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Original Article

Multiple Types of Autoimmunity Resulting from the same *CD40 Ligand* Mutation

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Abstract

Background/Objectives: Hyper-immunoglobulin M (HIgM) syndrome is a primary immunodeficiency disease in which impaired immunoglobulin class-switch recombination causes normal or high levels of serum IgM versus low or undetectable serum levels of class-switched immunoglobulins.

Methods: The diagnoses of all patients with HIgM in familial cases were evaluated based on genetic testing. Since this syndrome can present with either infectious diseases, malignancies, or autoimmune diseases, all medical complications were recorded in the index patients and relatives.

Results: Surprisingly, the evaluation identified a family with 3 males suffering from CD40 ligand deficiency, and each one had different autoimmune manifestations, including Guillain-barre syndrome and pauciarticular and polyarticular juvenile rheumatoid arthritis.

Conclusions: Based on the results, it is hypothesized that other genetic modifying factors or environmental parameters affecting epigenetics may have a significant role in the presentation of autoimmunity in CD40 ligand deficiency.

Keywords Hyper-IgM syndrome, Autoimmunity, Familial aggregation, Guillain-barre syndrome, Rheumatoid arthritis

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Introduction

Hyper-IgM syndrome (HIgM) can be a primary immune disease (1), or it can be secondary to neoplasia, congenital rubella, or the use of anti-epileptic drugs (2-5). Among primary deficiencies, there are different underlying genetic defects such as X-linked (CD40L, NEMO), autosomal recessive (activation-induced cytidine deaminase; AIDS, Uracil-DNA glycosylase; UNG, CD40, MSH2, MSH6, INO80) (6, 7) or possibly autosomal dominant (terminal AIDS, PI3KCD, PI3KR1) (8, 9)

with impaired class-switching recombination (CSR) and/or somatic hyper-mutation.

Although chronic or recurrent infection is the main presentation of patients with class switch recombination (CSR) defect, autoimmunity is also a major complication, especially in patients with mutations in the *AID* and *NEMO* genes (10). HIgM patients may present with autoimmune arthritis, autoimmune hepatitis, autoimmune cytopenia, hypoparathyroidism, or immune complex nephritis (11, 12). Although CD40L mutation is commonly seen in HIgM, the occurrence of autoimmunity in these patients is rare; it seems that patients most frequently present with autoimmune neutropenia (13, 14). Regarding to other complications, a family was identified with 3 males suffering from X-linked HIgM representing different autoimmune manifestations including Guillain-barre syndrome and pauciarticular and polyarticular juvenile rheumatoid arthritis with the same mutation. The result of this clinical investigation may increase insight into the role of environmental and epigenetic factors in CD40L-deficient patients.

Materials and method

Clinical Evaluation

Informed consent for participation in this study was obtained from the patients and their parents in accordance with the principles of the Ethics Committee of Tehran University of Medical Sciences. Patient information was recorded on an evaluation sheet and included patient name, gender, date of birth, age at onset of symptoms, clinical symptoms, age at diagnosis, family history or consanguinity, previous history of medications and vaccinations, and laboratory and molecular data.

Immunological assays

Complete blood count, serum immunoglobulin levels, specific antibody production, lymphocyte subpopulations, and proliferation tests were counted according to standard methods. The CD40L signalling pathway was evaluated using a previously described method (15).

Exome sequencing and analysis

Whole exome sequencing (WES) was performed for the patients. The extracted genomic DNA was randomly fragmented, amplified by ligation-mediated polymerase chain reaction (PCR), and captured and sequenced according to the protocol of the manufacturer as described previously (16). After raw image file processing, sequences were generated and aligned to the human genome reference (UCSC hg 19 version; build 37.1) using the SOAP software (SOAP v.2.21) (17). Duplicated reads were filtered out, and only uniquely mapped reads were kept for subsequent analyses. The SOAPsnp software (v.1.03) was subsequently used with default parameters to assemble the consensus sequence and call genotypes in target regions (18).

