Chapter 5
Hyper IgM Syndromes

Ramsay Fuleihan, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA

The Hyper-IgM Syndromes (HIGM) are rare inherited primary immunodeficiency diseases (PI) characterized by decreased blood levels of immunoglobulin G (IgG) and normal or elevated levels of IgM. Most individuals with HIGM are susceptible to recurrent and severe infections including opportunistic infections, which are infections by organisms that do not normally infect healthy individuals, and are susceptible to an increased risk of cancer. A number of different genetic defects can cause HIGM. The most common form is inherited as an X-linked disease affecting boys. The other forms of HIGM are inherited as autosomal recessive traits affecting both boys and girls. (See Inheritance Chapter.)

Overview

When B cells, which are the cells that make antibodies, develop, the first type of antibody they make is IgM. IgM is responsible for the immune system's initial response to an infection. Once healthy B cells make IgM, they can receive signals from T cells that tell them to switch from making IgM to IgG, IgA, or IgE depending on which type is needed to continue to fight infection. B cells from individuals with HIGM are unable to switch from the production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE type due to several different genetic defects in the signaling pathways between T cells and B cells. As a result, people with this disease have decreased levels of IgG, IgA, and IgE but normal or elevated levels of IgM in their blood. These different types of antibodies perform different functions and are all important in fighting infections. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) Since most individuals with HIGM are identified early and usually do not have elevated IgM levels, the name HIGM is not always accurate. Nevertheless, HIGM is used to denote that these diseases are characterized by the inability to switch antibody type--the B cells can only make IgM. Depending on the genetic defect causing HIGM, individuals may also be susceptible to opportunistic infections [such as *Pneumocystic jirovecii (carinii)*], cryptosporidium, certain forms of cancer, and autoimmune disease. Therefore, HIGM are severe immunodeficiency diseases and in the past have a guarded long-term outcome with few individuals surviving beyond the third or fourth decade of life. In recent years, hematopoietic stem cell transplantation (bone marrow, peripheral blood stem cells or umbilical cord blood stem cells) has been performed successfully in individuals with the X-linked form of XHIGM. (See Hematopoietic Stem Cell Transplantation Chapter.)

Immunobiology

People with HIGM have an inability to switch from the production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE types. As a result, individuals with this disease have absent or decreased levels of IgG, IgA, and IgE but normal or elevated levels of IgM in their blood. B cells, the cells that make antibodies, can produce IgM antibodies on their own, but they require interactive help from T cells in order to switch from IgM to IgG, IgA or IgE. HIGM syndromes result from a variety of genetic defects that affect this interaction between T cells and B cells, as well as cell signaling events that occur within B cells that are necessary for antibody switching.

The most common form of HIGM results from a defect or deficiency of a protein that is found on the surface of activated T cells. The affected protein is called CD40 ligand because it binds (ligates) to a protein on B cells called CD40. The interaction between CD40 and CD40 ligand signals the B cell to switch from production of IgM to other types of antibodies like IgG or IgA.

Some individuals with HIGM due to CD40 ligand deficiency have normal IgA levels, and the mechanism for this is not clear. It appears to occur via a CD40 ligand independent pathway. CD40 ligand is made by a gene on the X chromosome. Therefore, this form of PI is inherited as an X-linked recessive trait. X-linked recessive trait means that mothers can be carriers and boys are affected if they inherit the affected X chromosome from their mother. (See Inheritance Chapter.) CD40 ligand is also important for other functions carried out by T cells, so individuals with XHIGM have defective cellular immunity and thus are also susceptible to opportunistic infections and to some types of cancer.

Other forms of HIGM are inherited as autosomal recessive traits and have been observed in both girls and boys. (See Inheritance Chapter.) One of these forms results from a defect in CD40 and is clinically identical to XHIGM (the disease with the defect in CD40 ligand). Other autosomal recessive forms of HIGM result from defects in proteins that are involved in antibody class switching through the CD40 signaling pathway, these are known as Uracil-DNA glycosylase (UNG) deficiency and activation-induced cytidine deaminase (AID) deficiency. Autosomal recessive inherited genetic defects in two other proteins involved in antibody class switching, INO80 and MSH6 have also been seen in individuals with clinical HIGM.

