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**Review Article**

# A Review on Hyper-IgE Syndromes: Clinical Manifestations, Diagnosis and Therapeutic Approaches

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**Abstract**

Hyper IgE syndromes are classified as groups of primary immunodeficiency diseases, which are presented with a series of symptoms including recurrent infections accompanied by elevated serum IgE level and some atopic features. Both autosomal dominant and recessive mutations may lead to hyper IgE syndrome. The autosomal dominant forms are mutations in signal transducer and activators of transcription3 (STAT3), Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) and caspase recruitment domain family, member 11 (CARD11). The recessive forms are mutations in dedicator of cytokinesis8 (DOCK8), phosphoglucomutase3 (PGM3), Tyrosine kinase2 (TYK2) and interleukin-6 ST. moreover, there are some features that help distinguishing different types of hyper IgE syndrome. Connective tissue, skeletal and vascular abnormalities are prominent in autosomal dominant form, while in autosomal recessive form, viral infections, malignancies and neurological disorders are more prominent. The definite diagnosis is made by mutation analysis.

**Keywords** Hyper IgE syndromes, STAT3, DOCK8.

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## Introduction

Hyper-IgE syndromes are classified as a group of congenital primary immunodeficiency diseases with variable infectious and non-infectious manifestations (1). Although the presence of IgE had been hypothetically believed for decades, isolation of IgE and description of hyper IgE

syndrome occurred in the same year, and IgE was interestingly isolated later (2).

Since the first report of two female patients with fair skin, red hair, recurring antibiotic required respiratory infections, eczema, staphylococcal "cold abscesses", hyperextensible joints, was named as "Job's syndrome" by Davis et al. in 1966, several distinct syndromes with autosomal recessive or dominant inheritance were reported as hyper-IgE syndromes (1, 3). At first, mutations in signal transducer and activator of transcription 3 (STAT3) were described as the principal reason for hyper-IgE syndrome in both familial and sporadic cases (4). The pathogenesis of autosomal dominant hyper-IgE syndrome (AD-HIES) has been attributed to STAT3 dominant-negative mutations by Minegishi et al. in 2007 (5). Two distinct autosomal dominant disorders exhibiting by severe atopy have been described recently as a result of mutation in ERBB2-interacting protein (ERBIN) and CARD11 (6, 7). Autosomal recessive forms of HIES (AR-HIES) have been attributed to mutations of cytokinesis 8 protein (DOCK8) dedicator presenting with cutaneous viral infection, molluscum contagiosum, mucocutaneous candidiasis, severe atopy, malignancy and recurrent respiratory infection.

Mutations in phosphoglucomutase 3 (PGM3) was demonstrated in those patients with obvious atopy, high serum IgE level, autoimmunity and neurological impairment classified as AR-HIES (8, 9).

The clinical manifestations, diagnosis and therapeutic approach to HIES are reviewed here.

**Autosomal dominant hyper-IgE syndrome**

**STAT3 loss of function (STAT3 LOF)**

AD-HIES caused by STAT3 LOF was indicated by cutaneous eczema, recurrent pulmonary and skin infections and staphylococcal cold abscesses. At first, it was described by Davis et al. in 1966 as "Job's syndrome". However, the increased serum IgE level and characteristic facies, known as "Buckley syndrome", has been explained by Buckley et al. in 1972. Accordingly, Grimbacher et al. described the clinical features of hyper-IgE syndrome in 72 patients including primary teeth shedding delay and permanent teeth eruption failure, unique facial characters, skeletal and connective tissue abnormalities (1, 10).

