Original Article

Clinical Outcomes of a Cohort Study on Patients with CD40L Deficiency

Niloofar Razavi Khorasani, Saba Fekrvand, Arash Dooghaie Moghadam, Bobak Moazzami*

Abstract

Introduction: CD40 ligand (CD40L*)* deficiency is an X-linked form of hyper Immunoglobulin M syndrome (XHIGM), which is caused by mutations of *CD40L*gene*.* The aim of the present study was to investigate the clinical and molecular basis of this disorder with a long period of follow-up on an Iranian patients group.

Methods: Totally, 21 patients diagnosed with X-HIGM, who were referred to at Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran), and then were followed up, were enrolled in this retrospective cohort study. The medical and immunologic evaluations of patients were followed by mutation analysis to confirm the diagnosis.

Results: The median age of all participants was 7.50 (4.87-16.25) years old. The median age at the time of disease onset was 8.00 (6.00-13.50) months. Also, majority of patients showed their first manifestation before the age of 4 years old. The median age of diagnosis was 23.00 (12.50-48.00) months, with a median diagnostic delay of 9.00 (1.50-28.00) months.

Anemia was the most frequent hematologic manifestation, which was occurred in 71.4% of the patients. The median serum IgM concentration was 206 (82-335) mg/dL. Six patients had normal IgM levels, however, elevated IgM levels were observed in fifteen patients based on age-references. The mutation analysis among patients with the *CD40L* mutations revealed 15 missense, 5 frame shift-nonsense, and 1 splice-site mutation. Eight patients (38%) died in this study duration period. Respiratory infection such as pneumonia were the main cause of death in 5 patients.

Conclusions: Earlier diagnosis of X-HIGM may provide effective management and lead to patients' survival, and consequently better quality of life. Moreover, using whole-exome sequencing for detecting those patients with HIGM phenotype is strongly recommended in order to differentiate it from intrinsic humoral immunity defects and also to initiating the appropriate therapeutic procedures and management.

Keywords Primary immunodeficiency; Hyper-immunoglobulin M syndrome; Class switch recombination; Genetic diagnosis; Pneumonia.

* Corresponding author: Bobak Moazzami

E-mail: moazzami.bobak@gmail.com

Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran

Introduction

Hyper Immunoglobulin M syndrome (HIGM) is identified as a unique group of primary immunodeficiency disorders (PID) characterized by decreased or absent levels of serum switched immunoglobulins (Igs) and normal or increased levels of serum IgM (1). Mutations in several genes that are responsible for B cell signaling, class switch recombination (CSR), somatic hypermutation (SHM) and DNA repair mechanism are found to be involved in HIGM phenotype development, including cluster of differentiation 40 ligand (*CD40L*), *CD40*, nuclear factor-kappa-B essential modulator (*NEMO*), and activation-induced cytidine deaminase (*AICDA*) (2).

The most common form of HIGM syndrome is the X-linked HIGM(X-HIGM), with respect to mutations of the *CD40L* located at Xq26.3 and accounting for approximately 65–70% of all cases in Western cohorts (3). The frequency of this disorder occurrence among male subjects is estimated to be approximately 2:1,000,000 in the general population (4). In recent cohort study conducted on Iranian patient with HIGM, CD40L deficiency was accounted for 68% of the genetically diagnosed HIGM patients (5).

The CD40L protein is a type II integral transmembrane glycoprotein that is mainly presented by activated CD4$^+$T lymphocytes and is a member of tumor necrosis factor (TNF) family, which contains three main functional domains: intracellular, transmembrane and extracellular (6). Up to now, more than 120 unique mutations have been reported among X-HIGM patients mostly affecting the extracellular domain (http://structure.bmc.lu.se/idbase/CD40Lbas. Interactions between CD40L and CD40 [expressed by antigen-presenting cells (APCs) including B lymphocytes, monocytes, macrophages, and dendritic cells] is the first step for B cell growth and also CSR and SHM stimulation. This process results in the various Ig isotypes formation along with maturation of APCs, stimulating effector activities of macrophages, and antigen priming of T cells (7-9). Therefore, those patients with CD40L-deficiency have combined T- (cellular) and B-cell (humoral) immunodeficiency (10).