Low-quality single nucleotide polymorphisms (SNP) that met one of the four following criteria were filtered out: a genotype quality of less than 20; a sequencing depth of less than 4; an estimated copy number of more than 2; and a distance from the adjacent SNPs of less than 5 bp. Small insertions/deletions (Indels) were detected using the GATK Unified Genotyper (GATK, v.1.0.4705) (19)

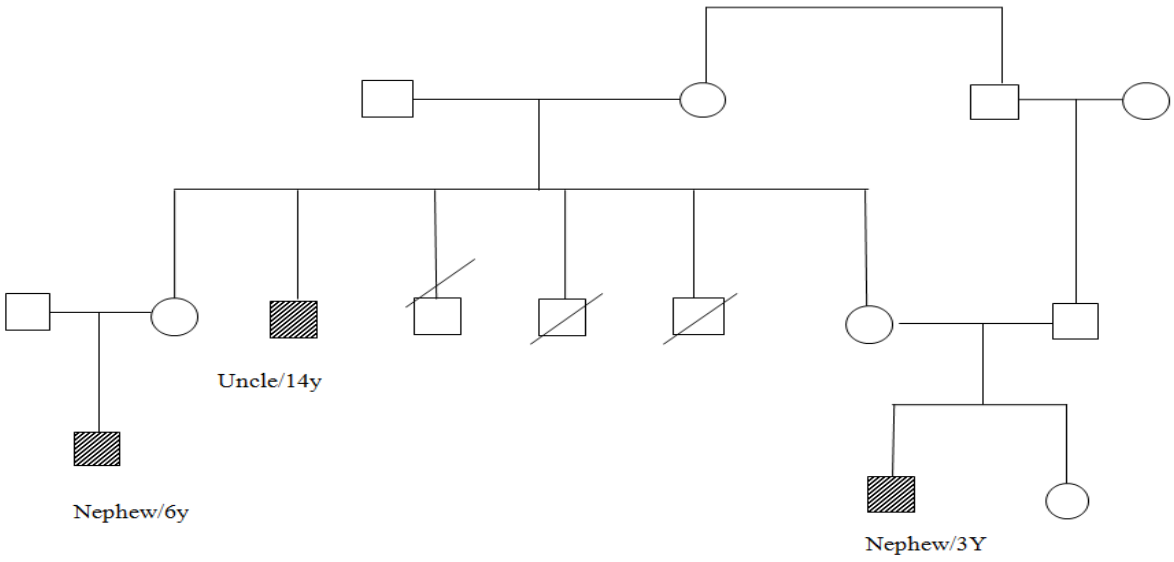
following the alignment of quality reads to the human reference genome using BWA (v.0.5.9-r16) (20). For analysis of WES, the protocol described previously for prioritizing candidate variants, predicting their effect on protein, homozygosity mapping, large deletion, and copy number variation detection was followed (16).

The pathogenicity of the disease-attributable gene variant was re-evaluated using the updated guidelines for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (ACMG), considering the allele frequency in the population database, computational data, immunological/functional data, familial segregation and parental data, and clinical phenotyping (21).

Results

CD40L is the most affected gene among HIgM patients registered in the national registry (21 out of 28 patients with a genetic diagnosis, 75%). Three of these 21 patients (14.2%) belonged to the index family (**Figure 1**). The proband from the index family was a 14-year-old boy who was diagnosed with HIgM at the age of 4 years. His parents were non-consanguineous, and 3 of his brothers had died from recurrent infections and liver problems. The patient had a history of recurrent infection before diagnosis. He had developed pneumonitis (4 times), parotitis, orchitis, sinusitis, and recurrent diarrhea when he was diagnosed with the disease. A complete blood cell count revealed a white blood cell (WBC) count of 10,000/ml with 30% neutrophil, 66% lymphocyte, and 2% eosinophil at the time of diagnosis. The serum concentration of immunoglobulins also showed IgG of 95 mg/dL and IgM of 360 mg/dL, but IgA was not detectable. After diagnosis, the patient received intravenous immunoglobulin (IVIG) regularly every month.

