Introduction

Hyper-IgE syndrome (HIES, Job’s syndrome) is a rare primary immunodeficiency (PID) characterized by recurrent skin abscesses, recurrent pneumonia with pneumatocele formation, eczema, eosinophilia and elevated levels of serum IgE. Most cases occur sporadically, however two distinct entities - classic HIES, which is inherited in an autosomal dominant pattern (AD-HIES), and an autosomal recessive HIES (AR-HIES), have been delineated. In the classic form associated facial, skeletal and dental abnormalities are also observed. In 2007 mutations in STAT3 gene were found in AD-HIES patients. We have reviewed literature concerning AD-HIES.

Key words: dermatitis, eosinophilia, hyper-IgE syndrome, STAT3 mutations, pneumatocele

Abstract

Hyper-IgE syndrome (HIES) is a primary immunodeficiency (PID) characterized by recurrent skin abscesses, recurrent pneumonia with pneumatocele formation, eczema, eosinophilia and elevated levels of serum IgE. Most cases occur sporadically, however two distinct entities - classic HIES, which is inherited in an autosomal dominant pattern (AD-HIES), and an autosomal recessive HIES (AR-HIES), have been delineated. In the classic form associated facial, skeletal and dental abnormalities are also observed. In 2007 mutations in STAT3 gene were found in AD-HIES patients. We have reviewed literature concerning AD-HIES.

Key words: dermatitis, eosinophilia, hyper-IgE syndrome, STAT3 mutations, pneumatocele
Current and severe infections caused by *Staphylococcus aureus*, *Haemophilus influenzae*, *Proteus mirabilis* and *Cryp
tococcus* were observed, but even more frequently severe, chronic, resistant to pharmacotherapy infection with mollu
scum contagiosum and *Herpes simplex* virus predominated. In this type either skeletal abnormalities, pathological bone
fractures, dental disorders, or characteristic facial features do not occur. On the contrary, in majority of affected persons
neurological complications were revealed. Diverse clinical manifestations facilitate a differentiation between autosomal
dominant and recessive form of the syndrome.

The first extensive review of the syndrome was pre
tented in 2000 by Erlewyne-Lajeunesse [8] and, in 2005 a
discussion was published by Grimbacher [11].

**Clinical presentation**

Manifestation of hyper-IgE syndrome of an autosomal domi
nant type consists of clinical triad of symptoms: 1. recurrent
skin, subcutaneous, lungs, bones, joints, and lymph nodes ab
scesses, 2. serious recurrent airway infections, 3. increased
concentration of total immunoglobulin E in serum [12] and
and a constellation of abnormalities in the immune and skeletal
systems, connective tissue, and teeth in various degree of se
verity [8, 11]. This multi-organ manifestations of hyper-IgE
syndrome leads to diagnostic difficulties in this immunode
ficiency syndrome, particularly in young patients and in aty
pical, less severe cases [13]. The frequency of typical clinical
manifestations and laboratory findings was summarized by

It has been stressed in the literature that neonatal rash is
typically the first clinical manifestation in hyper-IgE syn
drome [3]. Interestingly, although chronic dermatitis in hy
per-IgE syndrome is traditionally described as eczema, it is
doubtful if this rash virtually presents as atopic dermatitis [2]
Amongst infectious complications typical for the syndrome
bacterial, mainly staphylococcal infections predominate, in
cluding methicillin-resistant *Staphylococcus aureus* (MRSA), evoking generalized overwhelming infections [28].
Skin infections occur frequently as well and may be observed
early in the infancy presenting with furunculosis, „cold” ab
scesses, and cellulitis. Sporadically observed „cold” absc
seses are pathognomonic for hyper-IgE syndrome, but not ne
cessary for definitive diagnosis [7]. Severe recurrent respira
tory infections are usually caused by *Staphylococcus aureus*,
*Haemophilus influenzae* and *Streptococcus pneumoniae*. Pneumonias are typically complicated by lung abscesses
[21], bronchiectases, bronchopleural fistulas and pneumato
cele [8]. They are often colonized with microorganisms like
*Pseudomonas aeruginosa* and *Aspergillus fumigatus*. The
latter one can lead to invasive aspergillosis as well as forma
tion of aspergilloma which often requires surgical treatment.
Pulmonary complications lead invariably to the development of
chronic respiratory insufficiency and are the main cause of
mortality. Upper airway infections manifest as paranasal
sinusitis, exudative otitis media [14]. In approximately 80%
of cases mycotic infections of the skin and mucous membran
nes with *Candida albicans* and other fungal strains may co
exist [11]. There are also reports concerning *Pneumocystis ji
roveci (carinii)* infection [12], cryptococcosis [17], histoplas
mosis [24], disseminated pulmonary candidiasis [36], as
well as post-BCG vaccination complications [25]. In major
ity of affected individuals characteristic constitutional fea
tures are observed, such as coarse face, rough skin, deeply set
tled eyes, prominent forehead, prognathism, thick lower lip
and auricles, wide nose and increased interalar distance [3].
There are also reports concerning mid-face anomalies, ar
ched palate and a rare malformation – craniosynostosis [31].
Other characteristic manifestations include: delayed loss of
primary teeth, dental caries and abnormal development of
permanent teeth [3].