These patients were often present with respiratory and gastrointestinal tract infections and complications, increased susceptibility to opportunistic infections, and less commonly presented with autoimmune and inflammatory disorders along with malignancies (11, 12).

Due to the predominance of CD40L deficiency among diverse etiologies of HIGM syndrome, the purpose of this study was to determine the clinical outcomes of Iranian patients with CD40L deficiency.

Materials and methods

Study population

From 2001 to 2018, a total number of 21 patients diagnosed with X-HIGM, who were referred to at Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) and then were followed up, were included in the current retrospective cohort study (13, 14). The diagnosis of X-HIGM was made in terms of the newest criteria defined by the European Society of Immune Deficiencies (ESID) including low serum IgG (2 SD under age-related normal values in at least twice measurement) and normal or elevated serum IgM, exclusion of other hypogammaglobulinemia, also no evidence of Ataxia-telangiectasia, no evidence of profound T-cell deficiency, detecting mutation in *CD40L* gene along with at least one of the followings: increased susceptibility to infections, immune dysregulation, cytopenias, malignancy and affected family member (https://esid.org/Working-Parties/Registry-Working Party/Diagnosis-criteria). The ethics committee of Tehran University of Medical Science approved all of this study processes, and written informed consents were obtained from all participants or their parents or their legal guardians, before the study enrolment.

Data collection

A designed questionnaire was filled in order to retrospectively collect all information from the patients' medical records. These data consisted of demographic data, age at symptoms onset, age at diagnosis time, delay in diagnosis, the course of the disease, consanguinity, familial history, clinical manifestations, laboratory data

and mortality information. Accordingly, diagnostic delay was considered as the time between the symptoms onset and the diagnosis time. The course of the disease (follow up) was determined as the time period between diagnosis of the underlying PID and the date of either the patient's last visit or demise.

Genetic analysis

Genomic DNA was extracted from whole blood of the available patients for molecular diagnosis of the patients, and after that targeted Sanger sequencing for the *CD40L* gene was carried out in the patients, as described in earlier studies (15-17).

Statistical analysis

Statistical analysis was conducted using SPSS 21 software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were also applied to test the normality of data. Regarding quantitative data, central and descriptive statistics were reported. For variables with skewed distribution, median and interquartile ranges (IQR) were reported as data dispersion index. Analytical analyses were performed by the use of Mann-Whitney, and Chi-square or Fisher's exact tests. Moreover, *P value*<0.05 was considered statistically significant.

Results

Characteristics of studied patients

Totally, 21 male patients with a median age of 7.50 (4.87-16.25) years old, were included in this

study. Complementary data for demographic characteristics and clinical presentations of patients are displayed in **Table 1**.

Out of 21 patients, 12 of them (57.1%) had a history of consanguineous marriages. The median age at the time of disease onset was 8.00 (6.00-13.50) months. The first manifestations of the majority of patients were presented before the age of 4 years old. The median age of diagnosis was 23.00 (12.50-48.00) months, with a median diagnostic delay of 9.00 (1.50-28.00) months.

Laboratory and genetic findings

Neutropenia was found in 13 patients (61.9%) as shown in **Table 1**. Anemia was the most frequent hematologic manifestation, which was occurred in 71.4% (15 patients) of the total cohort. The median serum IgM concentration was 206 (82-335) mg/dL. Elevated IgM levels were observed in fifteen patients in terms of age, and also it is notable that six patients had normal IgM levels. Both serum IgG and IgA were uniformly decreased, and the median IgG and IgA levels were 76 (13-180) mg/dL and 9 (3-26) mg/dL, respectively. Other laboratory findings are summarized in **Table 2**.

Among patients with the *CD40L* mutations, we confirmed the mutations as followings: 15 individuals carry missense, 5 cases frame shift-nonsense, and 1 patient splice-site mutations. Among 21 patients with a molecular diagnosis, IgM levels were increased over the reference range of age-sex matched healthy controls in 15

of them (71.4%), and also normal one decreased in 6 (28.5 %) patients (**Table 1**).

