



Update on Hyper IgE syndrome (HIES)

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ABSTRACT

Hyper IgE Syndrome (HIES) is a rare primary immunodeficiency disease. Most of HIES cases are sporadic. Autosomal dominant HIES is caused by mutation in signal transducer and activator of transcription-3 (STAT-3). A number of mosaicism HIES has been reported that is associated with intermediate phenotype. Autosomal recessive HIES is due to mutation in Dock-8 or cytokine sis 8 and TYK2 or tyrosine kinase 2. The common manifestations are atopic eczema, staphylococcal dermatitis, cellulitis and folliculitis (cold dermal abscesses that are not warm, painful and without redness), recurrent pneumonia and pulmonary abscesses, osteopenia and recurrent bone fracture. The diagnosis of standard HIES is based on clinical suspicion. There is no specific treatment for HIES. The treatment should be based on the prevention of developing infections. Prophylactic antibiotics such as cotrimoxazole and IVIG are administered. Hematopoietic stem cell transplantation was done for all types of HIES, but there is a little information and experience about the long term results of this therapy.

Introduction

Hyper IgE Syndrome (HIES) was first described by Deiwis, Schuller and Wedgewood in 1966.¹ HIES (Job syndrome or Buckley's syndrome) is a rare immune deficiency disease due to mutations in the signal transducer and activator of transcription-3 (STAT-3) (chromosome 17, MIM=147060), Dedicator of Cytokinesis 8 (Dock-8) (chromosome 9, MIM=

243700) and Tyrosine Kinase-2 (TYK2) (chromosome 19, MIM= 611521) genes.² The incidence of the syndrome is about 1/100000 to 1/200000.²

HIES is characterized by high concentrations of the serum IgE level. It frequently occurs inheritance autosomal dominant, but autosomal recessive is also arisen. Both genders have been

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affected by the two types of HIES equally.³ Up to now, about 200 cases of HIES were reported.⁴

HIES symptoms that usually appear in early childhood are characterized by atopic eczema, recurrent infections such as skin abscess, sinusitis, otitis, pneumonia. Skeletal abnormalities in female like fractures, and delay of shearing of primary teeth are other symptoms that have also been described in HIES. Kyphosis and scoliosis are developed. The diagnosis of HIES is based on symptoms, family history of HIES and determining of mutation.

Treatment of the syndrome is included prophylactic drugs (Antibiotic and antifungal), management of infections, IVIG consumption and hematopoietic cell transplantation (HCT) is the last therapeutic method.⁵

Etiology and Pathogenesis

Most of the HIES cases are sporadic. HIES type AD is due to mutation in STAT-3. A number of mosaicism HIES have been reported that are associated with intermediate phenotype.⁶ Defect in STATA-3 causes decrease in T cell differentiation and leads to decrease of CD8 cells and Th-17 and IL-17. In cases of somatic mosaicism STAT-3, the Th-17 and CD8 cells are in normal range and neutrophil chemotaxis is normal.⁶ In AD-HIES, sometimes mutation in IL-21R occurs that lead to the decline of CD8 T-cells. So that IL21R/STAT3 pathway has an important role in CD8-T cells functions.⁷ CD8 cells have an important role in control of infection and anti-tumor effects. Autosomal recessive HIES (AR-HIES) is due to mutation in Dock-8 or cytokine sis-8 and TYK2.⁸ Mutation in Dock-8 is the most type of AR-HIES. In mutation TYK-2, there is a defect on Gama-interferon /IL-12.⁹ In most of HIES reported cases, parents are not related.¹⁰

Clinical manifestations

AD-HIES

Usually, Autosomal Dominant Hyper IgE Syndrome (AD-HIES) developed in the early months of life by presenting papular and pustular rash, eosinophilic dermatitis or eczema. The common manifestations are atopic eczema, staphylococcal dermatitis, cellulitis and folliculitis (cold dermal abscesses that are not warm, painful and without redness), recurrent pneumonia and pulmonary abscesses, osteopenia and recurrent bone fracture.^{1,11} The characteristics of patients with AD-HIES are included inflammation, infection, involvement of connective tissue and electrolyte imbalance. Mucocutaneous infections are developed due to bacterial and fungal agents. These pathogens include; Staphylococcus aureus, Streptococcus A and B, Haemophilus influenza and other Gram-negative microorganisms. Candida albicans is the most severe fungal infection. Chronic mucocutaneous candidiasis (CMC) is another fungal infection.^{1,8} Dermal abscesses were reported as furuncle and folliculitis.⁸ As a whole, viral infection is common infectious agent.¹¹ Cutaneous manifestations of AD-HIES in somatic mosaicism STAT3 type with intermediate phenotype are manifested by infections such as mucocutaneous candidiasis.⁷ Dermatitis is seen in 81-100% of total HIES patients. Of course, the manifestation of dermatitis in AR-HIES with mutation in Duck 8 is more severe than AD-HIES.¹² Eczematous rash occurs in 65-80% of neonates with STAT3 mutation.¹²

