HYPER IgM SYNDROME: A REVIEW OF 3 CASES.

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ABSTRACT

Hyper IgM syndrome (HIM SX) is a rare congenital primary immunodeficiency that affects males more than females (70%, x-linked recessive), but there are reports of autosomal recessive and autosomal dominant inheritances. In this study, we review medical histories of 2 affected girls and one affected boy. Our 3 cases fulfill clinical and laboratory criteria of this syndrome. Their clinical signs include recurrent pyogenic and opportunisitic infections especilly in skin, respiratory and GI tracts. case 2 suffered from recurrent urinary tract infections too. Case 3 experienced P. carinii pnemonia during a severe neutropenic episode.

Other signs were 1- Autoimmunities as neutropenia, throbocytopenia, Coomb's positive hemolytic anemia and chronic parotitis in second case, 2- lymphoid hyperplasia presenting as generalized lymphadenopathies, hepatosplenomegaly and nodular lymphoid hyperplasia of intestine. Case 3, the 5 year old boy had an ataxic gait and suffered from recurrent herpetic keratoconjunctivitis and stomatitis. All the cases had very high serum levels of IgM (>1000 mg/dl) while other immunoglobulins were low. Sm IgM + B lymphocytes were increased in the first two cases and CD40L on Tcell of the 3rd case was absent. Occurance of this syndrome in girls is a very rare phenomenon.

Presence of high or normal serum IgM level in a hypogammaglobulinemic patient should be a clue for diagnosing this syndrome and could be further confirmed either by studying CD40L/CD40 pathway or through a genetic survey.

Keywords: Hyper IgM syndrome, genetics, autoimmunity.

Abbreviations:
HIM SX = Hyper Immunoglobulin M Syndrom.
PCP = Pneumocystis carinii pneumonia
VZIG = Varicella zoster immunoglobulin
CXR = Chest X-ray
IVIG = intra venous immunoglobulin
CMV = Cytomegalo Virus
AD = Autosomal dominant
AR = Autosomal

Hyper IGM Syndrome

INTRODUCTION

Hyper IgM syndrome (HIM SX) is a rare primary immunodeficiency associated with decreased serum immunoglobulins while serum IgM is normal or increased.[7,25]Clinical manifestations are repeated bacterial and opportunistic infections, autoimmune and malignant disorders and lymphoid hyperplasia. Some functional derangements of cell malignant immunity have been reported. In this study, we review medical histories of 2 affected girls and one affected boy. It is more common in boys (70%)[25,29]. Its occurance in girls is a very rare phenomenon. The pathogenesis of disease in males is the absence of a surface glycoprotein called CD40 ligand on T helper cells which is the physiologic ligand of CD 40 on B cells. The presence of this ligation during cognate Antigen dependent cellular in the CD40 triggered B cell activation pathway.[16]

All our cases fulfill clinical criteria of this syndrome. In addition their serum IgM levels in several measurements were more than 1000 mg/dl, while other immunoglobulins were in normal ranges. CD40 ligand did not present on activated Tcells of the affected boy.

Additional confirmation of diagnosis in the second case either by studying CD40L/CD40 pathway or by genetic studies would be done in the future (at present inaccessible in our department).

PATIENTS

Case 1

A teenaged girl whose disease presentations were: chronic and recurrent otitis media resulting in sclerosis of both tympanic membranes, recurrent sinusitis, recurrent and severe pneumonia once cured only by antifugal drugs, eczema, recurrent skin infections, chronic idiopathic thrombocytopenic purpura, neutropenia, Coomb's positive autoimmune hemolytic anemia, reactive lymphadenopathies, huge and firm hepatosplenomegaly, chronic liver involvement, and chronic watery diarrhea. She was the lst affected family member and parents are not relatives. She received longterm monthly IVIG, life long antibiotic prophylaxis, corticosteroid for autoimmune disorders and at least 2 courses of antifungal therapy. Finally she died of severe pneuminia at the age of 20y while she was being prepared for elective laparatomy and splenectomy, an attempt to control progressive cytopenias. Her progressive weight loss, neutropenia, thrombocytopenia and increasing lymphocytosis implied malignant transformations.

Case 2

An eleven year old girl whose disease presented since infancy as protracted fever, recurrent urinary tract infections, chronic bloody diarrhea (due to recalcitrant giardiosis, nodular lymphoid hyperplasia, ulcerative colitis) gastroesophageal reflux and esophagitis, huge hepatosplenomegaly, esophageal varices and portal hypertension, recurrent otitis media, sinusitis and pneumonias, chronic bilateral parotitis, reactive arthritis, Coomb's positive hemolytic anemia and thrombocytopenia. She is the only affected family member and parents are not relatives.

