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Review Article

Job Syndrome and Its Management

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ABSTRACT

Job's syndrome is characterized by the clinical features of fair skin, red hair, recurrent cold, staphylococcal skin abscesses with concurrent other bacterial infections and skin lesions. Hyperimmunoglobulin E syndrome (HIES) is a rare immune deficiency presenting with a trial of recurrent skin and pulmonary infections elevated IgE and eczematous reactions. The aim of this article is to review the literature in order to consider clinical findings, pathophysiology and treatment of this syndrome.

Keywords: Hyperimmunoglobulin E syndrome, recurrent skin infections, eczema, STAT 3.

INTRODUCTION

Job syndrome is a rare, inherited disease that causes problems associated with the skin, sinuses, lungs, bones as well as teeth. Hyperimmunoglobulin E syndrome is also known as Job syndrome. Job syndrome is a rare immune deficient disorder with a possible occurrence of one in a million as yet approximately 250 cases already have been reported and many more remains concealed in the anonymous dusts of the third world countries. Patients with the hyperimmunoglobulin E and recurrent skin infection syndrome (HIE) characteristically have frequent skin and respiratory infections caused by *staphylococcus aureus*. The Job's syndrome was first described by Davis *et al* in 1966, often has it onset in childhood, sometimes shows familiar occurrence and is characterized by markedly elevated serum IgE levels, chronic dermatitis and recurrent pyrogenic infections[1,2]. Many people with Job syndrome have skeletal abnormalities such as an unusually large range of joint movement (hyper extensibility), an abnormal curvature of the spine (Scoliosis), reduce bone density (Osteopenia) and a tendency of bones to fracture easily. Dental abnormalities are also characteristic of this condition. The primary (baby) teeth do not fall out at the usual time during childhood but are retained as the adult teeth grow in. The other signs and symptoms of Job syndrome can conclude distinctive facial features and structural abnormalities of the brain, which typically do not affect a person's intelligence.

Sign and symptoms

An eye examination may reveal signs of dry eye syndrome.

- Curving of the spine.
- Osteomyelitis
- Repeated sinus infections.
- Bone and teeth defects, including fractures and losing the baby teeth late.
- Eczema.
- Large skin abscesses and infection.
- Osteoporosis
- Guilt
- Depression
- Increased number of eosinophils in blood.
- Mouth fungal infections
- Reduced bone density.

Causes

The exact cause of Job syndrome is unknown. Job syndrome is caused by a mutation in the STAT 3 gene, but it is thought to be a specific genetic abnormality affecting chromosome 4q. The result is defective immune response involving T-lymphocytes, neutrophils and the cytokines they produce, especially interferon-gamma. Excessive levels of interferon-gamma result in marked

elevation of immunoglobulin-E. Finding from a multipoint analysis confirm that the proximal 4q region contains the disease locus for Job syndrome[3].

Pathophysiology

The exact pathophysiology of Job syndrome is unknown. Patients consistently have a poor and delayed hypersensitivity response to antigens. This delayed response is also associated with alterations in T-lymphocyte populations and also various cytokine and interleukin abnormalities.[4] Chemotactic defects in neutrophils has since been attributed to defective production of interferon-gamma, a major activator of neutrophils when stimulated by interleukin (IL-12). The poor production of interferon-gamma in response to IL-12 results in the marked elevation of IgE levels[5]. Patients with Job syndrome have elevated levels of granulocyte-macrophage colony stimulating factor, which may also explain the decreased chemotaxis and increased oxygen radical production and tissue damage[6].

Although the cytokine deregulation plays a major role in its pathophysiology, the causative gene has not yet been identified[7]. The hyper-IgE syndromes have multiple genetic bases. The majority of patients have dominant mutations in the single transducer and activator of transcription-3 (STAT 3) gene[8]. Autosomal recessive mutations in DOCK 8 are linked with the autosomal receive hyper IgE-syndrome. Dominant- negative mutations in STAT-3 gene have been associated with the classic multisystem form of hyper IgE- syndrome[9].

