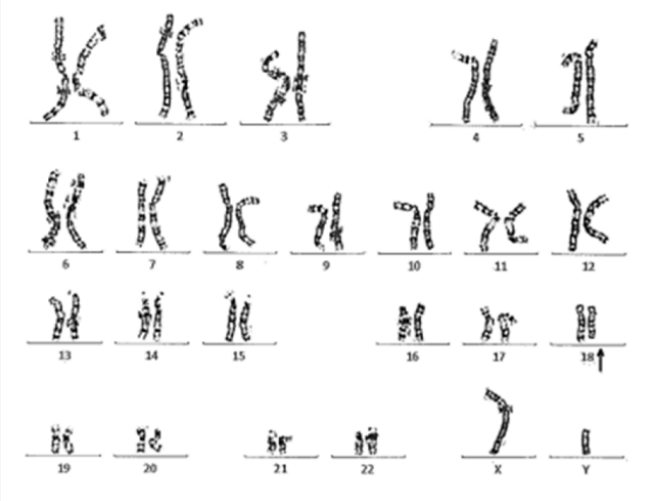

Figure 1 Karyotype showing chromosome 18q deletion.

Clinical course

Despite the patient's history lacking clinical consistency with Hyper IgE syndrome, intracellular phospho-STAT3 expression was performed by flow cytometry and found to be normal. DOCK 8 analysis was not done. The patient's dysmorphic facial features and other findings on physical exam prompted chromosomal analysis. The patient was found to have a distal 18q deletion and prompted further investigation (Figure 1). Array CGH analysis using Genzyme revealed a 12.77Mb copy loss in the region of 18q22.1-18q23 (Figure 2). This deletion is typically associated with demyelination seen on cerebral MRI.[6] and MRI done on this patient showed confluent nonspecific

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periventricular and subcortical white matter changes. The patient was treated for his atopic dermatitis using high dose corticosteroid preparations on his body and scalp and topical tacrolimus preparations on his face and groin.

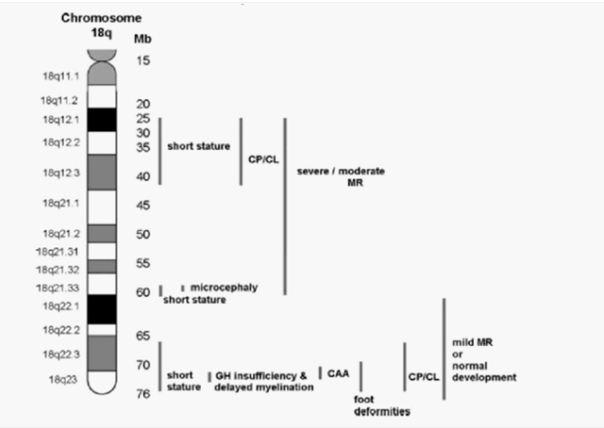

Figure 2 Phenotypic map of chromosome 18q indicating the critical regions for various clinical features. CAA, congenital aural atresia; CP/CL, cleft palate/cleft lip; MR, mental retardation.

Discussion

The 18q- syndrome represents a contiguous gene deletion syndrome and is one of the commonest of the human segmental aneusomies, with an estimated prevalence of about 1 in 40,000 live births. It is a terminal deficiency or macrodeletion syndrome characterized by mental retardation and congenital malformations. Common features include microcephaly, palatal defects, short frenulum, carp-like mouth, short palpebral fissures, external ear anomalies, and short stature but the phenotype is highly variable.[7] Most cases are sporadic, but an autosomal dominant transmission has also been reported.[8]

The patient described has several classical symptoms of 18q syndrome including short stature, hearing impairment, craniofacial dysmorphism, demyelination, low levels of growth hormone, and mental retardation. Autoimmune disease and low levels of Immunoglobulin A have been reported in some cases of the 18q-syndrome.[9] Distal 18q- is involved in neural development.[10]

This is the first patient reported to have this chromosomal deletion in addition to very high levels of IgE and severe atopic dermatitis. The deleted chromosome region 18q22.1- 18q23 comprises the genes DOK6, CD226, RTTN, SOCS6, CBLN2, NETO1, FBXO15, CYB5A, CNDP1, ZNF236, MBP, GALR1, SALL3, NFATC1, CTDP1, KCNG2, TXNL4A, and PARD6G, some of which are functional in the immune system.[11] This is the first reported case of extremely elevated IgE level in a patient with 18q-syndrome.

Final diagnosis

Atopic dermatitis and 18q deletion.

Conclusion

The patient was referred to us for evaluation of extremely elevated IgE. Increases in total serum IgE levels can be seen in many different conditions. The diagnosis is most often made on a clinical basis after synthesizing finding from the history, physical examination and laboratory studies. In our patient clinical and laboratory findings were not consistent with Hyper IgE syndrome (autosomal dominant or recessive) and further probing discovered a deletion of the distal 18q. Further studies are needed to clarify whether any of these genes would play a role in elevated IgE production or whether this association is coincidental.

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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