

Hyper-IgM syndromes

Definition of Hyper IgM Syndrome

Patients with Hyper IgM (HIM) syndrome have an inability to switch production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE type. As a result, patients with this primary immunodeficiency disease have decreased levels of serum IgG and IgA and normal or elevated levels of IgM. B-lymphocytes can produce IgM antibodies on their own, but they require interactive help from T-lymphocytes in order to switch antibody production from IgM to IgG, IgA and IgE. The hyper IgM syndrome results from a variety of genetic defects that affect this interaction between T-lymphocytes and B-lymphocytes.

The most common form of hyper IgM syndrome results from a defect or deficiency of a protein that is found on the surface of activated T-lymphocytes. The affected protein is called "CD40 ligand" because it binds to a protein on B-lymphocytes called CD40. CD40 ligand is made by a gene on the X-chromosome. Therefore, this primary immunodeficiency disease is inherited as an X-linked recessive trait and usually found only in boys. As a consequence of their deficiency in CD40 ligand, affected patients' T-lymphocytes are unable to instruct B-lymphocytes to switch their production of immunoglobulins from IgM to IgG, IgA and IgE. In addition, CD40 ligand is important for other T-lymphocyte functions, and therefore, patients with X-linked hyper IgM syndrome (XHIM) also have a defect in some of the protective functions of their T-lymphocytes.

Other forms of HIM syndrome are inherited as autosomal recessive traits (see chapter titled *Inheritance*) and have been observed in females

and males. The molecular bases for some of the other forms of HIM have been discovered. These forms of HIM syndrome result from defects in the genes that are involved in the CD40 signaling pathway. Genetic defects in CD40 are very rare and have been described in few families. The resulting disease is almost identical to XHIM because although the CD40 ligand is present on T-lymphocytes, the CD40 found on B-lymphocytes and other cells of the immune system is either not present or does not function normally. Two other genes (AID and UNG) have been identified that are necessary for B-lymphocytes to switch their antibody production from IgM to IgG, IgA or IgE. Defects in both of these genes have been found in patients with HIM syndrome. Since the function of these genes is limited to antibody switching, the other T-lymphocyte functions of CD40 ligand are not affected, and these patients are less likely to have infections caused by organisms that are controlled by T-cells.

Finally, a defect in another X-linked gene that is necessary for the activation of the signaling molecule NF- κ B has been identified in a form of HIM that is associated with a skin condition called ectodermal dysplasia. Patients have immunodeficiency with sparse hair and conical teeth among other abnormalities. NF- κ B is activated by CD40 and is necessary for the signaling pathway that results in antibody switching. NF- κ B is also activated by other signaling pathways that are important in fighting infections. Therefore, these affected boys are susceptible to a variety of serious infections.

Clinical Presentation of Hyper IgM Syndrome

Most patients with Hyper IgM (HIM) syndrome develop clinical symptoms during their first or second year of life. The most common problem is an increased susceptibility to infection including recurrent upper and lower respiratory tract infections. The most frequent infective agents are bacteria. A variety of other microorganisms can also cause serious infections. For example, *Pneumocystis jirovecii* (carinii) pneumonia, an opportunistic infection, is relatively common during the first year of life and its presence may be the first clue that the child has the X-linked form of HIM syndrome (XHIM). Lung infections may also

be caused by viruses such as Cytomegalovirus and fungi such as Cryptococcus. Gastrointestinal complaints, most commonly diarrhea and malabsorption, have also been reported in some patients. One of the major organisms causing gastrointestinal symptoms in XHIM is *Cryptosporidium* that may cause sclerosing cholangitis, a severe disease of the liver.

Approximately half of the patients with XHIM syndrome develop neutropenia (low white blood cell count), either transiently or persistently. The cause of the neutropenia is unknown, although most patients respond to treatment with the

Clinical Presentation of Hyper IgM Syndrome contined

colony stimulating factor, G-CSF. Neutropenia is often associated with oral ulcers, proctitis (inflammation and ulceration of the rectum) and skin infections. Enlargement of the lymph nodes is seen more frequently in patients with autosomal recessive HIM syndrome than in most of the other primary immunodeficiency diseases.

As a result, patients often have enlarged tonsils, a big spleen and liver, and enlarged lymph nodes. Autoimmune disorders may also occur in patients with HIM syndrome. Their manifestations may include chronic arthritis, low platelet counts (thrombocytopenia), hemolytic anemia, hypothyroidism, and kidney disease.