The function of these genes is limited to antibody switching (after the B cell has received the signal to switch from the interaction of CD40 and CD40 ligand), so the other T cell functions of CD40 ligand are not affected and these patients are less likely to have opportunistic infections or cancer. Unlike individuals with defects in CD40 or CD40 ligand whose B cells cannot receive the signal to switch due to faulty communication with the T cells, B cells from individuals with defects in AID or UNG do receive an activating signal, and this may lead to the development of enlarged lymph nodes (where B cells and T cells are found). Individuals with AID or UNG defects may be more susceptible to develop autoimmune disease.

Finally, since switching antibody types in B cells involves breaks and subsequent repair in DNA, defects in genes that are important for DNA repair may also present with HIGM. The main features of these diseases are related to the defect in DNA repair, but some have immunoglobulin levels similar to HIGM. These diseases include Ataxia-Telangiectasia, Nijmegen breakage syndrome, and PMS2 deficiency.

Clinical Presentation

Most individuals with HIGM develop clinical symptoms during their first or second year of life. The most common problem in all forms of HIGM is an increased susceptibility to infection including recurrent upper and lower respiratory tract infections. The most frequent serious infective agents are bacteria, but viral illnesses are also more frequent and severe.

In people with XHIGM and autosomal recessive HIGM due to a CD40 defect, a variety of other microorganisms can also cause serious infections. For example, *Pneumocystis jiroveci (carinii)* pneumonia, an opportunistic infection, is relatively common during the first year of life, and its presence may be the first clue that a child has HIGM.

Gastrointestinal complaints, most commonly diarrhea and malabsorption, also occur commonly in XHIGM and CD40 deficiency. One of the major organisms causing gastrointestinal symptoms in XHIGM is Cryptosporidium. A Cryptosporidium infection may cause sclerosing cholangitis—a severe, often fatal, disease of the liver.

Approximately half of the individuals with XHIGM or CD40 deficiency develop neutropenia (low count of granulocyte white blood cells), either transiently or persistently. The cause of the neutropenia is unknown, although most individuals respond to treatment with colony stimulating factor, G-CSF. Severe neutropenia is often associated with oral ulcers, inflammation, ulceration of the rectum (proctitis), and skin infections.

Autoimmune disorders may also occur in individuals with HIGM especially in those with defects in AID or UNG. Autoimmune manifestations may include chronic arthritis, low platelet counts (thrombocytopenia), hemolytic anemia, hypothyroidism and kidney disease.

Enlargement of the lymph nodes and the spleen is seen frequently in those with autosomal recessive HIGM due to defects of AID or UNG. As a result, they often have enlarged tonsils and adenoids that may cause snoring and obstructive sleep apnea.

Finally, the risk for cancer, particularly liver cancer, is increased in individuals with XHIGM or CD40 deficiency. A few individuals with HIGM have developed a rapidly progressive neuroendocrine carcinoma.

Diagnosis

XHIGM should be considered in any boy presenting with severe recurrent respiratory infections or an opportunistic infection who has low or absent IgG and normal or elevated IgM levels with normal T cell and B cell numbers. The presence of neutropenia in addition to the above features increases the likelihood of having XHIGM.

Failure to express CD40 ligand on activated T cells is a characteristic finding. Some express a defective CD40 ligand protein that may be detected by the antibody used in the test (falsely normal test result) but will not bind to a soluble form of CD40. Confirming the diagnosis of XHIGM depends on the identification of a mutation affecting the CD40 ligand gene. Carriers of XHIGM can be identified by finding decreased expression of CD40 ligand on activated CD4 T-lymphocytes (on average 50% of the cells will be normal) and confirmed by genetic testing.

The autosomal recessive forms of HIGM can be suspected if an individual has the characteristics of XHIGM but is either a female or is a male who has a normal CD40 ligand gene with normal expression on activated T cells. The diagnosis of the different forms of autosomal recessive HIGM can also be confirmed by mutation analysis of the genes known to cause these disorders.

Inheritance

X-linked Hyper IgM (XHIGM) is inherited as an X-linked recessive disorder, and typically only boys are affected. In girls, all cells randomly inactivate one of the X chromosomes. Very rarely, female carriers of XHIGM (or NEMO) may have markedly skewed X chromosome inactivation such that most of their cells (>95%) have the X chromosome with the defective CD40 ligand gene active in their cells and may present with a milder form of the disease.