She was treated with longterm regular monthly IVIG, antibiotic prophylaxis and steroid for autoimmunities. A trial of low dose azathioprine course in order to taper steroid failed and now she is on low dose steroids on alternate days. Cushingoid appearance and hypertricosis are present.

Case 3

A 5 year old boy who has a long-standing history of diarrhea since his infancy which got aggravated by cow's milk ingestion, allergy to egg and cow milk, failure to thrive, severe chicken pox requiring VZIG therapy, recurrent otitis media, sinusitis, CXR findings compatible with p.carinii pneumonia during a severe neutropenic episode, periorbital cellulitis, recurrent conjunctivitis, herpetic kerato conjunctivitis and stomatitis, oral ulcers, infectious dermatitis , lymphadenopthies, huge hepatosplenomegaly with stigmata of portal hypertension, neutropenia, thrombocytopenia, autoimmune hemolytic anemia and ataxia. He is the only child of a consanguine first degree relative marriage, with no birth difficulty. There is no history of immunodeficiency in other relatives.

The serum levels of IgM were markedly elevated with concomitant low IgG and the absence of IgA and IgE. CD40 ligand once detected by flowcytometry is absent. He has received longterm regular IVIG, Co-trimoxazole prophylaxis and GM-CSF for

Table 1. Immunologic laboratory findings

Test	Case 1	Case 2	Case 3
Immunoglobulins IgM IgA IgG	>1000mg/dl Absent or low low (IgG 1 low) (IgG 2 low)	>1000mg/dl Absent or low low	>1000mg/dl absent low
Bcells sm+IgM sm+IgA sm+IgG	Increased low low	Increased low low	———
Floweytometry	CD19 low CD4/ CD8 low	CD19 low CD4/ CD8 low	CD19 low CD4/ CD8 low
Specific antibody responces schick test isohemmaglotinin Blood group ASOTI	1+ negative AB	1+ negative AB normal	negative A
DTH PPD DT3 candida	negative	negative negative 1+	———
NBT4 chemiluminescence	normal	normal normal	———
complement components	———	Normal	Normal

ASOT = Anti streptolysin O
DT = Diphteroid-Tetunus
DTII = Delayed type Hypersensitivity skin tests
NBT = Nitro Blue Tetruzoliume test

concomitant thrombocytopenia and neutropenia.

He is a candidate for bone morrow and liver transplantation.

DISCUSSION

Hyper IgM syndrome is a rare congenital primary immunodeficiency characterized by decreased serum levels of IgG, IgA and IgE but normal or more frequently marked elevated concentrations of polyclonal IgM.[7,22] IgM primary and secondary antibody responses are intact while there is failure to switch to production of other isotypes.[25]

This disorder is inherited by x-linked transmission but there are reports of AR or AD inheritances. Secondary disorders e.g. following congenital rubella or the use of anti-epileptic drugs have been reported.[16,22,29]

Antigen driven cognate T-B cell cooperation needs 2 signals. First is delivered by cytokines and the second by the binding of CD40 to its ligand (CD154) on the activated T helper cells. The latter interaction is reponsible for immunoglobulins isotype switching and other B cell vital functions such as homotypic aggergation, proliferation and rescue from apoptosis.[4,16,17]

CD40/ CD40L system also plays an important role in mediating Tcell dependent immune response. This binding may lead to further activation of both the antigen presenting cells and the responding Tcells, thus amplifies the cell-cell interaction. There are reports of impaired in vitro T-lymphocyte proliferative response to candida antigen.[2]

Table 2. Other laboratory findings

Test	Case 1			Case 2			Case 3		
CBC	14yr	15yr	20yr	4yr	7yr	9yr	2yr	4yr	5yr
WBC	5300	4200	5300	2000	19500	6800	2800	6000	2740
PMN	58%	36%	18%	68%	75%	66%	68	8	4%
lymphocyte	34%	63%	82%	29%	22%	18%	31	63	66%
HB(g%)	8.2	5	10.4	7.6	4.5	13.2	9.5	9.6	7
MCV(FL)	85	107	84	74	272	94	186000	203000	60000
Platelette	3000	200000	26000	19000	67000	85000			
reticulayte count	1.5%				10%			14%	
Bone marrow aspiration	erythroid hyperplasia			Slightly erythroid hyperplasia			Myeloid arrest		
Liver Function tests	normal			slightly increased			increased		
HBS Ag	negative			negative			———		
Anti HIV	negative			negative			———		
Auto antibodies									
Anti DNA	negative			negative					
ANA	negative			negative					
LE cell	negative			negative					
Coom's test	Positive			Positive					
lymph node biopsy	reactive lymphadenitis			nonspecific hyperplasia					
liver biopsy				chronic active hepatitis			chronic active heptitis		
colon biopsy				Ulceratie colitis					
gastro intestinal endoscopy				Gastroduedenitis Esophageal verices Bulbar lymphoid Nodular hyperplasia			duodenitis		
abdominal sonography				hepatosplenomegaly, incrased portal vein diameter			huge hepato splenomegaly, stigmate of portal hypertnsion		