Clinical presentations

All of the patients presented various forms of clinical manifestations of predominantly respiratory and gastrointestinal tracts, as their initial clinical presentation (**Table 3**). Sixteen patients (76.2%) indicated some signs of infection before their diagnosis. Lower respiratory tract infection was the most common presenting feature that was occurred in 17 patients (81%). Bronchiectasis was detected in 2 patients (9.5%), due to CT scan findings (P1, P6). Pneumonia was detected in 14 patients (66.7%). *Pneumocystis Carinii pneumonia* was isolated from two patients (P1, P7). Also, BCGosis occurred in one patient (P5), and the autoimmune disease was detected in 4 patients (P1, P3, P15, and P19). In patient 1, marked splenomegaly was detected at time of diagnosis and was accompanied with oral candidiasis, osteomyelitis and cholecystitis. Nine patients (42.9%) were found to have failure to thrive. Eleven patients (52.4%) experienced recurrent diarrhea during their disease course. In one patient with severe diarrhea, *Cryptosporidium parvum* was the isolated pathogen (P8). In another patient (P19), chronic prolonged diarrhea was caused by *Giardia lamblia*. Moreover, Tonsilar hypertrophy was recorded in three patients (P4, P11 and P21). Finally, no case of malignancy was observed among our patient population.

Table 1. Descriptive of patients with CD40 ligand deficiency

Patients	Gender	Current age (y)	DOO (m)	DOD (m)	Diagnostic delay (m)	Status (D/A)	Family history	Immunoglobulin levels			Type of mutation	Deleterious variants	Method
								IgG	IgA	IgM			
P1	M	35	0	53	53	D	+	0.0	0.0	84.0	Splice-site	Ivs1+2T>C	Targeted Sanger
P2	M	16	4	30	26	A	-	90.0	0.0	245.0	Frameshift-nonsense	p.T29fsX36	Targeted Sanger
P3	M	12	6	12	6	D	-	155.0	119.0	327.0	Frameshift-nonsense	p.D62fsX79	Targeted Sanger
P4	M	6	11	13	2	A	+	0.0	45.0	158.0	Frameshift-nonsense	p.S89TfsX6	Targeted Sanger
P5	M	6	6	15	9	A	-	150.0	22.0	152.0	Frameshift-nonsense	p.S89TfsX6	Targeted Sanger
P6	M	5	12	12	0	A	+	0.0	0.0	65.0	Frameshift-nonsense	p.S89TfsX6	Targeted Sanger
P7	M	23	8	76	68	A	-	225.0	27.0	278.0	Missense	p.T254M	Targeted Sanger
P8	M	5	6	30	24	D	+	240.0	10.0	75.0	Missense	p.Q186X	Targeted Sanger
P9	M	9	7	12	5	A	+	316.0	6.0	34.0	Missense	p.G167R	Targeted Sanger
P10	M	12	84	84	0	D	+	114.0	169.0	344.0	Missense	p.M360T	Targeted Sanger
P11	M	-	8	15	7	D	-	76.0	6.0	217.0	Missense	p.G252D	Targeted Sanger
P12	M	6	1	18	17	A	+	42.0	4.0	164.0	Missense	p.G167R	Targeted Sanger
P13	M	3	7	7	0	A	+	17.0	15.0	80.0	Missense	p.Q186X	Targeted Sanger
P14	M	3	7	7	0	A	+	22.0	9.0	157.0	Missense	p.Q186X	Targeted Sanger
P15	M	-	12	23	8	A	-	27.0	3.0	206.0	Missense	p.L81X	NGS-panel
P16	M	4.5	30	42	12	D	+	140.0	8.0	12.0	Missense	p.Q186X	Targeted Sanger
P17	M	4	8	43	35	D	-	206.0	26.0	763.0	Missense	p.G144V	NGS-panel
P18	M	-	15	16	1	A	-	76.0	6.0	217.0	Missense	p.G252A	Targeted Sanger
P19	M	40	84	300	216	D	-	550.0	70.0	650.0	Missense	p.G219R	Targeted Sanger
P20	M	17	59	69	10	A	+	9.0	22.0	850.0	Missense	p.G167R	Targeted Sanger
P21	M	14	6	36	30	A	-	2.0	3.0	360.0	Missense	p.L161P	Targeted Sanger

Abbreviation: D; dead, A; alive, DOO; date of onset, DOD; date of diagnosis, NGS; next generation sequencing

