CASE REPORT

Hyper IgM Syndrome – An Immunodeficiency Disorder

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Abstract

A seven-year male child presented with history of recurrent life threatening infections associated with low IgA and IgG levels and significant elevation of IgM levels. He was diagnosed to have Hyper IgM syndrome. There was significant improvement after the immunoglobulin therapy. The child is now on regular immunoglobulin therapy and is free from recurrent infections. An index of suspicion to consider a possible diagnosis of immunodeficiency is stressed.

Keywords

Immunodeficiency disorder, Hyper IgM syndrome, Immunoglobulin replacement therapy

Hyper IgM Syndrome

Congenital immunodeficiency is a rare disorder, characterized by recurrent opportunistic infection, which may be often fatal. In a child, who develop recurrent infection either opportunistic or fatal one has to consider a possible immunodeficiency. A high index of suspicion help in early detection and appropriate intervention. Here we discuss a case of Hyper IgM syndrome, who had three life threatening infections before the deficiency could be established

Immunodeficiency with hyper-IgM syndrome (HIM) is characterized by normal or increased serum concentrations of IgM with decreased or absent IgG, IgA, and IgE (1). Case reports have revealed that Hyper-IgM may manifest as early as in infancy (2) and as late as 27 years (3). We present a case who was symptomatic at the age of five years.

Case Report

A seven-year male child was referred to our hospital with fever, headache, and altered sensorium for two days. He was born at term to non-consanguineously married parents. He had been immunized as per the schedule and had tolerated live vaccines well. He was reportedly well with normal developmental milestones till the age of five years. Then he presented to a hospital with history of fever of 8 weeks duration, pain abdomen and loose stools for 5 days. He was diagnosed to have enteric fever with perforation. Widal test was positive (titres 1:320 for Salmonella typhi O) and neutropenia (1300/cumm) was present with other hematological parameters within normal limits. Ultrasound examination and exploratory laparotomy confirmed perforation of intestine. Salmonella typhi was however not isolated in either blood or stool samples. The child improved with surgery

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(resection of the perforated bowel with end to end anastomosis) and treatment with ceftriaxone. Two months later, child presented again with high grade fever of four days duration, tremors and bleeding from nose and gums since one day. On examination, the child was pale and was in altered sensorium. He had purpuric rash, extensively over lower limbs with hepatosplenomegaly. Platelet count was low (27,000/cu mm). Bone marrow aspirate was normal. Cranial CT Scan revealed extensive bleed at basal ganglia . Autoimmune work-up (ASLO, ANA, Anti- ds DNA, Rh Factor) was normal. Work up for infection was negative as well. The child was treated with platelet-rich plasma and higher antibiotics. He was admitted for the third time two months later, this time with abscess over anterior abdominal wall. Staphylococcus aureus was grown from pus. Pus was drained and child was treated with cefazolin and ofloxacin (to which the organism was sensitive). Subsequently over next two months, the child had repeated respiratory infections requiring antibiotic therapy on outpatient basis. He also had an episode of otitis media, which was treated with antibiotics. Two months after the third admission, he developed fever, headache, and altered sensorium. He was referred to our hospital at this stage. Examination findings were concurrent with meningitis. He was emaciated, pale and had oral candidiasis. There was mild hepatosplenomegaly, but no lymphadenopathy. BCG scar was absent. There was leukocytosis (TC: 39,700/cumm, polymorphs 95%). CSF analysis revealed 121 cells/ cumm (polymorphs: 28% and lymphocytes: 72%), protein-126 mg/dl and sugar -12mg/dl. CSF grew Streptococcus pneumoniae. In view of recurrent infections with multiple organisms, especially capsulated bacteria, an immune- deficiency state was suspected.

The immunological evaluation showed (normal values indicated in parenthesis)-IgA: 22.1 mg/dl (30-250), IgG: 302 mg/dl (700-1650), IgE: 12.1 IU/ml (upto 90), IgM: 415 mg/dl (60-250) (tubidometric assay). On complement assay, C3: 168 mg/dl (60-120), C4: 30 dl (20-60), CD 19+ve (B-Cell): lymphocyt %(Normal range 7-23%), CD5+ve (Total T C lymphocyte72% (Normal range 62-83%) (analyse FACS). This child was diagnosed to have hyper- syndrome based upon the history of recurrent infect associated with low IgA and IgG and significant eleva of IgM.