Majority of the STAT3 LOF patients expressed loss or substitution of an amino-acid caused by missense or in-frame deletions in the DNA-binding or SH-2 domain of STAT3 gene, which were resulting in a normal but dysfunctional STAT3 protein. Extensive expression of STAT3 explains its role in wound repair and remodeling of vessels (matrix metalloproteinases) along with cancer prevention (leukemia inhibitory factor, oncostatin M) and cardiovascular system (cardiotrophin -1, cardiotrophin-like cytokine). Regarding, It plays a crucial role in signal transduction of cytokines (IL-6, 10, 11, 17, 21, 22 and 23) that was presented in AD-HIES as staphylococcus and candida infections, because of Th17 defect, abnormal dentition and craniosynostosis attributed to IL-11 signaling defect.

Moreover, increased serum IgE level, eczema, cutaneous and pulmonary infections, primary teeth retention, permanent teeth eruption failure, osteopenia, scoliosis, fracture not appropriate to severity of trauma and extent of osteopenia, typical coarse facies, central nervous system defects, arterial malformations (aneurysm); abnormalities in peripheral, coronary and brain circulation are among numerous manifestations of STAT3 LOF.

Although absolute and specific level of serum IgE is significantly high in STAT3 LOF, these patients had not indicate the manifestations of anaphylaxis and food allergy. Accordingly, this is attributed to the defect of STAT3 that mediates the effects of mast cell products on vascular permeability.

Generally, the cutaneous eczema of AD-HIES (STAT3 LOF) starts at the first days of neonatal period and enduring throughout adolescent. It is as same as atopic eczema; induced or exacerbated by staphylococcal infection and similarly, anti-staphylococcal antibiotics can improve eczema in these patients. Cold abscesses are among most recognized characteristic features of AD-HIES in terms of STAT3 LOF. It is also notable that these patients are vulnerable to cutaneous boils containing pus without apparent inflammatory manifestations such as soreness, warmness and painfulness. Also, chronic mucocutaneous candidiasis was observed requiring systemic antifungal treatment with mucosa, skin and nail involvement (11-13).

As same as other immunodeficiency diseases, STAT3 LOF patients are susceptible to pneumonia. Staphylococcus aureus as the most frequent pathogen, followed by *Streptococcus pneumoniae, Haemophilus influenzae* are among common causes of lower respiratory infections in these patients. Lung cold abscesses and pneumatocoeles are the characteristic pulmonary manifestations of STAT3 LOF. Tissue damage and bronchiectasis caused by prolonged and recurrent pulmonary infections predispose patients to fungal infection as well as pneumonia with opportunistic pathogens such as *Pseudomonas aeruginosa* and *Pneumocystis jiroveci*. Invasive fungal infection and aspergilloma are caused by aspergillus fumigatus. Gastrointestinal and meningeal infections with Cryptococcus are also reported. Although, Histoplasma is recognized as the other fungal pathogen in gastrointestinal tract and coccidioidomycosis in meninges (11, 13, 14) and Staphylococcus aureus is the most frequent pathogen either in skin or in lung cold abscesses (2). Furthermore, Herpes zoster infection and its recurrence are observed in relatively younger people who are attributed to the defect of central memory T cells (13).

Non-infectious manifestations of STAT3 LOF include typical coarse facies appearance (chin, forehead and nose prominence), along with vascular (coronary artery aneurysms, brain and peripheral vessels involvement), musculoskeletal (craniosynostosis, scoliosis, osteopenia, fracture vulnerability), gastrointestinal (gastroesophageal reflux disease, eosinophilic esophagitis, dysphagia and dysmotility) and neurologic

abnormalities, joint hyper-extensibility and also malignancies (Hodgkin and non-Hodgkin B cell or T cell lymphoma not related to EBV infection) (2, 11, 13).

Immunologic features of STAT3 LOF include non-protective antibody response to encapsulated bacteria in contrast with normal serum IgG and IgM level, extremely high serum IgE level (>2000 IU/ml) might be even found at the time of birth, serum eosinophilia, proportional neutropenia, increased level of γ-interferon and TNF-α, lack of Th17, Th2dominance and Th1 defect, decreased memory T and B cells and significant drop of T cells, which all are sources of IL-17 (11, 13, 15).