Recurrent pathological bone fractures reflecting the multi-system involvement in hyper-IgE syndrome are noted in
more than 50% of patients [11]. Typically long bones are
affected as a result of minor injuries [3]. More than 60% of
affected individuals present with scoliosis of various degree.
Giant chalasias are also frequently noted [5]. These compi
lations together with joint hyperextensibility is another cha
racteristic feature of AD-HIES. An increased incidence of
lymphoproliferative disorders (non-Hodgkin lymphomas,
Hodgkin disease) and autoimmune diseases (lupus erythema
thosus, dermatomyositis) have also been noted [20, 29, 30].

A hallmark of the syndrome is an increased concen
tration of immunoglobulin E in serum, exceeding 2000 U/ml
[11, 12]. Concentrations of other main classes of immuno
globulins remain normal in the majority of cases. Blood eosi
nophilia is usually higher than 700 cells/microliter [2, 11].
No correlation between eosinophilia and either the IgE con
centration in serum or the incidence of infectious complica
tions has been observed. Leucocyte blood count is usually
normal, but during acute infections often leucopenia may be
noted.

A score system taking into consideration both clin
ical and laboratory diagnostic criteria has been proposed by
Grimbacher and co-workers [11]. An analysis carried out on
the base of this scale and reaching the particular total score
indicates that the affected individual is probably a carrier of
the hyper-IgE genotype, or that the presence of this genoty
pe in uncertain, or at last, is less likely. However, several
symptoms like scoliosis, characteristic face, or delayed loss of
primary teeth can not be taken into account in children un
der the age of eight years, since they may not be expressed
until the adolescence. Likewise, the number of episodes with
infections, bone fractures and pulmonary disorders leading to
the development of pneumatocele increases with age. Assess
ment of the suspected patient according to this scoring sys
tem and gaining ≥15 points makes the recognition of hyper
-IgE phenotype carrying highly probable.

**Principles of treatment**

Therapeutic strategy in hyper-IgE syndrome is directed ma
inly toward prevention and management of infections. Intro
duction of regular long-term in-take of systemic antibiotics
and antifungals in suspicion of HIES is of great importance as it can prevent from overwhelming serious infections. Active infections are treated with the early introduced, long-term antibiotic therapy in high doses, antifungal agents, as well as immunoglobulins.

In empirical treatment of respiratory infections antibiotics covering in their spectrum such microorganisms like Staphylococcus aureus, Haemophilus influenzae and Streptococcus pneumoniae are recommended. Lung abscesses, being frequent complications, particularly of staphylococcal pneumonia require a surgical intervention. An important therapeutic problem are also pneumatocele and bronchiectases, superinfected with Pseudomonas aeruginosa and other Gram negative bacteria or with fungi, such as Aspergillus fumigatus. In these cases invasive procedures such as resection of the lung parenchyma limited to pneumatocele or confined bronchiectases are recommended [11].

In contradistinction to atopic dermatitis in hyper-IgE syndrome skin changes frequently improve solely after antibiotic therapy [15], therefore intensive antibacterial and antifungal agents are recommended in the treatment strategy of cutaneous complications. Skin abscesses should be incised and drained. In superficial skin and mucosal candidiasis – onychomycosis, vaginomycosis and oral thrush treatment with tiazoles is effective, yet in systemic mycoses it's spectrum antistaphylococcal activity, eg. trimethoprime/sulfamethoxazole, semisynthetic penicillins or cephalosporins, significantly contributes to the reduction of such complications like skin abscesses and staphylococcal pneumonias [11, 32]. Development of resistance in the course of long-term therapy outweighs the risk of severe infections and lung damage when it is given up [11]. The use of immunoglobulins in hyper-IgE syndrome is controversial. Kimata et al [19] reported positive results of high-dose intravenous immunoglobulins, however other authors did not note any positive effect of this therapy [34]. A relatively positive clinical effects were achieved on prophylactic treatment with H2 – receptor antagonists [33]. In vitro studies revealed an improvement of neutrophil chemotactic function with interferon-gamma [18], however in one patient autoimmune thrombocytopenia was noted [1]. Reports concerning the use of cyclosporine A are encouraging; a positive clinical effect was observed by Wolach [35] and Etzioni [9]. Ishikava et al noted an improvement after plasmapheresis [16]. Currently there is a lack of data referring to a therapeutic option with monoclonal anti-IgE antibody (omalizumab). Attempts of bone marrow transplantation have also been undertaken, however the efficacy of this procedure is discouraging [10, 23].

Patients with hyper-IgE syndrome require interdisciplinary care of specialists in pediatrics / internal medicine, pneumonology, dermatology, surgery, oncology, neurology, stomatology, and psychology under the clinical immunologist’s supervision.

Conclusions

Hyper-IgE syndrome seems to be not a solemn disease but rather a group of similar diseases with different underlying genetic defects, so it is still a challenge for scientists working in genetic field. It is also a great difficulty for clinicians, as there are no ESID criteria for recognition of the suspected case, which are so supportive in doctor’s every-day work. Grimbacher’s scoring scale is very supportive in AD HIES before performing genetic analysis of STAT3 gene.

References