Pulmonary manifestations

Bronchiectasis and pneumatoceles usually occur due to recurrent pulmonary infections.¹³ The main causes of pneumonia include: Staphylococcus aureus, Streptococcus pneumoniae and Haemophilus influenza.^{13,14} Pseudomonas Auroginosa and Aspergillus

fumigatus are also considered as the other causative agents. Pulmonary involvement is one of the main causes of mortality and morbidity and poor quality of life. Bronchiectasis and pneumatocoeles occur in 70% of the patients following pulmonary infection.^{14, 15} These patients are prone to pulmonary hemorrhage. Antiseptic mycobacterial infection is reported.¹⁶ Recurrent pneumonia (with purulent sputum but non-febrile) occurs in the early years of life.¹¹ Renal infection such as pyelonephritis was reported due to *Aspergillus fumigatus* in patients with AD-HIES.¹⁷

Musculoskeletal manifestations

Musculoskeletal abnormalities composed of hyper extensibility of joints, forehead protrusion, arthritis, macrocephaly, broad nasal bridge and delay shearing of primary teeth.¹⁸ kyphosis, clubbing of fingers, shortness of height, failure to thrive, delay in bone age associated with coarse facial appearance also developed in these patients.⁸ There are also multiple fractures, scoliosis, cystic changes of bone and osteopenia. In an investigation, the mean z scores of patients with and without fracture was -1.8 ± 0.7 and -0.9 ± 0.5 respectively. However, the z scores of all the investigated patients were less than normal limit. Facial asymmetry, broad nasal bone with deep eyes and rough skin.¹¹ Deep hard palate were reported in 44 to 71% of cases.³ Failure of primary dentition shedding occurs in 64% of all cases leading to the emergence of asymmetric secondary teeth (malocclusion).^{3, 19} Bone density decreases in these patients by increasing age and the administration of Alendronate Sodium has been suggested.²⁰ Craniosynostosis and deep roof of mouth have been reported.²¹ It should be reminded that scoliosis occurs in about two thirds of patients.²¹

Gastrointestinal manifestations

There are Gastrointestinal (GI) symptoms like gastro-esophageal reflux, esophageal dysmotility, diverticula, dysphagia and rarely bowel perforation. Eosinophilic esophagitis is common. Histoplasmosis, coccidioides and *Cryptococcus* are the causes of GI infections and even meningitis.^{22, 23} Dental infections, dental decay, oral fungal infections, mucosal plaques and inadequate transverse mandibular diameter are the other manifestations of these patients.²⁴ Diverticulitis, pelvic abscess and spontaneous colon perforation also occurred.²⁵ Oral wounds, gingivitis and prolonged infection on scalp and face have been reported in 75% of all cases.³ Oral thrush and plaques as a form of glossitis and angular cheilitis have developed,^{3, 22} both lymphoma and leukemia malignancies were reported in these patients.^{26, 22} The incidence of lymphoma is about 259 folds more common than normal population. T-Lymphocytes, B-Lymphocytes, Hodgkin's and Burkett's lymphoma have also occurred.²⁵

Neurovascular manifestations

Neurologic manifestations include partial facial paralysis, hemiplegia and central nervous system hemorrhage may have occurred.^{26, 22} Vasculitis, partial infarction of right hemisphere, left posterior inferior cerebral vascular thrombosis occur.²⁷ Vascular changes such as coronary arteries aneurysms and Arnold Chiari malformations may be seen in 20% of all cases.^{17, 24, 26, 28} Tortuosity/ dilatation (50%), aneurysm, hypertension and subarachnoid hemorrhage can develop.²⁸ The other manifestations including patent ductus venosus, pseudoaneurysm and vana cava syndrome were also reported.²¹ In 70% of the patients, focal hyperdensity in white matter may be seen in type T2 MRI that increase by age.²⁸ A combination of tortuosity/ dilatation occurred in 50% of cases but in 70% of the patients they occur separately that creates low side effects. Myocardial infarction may also develop.^{21, 29}