Figure 1. Pedigree of 3 patients with X-linked hyper-IgM syndrome associated with different autoimmune disorders



At age 7, he showed symptoms of pharyngitis and tonsil hypertrophy. At age 11, he presented to our center with sudden symmetrical weakness in the upper and lower limbs and ataxic gait. He did not mention any dysesthesia or paresthesia in his limbs, nor did he complain of blurry vision, dysphagia, respiratory distress, or urinary incontinency. On physical examination, the patient was found to be afebrile. His muscle force in distal upper and lower extremities had decreased, but the legs were more affected. Deep tendon reflex in the upper limbs was reduced to one, and the legs were unresponsive to reflex hammer blow, but the patient had no sensory loss. The patient did not mention any recent respiratory infection, diarrhea, vomiting, or urinary tract infection. His laboratory data showed a leukocyte count of 7,600/ml with 55% neutrophils. His urine analysis was normal and urine culture was negative. A cerebral spinal fluid collection through lumbar puncture was performed for the patient, and the results are demonstrated in **Table 1**. An electromyography was also done. The results indicated an axonal-type Guillain-barre syndrome, and the patient was given 40 grams of IVIG for 2 consecutive days. He improved and his symptoms disappeared. The patient was discharged after one week in a generally good condition.

Three months later, the patient presented again to our center with complaints of abdominal pain in the right upper quadrant associated with nausea and vomiting. The pain was worse at postprandial times. These symptoms had continued from the previous week. He also complained of massive non-bloody diarrhea from the previous day. In his physical exam, his vital signs were stable and he was not icteric. He had a leukocyte count of 7,000/ml with 56% lymphocytes. His liver enzymes were 15-fold higher than normal, and alkaline phosphate and gamma glutamyl transpeptidase (GGTP) were also higher than normal (**Table 1**). A stool exam revealed fecal occult blood of 2+ and infection with Blastocystis hominis. An abdominal ultrasonography showed mild dilation of the intrahepatic biliary ducts and dilation and thickness of the gallbladder. It also showed cholangitis and constriction of ducts which were consistent with hydrops of the gallbladder. The patient was treated conservatively and referred for an elective cholecystectomy.

Two nephews of the proband were also diagnosed as having HIgM syndrome. The first nephew was a 5-year-old boy who was referred to our department at the age of 11 months with swelling and pain in the right hip, left ankle, and right wrist. He also mentioned a history of recurrent respiratory infections and diarrhea. One month later he presented with bilateral and symmetrical arthritis of the same joints. The affected joints had limited movements, and he had no fever or any other constitutional symptoms. The patient's tonsils were smaller than normal, and no lymphadenopathy was detected. He had no signs of skin rashes or eye involvement. Based on immunoglobulin titers and his positive family history, the patient was diagnosed with HIgM, and he was also included in the diagnostic criteria for polyarticular juvenile

idiopathic arthritis (JIA). Thus, prednisolone was initiated as the main treatment for his JIA, and he was also placed on IVIG treatment (**Table 1**).

The second nephew of the proband was a 3-year-old boy whose parents were first-degree relatives. He presented to our department at the age of 1 year with fever and recurrent non-bloody diarrhea. He also had a history of three admissions to the hospital for sinopulmonary infections during the previous 6 months. The measurement of immunoglobulins indicated IgM of 83 mg/dl, IgA of 2, and IgG of 47 mg/dl. The patient was also diagnosed with HIgM and placed on treatment. At age 3 years, he was referred to our hospital for pain and swelling of wrists and ankle joints from 2 weeks prior to this visit. There was no deformity in his joints, but a mild swelling of the soft tissue with no tenderness was observed in his ankles and wrists. Based on the laboratory data, he was also diagnosed with pauciarticular-onset JIA and placed on prednisolone and 3 high doses of IVIG for treatment; his symptoms gradually improved. A genetic analysis of all of the patients was performed, and the results showed a known mutation in the *CD40L* gene within exon 5 of the TNFH domain of the protein, at c.499 G>C (p.G167R).