Since the autosomal recessive forms of HIGM require that the gene on both chromosomes be affected, by inheriting one mutation from each parent, they are less frequent than the X-linked conditions. The likelihood of having an autosomal recessive form of HIGM is increased if the parents are related prior to marriage.

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. Early diagnosis of any HIGM will allow initiation of treatment prior to the development of long-term consequences of serious infections.

Treatment

Since individuals with all forms of HIGM have a severe IgG deficiency, they require immunoglobulin (Ig) replacement therapy. The Ig replaces the missing IgG and often results in a reduction or normalization of the serum IgM level, if it was elevated. Ig replacement therapy can be given intravenously or subcutaneously. (See Immunoglobulin Therapy Chapter.)

Since individuals with XHIGM or CD40 deficiency also have a marked susceptibility to *Pneumocystis jiroveci (carinii)* pneumonia (PJP, or PCP), they should be started on prophylactic treatment with the antibiotic trimethoprim-sulfamethoxazole (orally) as soon as the diagnosis of XHIGM is made. Other drugs for PJP prophylaxis are available if the individual is allergic to sulfa drugs.

When present, neutropenia may also improve during Ig replacement therapy. Individuals with persistent neutropenia may also require granulocyte colony stimulating factor (G-CSF) therapy, especially if they have infections, mouth sores or other complications associated with the neutropenia. G-CSF treatment, however, is only necessary in select individuals and long-term treatment with G-CSF is usually not recommended.

Individuals with XHIGM or CD40 defects should not receive live virus vaccines since there is a remote possibility that the vaccine strain of the virus may cause disease. Bottled water should be used to avoid exposure to Cryptosporidium if using well water or water outside the U.S.

Individuals with XHIGM or CD40 deficiency have defects in T cell function in addition to their antibody deficiency, and treatment with Ig replacement therapy may not fully protect them against all infections and does not protect them from some opportunistic infections or cancer. Hematopoietic stem cell transplantation (bone marrow, peripheral blood stem cells, or cord blood stem cells) has been performed successfully in individuals with XHIGM. (See Hematopoietic Stem Cell Transplantation Chapter.) While a permanent resolution of the PI is anticipated after successful stem cell transplantation, the long-term prognosis for these individuals is not yet known. Earlier transplant is associated with improved survival.

Since individuals with autosomal recessive HIGM caused by mutations in AID or UNG only have defects of antibody production with no defect in T cell function, stem cell transplantation is not recommended at this time.

While gene therapy has been effective in treating some severe forms of PI, there are a number of issues that make it difficult for HIGM:

- The genetic defect in HIGM does not affect the development of T cells or B cells, and thus gene therapy will have to be very efficient to correct a sufficient percentage of stem cells.
- CD40 ligand is expressed only transiently on activated T cells, and thus gene therapy will have to mimic the regulation of expression of normal CD40 ligand, which remains a difficult task.
- Dysregulated expression of CD40 ligand is associated with autoimmune diseases and lymphoproliferation (increased numbers of lymphocytes with enlarged lymphoid tissues).

Gene therapy researchers are testing new approaches to correct the defect in the CD40 ligand gene in its location on the X chromosome in order to provide normally regulated expression of a normal CD40 ligand gene. Efficiency of correction in stem cells remains an obstacle currently.

Expectations

There is a broad range of severity seen amongst individuals with different genetic forms of HIGM. Those with defects primarily involving antibody switching can be effectively treated by Ig replacement therapy and can live long, productive lives. Those with associated defects in T cell activation characteristically have more significant immune deficits and may encounter additional problems including susceptibility to more dangerous types of infections as well as the development of cancer as further challenges. The experience with hematopoietic stem cell transplantation (HSCT) is encouraging for those with more severe diseases. A recent study looking at the outcome of individuals treated with HSCT as compared to those who were not did not show an overall decrease in mortality. When the data was examined over time, however, there was a trend for decreased mortality if the transplant was done more recently. In addition, those who had survived HSCT had a better quality of life and none had developed cancer at the time of the study. Further studies are needed to evaluate the long-term outcomes of HSCT.

Adapted from: Chapter 11 Hyper IgM Syndromes. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.