IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

MANAGEMENT OF **HYPER IGM SYNDROMES**

ABBREVIATIONS

G-CSF	Granulocyte colony stimulating factor
IEI	Inborn errors of immunity
Ig	Immunoglobulin
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PIDs	Primary immunodeficiency

Hyper IgM Syndromes (2nd edition)

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SUMMARY

Hyper IgM syndromes are a group of rare primary immunodeficiencies that occur when people have abnormal levels of antibodies, called immunoglobulins. People with these disorders are unable to switch the production of antibodies from the IgM type to the IgG, IgA or IgE types resulting in decreased levels of IgG, IgA and/or IgE combined with normal or increased levels of IgM. The decreased levels of IgG, IgA and/or IgE result in an increased risk of recurrent and severe infections. Hyper IgM syndromes are inherited disorders; X-linked recessive hyper IgM syndrome is the most common form, occurring in about 70% of individuals, and affects only males while females can be “carriers” for the disorder. There are at least four types of autosomal recessive hyper IgM syndrome which affect men and women equally and are known as hyper IgM syndrome type 2, 3, 4, and 5.

Most persons with hyper IgM syndromes develop clinical symptoms during the first or second year of life. The most common issue across all hyper IgM syndromes is an increased susceptibility to infection including recurrent upper and lower respiratory tract infections. Gastrointestinal symptoms, most often diarrhoea and malabsorption, also commonly occur, as does neutropenia. A diagnosis of hyper IgM syndrome requires identification of a mutation in one of the genes known to cause these disorders.

Immunoglobulin replacement therapy can be very helpful for all forms of hyper IgM syndrome as it markedly reduces the frequency of bacterial infections, and prophylactic treatment with trimethoprim-sulfamethoxazole should also be considered in persons with X-linked hyper IgM syndrome. Persistent neutropenia may require granulocyte colony stimulating factor therapy and haematopoietic stem cell transplantation can be a possibility in some individuals.

INTRODUCTION

This booklet explains what hyper IgM syndromes are, the signs and symptoms of the diseases, and how they are diagnosed, treated and managed.

Hyper IgM syndromes are a group of rare disorders in which the immune system does not function properly. They are classified as primary immunodeficiencies (PIDs), sometimes referred to as inborn errors of immunity (IEI), and are characterized by irregularities in the development and/or maturation of certain cells in the immune system. This results in persons with a hyper IgM syndrome being susceptible to recurrent and severe infections, opportunistic infections and an increased risk of cancer.

WHAT ARE HYPER IGM SYNDROMES?

Hyper IgM syndromes comprise a group of PIDs that occur when people have abnormal levels of antibodies, also called immunoglobulins (Igs). People with hyper IgM syndromes are unable to switch the production of antibodies from the IgM type to the IgG, IgA or IgE types. This results in them having decreased levels of IgG, IgA or IgE but normal or increased levels of IgM in their blood. As these different types of antibodies perform different immune functions, the decreased levels of IgG, IgA and/or IgE result in an increase in the risk of recurrent and severe infections. There are also several PIDs not typically classified as hyper IgM syndromes that can present with elevated IgM levels.

Normally, B cells can produce IgM antibodies on their own, but they require interactive help from T cells in order to switch production from IgM to IgG, IgA or IgE. Hyper IgM syndromes result from a variety of genetic defects that affect this interaction between T cells and B cells. The most common form of hyper IgM syndrome arises when a protein on the surface of T cells – CD40 ligand – is defective and is unable to bind to the matching CD40 protein on the surface of B cells.

WHO IS AFFECTED BY HYPER IGM SYNDROME?

Hyper IgM syndromes are inherited disorders; the most common form, occurring in about 70% of individuals, is inherited in an X-chromosome linked recessive pattern and affects only males while females can be “carriers” for the disorder. Less often, affected individuals inherit the disorder in an autosomal recessive pattern and few cases have been described in an autosomal dominant pattern. There are at least four types of autosomal recessive hyper IgM syndrome; these forms affect men and women equally and are known as hyper IgM syndrome type 2, 3, 4, and 5.

