International Journal of Contemporary Pediatrics
Singh A et al. Int J Contemp Pediatr. 2016 May;3(2):674-677
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291
DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20161064

Case Report

Hyper IgE syndrome: often a missed diagnosis

Amitabh Singh[1]*, Anirban Mandal[2], Rachna Seth[2]

[1]Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, New Delhi 110031, India
[2]Department of Pediatrics, AIIMS, New Delhi 110029, India

Received: 27 December 2015
Revised: 31 January 2016
Accepted: 17 February 2016

***Correspondence:**
Dr. Amitabh Singh,
E-mail: dramit_amy@yahoo.co.in

ABSTRACT

The hyper immunoglobulin E syndromes (HIES) are a group of primary immunodeficiency manifesting with very high levels of serum immunoglobulin E (IgE), recurrent skin abscesses, pulmonary infections, neonatal onset dermatitis and a myriad of connective tissue, vascular and skeletal abnormalities. The diagnosis of HIES relies on a combination of clinical features and laboratory studies. Heterogeneous manifestations of HIES mimics common infections prevalent in tropical areas and results in delayed diagnosis. Primary goal of treatment lies in prevention of infections with prophylactic antibiotics. We report a 6 year old boy symptomatic since early infancy with recurrent respiratory problems, rash, organomegaly, suppurative generalised lymphadenopathy. He was misdiagnosed as tuberculosis twice. Following extensive investigations, infectious causes for such manifestations were ruled out and the final diagnosis of possible HIES was made as genetic studies could not be done. He remained relatively asymptomatic on antibacterial and antifungal prophylaxis during subsequent follow up for 2 years.

Keywords: Hyper IgE syndrome, Recurrent infection, Immunodeficiency

INTRODUCTION

Hyper IgE syndrome (HIES) or Job's syndrome, first described by Davis et al in 1966, is a rare, complex, primary immunodeficiency disorder where immunodeficiency seems to meet allergy.[1] Most of the cases are sporadic but two forms based on inheritance pattern have been recognized-autosomal dominant and autosomal recessive. HIES presents with a vast array of symptoms leading to diagnostic difficulties, particularly in less severe cases and in young children.[2] The diagnosis of pediatric hyper-IgE syndrome is also based upon a compilation of symptoms, not necessarily expressed at the time of first presentation.[3] There have been a number of diagnostic recommendations published till date, the recent one being by Woellner, et al.[4] They have established a scoring system for STAT3 mutant HIES and also divided the diagnosis in to possible, probable and definitive HIES. We report a 6 year old boy who was symptomatic since first week of life with multisystemic involvement manifesting with some atypical facial features, neonatal rash, recurrent pneumonia, organomegaly and suppurative lymphadenopathy. He received treatment for tuberculosis twice being a resident of endemic region for the same and ultimately was diagnosed with hyper IgE syndrome after going through extensive investigations.

CASE REPORT

A 6 year old boy, born to non-consanguineous marriage, presented with history of recurrent cough, cold and fever since early neonatal period with generalized skin rash, intermittent swelling over bilateral lower limbs for 2 years, progressive abdominal distension for 1 year, multiple nodular neck swelling for 4 months and

spontaneous rupture of the neck swellings with pus discharge for last 2 months. He was appropriately immunized for age and was also developmentally normal.

Review of history and available previous medical records revealed, recurrent episodes of fever since day 4 of life with generalized erythematous, macula-papular rash since day 7 of life. There was no history of delayed umbilical cord fall. He had fever with seizure at 1 month of age and was diagnosed as tubercular meningitis. Though the basis of diagnosis of TB was not clear, he received anti-tubercular therapy (ATT) for 6 months along with antiepileptic. During his 2nd and 3rd year of life, he persisted to have recurrent pneumonia documented by several chest x-rays. He required infrequent hospital admissions with one episode of E. coli urinary tract infection and symptoms used to relieve with both oral and intravenous antibiotics. At around 3 ½ years of age, he was diagnosed with pulmonary tuberculosis (primary complex) on the basis of chest x-ray alone and again received category 1 ATT for 9 months with transient improvement in symptoms. Abdominal distension was insidious in onset and slowly progressive, with associated history of pain abdomen, constipation and vomiting during initial days. Bilateral discrete, nodular neck swellings were painless and increasing in size with spontaneous rupture yielding purulent blood tinged material. He also required blood transfusion twice during last 8 months. There was history of one sib death at 2 ½ months of age with pneumonia, rest of the siblings and parents were healthy. There was no history of bleeding from any site, jaundice, ear discharge, loose stools, recurrent fractures, abnormal sensorium or seizures.