The child was treated with IV Immunoglobul (IgG concentrates – 400 mg/kg/day × 3 days) in addit to mannitol and injectable ampiciliin, chloramphenic crystalline penicillin, metronidazole and Phenobarbito There was a dramatic improvement after t immunoglobulin replacement therapy. The child is n on regular immunoglobulin replacement (Ig concentrates – 400 mg/kg/month) from past two yea He is being followed-up at regular interval and has n suffered from any life-threatening infections ever sin he is receiving immunoglobulin replacement.

Discussion

Children with recurrent infections is one of the mo frequently encountered challenges by a pediatrician i his routine practice. The immunodeficiency wit reference to number of such patients is very rare. S pediatrician must have a high index of suspicion, i defects of immune system are to be diagnosed early. The recurrent infections can occur because of several different reasons. The condition may be an acquired transient phenomenon, or an inherited congenital condition. The correct estimation of immune deficiency in Indian context is not clear. The diagnosis often goes undiagnosed because of lack of clinical suspicion. The case in discussion was a healthy child till age of five years and had three fatal infections and an autoimmune phenomenon. This should have lead the treating pediatrician to suspect immunodeficiency.

The guideline for suspecting immunodeficiency such as (A) Two or more systemic bacterial infection (e.g.,

sepsis, osteomyelitis or meningitis) , (B) Three or more serious respiratory or documented bacterial infection (e.g., cellulitis , draining otitis media or lymhadenitis within one year), (C) Infections occurring at unusual sites (e.g., liver or a brain abscess)(D) Infection with unusual pathogens (e.g.,Aspergillus species, Serratia marcescens , Nocardia species or Pseudomonas cepacia) and (E) Infections with common childhood pathogens but of unusual severity (4).

In our case the child prior to evaluation for immunodeficiency, had met these criteria like recurrent respiratory infections, abdominal abscess etc. This should have lead them to suspect immunodeficiency disorder. But there was a delay in such suspicion , the child could have been avoided of another catastrophic infection. Simple widely available investigation could have helped in making diagnosis of Hyper IgM syndrome, what the present case was suffering.

Primary hypogammaglobulinemia associated with normal or increased IgM (the hyper-IgM syndrome) was first described in 1961(1). Inheritance of this rare disorder is usually X linked, but genetic heterogenecity is known and the disease can be inherited as autosomal recessive or dominant (1). X linked hyper IgM syndrome is distinguished from more common X linked agammaglobulinemia by the presence of circulating B-lymphocytes and polyclonal IgM in the former.

The clinical spectrum of the disease indicates that T lymphocyte deficiency may underlie hypogammaglobulinemia (5). The common clinical manifestations include upper and lower respiratory tract infections, otitis media, diarrhoea, oral ulcers, lymphoid hyperplasia and autoimmunity. Recurrent neutropenia is common (1,2). High titres of IgM antibodies to Salmonella O antigen are found in some patients (4). Immunological abnormalities consist of lack of IgG and IgA and failure to respond to vaccination. Pathogenetic hypotheses include failure of B-Cell differentiation, and defective regulation of immunoglobulin isotype switching due to abnormal T-Cell-mediated signals (6,7).

Treatment is often based on regular administration of IV Immunoglobulins (1). Steroids may be helpful in treatment of neutropenia and of severe autoimmune manifestations (1). Studies suggest that bone marrow transplantation can provide cure for these patients (8).

In our case, the levels of IgM were high which gradually reduced to normal levels with continued replacement of IgG concentrate. This case illustrates the need for investigations for immunodeficiency in a clinical setting of recurrent often-fatal infections in a child.

In conclusion, high index of suspicion of a probable immunodeficiency will improve the pick up rate of immunodeficiency and help in appropriate management of these unfortune children.

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