

# **Hyper IgM syndrome: a review of immunological disorder.**

## **Introduction.**

The term “Hyper IgM syndrome” refers to a family of immunological disorders caused by various genetic mutations. Regardless of a particular type of disorder, the level of IgM becomes much higher than the level of other immunoglobulins. This results in immunodeficiency and susceptibility to infections.

## **Symptoms**

Symptoms of this disorder tend to manifest themselves very early (during first two years of life), usually in the form of various recurrent infections of respiratory tract (Immune Deficiency Foundation, 2012). Infants with Hyper IgM syndrome often suffer from a form of pneumonia, pneumocystosis, caused by yeast-like fungus *Pneumocystis jirovecii*. This form of pneumonia is also common among other people with weak immune system such as people with cancer, HIV/AIDS or those taking the immune suppressing medication. Gastrointestinal disorders are also very often. Low white blood cell count (neutropenia) is observed in approximately half of the patients. Enlargement of lymph nodes and tonsils, as well as enlarged liver and spleen are also seen very often.

## **Mechanisms**

All B cells initially produce IgM. Upon exposure to a recognized antigen, processed and presented with MCH II by CD4 T helper cells, healthy B cells undergo the class switching and start producing other antibodies. This is a part of normal adaptive immune response. If, however, B cells carry one of the mutations causing the Hyper IgM Syndrome, class changing becomes impossible and B cells keep expressing IgM resulting in its overproduction and low level of expression of other antibodies (IgA, IgB, IgE) that are required for effective immune response.

Only cells that undergo the class switching can differentiate into memory cells. IgM cells can't do it. On the next encounter with antigen there will be more memory B cells than naïve cells. Memory B cells have already undergone the affinity maturation so they will produce high affinity antibody. If class switching is not possible, no secondary response will be produced.

Seven types of Hyper IgM syndrome are currently known (Jesus et al., 2008). They differ by the nature of underlying genetic defect. The most common type 1 has a point mutation in gene *CD40LG* which results in the production of nonfunctional CD40 ligand protein (also known as CD154). As a result of this mutation, CD40LG protein is not capable of binding to the cell surface CD40 receptor, and T cell cannot tell B cell to switch classes (Allen et al., 1993; Lougaris et al., 2005). CD40LG gene is located on X-chromosome, and therefore this type of Hyper IgM deficiency is often referred to as X-linked one. This type of hyper IgM deficiency is found only in boys.

The problems leading to the lack of class switching can be caused by defects in both T and B cells. Class switching involves the formation of immunological synapse between primed antigen-bound B leukocyte and CD4+ T helper cell. One of the steps in the formation of immunological synapse involves activation of CD40 gene in B cells in response to the CD40LG and T cells cytokines. CD40 expression promotes differentiation of naïve B leukocyte into plasma cell. Proteins CD40 and CD40LG bind directly to each other in the synapse. If CD40 is mutated and unable to bind, or if it is not expressed, class switching becomes impossible and Hyper ImG syndrome develops. Type 3 hyper IgM syndrome is caused by mutation in CD40 gene which affects communication between B and T cells.

Other types of hyper IgM syndrome are much more rare and involve abnormalities of CD40 signal transduction pathway or DNA processes involved in class switching and somatic hypermutations. Type 2 is characterized by mutation in AICDA (Activation-Induced Cytidine Deaminase) gene. The product of this gene converts cytidine residues into uracils in DNA . This mutation also affect the switching of classes, but works on the level of B cells which are unable to undergo recombination required to change the heavy chain production (Revy et al., 2000). Type 4 syndrome affects recombination downstream of the AICDA gene. Type 5 syndrome involves mutation in gene UNG (Uracil DNA glycosidase, which eliminate uracil moieties from DNA).

## **Treatment**

Regular immunoglobulin replacement therapy helps to reduce the number of infections. Gammaglobulin transfusions help to keep the normal balance of antibodies. Generally observed infections are manageable and often treated with antibiotics. Preventive treatment with trimethoprim-sulfamethoxazole is often given due to a very high probability of developing the pneumonia caused by *Pneumocystis jirovecii*.

Bone marrow transplantation and cord blood stem cell transplantation were successfully used for the complete immune reconstruction, which opens a possibility of the complete cure. Transplant donors, however, should be closely matched or related to the patient for the success of the procedure (affected child's siblings are usually the best). Human leukocyte antigen (HLA) match should be close enough to avoid the transplant's rejection (Encyclopedia of Children's Health).

### **Conclusion**

Hyper IgM syndrome is caused by genetic mutations of genes involved in immune response and affects a very small part of population. It causes immunodeficiency and susceptibility to infections. Due to the progress in understanding of this condition, achieved in the recent years, it is now possible not only to manage the condition effectively, but also achieve a permanent cure in some cases.

## References:

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