By considering the vital role of STAT3 in control of IL-6, IL-10, IL-17, IL-21 and IL-22 as strategic human cytokines, the spectrum of AD-HIES clinical manifestations including fungal infection, pneumatoceles and the variety of inflammatory responses could be explained (16).

Management of AD-HIES caused by STAT3 LOF is concentrated mainly on the infections prevention and controlling. Due to the fact that infections are frequently asymptomatic in those patients with STAT3 LOF, recurrent and carefully organized history taking and physical examination also along with applicable paraclinical study will help diagnosis of the infections on the right time and adopting an appropriate measure. According to the skin involvement and defects of innate immunity, these patients are susceptible to cutaneous infections. Therefore, applying chlorhexidine and diluted bleach as local antiseptic, can decolonize the skin. However, pathogens couldn't be cleaned from groin and axilla. Using antibiotics with staphylococcus aureus coverage with preventive and therapeutic doses, can properly help the prevention and management of cutaneous and pulmonary bacterial infections, and also prevent from the secondary damage of lung parenchyma. Subsequently, this improves patients' prognosis and enhances their quality of life.

These patients are vulnerable to mucocutaneous and lung infection with candida; as a result, prevention and as-needed treatment with antifungals are required. Choosing the antifungal drug depends on the presence of lung parenchymal diseases such as pneumatoceles (need anti-aspergillus) or living in an area that is endemic for mycoses (need coccidioides and Histoplasma coverage)

It is crucial to clean the airway in those patients with parenchymal defects of the lung and bronchiectasis changes to prevent secondary infections. However, the physiotherapy maneuvers should be accomplished with caution, due to the risk of hemoptysis. Decision about using intravenous or subcutaneous immunoglobulin replacement therapy is individually made. In case of lung parenchymal damages, recurrent infections uncontrolled with prophylactic antibiotics and impaired specific antibody response, patients greatly benefit from immunoglobulin replacement therapy.

There is no contraindication about regular vaccination except for unconjugated pneumococcal 23-valent vaccine, which is

recommended to be replaced with conjugated form, due to its considerable local reactions. There is no consensus about using topical or systemic steroids along with H2 blockers or proton pump inhibitors for managing the gastrointestinal presentations. Hematopoietic stem cell transplantation (HSCT) has been used in STAT3 LOF patients, which had inconsistent results. Also, non-hematopoietic problems of the AD-HIES are not expected to be solved by HSCT (13).

**Autosomal recessive hyper-IgE syndrome**

Autosomal recessive hyper IgE syndrome (AR-HIES) is a group of combined primary immunodeficiency disorders similar to AD-HIES, however, with some different features that are secondary to several autosomal recessive mutations including mutations in dedicator of cytokinesis 8 (DOCK8), phosphoglucomutase 3 (PGM3) and thyrosin kinase2 (TYK2).

**Dedicator of cytokinesis 8 deficiency (DOCK8 deficiency)**

Among autosomal recessive forms of HIES, DOCK8 deficiency is associated with combined immunodeficiency that is presented with elevated serum level of IgE, severe respiratory and dermatologic viral infections, atopic disorders and malignancies (8, 17). Features of AR-HIES was described at first in 2004 by Renner et al. who presented 13 patients from 6 consanguineous families with some features of HIES such as recurrent pneumonia and pulmonary abscesses, atopic dermatitis, elevated serum IgE levels and peripheral blood eosinophilia, but with some differences in AD-HIES (e.g. not having the connective tissue and skeletal abnormalities, for example minimal trauma fractures, retained primary teeth, and characteristic facies ) and with increased rate of viral skin infections, neurological symptoms and autoimmunity. The disease entity is known as the most common autosomal recessive (AR) form of HIES (18).