Table 2. Demographic and laboratory features of 21 CD40lignad deficient patients

Parameter	Results
Age at the time of the study, years, median (IQR)	7.50 (4.87-16.25)
Age at the onset of symptoms, months, median (IQR)	8.00 (6.00-13.50)
Age at diagnosis, months, median (IQR)	23.00 (12.50-48.00)
Delay in diagnosis, months, median (IQR)	9.00 (1.50-28.00)
Consanguinity, n (%)	12 (57.1)
Dead/alive/unknown, n (%)	7/13/1 (33.3/61.9/4.7)
Family history, n (%)	11 (52.4)
White blood count, cells/mL, median (IQR)	13700 (7800-24265)
Lymphocytes, cells/mL, median (IQR)	8816 (4666-16279)
Lymphocytes, %, median(IQR)	66 (52-75)
Neutrophil, cells/mL, median (IQR)	1836 (898-4900)
Neutrophil, %, median (IQR)	17.5 (9.2-29.2)
CD3, cells/mm3, median (IQR)	5715 (1880-9848)
CD3, %, median (IQR)	63 (61.2-76)
CD4, cells/mm3 (IQR)	4093 (823-5253)
CD4, % (IQR)	38.0 (31.7-48.5)
CD8, cells/mm3, median (IQR)	2141.7 (898.9-3275.4)
CD8, %, median (IQR)	24 (15-33)
CD56, %, median (IQR)	5 (5-5)
CD16, %, median (IQR)	6.1 (3.5-8.5)
CD19, cells/mm3, median (IQR)	1469.9 (564.8-2808.9)
CD19, %, median (IQR)	18.0 (13.2-24.2)
CD20, %, median (IQR)	16.5 (8.2-27.7)
IgG, mg/dL, median (IQR)	76 (13-180)
IgA, mg/dL, median (IQR)	9 (3-26)
IgM, mg/dL, median (IQR)	206 (82-335)
IgE, IU/mL, median (IQR)	3 (1-7)

Abbreviation: IQR; inter quartile range, Ig; Immunoglobulins, CD; Cluster of Differentiation, N; count

Follow-up and survival analysis

Patients were followed-up for a median period of 70 months (range, 12-189 months). Eight patients (38%) died during this study period. Respiratory infections such as pneumonia were identified as the main cause of death in 5 patients. The Kaplan Meier survival curve for all patients is indicated in **Figure 1**.

Discussion

The present study purpose was to provide the clinical, immunological, and molecular profiles of 21 Iranian patients diagnosed with CD40L deficiency. The genetic analysis provides an extensive variety of CD40L gene mutations described in the present series. Generally, the diagnostic delay was relatively lower in our series in comparison with previous studies and this may be caused by recent significant improvement in diagnostic techniques and obtaining greater

understanding of PIDs among physicians in the country (18, 19).

Normal levels of serum IgM was detected in 6 patients, while serum IgA and IgG were normal

for age in 3 and 3 patients, respectively. Interestingly, normal levels of serum IgA were also identified among patients with CD40L mutation.

Table 3. The frequency of different organ involvement of 21 CD40 lignad deficient patients

Organs	Results, n (%)
Respiratory tract	18 (85.7)
Hematologic	17 (80.9)
Gastrointestinal	12 (57.1)
Neurodevelopmental	8 (38)
Urinary tract	5 (23.8)
Rheumatoid	5 (23.8)
Endocrine	2 (9.5)
Musculoskeletal	4 (19)
Cardiovascular	2 (9.5)
Ophthalmologic	3 (14.2)
Abbreviations: N; count	

This finding may propose the involvement of underlying molecular mechanisms instead of CD40L in the regulation of class switching (20, 21).

In the majority of our HIGM patients, clinical manifestations were developed within the first 2 years of life. Complications including recurrent respiratory infections, hematologic and gastrointestinal manifestations were observed in almost all of the patients with the ages under 10 years old. After the initiation of the IVIG replacement therapy, these infections rate was significantly decreased. However, chronic pulmonary complications including bronchiectasis had developed in two patients. The delay in diagnosis and late administration of IVIG therapy may be associated to these complications developing (22).

It should be noted that lower respiratory tract infection was the most common pulmonary manifestations found in the majority of these patients. Also, the most frequent etiology of pneumonia in HIGM patients is caused by an opportunistic infection known as *Pneumocystis jiroveci, however, P. jiroveci was found in two patients.*

Although identifying the pathogenic microorganisms responsible for infections should be performed for any patients with recurrent infectious manifestation, this was not feasible in our study partly because of patients lost to follow-up along with lack of precision and cost-effectiveness of conventional microbiologic methods as well as empirical antibiotic treatment that could lead to false-negative results.