The gene for CD40L maps to xq26 on the long arm of the X chromosome and its mutations result in x-linked HIM syndrome.[8,23,28]

In cases with other inheritance patterns CD40L is expressed normally on activated T cells but there is an intrinisic B cell deficiency and a defect in the CD40-triggered B cell activation pathway[16]

There is a highly polymorphic micro satellite dinucleotide (CA) repeat region at 3 end of CD40L gene which provides a good marker to detect carriers and for prenatal diagnosis.[7,15] The congenital disorder presentations commence since infancy parallel to the nadir of child's maternal driven imunoglobulins. Charcteristic clinical features are repeated pyogenic bacterial infections involving skin, respiratory and GI tracts. Chronic diarrhea so severe to cause growth retardation due to giardiosis, cryptosporidia infestation or nodular lymphoid hyperplasia of intestine is a frequent manifestation. Neutropenia is common and presents as gingivitis, oral ulcers, and perianal abscesses[12,29]. There are stigmata of cell mediated immunity impairement such as higher susceptibility to opportunistic infections such as PCP, generalized CMV infections, and

extensive verruca vulgaris,[2,6,7,21] The frequency of autoimmunity is even higher than other antibody deficiency syndromes.[7,19] They are prone to autoimmune disorders involving formed elements of the blood as hemolytic anemia, thrombocytopenia and recurrent often severe neutropenia.[27] Chronic liver disease such as sclerosing chollangitis, hepatitis progressing to Cirrhosis or hepatocellular carinoma is a frequent presentation found in majority of patients who reach teenage.[21,18] Frequency of GI tumors is 17% the most commonly being adenocarcinomas[18].

Other less common manifestations are neurologic disorders as meningitis, progressive degenerative encephalopathy, CNS infections with toxoplasma, echovirus, CMV, Mycobacterium Bovis and cryptococcus.[20,21]

Lymphoid hyperplasia such as lymphadenopathies, hepatosplenomegaly is a frequent presentation of the syndrome, often abstracting from a diagnosis of immunodeficiency although it is a significant cause of their morbidity.[7,29].

Aggressive treatment of infections and regular IVIG are the mainstay of therapy[29]. Neutropenia improves during IVIG therapy. Other options include G-CSF or leukocyte transfusion from healthy donors.[1,5,27,31]

They are especially susceptible to PCP and should receive prophylaxix with trimethoprime-sulfamethoxazole. Allogenic HLA-matched bone marraw transplantation is the treatment of choice. It has the potency to cure genetic disorders affecting marrow derived cells.[30]

Liver transplantation is beneficial in patients suffering from hepatic failure, cirrhosis or sclerosing chollangitis.[21]

Novel treatments involving replacement therapy with recombinant, soluble forms of CD40L are future options.[25]

Natural courses of all our patients fulfill clinical and laboratory criteria of this syndrome. In addition to recurrent infections, all suffered from various autoimmune hematopoetic disorders, lymphoid hyperplasia and chronic liver involvement.

Case 1 and case 3 were suspected to have malignant transformations.

Their serum level of IgM in several measurements were very high (1000mg/dl), while other immunoglobulins were under lower limitis of normal age matched controls. In the case 3, the diagnosis was further confirmed by an absence of CD40L on Tcells. Additional confirmation of diagnosis in second case either by studying CD40L/CD40 pathway or by genetic studies should be done in the near future (now inaccessible in our department).

The case 1 suffered from progressive neutropenia, lymphocytosis and cachexia implying malignancies. Unfortunately, while she was being prepared for elective splenectomy in an attempt to control progressive cytopenia, she died due to a fulminant pneumonia at 20 th yr of age.

Patients with HIM SX syndrome are noted to be sicker than most patients with other aggamaglobulinemias.

Patients with defects in the CD40L have a poor prognosis [13,21].The high incidence of autoimmune disorders, bowel disease, neutropenia and increased incidence of malignancies are responible for additional morbidity and mortality.

Failure to respond promptly to IVIG therapy indicates poor prognosis.

CONCLUSION

Hyper IgM syndrome is a rare primary immunodeficiency with gaurded prognosis due to high incidence of opportunistic infections, autoimmunities, and malignancies [21]. This fact allows us to use more aggressive therapy such as bone marrow transplantations [13].

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