Table 1. Auto-antibody titers, liver enzymes, and cerebrospinal fluid analysis (CSF) for the index patient

Parameters	**Results**
Volume of CSF, ml	50
Lactate of CSF, mg/dl	11
Glucose of CSF, mg/dl	45
Protein of CSF, mg/dl	22
WBC of CSF/ul	1
RBC of CSF/ul	228
Direct smear of CSF	Neg
CSF culture	Neg
Aspartate aminotransferase, IU/L	615
Alanine aminotransferase, IU/L	568
Alkaline phosphatase, IU/L	1308
Gamma-glutamyl transferase, IU/L	285
IgM, mg/dL	34
IgA, mg/dL	6
IgG, mg/dL	0
Anti-nuclear antibody (ANA), IU/ml	Neg
Rheumatoid factor (RF), IU/ml	Neg
Anti-cyclic citrullinated peptides (CCP), IU/ml	Neg
Smooth muscle antibody (SMA), IU/ml	Neg
Anti-neutrophil cytoplasmic antibodies (ANCA), IU/ml	Neg
Anti-liver-kidney microsomal type 1 (LKM1), IU/ml	Neg

Discussion

One major type of autoimmunity with c.499 G>C (G167R) mutation is a different type of autoimmune arthritis. About 9% of HIgM patients develop arthritis during their lifetimes (22). Most cases are affected by polyarthritis, but monoarthritis, oligoarthritis, tenosynovitis, subcutaneous nodules, and periarticular masses can be seen (23-25). There are a lot of hypotheses about the mechanism of

autoimmunity and arthritis in HIgM patients. CD40 receptors which are on B cell surfaces can also be revealed on cells like macrophages, endothelial cells, fibroblasts, and other cells in inflamed joints (26). Unlike the activation of B cells which is exclusively dependent on CD40-40L interaction, these cells can be activated by other stimuli, like TNF-α (27). Based on these observations, some scientists believe that infections and unregulated cytokines in CD40L patients can activate cells other than B cells, like fibroblasts, macrophages, endothelial cells, and osteoclasts, which can represent inflammatory arthritis. Some others believe that the interaction between CD40 and CD40L has a protective and regulatory role in immune responses to autoantigens (26). Recently, a new model suggested that infections can affect thymus function and induce autoreactive T cells, which can cause arthritis in mice (28).

Although some physicians refer to this disease as rheumatoid arthritis, there are a lot of reasons that arthritis in HIgM patients is different from classic idiopathic RA. First of all, the rheumatoid factor (RF) is usually negative in HIgM patients in contrast with RA patients (23-25). It is thought that CD40-40L interaction is essential for the production of this autoantibody, and the absence of this interaction leads to RF negativity in these patients (23). Secondly, a biopsy of the synovial membrane shows synovial hyperplasia and capillary proliferation without lymphocytic or polymorphonuclear infiltration. B cells and plasma cells can rarely be seen, while there are a lot of CD8+ T cells. In contrast, B cells and CD4+ T cells are the main cells in the synovial fluid of classic RA patients (29-31). Thirdly, the HLA findings are incompatible with those of RA patients; for example, HLA A1, B8, and DR3 are more common in HIgM patients than HLA DRB1*04 and DRB1*01 (29, 32).

There are many hypotheses about the factors involved in autoimmune diseases in HIgM which may interpret the autoimmune neurologic disorders as being Guillain-barre syndrome in the proband. Interactions of CD40 L and Fas L with B cell receptors can propel these cells to maturation or elimination (33). Hervé et al. have suggested that impaired peripheral B cell tolerance can be seen in CD40L deficient patients (34). In fact, CD40L on T cells and MHC II are essential in suppressing autoreactive mature naïve B cells which express antibodies with highly positively charged IgH CDR3s. It is suggested that central B cell checkpoints are intact in both patients and the control group, but the peripheral elimination of autoreactive B cells is decreased due to impaired regulatory T system and B-cell activating factor (BAFF) accumulation. BAFF is a serum cytokine, high levels of which can be seen in autoimmune diseases; BAFF can act as an inhibitor in suppressing autoreactive B cells (35, 36).