At first, mutations in the *DOCK8* gene were identified in 2009, and based on current data available they were considered for the majority of these AR-HIES patients (17, 19). Homozygous and compound heterozygous mutations can be considered as underline of the diseases, but large deletions were also very frequent in these patients, leading to absent or reduced levels of protein in the majority of investigated cases. DOCK8 is a member of family of DOCK180 proteins, which allow cell migration, adhesion and growth as they are a part of cytoskeletal structure. Therefore, the absence of DOCK8 protein results in defective migration of dendritic cells to lymph nodes and defective priming of CD4+ T-cells (20). In B cells, DOCK8 is an adaptor protein downstream of TLR9 and upstream of STAT3 that affects B cell proliferation and immunoglobulin production (21). DOCK8 deficiency results in dysfunction of long-lived memory B cells and virus-specific CD8+ T cells. Moreover, the detailed mechanisms of action of DOCK8 protein are more complex and are beyond the

domains of this study (22-24). Dysfunction of cytotoxic and helper T cells in addition to B cells, explains the susceptibility to an extensive variety of bacterial and viral infections.

Patients with DOCK8 deficiency have high serum IgE levels, peripheral blood eosinophilia, severe early-onset eczema, recurrent sinopulmonary infections, dermal and less frequently pulmonary staphylococcal abscesses, mucocutaneous candidiasis, high malignancies rates and several allergic disorders including food allergy or respiratory allergies. Disseminated viral infections of skin with molluscum contagiosum, human papillomavirus (HPV), herpes zoster and herpes simplex are the most prominent complications in DOCK8 deficiency. Less commonly, other severe systemic viral infections such as cytomegalovirus disease or progressive multifocal leukoencephalopathy occur secondary to a variety of systemic viral infections (8, 25, 26).

The rate of mortality in DOCK8 deficiency is high at young ages, and patients often die before the age of 20 years old. Sclerosing cholangitis associated with cryptosporidial colitis, granulomatous soft tissue lesions, primary central nervous system lymphomas and fatal leiomyosarcomas are also reported in some patients with DOCK8 deficiency (27-29).

Typically, allergic manifestations are more common in DOCK8 deficient patients in comparison with loss of function of STAT3 mutant patients, including atopic dermatitis, food allergies, asthma, and eosinophilic esophagitis. Recurrent sinopulmonary infections, including *pneumocystis jiroveci* pneumonia and complications like bronchiectasis formation, are also common (13, 26).

Malignancy, often aggressive and at early onset, is a key feature of DOCK 8 deficiency (18). Some malignancies occur secondary to poor control of viral infections such as HPV-associated squamous cell carcinomas, Ebstein barr virus (EBV) related lymphomas and soft tissue tumors like leiomyosarcomas (26, 30). Cancers that are not typically associated with viral infections, such as microcystic adnexal carcinoma and rapidly progressive T-cell lymphoma and leukemia have also been reported (8, 26).

Vascular abnormalities in AR-HIES are thought to be secondary to vasculitis. Cerebral arterial aneurysms and stenosis were observed and have been indicated to be associated with stroke and moyamoya. Accordingly, Vasculitis of aorta and other arteries has been also described. Other autoimmune conditions like autoimmune hemolytic anemia may rarely occur (18, 31).

In DOCK8 deficiency, dermatitis is more severe than AD-HIES (32). There are some rare presentations in reports of DOCK8 deficiency including eosinophilic pneumonia associated with other symptoms of AR-HIES, non-tuberculosis disseminated m ycobacterial infection, eosinophilic

esophagitis, anaphylaxis, autoimmune hemolytic anemia have been reported (8, 17, 33, 34).

**Thyrosin kinase 2 (TYK2) deficiency**

Mutation in Tyk2 was firstly described in a patient who was under treatment because of Bacille Calmette-Guérin infection, and had recurrent salmonella infections and also indicated some features of HIES. Usually, these features are found in interferon-gamma/ IL-12 pathway defects (35). A second patient with Tyk2 gene mutation was described with atypical mycobacterial infections along with viral disorders without infections caused by pyogenic bacteria. These findings propose that the presence of the HIES phenotype in Tyk2 deficient patients also depends on other genetic loci (31). TYK2 deficiency results in predisposition to intracellular bacteria, mainly mycobacteria and occasionally viruses by impairing signal transduction from IL-12, IFNα/β (36).