Ophthalmic manifestations

Ocular manifestations such as xantolasma, Giant chalaza and strabismus have been reported.^{28, 17} Recurrent otitis media and external otitis may occur in these patients.⁸ There are several reports about reactivation of varicella zoster virus in these patients.³⁰

AR- HIES (Dock-8)

The viral infection and neurologic complications are prominent in this kind of HIES.⁸ The symptoms of AR-HIES are milder than AD-HIES. Although, in Dock-8 type, the phenotype is similar to AD-HIES, pulmonary involvement is less common. Allergy, viral infections such as Herpes Zoster, disseminated varicella infections and Molluscum contagiosum have been seen.^{31, 32} Dermatitis is seen in 91-100% of all patients with HIES, but in Dock-8 type, dermatitis is more severe than AD-HIES.¹² Eczematoid rash appears in 24% of cases in the newborn period.¹² Dental infections, dental decays, oral fungal infections, mucosal plaques and inadequate transverse diameter of mandible are the other manifestations in these patients.²⁴ A case of acute eosinophilic pneumonia associated with recurrent pulmonary infections, severe atopic dermatitis and viral infection has been reported. In this case, there was an increase in IgE and decrease of IgM, CD4 T cells, B-cells, CD19+ and CD27+.³² A case of disseminated Molluscum contagiosum with polyclonality lymphocyte, follicular hyperplasia and unusual IgE+ plasma cells that revealed.³³ There was a non-tuberculosis disseminated mycobacterial infection in one case.³⁴ Severe eczema, recurrent cutaneous infections and/or Staphylococcus aureus abscess are prominent. However, viral infections including Molluscum contagiosum, warts, herpes simplex and varicella zoster are prominent infectious agents

in AR-HIES type compared with AD-HIES. Food and environmental allergies are more common.³⁵ Also, asthma, eosinophilic esophagitis and anaphylactic reaction have been observed.³⁶ Respiratory infection composed of otitis media, external otitis and sinusitis are common. But mastoiditis and frequent croup are less common.³⁵ Staphylococcus aureus, Haemophilus influenzae, Pneumonia jiroveci, Proteus mirabilis, Pseudomonas aeruginosa, cryptococcus, adenovirus and RSV are common pathogens in AD-HIES. Facial manifestations and delay shearing of primary teeth have not been seen.³⁵ Neurological manifestations in AD-HIES that are more common include facial paralysis, hemiplegia and CNS vasculitis.³⁷ Progressive Multifocal Focal Encephalopathy associated with JC virus, Cryptococcus meningitis and hemophilus influenza have been reported.³⁵ Vascular abnormalities in AR-HIES are more common than AD-HIES. Salmonella enteritis and giardiasis are also presented. Cutaneous malignancies such as squamous cell carcinoma (SCC) and leukemia/ cutaneous T cell lymphoma are more common. Also, autoimmune hemolytic anemia has been reported.³⁵

AR-HIES Type-2

The level of serum IgE in this kind of HIES is less than others. There is no somatic phenotype, but mycobacterial pulmonary infections are more prominent.^{9, 31} So, type-2 AR-HIES has not specified (typical) manifestations of AD-HIES, but BCG-osis is common. Viral infections such as cutaneous herpetic infections, brucellosis and pneumonia have been reported. There are cerebral infarction, cutaneous infections, oral candidiasis and recurrent otitis media.³⁰

Laboratory findings

AD-HIES: The serum level of IgE is usually higher than 2000 IU/ml.¹⁴ Increasing age may be associated with gradual decrease in IgE and even reach to normal level. Spirometry abnormalities such as decrease of FVC, FEV1, FEF 25-75 and FEV1/FVC occur due to pulmonary involvement. The obstructive pattern are present in early stage of the disease that will ultimately progress to restrictive pattern.¹³ Serum eosinophilia is another laboratory finding.^{1, 6} The serum levels of IgM, IgG, IgA are at normal range. Chemotaxis of neutrophilia and bactericidal activity are decreased. Therefore, there is a native immune deficiency response.¹¹ Also, B and T- memory cells are decreased.