On examination, there was pallor, grade 1 pan digital clubbing and bilateral cervical lymphadenopathy in both anterior and posterior triangle of neck with discharging sinuses (Figure 1). Erythematous, macula-papular skin lesions were noted over the lower abdominal wall with hyperpigmentation and dermatitis in both lower limbs. His weight, height, BMI all were below 3rd centile and systemic examination revealed hepatosplenomegaly.

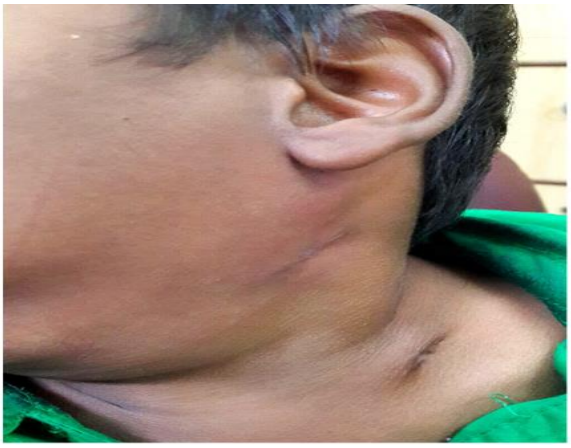

Figure 1: Discharging sinuses over cervical lymph nodes.

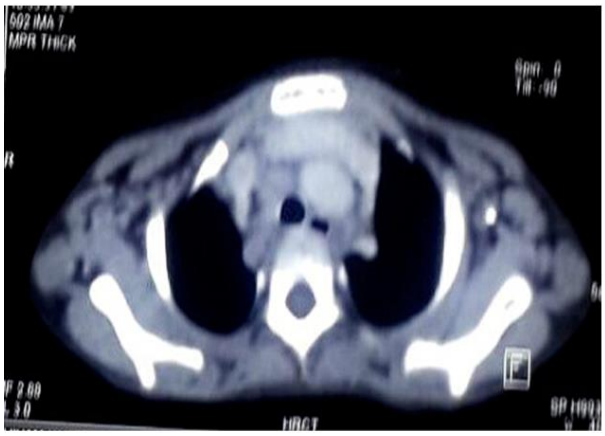

Figure 2: Contrast enhanced CT scan of thorax showing conglomerate, homogenously enhancing mediastinal lymphadenopathy.

Investigations showed microcytic, hypochromic anaemia (Hemoglobin-6.1 gm/dl), elevated total counts with 12 % eosinophil's on differential count with normal liver and renal function tests. Contrast enhanced CT scan of neck, thorax and abdomen reported multiple, enlarged, homogenous, discrete as well as conglomerate lymph nodes in cervical, mediastinal, intra-abdominal, and retroperitoneal locations (Figure 2). Ultrasonography of abdomen revealed multiple hypoechoeic leions in spleen. Gram stain, KOH stain, bacterial and fungal culture from the lymph node discharge failed to reveal any organism. Serology (IgG & IgM) for Bartonella henselae was negative. Work up for tuberculosis in the form of Mantoux test, induced sputum and skin discharge for acid fast bacilli (AFB) and MGIT (Mycobacterium growth indicator tube) cultures were negative. FNAC and biopsy of cervical lymph nodes was suggestive of reactive follicular hyperplasia with focal sinus histiocytosis, repeat FNAC and biopsy from axillary and retroperitoneal lymph nodes were also non-contributory. Bone marrow aspiration and biopsy revealed only cellular reactive bone marrow response and serum Lactate dehydrogenase (LDH) was within normal limits. His immunoglobulin profile was normal and further work up for immunodeficiency showed normal CD3, CD4, CD8, CD19, CD11a, CD11b, CD11c, CD18 values. Flow cytometry for Chronic Granulomatous Disease (CGD) using 2, 7-dichlorofluorescin diacetate (DCFDA) was within normal limits and HIV serology was negative. Skin biopsy done twice was suggestive of leucocytoclastic vasculitis with no evidence of Granuloma or AFB. Double negative (CD4- CD8-) T lymphocyte (DNT) was also within normal limits. Serum IgE level came out to be very high (3109.8 IU/mL), indicating a diagnosis of hyper IgE syndrome. The facial characteristics were re-examined and coarse facial features were noticed with a prominent forehead, broad nasal bridge and wide fleshy nasal tip, though there was no deep set eyes or prognathism (Figure 3). Oral examination revealed a high arched palate with normal dentition. There was no history of fractures. Mutational

studies for STAT3 gene was not available but diagnostic scoring for Hyper IgE syndrome yielded a score of 39.98 (Table 1), predicting a likelihood of the mutation. Family history was not suggestive of HIES except unexplained death of one sibling during infancy. The facilities for TH17 cell testing were not available, therefore a diagnosis of possible HIES was made.