**Phosphoglucomutase 3 (PGM3) deficiency**

A hypomorphic mutations in *PGM3* were described in 2014, in 9 patients from four consanguineous families who all indicated autosomal recessive pattern (37). The human PGM3 belongs to the phosphohexose mutases, which has function in the conversion of glucose-1-phosphate to glucose-6-phosphate (38). Clinical findings of these patients were ranged from severe combined immunodeficiency (SCID) to HIES (9, 37, 39). Hypomorphic mutations in PGM3 gene in mice caused bone marrow failure, tindolent course, with frequent respiratory tract infections and bronchiectasis, elevated serum IgE levels, atopy, neurologic disorders and autoimmunity (9, 37). Connective tissue and skeletal abnormalities such as joint hyperextensibility, scoliosis, and short limbs have been reported, however, they were not as frequent as AD-HIES patients. Increased Th17 cells and autoimmunity is a unique feature of PGM3 patients with hyper-IgE phenotype (40). Recently, a patient with homozygous IL6ST mutations that was manifested by eczema, high serum IgE levels, and peripheral blood eosinophilia and craniosynostosis and scoliosis was diagnosed with HIES. In addition, severe infections, bronchiectasis, low switched memory-B cells, and an abrogated acute-phase inflammation were also indicated. Furthermore, IL6ST is required for transformation of the message through IL-6, IL-11, IL-27, and leukemia inhibitory factor, so it plays a role in phosphorylation of STAT3 and STAT1 (43).

**Rare genetic syndromes with features of HIES**

There are some rare genetic syndromes with features of HIES in reports, which are as followings: coexistence of HIES and Dubowitz syndrome (postnatal growth retardation, microcephaly and characteristic facies), HIES and pentasomy X and HIES and Saether-Chotzen syndrome (acrocephalosyndactyly, hypertelorism and ptosis because of mutations

in TWIST gene) (41-43). The mutual mechanisms among these syndromes and STAT3 and DOCK8 deficiency still remain undefined.

**Laboratory findings and diagnosis in AR-HIES**

As it was mentioned earlier, DOCK8 deficiency indicate both involvement of T and B cells, and defective patients were often indicated with progressive lymphopenia and the absence of memory B cells and switched memory B cells (44, 45). Naiive T cells and recent thymic emigrant T cells were low, and Th2 skewing was observed in a report (45). The number of memory T cells is variable (22, 44).

Almost always, high IgE level and blood eosinophilia are presented. Serum IgG level tends to be either normal or elevated, serum IgA level is normal, and serum IgM level is usually low, and after that it gradually decreases. Specific antibody responses to protein and polysaccharide vaccine antigens are variable (22, 42). There are many laboratory features, which differentiate between DOCK8 deficiency and AD-HIES to some extent. Generally, the peripheral blood eosinophil count is low. In addition, the number of absolute lymphocyte count, T-lymphocytes, CD4+ T-cells, and CD8+ T-cells are reduced. However, a normal CD4/CD8 ratio is maintained. Neutrophils and monocyte numbers are normal. The number of B-cells and Natural killer (NK) cells is variable (8). Also in comparison with AD-HIES, those patients with DOCK8 deficiency have lower levels of serum IgM and IgE and more profound lymphopenia attributable to reductions in T cells, while normal levels were observed in some patients (8, 46). Regarding, there is less increase in IgE level. Serum levels of other switched Igs and specific antibody production vary a lot. Lymphocyte proliferative responses can be abnormal and main defect is in the CD8+ T cell compartment among DOCK8 deficiency (29).