Dock 8 AR-HIES

There is less increase of IgE level. There is also an increase in Eosinophil but decrease in lymphocytes, T-lymphocytes, CD4 T-cell, CD8 T-cell with normal CD4/CD8 ratio have been seen. Neutrophils and monocyte numbers are at normal levels. The number of B-cells and Natural killer (NK) cells varies. The serum level of IgG decreases or at normal level, serum IgA level is different and IgM may decrease.³⁵

TYK-2 AR-HIES

There is less increase in serum IgE level. Other serum immunoglobulins are in normal levels. Nitroblue tetrazolium (NBT) test is normal. T-cells, B-cells, NK cells and neutrophils activities are at normal levels. More expression of HLA class I, deficiency in response to interferon type I and no production of Gamma interferon by stimulation of IL12 were reported.³⁸

Diagnosis

The diagnosis of standard HIES is based on clinical suspicion. Diagnosis should be easier using NIH scale that is composed of 21 signs.³⁹ The signs in AD-HIES include internal organ

abscess, pneumatocele, mucocutaneous and nail candidiasis, bone fracture, scoliosis and positive family history of HIES.⁴⁰ Positive family history of HIES and scoring equal or more than 40 is suggested as the diagnosis of HIES. Scores between 20- 40 is considered as intermediate HIES score and score less than 20 are suggested unlikely of HIES diagnosis. Also, there are other diagnostic criteria for AD-HIES,⁴¹ that have signs and symptoms including IgE equal or more than 1000 IU/ml and a score more than 30 belongs to recurrent neonatal rash, bone fracture, specific facial appearance and high arch palate. These criteria were not confirmed for AR-HIES. Determining the mutations of STAT-3, Dock-8 and TYK-2 can confirm the diagnosis.⁴²

Differential diagnosis

Increasing of IgE is also observed in other immunodeficiency syndrome such as; Wiskott-Aldrich syndrome (eczema, recurrent infections, thrombocytopenia with small size), Omenn syndrome (neonatal rash, high IgE), Complete atypical DiGeorge syndrome, Netherton syndrome (autosomal recessive with increasing IgE, skin rash, entropathy, failure to thrive, bamboo hair). Hyper IgE may be presented in allergy, parasitic disorders and/ or hematologic malignant disorders that are almost associated with eosinophilia. CGD associated with staphylococcus infections is also considered as differential diagnosis.¹⁸

Olmsted syndrome is also associated with hyper IgE and eosinophilia. There are several defects in this syndrome including periorificial hyperkeratotic lesions and mutilating pulmpalmar keratoderma.⁴³ There are associations between HIES and other syndromes like Dubowitz syndrome (postnatal failure to thrive, microcephaly, typical face); pentasomy X and Saethre-Chotzen syndrome (acrocephalosyndactyly, hypertelorism and ptosis due to Twist mutation).^{44, 45} Atopic

dermatitis is almost associated with hyper IgE and staphylococcal dermatitis develops, but there are other manifestations of HIES. However, food and environmental allergies and even anaphylactic are common.^{28, 18}

Treatment

There is no specific treatment for Hyper IgE. The treatment should be based on the prevention of developing abscess and staphylococcal pneumonia. Pneumonia should be treated seriously. Prophylactic antibiotics such as cotrimoxazole, IVIG are administered.¹³ Itraconazole is prescribed to prevent fungal infections such as aspergillus microorganism. Chlorhexidine and bleach baths are useful for the treatment of cutaneous staphylococcal infections.¹⁶ In infectious cases, preparing culture from skin; sputum and blood are very helpful to determine proper antibiotics. Surgical treatment is seldom used to treat the complications of the disease such as pneumatocele that is also associated with many hazards.^{46, 35} The role of Bone Marrow Transplant (BMT) has still remained questionable.⁴⁷ Hematopoietic stem cell transplantation (HSCT) was done for all type of HIES, but there is a little information and experience about the long term results of this therapy.⁴⁷ However, there are no acceptable reported results in this regard because of fatal side effects such as fulminant infections, malignancies, CNS infarctions and hemorrhage.⁴⁸ Successful results using HCT in patients with AD-HIES were more than the other type of HIES and associated with better prognosis.

Antihistaminic agents are used to relieve the itching of cutaneous lesions.^{3, 19} Calcium consumption of Vitamin D is considered in improving and repairing a bone fracture.²¹ Regular follow-up of dental and mouth problems is suggested and primary teeth

exfoliation may be necessary. If mutation is known in the family, prenatal diagnosis is possible when performed by Amniocentesis and DNA analysis in 15-18 weeks of gestation or Chorionic villus sampling (CVS) in 12 weeks of gestation.²¹

Conclusion

Hyper IgE syndrome is a rare immune deficiency disorder with autosomal dominant and recessive inheritance. Multi-organ involvement such as skin, bone, respiratory and dental infections and decay were seen. Diagnosis is made based on clinical manifestations and molecular component. There is not specific treatment for HIES yet.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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