 Neutropenia was identified as the most common

presenting feature of hematological manifestations reported in 21 patients of our study population. Most of these cases had concomitant gastrointestinal mucosal involvement like oral, rectal, and esophageal ulcers along with neutropenia. The interactions between CD40:CD40L plays a crucial role in production of granulopoiesis-promoting factors (23). Therefore, a defect exhibited in CD40L signaling pathway may be associated with impaired neutropenia, and also displayed lesions among CD40Ldeficient HIGM cases (24). It should be noted that identifying neutropenia in a patient with HIGM phenotype, should prompt the evaluation for CD40L mutation analysis.

In regard with gastrointestinal manifestation in CD40L deficiency, the role of opportunistic infection responsible for chronic diarrhea including cryptosporidium infection should take into account.

Figure 1. The survivals function of patients after diagnosis
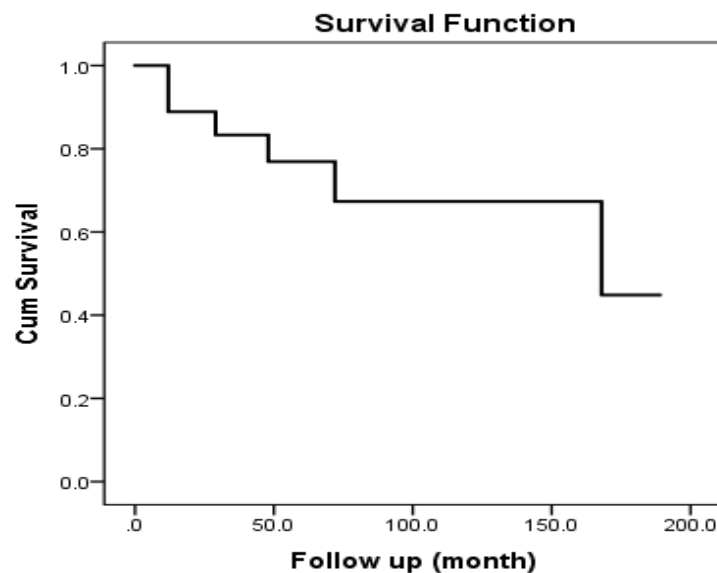
Although this microorganism was isolated in only one patient, its incidence rate could be accurately measured in our survey. The reason for this low number of diagnosed patients with these organisms may be caused by lack of systematic evaluation for such infection. On the other hand, the rate of gastrointestinal manifestation was observed only in half of the CD40L deficient cases, suggesting a sufficient defensive mechanism owing to the presence of IgM antibodies, even in absence of the somatic hypermutations.

The most common etiology for mortality was with respect to the pneumonia in our series, which is consistent with earlier reported surveys (21, 25). The main reason for these severe adverse outcomes and higher mortality rate in our patients may be partly due to socio-economic and environmental factors, also along with inadequate awareness of physicians of its importance of earlier detection and management of such disorders to minimize irreversible complication.

In conclusion, earlier diagnosis of this disorder may provide effective management and enable physicians for performing hematopoietic stem cell transplantation in those individuals with cellular immunodeficiency, collectively resulted in patients' survival, and consequently better quality of life. Moreover, using whole-exome sequencing for detecting those patients with HIGM

phenotype is strongly recommended for initiating the appropriate therapeutic procedures and management.

Disclosure Statement: The authors declare no conflicts of interest in regard with this study.

References

1. Etzioni A, Ochs HD. The hyper IgM syndrome—an evolving story. Pediatric research. 2004;56(4):519.

2. Leven EA, Maffucci P, Ochs HD, Scholl PR, Buckley RH, Fuleihan RL, et al. Hyper IgM syndrome: a report from the USIDNET registry. Journal of clinical immunology. 2016;36(5):490-501.

3. Allen RC, Armitage RJ, Conley ME, Rosenblatt H, Jenkins NA, Copeland NG, et al. CD40 ligand gene defects responsible for X-linked hyper-IgM syndrome. Science. 1993;259(5097):990-3.

4. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine. 2003;82(6):373-84.