INHERITANCE

For X-linked recessive hyper IgM syndrome, the gene causing disease is present on the X chromosome. Males have only one X chromosome that is inherited from their mother so if a male inherits an X chromosome that contains a defective gene, he will develop the disease (**Figure 1**). Females have two X chromosomes, so those that have a defective gene present on one of their X chromosomes are “carriers” for that disorder (**Figure 1**).

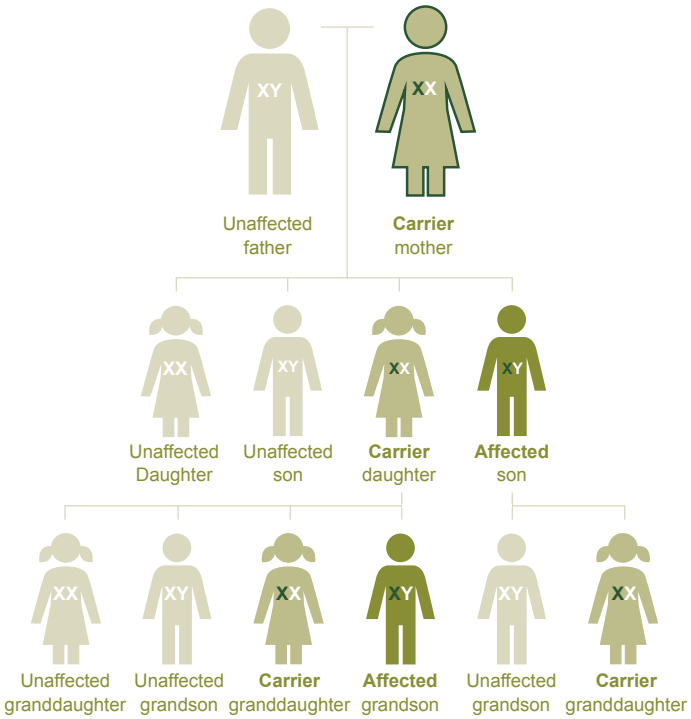

FIGURE 1. Inheritance pattern of X-linked hyper IgM syndrome with a carrier mother

As can be seen from Figure 1, women who are carriers of an X-linked disorder, such as X-linked hyper IgM syndrome, have with each pregnancy a 25% chance of having an unaffected (non-carrier) daughter, a 25% chance of having an unaffected son, a 25% chance of having a carrier daughter like themselves, and a 25% chance of having a son affected with the disease (**Figure 1**).

A man with X-linked hyper IgM syndrome will pass the defective gene to all of his daughters, who will be carriers, while none of his sons will be affected as he cannot pass an X-linked gene to his sons because males always pass their Y chromosome to male offspring (**Figure 2**).

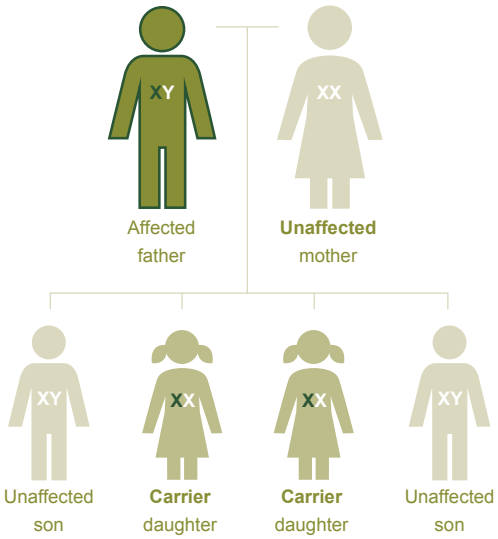

FIGURE 2. Inheritance pattern of X-linked hyper IgM syndrome with an affected father

For autosomal recessive hyper IgM syndrome, two abnormal copies of the gene, one from each parent, must be inherited to cause symptoms of the condition. Usually, parents of the affected child each carry one copy of an abnormal gene and are unaffected themselves because of the normal functioning of the other gene. If both parents are carriers of an abnormal autosomal recessive gene, this leads to a 25% chance (1 in 4) that any offspring, irrespective of gender, will be affected by the disorder. There is a 50% chance (1 in 2) that the offspring will be a carrier (have one abnormal gene), and a 25% (1 in 4) that the baby will not inherit the faulty gene from either parent, and therefore will not be affected by the condition or be able to pass it on to their children (**Figure 3**). Since the autosomal recessive forms of hyper IgM syndrome require that the gene on both chromosomes be affected, they are less frequent than the X-linked conditions.