Lacroix-Desmazes et al. also believe that the interactions of CD40-CD40L are essential modulators for the selection of autoreactive B cell repertoires (37). They found a significant bias in IgM autoreactivity in HIgM patients versus the normal activity of these immunoglobulins against foreign antigens. They have also suggested that the autoreactivity of the serum IgG of these patients does

not differ from that of the control group in the same concentrations.

Kumanogoh et al. studied the defects of T cells by transferring T cells from CD40-deficient mice to syngenic athymic (nude) mice. They observed that the rate of autoimmunity increased in these mice, while it stayed the same when the cells were from wild-type mice. They also noticed lower levels of $CD25^{+}CD45RB^{low}CD4^{+}$ subpopulations (which is essential in the regulatory T cell system) in CD40-deficient mice. Moreover, CD40-deficient antigen-presenting cells fail to provoke T regulatory cells, which this leads to T cell autoreactivity (38).

The proband also suffers from hydrops of the gallbladder associated with Blastocystis hominis infection; however, the probability of the role of autoimmune inflammation in this complication cannot be ruled out. It is evidenced that prolonged diarrhea in CD40L patients can be commonly caused by *Cryptosporidium parvum*, which also can be involved in cholangiopathy or liver cirrhosis (39, 40). Liver involvement seems to be severe in these patients and is estimated to be the cause of death of 75% of patients in the third decade of life (1). This infection can be transported from the bowels to the bile duct retrogradely or it can be transported to the liver by portal blood (41). Some studies have stated that the excessive proliferation of IgM-producing plasma cells can cause a kind of autoimmunity against the liver, gallbladder, and gastrointestinal tract in response to parasites in CD40L patients (42). It is suggested that primary biliary cirrhosis is more prevalent in these patients, which involves small and medium-sized intrahepatic bile ducts and leads to inflammation and progressive fibrosis due to remarkably high levels of pentameric IgM (43, 44). It is also distinguished with anti-mitochondrial auto-Abs (AMA) in about 90% of affected individuals (45).

Cellular immunity also has a role in the pathogenesis of this disease, as it has been found autoreactive T cells in the patients (46). This disease can be more common in HIgM patients due to the higher rate of infections seen in these patients, because their antigens can mimic the superficial antigens of biliary ducts (47, 48). Unfortunately, in our patient, the surveys were not completed to understand which one of the pathologies, autoimmunity, infection, or malignancy of ducts, was responsible for the hydrops of the patient's gallbladder.

Until 2011, the database of CD40L mutations causing X-linked hyper-IgM syndrome (X-HIgM) contained over 250 public entries about different known mutations of this gene (http://bioinf.uta.fi/CD40Lbase). Most of the detected mutations occur in the extracellular TNFH domain encoded by exon 5. It is noteworthy that there is no specific correlation between clinical presentations and the site of the mutation; in other words, each mutation can cause any manifestation of the disease (49). The gene mutation in our patients is a known missense mutation in exon 5, which is related to the TNFH domain of the CD40L. This gene mutation was reported to be responsible in other patients with tonsillar atrophy and low IgM levels but without autoimmunity (50). This comparison also

represents the role of epigenetics or environmental factors (like different infections) in the final manifestation of the disease.

Monthly treatments with IVIG and intravenous antibiotics (400–600 mg/kg/month) seem to be useful in decreasing the severity of infections and the related mortality, but they have failed to prevent autoimmune disorders (51). Recent studies have suggested that the autoimmunity of X-linked HIgM can be cured with bone marrow transplantation; unfortunately, however, the conditioning regimen can be toxic to the liver itself and can be fatal in patients who already have a liver complication of the disease (52, 53).

Conflicts of interest The authors declare that they have no conflicts of interest.

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