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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 cytokinesis-8 and TYK-2 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.

Keywords: Hyper IgE Syndrome, Infection, Immunodeficiency.

1. 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. The incidence of the syndrome is about 1/100000 to1/200000 [2].

HIES is characterized by high concentrations of the serum IgE level. The most common inheritance pattern is autosomal dominant, but autosomal recessive is also arisen. Both genders have been affected by the two types of HIES equally [3].

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, delay of shearing of primary teeth, kyphosis and scoliosis are other symptoms that have also been described in HIES. 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].

2. CASE REPORT :

9 year old girl, first born of a non consanguineous couple with history of recurrent respiratory infections, skin lesions and death due to meningitis in younger brother presented with complaints of cough with white mucoid expectoration, breathlessness for 1 week. She was born as preterm with birth weight of 2.5kg, was admitted for pneumonia when 10 days old. Thereafter repeated admission for RTI. She also has eczemas since 1 ½ months of age with itching and exacerbations during summer.

On examination child was afebrile and had tachypnoea and tachycardia. Weight of the child was 10.5kgs (<3rd centile) and height was 92 cm (<3rdcentile) with BMI of 12.4 (at 3rd centile).

Head to toe examination revealed frontal

bossing, multiple dental caries, onycholysis and multiple swelling over the scalp, back, elbow with eczematous lesions and hyperpigmentation all over the body.
Respiratory system: Tachypnoea with chest indrawing was present along with bilateral rhonchi and crepitations. Child had decreased vision on right eye. Other system examination was within normal limits.
Investigation Report:
Blood Group: A +;
Hb: 13.5 g/dl;
TLC:17,700/cu.mm;
DC: N 95, L 05;
Absolute Eosinophils count:190/cu.mm ;
IgE > 2500 IU/ml [0 – 200];
Sodium: 127 mmol/L;
Potasium: 4.7 mmol/L;
Chloride: 88.7 mmol/L;
Sputum C/S: S.pneumoniae resistant to ampicillin, Cotrimoxazole, Gentamicin, Cefalotihin.
Blood Culture: No growth.
Workup for immunodeficiency:
HIV: negative;
IgE 420 IU/ml [less than 100]
IgG 790mg/dl [800 - 1500]
IgA 210 mg/dl [150 - 300]
IgM 88 mg/dl [80 - 280]
Sweat Chloride: 77.04 mmol/L
Plain Axial CAT section of Thorax with HRCT Section: CAT features are suggestive of sub segmental collapse involving medial segment of right middle lobe.
USG abdominal &Pelvis: Right renal calculus.
Orbital Scan: USG features retinal detachment of right eye.
2 years back child had multiple abscesses, histopathology of which showed- Necrotising granulomatous lesion cystic changes.
Child was initially treated with inj. Cloxacillin, gentamicin and ceftriaxone with bronchodilators. After sputum c/s report Amikacin & Metronidazole were added. IV Ig 2 gm/kg was given.

3. DISCUSSION :

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 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]. Autosomal recessive HIES (AR-HIES) is due to mutation in Dock-8 or cytokine sis-8 and TYK2 [8].

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, 9]. 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 can present as severe fungal infection and also as chronic mucocutaneous candidiasis. These children can also have dermal abscess, Dermatitis and other viral infections.
Pulmonary manifestations seen are bronchiectasis and pneumatocoeles which usually occur due to recurrent pulmonary infections [10]. The main causes of pneumonia include: Staphylococcus aureus, Streptococcus pneumoniae and Haemophilus influenza [10, 11]. Pseudomonas aeruginosa and Aspergillus fumigatus.
Musculoskeletal abnormalities composed of hyper extensibility of joints, forehead protrusion, arthritis, macrocephaly, broad nasal bridge and delay shearing of primary teeth. 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.

Gastrointestinal (GI) symptoms like gastro-esophageal reflux, esophageal dismotility, diverticula, dysphagia and rarely bowel perforation. Eusinophilic esophagitis is common. Histoplasmosis, coccidiodomycosis and Cryptococcus are the causes of GI infections and even meningitis [13, 14].

Neurologic manifestations include partial facial paralysis, hemiplegia and central nervous system hemorrhage may have occurred [13, 15]. Vasculitis, partial infarction of right hemisphere, left posterior inferior cerebral vascular thrombosis occurs [16].

Ocular manifestations such as xantolasma, Giant chalazae and strabismus have been reported [17]. Recurrent otitis media and external otitis may occur in this patient [8].

AR- HIES (Dock-8)

The viral infection and neurologic complications are prominent in this kind of HIES. The symptoms of AR-HIES are milder than AD-HIES [8]. 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 [18,19]. Dermatitis is seen in 91-100% of all patients with HIES, but in Dock-8 type, dermatitis is more severe than AD-HIES. Eczematoid rash appears in 24% of cases in the newborn period. Dental infections, dental decay, oral fungal infections, mucosal plagues and inadequate transverse diameter of mandible are the other manifestations in these patients. Facial manifestations and delay shearing of primary teeth have not seen.