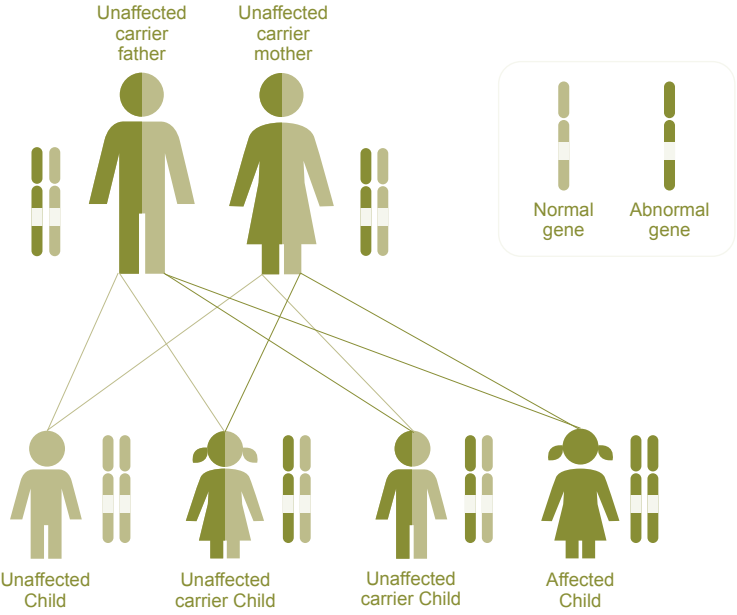

FIGURE 3. Inheritance pattern of autosomal recessive hyper IgM syndrome with a carrier mother and a carrier father

If the precise mutation in the affected gene is known in a 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 of the hyper IgM syndromes will allow initiation of treatment prior to the development of long-term consequences of serious infections.

CLINICAL PRESENTATION OF HYPER IGM SYNDROMES

Most persons with hyper IgM syndrome develop clinical symptoms during the first or second year of life. The most common issue across all hyper IgM syndromes is an increased susceptibility to infection including recurrent upper and lower respiratory tract infections. The most frequent serious infectious agents are bacteria, but viral illnesses are also common and severe.

In persons with X-linked and autosomal recessive hyper IgM syndrome due to a CD40 defect a variety of other microorganisms can also cause serious infections. For example, Pneumocytis jiroveci (*carinii*) pneumonia, an opportunistic fungal infection, is relatively common during the first year of life of infants with hyper IgM

syndrome and may be an early clue that the child has the disorder. Viruses such as Cytomegalovirus and fungi such as Cryptococcus may also cause lung infections. Gastrointestinal symptoms, most commonly diarrhoea and malabsorption, also commonly occur in X-linked hyper IgM syndrome or CD40 deficiency. One of the major organisms causing gastrointestinal symptoms in these infants is *Cryptosporidium*, which may cause sclerosing cholangitis, a severe liver disease. Long-term liver inflammation caused by viruses such as Cytomegalovirus, Hepatitis B and Hepatitis C can lead to chronic hepatitis. Additionally, severe liver damage, known as cirrhosis, may occur in some individuals. This damage could become so severe that it might lead to liver failure or serious issues with bile flow, requiring a liver transplant.

Low white blood cell count (neutropenia) occurs in about half of people with hyper IgM syndrome, either transiently or persistently, and severe neutropenia is often associated with oral ulcers, proctitis (inflammation and ulceration of the rectum) and skin infections. People with hyper IgM syndrome may present with enlarged lymph nodes and hepatosplenomegaly, and autoimmune disorders may occur in those with X-linked hyper IgM syndrome or CD40 deficiency which may manifest as diabetes, chronic arthritis, low platelet count (thrombocytopenia), haemolytic anaemia, hypothyroidism, chronic uveitis, and kidney disease.