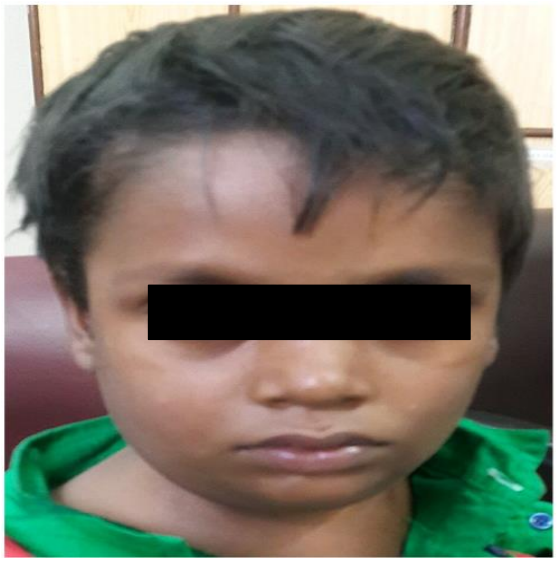

Figure 3: Facial features of the patient: coarse facies, prominent forehead, broad nasal bridge and wide fleshy nasal tip.

Table 1: Diagnostic scoring for Hyper IgE syndrome in our patient.

Clinical features	Points	Scale	Scaled points
Pneumonias (>3) (present)	8	2.5	20
Newborn rash (present)	4	2.08	8.32
Pathologic bone fractures (absent)	0	3.33	0
Characteristic face for Job syndrome (mild)	2	3.33	6.66
Cathedral palate (present)	2	2.5	5
Total points 39.98			

The patient was started on antibacterial and antifungal prophylaxis with Trimethoprim-sulfamethoxazole and Itraconazole and is being followed up regularly for last 2 years. He remained well with only minor respiratory complaints and no requirement of hospitalizations subsequently.

DISCUSSION

Hyper IgE syndromes have heterogeneous genetic origins and manifest with diverse clinical manifestations.[5] Hypomorphic mutations in the signal transducer and the activator of transcription 3 (STAT3) gene result in the classical multisystem, autosomal dominant form of HIES (AD-HIES), associated with facial, dental, skeletal, and connective tissue abnormalities.[6] A STAT3 mutation results in a defective multiple cytokine signal transduction, including interleukin (IL)-6 and IL-22, leading to impaired Th17 function and thus explaining the susceptibility to infections in HIES.[7] The clinical triad of recurrent staphylococcal skin infections, recurrent pneumonia and increased serum IgE characterizes the classical or the autosomal dominant form of hyper IgE syndrome.[3] Autosomal recessive forms of HIES (AR-HIES) are due to deficiency of dedicator of Cytokinesis 8 (Dock-8) and Tyrosine Kinase-2 (TYk2).[8] AR-HIES cases lack the facial, dental and skeletal abnormalities but central nervous system involvement is more common.[9] The commonest organisms causing infection in AD-HIES includes bacterial agents namely Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae etc, fungal agents such as Candida and Aspergillous, while viral infections are less common. Whereas, AR-HIES patients also demonstrate an increased susceptibility for viral and mycobacterial infection including disseminated BCG disease.[9] Though our patient was diagnosed twice with tuberculosis, it was based solely upon symptomatology supported by a high prevalence of the infection in the given population. Absence of any skeletal manifestations in our patient can be explained by the fact these manifestations in HIES become prominent from adolescence onwards.[9] Vascular abnormalities in AD-HIEs include aneurysm and rupture of aorta, non-atherosclerotic dilatation of coronary and CNS vasculitis.[9] Eosinophilia is present in majority of patients, at least at some point in their life, though our patient was not detected to have the same.[7] An increased risk of malignancy has also been described with STAT3 deficiency, including lymphoma (Hodgkin's and Non-Hodgkin's), leukaemia and adenocarcinoma of lungs.[10-12]

The laboratory hallmark of HIES is very high serum IgE levels, typically above 2,000 IU/ml and is found to be elevated even at birth. The serum IgE levels may decrease over time and can even normalize. The differential diagnosis of such severe IgE levels include atopic dermatitis, inflammatory diseases such as Kimura disease and Churg Strauss syndrome, Specific syndromes such as Olmsted syndrome (periorificial hyperkeratotic lesions and mutilating palmoplantar keratoderma) and also other primary immunodeficiency diseases such as Wiskott-Aldrich syndrome (eczema, recurrent infections, thrombocytopenia with small platelets), Netherton syndrome (skin rash, entropathy, failure to thrive, bamboo hair), Omenn syndrome (exudative erythroderma with desquamation, lymphadenopathy, hepatosplenomegaly, intractable diarrhea and failure to thrive) and Nezeloff Syndrome (dermatitis, pondostatural retardation, candidiasis, diarrhea).[13] Co-existance of Hyper IgE syndrome has also been reported with