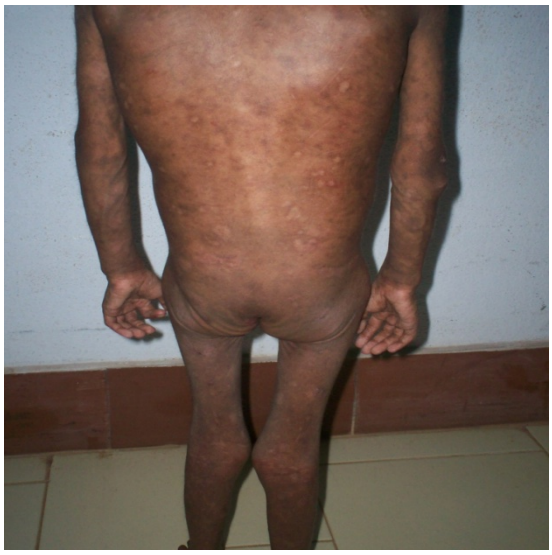

Fig. 2: Note the multiple swellings over the back with eczematous lesions.

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 [18]. So, type-2 AR-HIES has not specified (typical) manifestations of ADHIES, but BCG-osis is common. Fig 1, 2, & 3 shows the different features of this child. Table 1 shows the features of Hyperimmunoglobulin E syndromes.

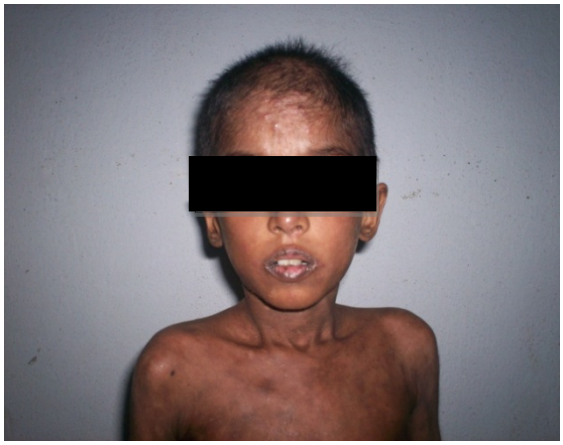

Fig. 1: Job Syndrome. 9 Year Old Female. (Note: the frontal bossing and multiple swelling over scalp.)

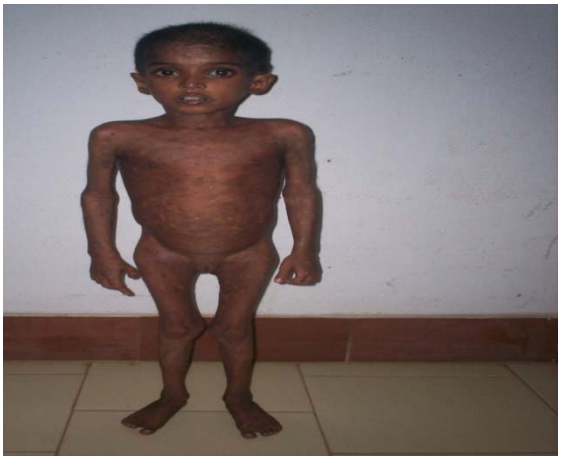

Fig. 3: Note the multiple eczematous lesions and hyperpigmentation all over the body.

Table: 1 shows Hyperimmunoglobulin E syndromes

	Autosomal dominant or sporadic(JOB SYNDROMES)	**Autosomal recessive**
Gene	STAT3	DOCK8:less often TYK2
Infections		
Sinopulmonary		
Recurrent bacterial	S.aureus, Pneumococcus, H.influenza	No
Pneumatoceles/bronchiectasis	Common	No
Fungal	Aspergillus species	
Cutaneous		
Abscesses	S.aureus	S.aureus
viral	No	HPV, HSV, VZV, MCV
Mucocutaneous candidiasis	Common	Common
Atopic disorders		
Newborn eosinophilic pustules	Common	No
Eczema	Common	Common
Asthama	No	Common
Allergies/Anaphylaxis	No	Common
Musculoskeletal		
Osteopenia, Pathological fractures	Common	No
Scoliosis	Common	No
Retained primary teeth	Common	No
Hyperextensible	Common	No
Other features		
Coarse facies	Common in adolescent	No
Coronary artery tortousity/aneurysm	Common	No
UBO on brain MRI	Common	No
Lymphomas	Yes	Higher incidence
Cutaneous malignancy	No	Yes
Mortality	Adulthood	Childhood

4. LABORATORY FINDINGS :

AD-HIES: The serum level of IgE is usually higher than 2000 IU/ml [11]. Increasing age maybe 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 patterns are present in early stage of the disease that will ultimately progress to restrictive pattern [10]. Serum eosinophilia is another laboratory finding [1,6]. The serum levels of IgM, IgG, IgAare at normal range. Chemotaxis of neutrophilia and bactericidal activity are decreased. Therefore, there is a native immune deficiency response [9]. 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, CD8T-cell with normal CD4/CD8 ratio have been seen. The serum level of IgG decreases or at normal level, serum IgA level is different and IgM may decrease [20].

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.

5. 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, pneumatocoele, mucocutaneous and nail candidiasis, bone fracture, scoliosis and positive family history of HIES [22]. 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, [23] 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 arched palate. These criteria were not confirmed for AR-HIES. Determining the mutations of STAT-3, Dock-8 and TYK-2 can confirm the diagnosis [24].

6. 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 [10].

Itraconazole is prescribed to prevent fungal infections such as aspergillus microorganism. The role of Bone Marrow Transplant (BMT) has still remained questionable [25]. 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 [25]. Antihistaminic agents are used to relieve the itching of cutaneous lesions [3, 27].Calcium consumption of Vitamin D is considered in improving and repairing a bone fracture [26]. 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 [26].

7. 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.

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