Hyper IgM syndrome can also be suspected in infants with features of ectodermal dysplasia (such as sparse hair and conical teeth) along with recurrent infections.

Finally, people with X-linked hyper IgM syndrome have an increased risk for cancer, particularly liver cancer and lymphoma. Neuroendocrine tumours can also occur.

DIAGNOSIS OF HYPER IGM SYNDROME

A diagnosis of X-linked hyper IgM syndrome should be considered in any boy presenting with severe recurrent respiratory infections or an opportunistic infection who also has hypogammaglobulinaemia (low or absent IgG and IgA and normal or elevated IgM) and positive family history or early death in male family members. The final diagnosis requires identification of a mutation affecting the CD40 ligand gene.

Diagnosis of autosomal recessive forms of hyper IgM syndrome can be suspected if a person has the characteristics of X-linked hyper IgM syndrome but is either a female and/or has a normal CD40 ligand gene with normal expression on activated T cells. The final diagnosis of autosomal recessive forms of hyper IgM syndrome also requires identification of a mutation in one of the genes known to cause these disorders.

WHAT TREATMENT IS SUGGESTED FOR HYPER IGM SYNDROME

The treatment of hyper IgM syndrome is directed toward the specific symptoms that are apparent in each individual. Treatment is likely to require the coordinated efforts of a team of specialists – possibly including a paediatrician, immunologist, haematologist and infectious diseases specialist to systematically and comprehensively plan treatment. Genetic counselling is recommended for affected individuals and their families, as is psychosocial support.

CONSERVATIVE TREATMENT: IMMUNOGLOBULIN SUBSTITUTION, ANTIMICROBIALS, GROWTH FACTORS

Since persons with all forms of hyper IgM syndrome have a severe IgG deficiency, they require regular Ig replacement therapy. This can be administered by direct infusion into the vein in an arm (intravenously) or just below the surface of the skin (subcutaneously). This therapy can be very helpful for all forms of hyper IgM syndrome as it markedly reduces the frequency of bacterial and viral infections and reduces the likelihood of developing lymphoid hyperplasia.

Since persons with X-linked hyper IgM syndrome or CD40 deficiency also have a marked susceptibility to *Pneumocystis jiroveci* (*carinii*) pneumonia, prophylactic treatment with trimethoprim-sulfamethoxazole should also be considered.

Persistent neutropenia may require granulocyte colony stimulating factor (G-CSF) therapy, especially if the person has infections, mouth sores or other complications associated with neutropenia. However, G-CSF treatment is only necessary in selected persons and long-term treatment with G-CSF is usually not recommended.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Some people with hyper IgM syndrome may also have defects in T-cell function and other aspects of their immune system and may not be fully protected from serious infections by Ig replacement therapy. For X-linked hyper IgM syndrome the infection with *Cryptosporidium parvum* can lead to chronic cholangitis and an increased risk for cholangiocarcinoma. The clinical literature suggests that haematopoietic stem cell transplantation (bone marrow or cord blood stem cell) can be considered for these people and offers a potential cure, although the long-term prognosis for these persons is not yet known.

LIVING WITH HYPER IGM SYNDROME

It is important to reduce the possibility that drinking water is contaminated with Cryptosporidium and families should contact their local water supply company to make sure the water is tested and safe. Bottled water is an alternative, as is boiled water or water filtered through a reverse osmosis process. Swimming in lakes or communal pools should be avoided. Some medical sources recommend that young children avoid daycare and preschool because children there are often sick, avoid contact with farm animals, and minimize contact with kittens and puppies.

People with hyper IgM syndrome should not receive live virus vaccines since there is a remote possibility that the vaccine strain of the virus may cause disease.

Boys with X-linked hyper IgM syndrome should undergo regular screening for liver disease and all persons with hyper IgM syndrome should be regularly monitored for autoimmune disorders and other complications at follow-up visits.

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FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

'Information presented within this leaflet is based on published literature at the time of production. The leaflet is intended to provide a broad overview rather than be a guide on clinical practice – for this, please consult the treatment guidelines in your country.'

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