Diagnosis

Other than IgE level, laboratory tests are not helpful in diagnosing HIES, and even high IgE levels are not specific since these can be found in other conditions. Many studies have already focused on the immune aspects of HIES, such as migration of neutrophils toward damaged or infected tissue. However no specific immune defect has been found consistently in all patients with HIES. An elevated level of serum IgE alone is not sufficient to make the diagnosis since patients with certain conditions such as severe allergic skin rashes occasionally have IgE levels in the HIES range without having HIES.

In infants, in whom normal IgE levels are very low, an IgE of 10 times the age appropriate level is a reasonable guide for HIES. It should be noted that in some adults with HIES, IgE may decrease and even become normal. The presence of the other clinical features involving the skeleton and teeth can be very useful in supporting the clinical diagnosis.

Elevated IgE is the hallmark of HIES, usually more than 10 times normal. However, patients younger than 6 months of age may have very low to non-detectable IgE levels. Eosinophilia is also a common finding with greater than 90% of patients having eosinophil elevations greater than two standard deviations above the normal mean.[10]

Treatment

No definitive therapy is available for the treatment of hyper-IgE Syndrome (HIE syndrome or Job syndrome). The mainstay of treatment is the control of bacterial infections. Early incision and drainage followed by the intravenous administration of antibiotics are used for cutaneous infections. Coverage is usually aimed at Staphylococcus and Haemophilus species. [11]

Job syndrome's therapy is usually longer than typical treatment because the disease in these patients responds more slowly than that of patients without Job syndrome. Intravenous antibiotic treatment for 2 weeks is typical, chronic onychomycosis responds well to oral ketoconazole and fluconazole. Eczematous dermatous dermatitis has a varied response to high dose tropical steroids. Chemoprophylaxis in patients with Job syndrome has varied results. Levamisole an immunopotentiating drug, has been investigated as a therapeutic agent; in one study it was unhelpful. Long term trimethoprim-sulfamethoxazole treatment was used in one patient with recurrent pruritic dermatitis, with resolution of symptoms.[12]

Surgical excision and drainage of cutaneous infections are often performed in patients with Job syndrome. Drainage is usually followed by intravenous antibiotic therapy. Chronic hidradenitis suppurative occurs in some patients with Job syndrome. The treatment consists in local care of the skin, steroid administration (topical steroids together with oral prednisone 0.5 mg/kg/24hrs, with slight decrease of the dose over 3 weeks), antibiotic therapy based on the results of bacterial cultures. Anti-H_1 medication (claritine) and Vitamin-C were added. The immunomodulatory therapy with cyclosporine A at 0.3 mg/kg/day was started with a favorable outcome, regarding as well the clinical and biological aspects. Treatments consist of intensive skin care and use of topical agents; moisturizing creams, anti-bacterials, topical steroids. Prophylactic antibiotics are given in order to reduce severe infections. Ascorbic acid and anti-H_1 are prescribed in order to improve chemotactic responsiveness of neutrophils.

Other therapeutic options have been tried in several studies, with different results: Methotrexate[13],Interferon gamma[14], intravenous gamma-globulin[15], plasmapheresis[16] and bone marrow transplant[17].

In two studies, cyclosporine A was followed by a dramatic improvement of clinical manifestations and IgE serum levels, without side-effects but with a relapse at the time of discontinuation and with

clinical and laboratory improvement after reintroducing this therapy.[18,19]

CONCLUSION

Job syndrome is a rare immune-deficiency disorder that comprises essentially of generalized eczema and susceptibility to skin and pulmonary infections. Characteristic facial features comprising of broad-based nose and prominent eye-brows are seen in majority of cases. Symptoms of recurrent skin and sinu- pulmonary infections usually start during the first two years of life; they may be delayed upto 17years. Job's syndrome can be transmitted as an autosomal dominant trait with variable expressivity. Though no specific satisfactory treatment is available for the illness but antibiotics are the mainstays of therapy during infective episodes. Though there is no known cure for Job syndrome, antibiotics are used to control the bacterial infections, often requiring a longer course of treatment than is usually necessary. Several doctors from different specialties may need to help care for affected children.

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