Review Article

Hyper immunoglobulin-M Syndrome in children

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Abstract:

Introduction: Hyper immunoglobulin-M syndrome (HIGM) is a rare, x-linked recessive inherited disorder with Increased or normal serum IgM and decreased IgA, IgG and IgE and normal peripheral B cells. In this disease, we have defect in class switch recombination (CSR) and somatic hyper mutation that is caused by defects including the enzymes required for CSR and SHM. (SHM)

Methods: To update about HIGM, PubMed and Google Scholar database were searched for term, X linked Hyper IgM syndrome and CD40 ligand. In our first search, we received about 90 updated articles, and then we distributed these articles among the authors. After reading the articles and sharing together, finally 33 articles were selected that fully related to the topic as references.

Findings: In conclusion, HIGM is rare disease that starts early in life with lifelong recurrent attacks of various infections by a variety of symptoms, including lymph Adenopathy, vomiting, diarrhea, skin lesion and abdominal pain. Allogenic hematopoietic cell transplantation and BMT can be effective in these patients.

Conclusion: In conclusion, HIGM is rare disease that starts early in life with lifelong recurrent attacks of various Infections by a variety of symptoms, including lymphadenopathy, vomiting, diarrhea, skin lesions and abdominal pain. Allogenic hematopoietic cell transplantation and BMT can be effective in these patients.

Keywords: CD40 ligand, X linked hyper-IgM, Immune Deficiency Syndromes

Introduction:

Hyper Immunoglobulin-M syndrome (HIGM) is a rare, x-linked recessive inherited disorder with increased or normal serum IgM and decreased IgA, IgG and IgE and normal peripheral B cells (1). HIGM was initially described in 1960 (2). In 1974 the number of scientist of WHO due to IgM levels in These patients, called it hyper Immunoglobulin-M syndrome (3). In this disease, we have defect in class switch recombination (CSR) and somatic hyper mutation (SHM) that is caused by defects including the enzymes required for CSR and SHM. The classical form of HIGM occurs due to CD40L deficiency in 70% of total patients. Clinical symptoms in patients become apparent in the first year of life by sever ear, throat and lung infections that don't respond to antibiotics (4). As well as children can be suffered from pneumonia, upper respiratory tract, opportunistic infections, Chronic recurrent diarrhea or lower long-term oral ulcers, arthritis, hepatitis and malignant tumors of digestive and liver (5,6,7,8,9).

Methods:

To update about HIGM in children, PubMed and Google scholar database and up to date were searched for term, X linked hyper IgM Syndrome and CD40 ligand. In our first search, we received about 90 updated articles, and then we distributed these articles among the authors. After reading the articles and sharing together, finally 33 articles were selected that fully related to the topic and limited to the articles published in English-language journals as references. The qualitative results are presented here.

Findings:

1: Etiology and pathology

1. Hyper IgM syndrome can take several forms. The most important common x-linked recessive disease or type HIGM1 (XHIGM), which is CD40R gene disorder affects only males. Also NEMO syndrome or HIGM-ED is another form x-linked recessive HIGM1 that there is defect in NEMO gene. This form is Associated with Hypohidrotic Ectodermal dysplasia (2,10).

2. HIGM2 syndrome: HIGM2 syndrome is caused by multiple mutations in AICDA10 genes and affects both sexes. This mutation causes abnormal growth and differentiation B lymphocyte (5).

3. HIGM3 syndrome caused by a mutation in the CD40 gene that is clinically significant and it is not different from HIGM1 (7, 11).

4. HIGM4syndrome: In this type, serum Ig G has decreased. As a result of milder disease Compared HIGM1 syndrome occurs. Ultimate etiology HIGM4 syndrome is unknown (7, 13).

5. HIGM5 syndrome: It caused by a mutation in uracil N-Glycosylate (UNG) gene and inherited with Autosomal recessive (7, 12).