Impaired differentiation of Th17 cells is more prevalent in AR-HIES, in comparison with AD-HIES, but reduced Th17 counts are found in both dominant and the recessive forms of HIES (47-49). Also, normal counts of Th17 cells have been documented in patients with atopic dermatitis. Atopic dermatitis share many clinical features with HIES, enumeration of Th17 cells could be a clue toward clinical finding for the differentiation between isolated atopic dermatitis and HIES (50).

TYK2 deficient patients also have less increase in level of serum IgE. The other immunoglobulin's serum levels and Nitroblue tetrazolium (NBT) tests are usually normal. The T-cells, B-cells, NK cells and neutrophils function are also normal. There is increased in HLA class I along with decreased response to type I interferons and absence of gamma interferon production by stimulation through IL-12 (31). There are no evident diagnostic criteria

for AR-HIES. Determining the mutations in STAT-3, DOCK-8 or TYK-2 using next-generation sequencing are recommended since it can confirm the diagnosis (51).

**Treatment of AR-HIES**

No specific treatment is approved for HIES, up to now. Management is based on prevention from abscess formation and other infections. Any infection especially pneumonia should be promptly treated. Prophylactic use of anti-bacterial drugs such as trimethoprim-sulfamethoxazole to prevent from bacterial infections and itraconazole to prevent from fungal infections (*e.g.* aspergillus infections) and antivirals is recommended. In treating severe viral infections, salicylic acid, cryotherapy and imiquimod as a standard therapies have been reported to indicate limited success, but treatment with systemic INF-α, which may activate effector lymphocytes and decrease viral replication, was proved with appropriate efficacy (41, 43, 46). Also, Intravenous immunoglobulin replacement therapy is strongly recommended (52-55).

To prevent cutaneous infections (especially staphylococcal infections), topical use of chlorhexidine and bleach baths may be recommended (53). At the time that infection occurs, prompt seeking for organism should be performed using the culture from skin; sputum and blood, so that the antibiotic therapy would be more targeted. Surgical intervention is rarely essential, for controlling the complications of the disease such as pneumatocele or abscesses (8, 56). Hematopoietic stem cell transplantation (HSCT) has been accomplished for all types of HIES (29, 57, 58). Previously, it was believed that considering the risk of complications after HSCT such as fulminant infections, risk of secondary malignancy and cerebrovascular accidents, HSCT may be an inappropriate selection for treatment of HIES patients (59). Currently, HSCT could be considered as the only curative option for DOCK8 deficiency mainly at early stages of the disease, with respect to the high morbidity and mortality rate in this genetic defect (~50% of patients die < 20 years). It is vital to keep in mind that severe complications related to infection/malignancy must be precisely control at the time that transplantation process is ongoing (54, 55). Resolution of infections (mainly cutaneous Molluscum spp. infections) and eczema occur after HSCT, however, in rare cases food allergies continue. Normalization of IgE levels and vasculitis were also reported.

With respect to the high morbidity and mortality occurrence rate of the disease, stem cell transplantation in AR-HIES may represent an excellent curative option (46). Patients should be recommended to avoid potentially water contaminated with Cryptosporidium. To prevent from stroke, physicians can perform vascular imaging of cerebral vessels for stenosis detection (13). Histamine receptor blockers are used for itching (60, 61). If pathologic fractures occur, Calcium and Vitamin D using is

considered (62). Allergic and atopic disorders are more prevalent in AR-HIES, which can be managed by conventional treatment using corticosteroids (inhaled-forms) and antihistamine. Patients should regularly visit dentists and primary teeth may be extracted (46). Using genetic evaluation and identifying mutation and carriers in the family, prenatal diagnosis can be offered through amniocentesis or chorionic villus sampling and DNA analysis (62).

**Conclusion**

Hyper IgE syndromes are a series of primary immunodeficiency syndromes, which were presented with some features of allergic diseases, unusual infections and some syndromic non-immunologic features. The distinction among different types needs the knowledge about special characteristics of each syndrome, however, the definitive diagnosis is made by mutation analysis.

**Conflict of interest:** The authors declare no conflicts of interests in regard with this study.

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