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Job Syndrome (Hyperimmunoglobulin E)

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Introduction

Hyper-IgE syndrome (HIES) is a rare, primary immunodeficiency distinguished by the clinical triad of atopic dermatitis, recurrent skin staphylococcal infections, and recurrent pulmonary infections. Furthermore, there are elevated IgE levels of early onset in primary childhood.

David et al. first described reported "Job syndrome" in 1966 in two patients with eczema, recurrent pulmonary infections, and cold lung abscesses. Later, in 1972, Buckley et al. reported the association of this condition with increased serum immunoglobulin E (hyper-IgE) levels and a series of phenotypic features called HIES.

The HIES is classified into 2 types.

- Type I: Autosomal dominant hyper-IgE syndrome (AD-HIES), in which patients have abnormalities in different systems, including the immune system, connective tissue, skeletal and vascular among others
- Type II: Autosomal recessive hyper-IgE syndrome (AR-HIES), which also affects the immune system, manifesting in high IgE, recurrent skin and lung infections, sensitivity to viral infections such as molluscum contagiosum, and central nervous system (CNS) involvement, but does not have musculoskeletal alterations

Most recently, the International Union of Immunology Societies describes primary immunodeficiencies (PID) with well-defined syndromes as AD-HIES (Job syndrome) and 3 subtypes of AR-HIES that do not present skeletal or pneumatocoeles alterations. These are further subdivided into TYK2 deficiency, DOCK8 deficiency, according to a molecular abnormality, and one of unknown origin.[1][2][3]

Etiology

Job syndrome is due to a mutation in the *STAT3* gene in more than two-thirds of cases (70%). The transmission of this syndrome is autosomal dominant and variable expressivity. More than 90 different mutations have been reported. In the rest of the cases, the etiology of Job syndrome remains unclear.[1][4]

Epidemiology

The annual incidence of Job syndrome is estimated at around 1: 1,000,000. Although initially described in female subjects, both genders are affected, with no ethnic factor. A family character has only rarely been described.[1]

Pathophysiology

Job syndrome is due to a specific genetic mutation of autosomal dominant inheritance in the *STAT3*. *STAT3* is involved in healing mechanisms and immune mechanisms. The mutation of this gene will lead to an intensification of the production of immunoglobulin E by B lymphocytes, the loss of the modulation capacity of their production by IL-6, IL-10, and IFN-gamma, and a defect chemotaxis of neutrophils. The lack of anti-inflammatory effects of IL-10 is probably the cause of the inappropriate inflammatory response observed in patients with Job syndrome. IL-6 plays an essential role in the genesis of Th17 cells; therefore, the lack of this cytokine leads to a deficiency of Th17 cells in Job syndrome. The CD4 + Th17 cells play an important role in the defense against infections mainly bacteria and extracellular fungi.

In addition, aside from its immunological role, this molecule has the role of pleiotropic signaling, which explains other non-immunological findings observed in the Job syndrome, such as long bone fractures and a late rash. Secondary

teeth with primary teeth retained among immunodeficiencies.[4][1]

History and Physical

Job syndrome is characterized by clinical signs of immunological and non-immunological order.

Immunological and Infectious Features

They are mainly about a chronic eczematoid eruption and recurrent skin and pulmonary bacterial infectious and mucocutaneous candidiasis. The skin manifestations appear usually very early, few weeks after birth. They include a pruriginous eczematoid rash affection the scalp and the face, that is rapidly superinfected with *Staphylococcus aureus*, resulting in weeping, crusty and follicular infectious lesions, as well as cold skin abscesses that are little or non-inflammatory. *Candida* infections are also common: they affect the skin, mucous membranes and nails. Sinopulmonary infections are also common in Job syndrome. These are recurrent or chronic infections such as bronchitis, pneumonia (with pneumatoceles) predominately due to *S. aureus*, more rarely *Streptococcus pneumoniae* and *Haemophilus*. The evolution of pneumonia is classically marked by the installation of cystic dilatation with bronchiectasis and pneumatoceles, which are at the origin of other manifestations close to those observed in cystic fibrosis, such as bacterial infections with *Pseudomonas aeruginosa* and nontuberculous mycobacteria, *Aspergillus* and *Scedosporium*. These secondary infections are very difficult to treat and cause significant morbidity and mortality. Other infectious manifestations such as sinusitis, otitis, gingivitis, dental abscess, septic arthritis and osteomyelitis are also common. Bone density is decreased and is the source of multiple fractures leading to functional discomfort and significant pain. There is an increased risk of malignancies in Job syndrome especially Hodgkin lymphoma. Other cancers have also been reported as Hodgkin lymphoma, leukemia, and cancers of the vulva, liver, and lung.[5][6][7][8][9][10][11][12][13][8]