Dubowitz syndrome, pentasomy X syndrome and Saethre-Chotzen syndrome.[14-16]

Till curative or any other specific therapy becomes available for HIES, the consensus is to give life-long prophylactic therapy with anti-staphylococcal antibiotic such as Trimethoprim/sulfamethoxazole.[3] Usefulness of antifungal prophylaxis remains uncertain and interferon gamma also had inconsistent effects on the elevated IgE levels.[17,18] IVIG may be able to decrease the number of infections.[19] The natural history of this immunodeficiency mandates close follow up of the patient for subsequent development of other immunological and non-immunological complications, timely diagnosis and appropriate management of infections and surveillance for vascular complications and malignancies.

CONCLUSION

This case reemphasizes the fact that paediatricians should keep the possibility of primary immunodeficiency when encountered with a child who is symptomatic since early infancy with recurrent infections. Diagnosis of HIES in children remains challenging and it should be considered when common causes of such manifestations are ruled out with appropriate investigations and the diagnosis still remaining elusive.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Davis SD, Schaller J, Wedgwood RJ. Job's syndrome: Recurrent, "cold" staphylococcal abscesses. Lancet. 1966;1:1013-5.
2. Grimbacher B, Belohradsky BH, Holland SM. Immunoglobulin E in primary immunodeficiency diseases. Allergy. 2002;57:995-1007.
3. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. Immunol Rev. 2005;203:244-0.
4. Woellner C, Gertz EM, Schäffer AA. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125:424-32.
5. Minegishi Y, Karasuyama H. Genetic origins of hyper-IgE syndrome. Curr Allergy Asthma Rep. 2008;8:386-91.
6. Holland SM, DeLeo FR, Elloumi HZ. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007;357:1608-19.
7. Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. Arthritis Res Ther. 2012;14:228-38.
8. Szczawinska-Poplonyk A, Kycler Z, Pietrucha B, Heropolitanska-Pliszka E, Breborowicz A, Gerreth K. The hyperimmunoglobulin E syndrome--clinical manifestation diversity in primary immune deficiency. Orphanet J Rare Dis. 2011;6:76-85.
9. Rael EL, Marshall RT, McClain JJ. The Hyper-IgE Syndromes: Lessons in Nature, from Bench to Bedside. World Allergy Organ J. 2012;5:79-87.
10. Leonard GD, Posadas E, Herrmann PC. Non-Hodgkin's lymphoma in Job's syndrome: a case report and review of the literature. Leuk Lymphoma 2004;45:2521-5.
11. Gorin LJ, Jeha SC, Sullivan MP, Rosenblatt HM, Shearer WT. Burkitt's lymphoma developing in a 7 year old boy with hyper IgE syndrome. J Allergy Clinical Immunol. 1989;83:5-10.
12. Oztop I, Demirkan B, Tarhan O. The development of a pulmonary adenocarcinoma in a patient with Job's syndrome, a rare immunodeficiency condition. Tumori. 2004;90:132-5.
13. Yasharpour MR, Agarwal S, Jerome D, Yel L. Is It Hyper IgE Syndrome Or Something Else? MOJ Immunol. 2014;1:00010-4.
14. Antoniades K, Hatzistilianou M, Pitsavas G, Agouridaki C, Athanassiadou F. Co-existence of Dubowitz and hyper-IgE syndromes: a case report. Eur J Pediatr. 1996;155:390-2.
15. Boeck A, Gfatter R, Braun F, Fritz B. Pentasomy X and hyper IgE syndrome: co-existence of two distinct genetic disorders. Eur J Pediatr. 1999;158:723-6.
16. Boeck A, Kosan C, Ciznar P, Kunz J. Saethre-Chotzen syndrome and hyper IgE syndrome in a patient with a novel 11 bp deletion of the TWIST gene. Am J Med Genet. 2001;104:53-6.
17. Freeman AF, Holland SM. The hyper-IgE syndromes. Immunol Allergy Clin North Am. 2008;28:277-91.
18. King CL, Gallin JI, Malech HL, Abramson SL, Nutman TB. Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon gamma. Proc Natl Acad Sci U S A. 1989;86:10085-9.
19. Wakim M, Alazard M, Yajima A, Speights D, Saxon A, Stiehm ER. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann Allergy Asthma Immunol. 1998;81:153-8.

Cite this article as: Singh A, Mandal A, Seth R. Hyper IgE syndrome: often a missed diagnosis. Int J Contemp Pediatr 2016;3:674-7.