Diagnosis of Hyper IgM Syndrome

The diagnosis of X-linked Hyper IgM (XHIM) syndrome should be considered in any boy presenting with hypogammaglobulinemia, characterized by low or absent IgG and IgA and normal or elevated IgM levels. Failure to express CD40 ligand on activated T-cells is a characteristic finding. However, some patients with other forms of immunodeficiency may have a markedly depressed expression of CD40 ligand while their CD40 ligand gene is perfectly normal. Therefore, the final diagnosis of XHIM syndrome depends on the identification of a mutation affecting the CD40 ligand gene. This type of DNA analysis can be done in several specialized laboratories.

The autosomal recessive forms of HIM can be suspected if a patient has the characteristics of

XHIM but is either a female patient and/or has a normal CD40 ligand gene with normal expression on activated T-lymphocytes.

Ectodermal Dysplasia with Immunodeficiency, another X-linked form of HIM, can be suspected in a patient who has features of ectodermal dysplasia (e.g. sparse hair and conical teeth) and recurrent infections, normal or elevated IgM and low IgG, IgA and IgE.

The diagnosis of the different forms of autosomal recessive HIM or of Ectodermal Dysplasia with Immunodeficiency can be confirmed by mutation analysis of the genes known to cause these disorders.

Inheritance of Hyper IgM Syndrome

X-linked Hyper IgM (XHIM) and Ectodermal Dysplasia with Immunodeficiency are inherited as X-linked recessive disorders. As a result, only boys are affected. See chapter titled *Inheritance* for more complete information on how X-linked recessive disorders are passed on from generation to generation. Since these are inherited diseases, transmitted as an X-linked recessive trait, there may be brothers or maternal uncles (mother's brothers) who have similar clinical findings. As in

other X-linked disorders, there also may be no other affected members of the family.

Since the autosomal recessive forms of HIM require that the gene on both chromosomes be affected, they are less frequent than the X-linked conditions.

If the precise mutation in the affected gene is known in a given family, it is possible to make a prenatal diagnosis or test family members to see if they are carriers of the mutation.

Treatment of Hyper IgM Syndrome

Patients with Hyper IgM (HIM) syndrome have a severe deficiency in IgG. Regular treatment with immunoglobulin replacement therapy every 3 to 4 weeks is effective in decreasing the number of infections (see chapter titled *Specific Medical Therapy*). The immunoglobulin replaces the missing IgG and often results in a reduction or normalization of the serum IgM level. Since patients with the XHIM syndrome also have a marked susceptibility to *Pneumocystis jiroveci* (carinii) pneumonia, many physicians feel it is important to initiate prophylactic or preventative treatment for *Pneumocystis jiroveci* pneumonia by starting affected infants on trimethoprim-sulfamethoxazole (Bactrim, Septra) prophylaxis as soon as the diagnosis of XHIM syndrome is made. Sometimes, neutropenia may improve during treatment with IVIG. Patients with persistent neutropenia may also respond to granulocyte colony stimulating factor (G-CSF) therapy. However, G-CSF treatment is only necessary in selected patients and long-term treatment with G-CSF is usually not recommended. Boys with HIM, similar to other patients with primary immunodeficiency diseases, should not receive live virus vaccines since there is a remote possibility that the vaccine strain of the virus may cause disease. It is also important to reduce the possibility of drinking water that is contaminated with *Cryptosporidium* because exposure to this

organism may cause severe gastrointestinal symptoms and chronic liver disease. The family should be proactive and contact the authorities responsible for the local water supply and ask if the water is safe and tested for *Cryptosporidium*.

Patients with XHIM syndrome have defects in T-lymphocyte function in addition to their antibody deficiency, and patients with Ectodermal Dysplasia with Immunodeficiency also have defects in other aspects of their immune system. Treatment with immunoglobulin may not fully protect these patients against all infections. In recent years, bone marrow transplantation or cord blood stem cell transplantation have been advocated (see chapter titled *Specific Medical Therapy*). More than a dozen patients with XHIM have received an HLA identical sibling bone marrow transplant with excellent success. Thus, a permanent cure for this disorder is possible. Cord blood stem cell transplants, fully or partially matched, have also been successfully performed, resulting in complete immune reconstitution. Matched unrelated donor (MUD) transplants are nearly as successful as matched sibling transplants. Since patients with the XHIM syndrome may have strong T-cell responses against organ transplants, including bone marrow transplants, immunosuppressive drugs or low dose irradiation are usually required.

Expectation for the Hyper IgM Syndrome Patient

Although patients with the Hyper IgM syndrome may have defects in the production of IgG and IgA antibodies and in some aspects of their T-lymphocyte function (XHIM), a number of effective therapies exist which allow these children to grow into happy and successful adults.