2: Epidemiology:

All forms of HIGM syndrome are rare. The estimated minimal incidence was nearly 1/1.030.000 In live birth and its frequency of CD40 ligand (CD40L) deficiency is 2/1.000.000 males (4).In Contrast to, there are a few reported cases of CD40(7,13,14,15) and uracil N-glycosylos (UNG) Deficiencies (16). As well as, a cohort study is investigated by Leewi and colleagues about prevalence of mutations

effectively. These genes are: Inducible co-stimulator molecule (ICOS), ICOS ligand (ICOSL), and if male, Brutontyrosine kinase (Btk) and SLAM-associated protein. They found mutations of CD40L in 98 males, AICD in 4 patients (3 males, 1 females), UNG in one adult male and Btk in 3 boys of the remaining 25 males, one infant with Hypohidrotic ectodermal dysplasia had a mutation of NEMO. None of residual 33 patients had alterations affecting CD40, ICOS, ICOSL or SH2D1 and are best classified as common variable immune deficiency (CVID). Although other genes not yet identified and may be affective (6).

3: Clinical figure:

Clinical figure of the HIGM syndrome depending on the nature of genetic mutation, such that CD40L and CD40 deficiencies are combined immune deficiencies, while AID and UNG deficiencies are humoral immune deficiency. Typically, patients with HIGM have chronic and recurrent infections of the lung and sinuses, which can be caused bronchiectasis pneumonia, sinusitis and otitis media (17). At first caused by encapsulated bacteria (4,8,18).In addition opportunistic infection are common and may occur in the first few months of life. In these patients chronic diarrhea lead to weight loss. Chronic diarrhea happens about in one-third of patients (2, 4, 19).Delayed growth and weight loss will be in Children. Some of these patients need TPN (total parenteral nutrition).Nodular lymphoid hyperplasia, inflammatory bowel disease, recurrent oral ulcers, gingivitis, skin infections,

3, perianal ulcers neutropenia, cellulitis, candida esophagitis,19-parvavirus infection, warts and molluscum have been reported in such patients (2,17,19,4,8,20,21). Diseases of the liver (including cirrhosis and carcinoma) and gastrointestinal tumors including. Another common clinical problem in these patients (4,22). Nervous system is affected by this disease because of meningoencephalitis disorder.as well as, they suffering from cognitive disorders and walking problems (4,6,23). In some patient osteomyelitis, hypothyroidism and general lymphadenopathy have been reported (2,5).

4: Laboratory finding:

Levels of serum immune oglobulins were measured at the time of diagnosis in which the median Value for IgG, IgA, IgM were 100 (range,0-320) mg/dl, 10 (range,0-270) mg/dl and 371.5 (range,27-850) mg/dl, respectively.

5: Diagnosis:

The diagnosis of HIGM syndrome due to mutation of CD40 gene is accomplished by inability of Peripheral blood B cells to express the CD40 molecule, as assessed by the binding of monoclonal Antibodies to CD40 in patients with profile suggestive of HIGM. If seen ten alarming sign of following, must see a doctor:

1. Getting at least 8 case of ear infections in one year
2. Getting at least 2 case of sinusitis in one year
3. Antibiotics has little effect, if you use drugs for at least 2 months.
4. Diagnosis of 2 cases of pneumonia in one year
5. Not having a normal weight and growth in a child
6. Risk of recurrent deep skin abscess

7. Persistent thrush infection in children over 12 months
8. Need for intravenous antibiotics to treat the infection in children
9. Diagnosis of primary immunodeficiency in other family members
10. Among children at least two deep infections, such as meningitis, osteomyelitis, sepsis, and cellulitis. Also, to diagnosis, we can use the finding of the family tree and evaluate the expression of molecules with flowcytometry method and the final outcome molecular genetic test of ligand gene (CD40) used (11, 24, 25, 26, 27).

6: Prevention and Treatment:

For prevention of early symptoms, recommended to full observance of hygiene, perfect care of their teeth disinfection and cleaning any cuts with antiseptic and water sanitation domestic consumption. Avoid crowded places, especially in the influenza season, the lack of use the vaccine is made from live Viruses noted (2, 8, 28).

Allogenic hematopoietic cell transplantation of cord blood stem cell or bone marrow transplantation (BMT) and administration of synthetic CD40 ligand are successful treatments (29, 30, 31, 32,33). Also IVIG and specific antimicrobial antibiotics for specific pathogen have been used in the treatment of established infections in patients with XHIGM syndrome. Using gene therapy to treat, is under consideration.

Conclusion:

In conclusion, HIGM is rare disease that starts early in life with lifelong recurrent attacks of various Infections by a variety of symptoms, including lymphadenopathy, vomiting, diarrhea, skin lesions and abdominal pain. Allogenic hematopoietic cell transplantation and BMT can be effective in these patients.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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