5. Delbari MT, Cheraghi T, Yazdani R, Fekrvand S, Delavari S, Azizi G, et al. Clinical Manifestations, Immunological Characteristics and Genetic Analysis of Patients with Hyper-Immunoglobulin M Syndrome in Iran. International archives of allergy and immunology. 2019:1-12.

6. Hollenbaugh D, Grosmaire L, Kullas C, Chalupny NJ, Braesch-Andersen S, Noelle R, et al. The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity. The EMBO journal. 1992;11(12):4313-21.

7. Noelle RJ, Roy M, Shepherd DM, Stamenkovic I, Ledbetter JA, Aruffo A. A 39-kDa protein on activated helper T cells binds CD40 and transduces the signal for cognate activation of B cells. Proceedings of the National Academy of Sciences. 1992;89(14):6550-4.

8. Miga A, Masters S, Gonzalez M, Noelle R. The role of CD40-CD154 interactions in the regulation of cell mediated immunity. Immunological investigations. 2000;29(2):111-4.

9. Noelle RJ. CD40 and its ligand in host defense. Immunity. 1996;4(5):415-9.

10. Tsai H-Y, Yu H-H, Chien Y-H, Chu K-H, Lau Y-L, Lee J-H, et al. X-linked hyper-IgM syndrome with CD40LG mutation: two case reports and literature review in Taiwanese patients. Journal of Microbiology, Immunology and Infection. 2015;48(1):113-8.

11. Yazdani R, Fekrvand S, Shahkarami S, Azizi G, Moazzami B, Abolhassani H, et al. The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clinical Immunology. 2018.

12. Qamar N, Fuleihan RL. The hyper IgM syndroms Clinical reviews in allergy & immunology. 2014:46 (2):120-30.

13. Chavoshzadeh Z, Mahdaviani SA, Momen T, et al. Fourth Update on the Iranian National Registry of Primary Immunodeficiencies: Integration of Molecular Diagnosis. Journal of clinical immunology. 2018;38(7):816-32.

14. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. Journal of clinical immunology. 2014;34(4):478-90.

15.   Miller S, Dykes D, Polesky H. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic acids research. 1988;16(3):1215.

16. Abolhassani H, Chou J, Bainter W, Platt CD, Tavassoli M, Momen T, et al. Clinical, immunologic, and genetic spectrum of 696 patients with combined immunodeficiency. Journal of Allergy and Clinical Immunology. 2018;141(4):1450-8.

17. Abolhassani H, Aghamohammadi A, Fang M, Rezaei N, Jiang C, Liu X, et al. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. Genetics in Medicine. 2019;21(1):243.

18. Tang WJ, An YF, Dai RX, Wang QH, Jiang LP, Tang XM, et al. Clinical, molecular, and T cell subset analyses in a small cohort of Chinese patients with hyper-IgM syndrome type 1. Human immunology. 2014;75(7):633-40.

19. Ouadani H, Ben-Mustapha I, Ben-ali M, Ben-khemis L, Largueche B, Boussoffara R, et al. Novel and recurrent AID mutations underlie prevalent autosomal recessive form of HIGM in consanguineous patients. Immunogenetics. 2016;68(1):19-28.

20. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, et al. Clinical spectrum of X-linked hyper-IgM syndrome. The Journal of pediatrics. 1997;131(1 Pt 1):47-54.

21. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine. 2003;82(6):373-84.

22. Davies EG, Thrasher AJ. Update on the hyper immunoglobulin M syndromes. British journal of haematology. 2010;149(2):167-80.

23. Hirbod-Mobarakeh A, Aghamohammadi A, Rezaei N. Immunoglobulin class switch recombination deficiency type 1 or CD40 ligand deficiency: from bedside to bench and back again. Expert review of clinical immunology. 2014;10(1):91-105.

24. Mavroudi I, Papadaki V, Pyrovolaki K, Katonis P, Eliopoulos AG, Papadaki HA. The CD40/CD40 ligand interactions exert pleiotropic effects on bone marrow granulopoiesis. Journal of leukocyte biology. 2011;89(5):771-83.

25. Rawat A, Mathew B, Pandiarajan V, Jindal A, Sharma M, Suri D, et al. Clinical and molecular features of X-linked hyper IgM syndrome-An experience from North India. Clinical immunology (Orlando, Fla). 2018;195:59-66.