Morphologic Features

Patients with Job syndrome have characteristic facial features that appear in early adolescence or earlier in late childhood, for example, facial asymmetry, prominent forehead, sunken eyes, broad nasal ridge and fleshy nose, prognathism, and craniosynostosis. Musculoskeletal abnormalities are common. They include hyperextensibility of the joints, scoliosis, and osteopenia. The hyperextensibility may result in early onset of degenerative joints disease. Bone density is decreased and is the source of multiple pathological fractures that occur in approximately 50% of patients (long bones and ribs). Scoliosis of variable severity is observed in approximately 60% of patients. Anomalies of dentinogenesis are possible manifestations. Decreased resorption of the roots of the deciduous teeth may result in prolonged retention of the deciduous teeth, preventing the appearance of definitive teeth. Vascular manifestations include coronary and aortic aneurysms, tortuosity or dilatation, lacunar infarctions, thrombosis of the cerebral artery, and persistence of the congenital arterial duct. Ocular complications may include xanthelasma, giant chalazion, nodules on the eyelids, strabismus and retinal detachment with complicated cataract. There is also a high risk of autoimmune and lymphoproliferative diseases. MRI may detect brain abnormalities. They could be secondary to infectious or vacuogous manifestations.[5][6][7][8][9][10][11][12][13][8]

Evaluation

The main diagnostic feature is an increase in serum IgE levels of more than 2000 U/mL, and often 500 U/mL. A clinical score has been developed to define the probability of diagnosis. A total IgE concentration greater than 1000 IU/mL and a weighted score of greater than 30 indicate an AD-HIES of the defect in *STAT3*, and a dominant-negative heterozygote mutation in *STAT3* confirms the diagnosis.[5][1]

Treatment / Management

The most effective treatment, for now, for this condition is the long-term, sometimes continuous, use of antibiotics (penicillinase-resistant penicillins, cephalosporins, other antibiotics, and antifungal agents) by adapting the treatment to infections occurring in these patients and sometimes using surgical procedures during abscess development.

Interferon-gamma has shown no clinical benefit in this condition, nor does bone marrow transplantation. Thanks to antibiotics, and if the diagnosis is made early, patient survival can be long. The management of non-immunological manifestations must be interprofessional. It aims to treat complications. Thus, scoliosis, depending on its severity, as well as bone fractures and degenerative joints diseases may require orthopedic surgery. Dental abnormalities require

adequate stomatological treatment. Cardiovascular complications are managed in a specialized environment.^{[5][1][6][8][1]}

Differential Diagnosis

According to the clinical presentation, the diagnosis of Job syndrome could be difficult and arise with other diagnoses including in particular other types of primitive (chronic granulomatous disease) or acquired (HIV infection) immunodeficiency, severe atopic dermatitis, or cystic fibrosis.^{[1][10]}

Prognosis

Although AD-HIES is associated with high morbidity and mortality, advances in medical care, close monitoring and patient compliance have led to improved prognosis, with survival up to 50 years or more.^{[1][14]}

Pearls and Other Issues

Job syndrome is a rare, primary immunodeficiency due to mutations in *STAT3* and characterized by defects in immunity with eczematous and non-immunologic system disorders. Antenatal diagnosis is theoretically possible. However, the very low incidence and the sporadic nature in the majority of cases make this method without much interest. The treatment at the moment is purely symptomatic. A biological or gene therapy in the future could change the prognosis of this syndrome.

Questions

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