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Clinical and Laboratory Findings in Hyper-IgM Syndrome with Novel *CD40L* and *AICDA* Mutations

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Abstract
Background Hyper-immunoglobulin M (HIGM) syndromes are a heterogeneous group of primary immunodeficiency disorders, characterized by recurrent infections associated with decreased serum levels of immunoglobulin G (IgG) and IgA and normal to increased serum levels of IgM. These patients have immunoglobulin class switch recombination defects, caused by mutations in several genes.
Methods In order to investigate clinical and immunological manifestations of HIGM in Iran, 23 Iranian patients with an age range of 5 months to 35 years, who were followed up over a period of 17 years, were studied. Fourteen of the 23 patients were screened for *CD40L*, *AICDA*, *UNG*, and *CD40* gene mutations, using polymerase chain reaction followed by direct sequencing.
Results All patients, except one, initially presented with infectious diseases; the most common manifestations were respiratory tract infections. Six different *CD40L* mutations were identified, five were novel, one splicing (IVS1+2T>C), three missense (T254M, G167R, L161P), and two frame shift deletions (T29fsX36 and D62fsX79). In addition, one novel *AICDA* mutation (E122X) was detected. No mutation was found in six out of 14 analyzed patients.
Conclusion *CD40L* mutations comprise the most common type of immunoglobulin class switch recombination defects. There are several patients with HIGM phenotype, in which the underlying genetic defects remain to be identified. Other defects such as those in components of the mismatch repair mechanism could be potential candidates for the latter.

Keywords Hyper IgM syndromes · *AICDA* · *CD40L* · mutations · infection

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Introduction

Hyper-immunoglobulin M (HIGM) syndromes or immunoglobulin class switch recombination (Ig-CSR) deficiencies are a heterogeneous group of primary immunodeficiency disorders, characterized by recurrent infections associated with decreased serum levels of IgG, IgA, and IgE and normal to increased serum levels of IgM [1, 2]. Defects in Ig-CSR have previously shown to be caused by mutations in the genes encoding CD40 ligand (*CD40L*) [3, 4], CD40 (*CD40*) [5, 6], activation-induced cytidine deaminase (*AICDA*) [7], and uracil-DNA glycosylase (*UNG*) [8].

Mutations in the gene encoding the CD40 ligand molecule, which result in X-linked hyper-IgM syndrome (X-HIGM) [9], is the most frequent variant of Ig-CSR deficiencies and is generally associated with reduced somatic hyper-mutation (SHM) in the Ig variable (V) region [10].

Mutations in the *CD40* gene lead to an autosomal recessive form of disease, phenotypically similar to X-HIGM [6]. Defects in the genes encoding the AICDA and UNG result in autosomal recessive HIGM, which are associated with impairment of both CSR and SHM [11–13]. There are several HIGM cases where no mutation has been detected in the described genes [14]. Components of the mismatch repair mechanism could be potential candidates, as mutations in *PMS2* have recently been reported in three patients [15].

In this study, we reviewed the clinical features of Iranian patients with HIGM and described the molecular defects in the selected cases.

Patients and Methods

Subjects

Twenty-three patients with HIGM, whom were diagnosed or referred to Children's Medical Center during 1993–2009, were enrolled in this study. The criteria for diagnosis of HIGM were low serum IgG and IgA [≤2 standard deviation (SD) below normal values for age], normal or elevated IgM, and recurrent or severe infections. Informed consent was obtained from all patients, and blood was collected under institutional guidelines. Clinical and laboratory data on each patient was obtained using a designed questionnaire. We also studied 244 ethnically matched controls for the found mutations.

Methods

Serum immunoglobulin levels were determined by nephelometry (Behring Nephelometer, Behringwerke, Marburg, Germany) and lymphocyte subpopulations by flow cytometry (Partec PAS, Münster, Germany) at the time of diagnosis.

Genomic DNA was extracted from whole blood by the conventional salting out method. The polymerase chain reaction (PCR) was carried out using primers encompassing each exon/intron boundary of the *CD40L* [16]. In the absence of any *CD40L* mutation, the patients were analyzed for the mutations of *CD40*, *AICDA*, and *UNG* [6, 11]. The PCR products were resolved in a 1% agarose gel, and specific bands were excised using a sterile scalpel. The PCR products from agarose slices were purified using PCR purification kit-QIAquick Gel extraction Kit (Qiagen) and sent for direct sequencing (Macrogen, Seoul, Korea).

Statistical Analysis

Data analysis was done using the SPSS statistical software (version 15; SPSS Inc., Chicago, IL). Diagnostic delay was considered as the time between the onset of symptoms and the age of diagnosis. Follow-up time was counted as the time between the diagnosis and either the date of death or of the last visit. Probabilities of survival after diagnosis of HIGM were estimated via Kaplan–Meier life tables.

Results

Characteristics of Patients

In this study, a total of 23 patients (19 male and four female), aged 1–32 years, were included. Demographic and clinical data of patients are presented in Table I. The parents of eight (35%) patients were first cousin consanguineous.

The median age at the time of disease onset was 1 year (range, 0.5–9 years) in which 15 (65%) patients showed their first manifestation before 1 year of age. The median age of diagnosis was 5 years (range, 1–25 years), with a median diagnostic delay of 2.7 years (range, 1 month to 18 years).

Clinical Presentation

Twenty-two patients (96%) presented with various forms of infections, mainly in the respiratory and gastrointestinal tracts, as the first clinical manifestation. In one patient (P7), although he was initially asymptomatic, a diagnosis was made based on family history of immunodeficiency in his uncle (P3).

All patients experienced chronic and recurrent infections, particularly involving the respiratory and gastrointestinal systems, during the course of the disease (Table II). Chronic otitis media resulting in permanent hearing loss developed in two patients (P8 and P17) before a diagnosis was made. Bronchiectasis was detected in three patients (P9, P13, and P18), with recurrent pneumonias and long diagnostic delays. One patient (P3) primarily experienced severe pneumonia, occurring at 5 years of age, and the diagnosis of HIGM was made following hospitalization and identification of *Pneumocyctis jiroveci*, as the etiologic agent.

Protracted or recurrent diarrhea was present in 14 patients. *Cryptosporidium parvum* was the isolated patho-

Table I Descriptive Data of Patients with Hyper IgM Syndromes

Number	Gene	Status	Sex	Consanguinity	Current age (years)	Onset age	Diagnosis age	Immunoglobulin levels at diagnosis (mg/dl)			CD3 (%)	CD4 (%)	CD8 (%)	CD19 (%)	Neutropenia (ANC, cells/mm^3)
								IgG	IgA	IgM					
P1	*CD40L*	D	M	Yes	18	6 months	2 years 5 months	120	110	82	63.5	30.8	21.5	24.4	336
P2	*CD40L*	A	M	No	15	8 months	7 years	0	0	204	99	50	35	3	–
P3	*CD40L*	A	M	No	9	5 years 3 months	5 years 9 months	5	22	850	N/A	27	35	19	864
P4	*CD40L*	A	M	No	6	8 months	3 years 1 month	2	3	360	79	60	20	14.9	590
P5	*CD40L*	A	M	No	8	7 months	2 years 3 months	90	0	245	82	41	14	11	120
P6	*CD40L*	A	M	No	4	6 months	2 years 8 months	120	270	355	N/A	N/A	N/A	N/A	528
P7	*CD40L*	A	M	No	1	11 months	1 year	0	7	27	58.6	37.9	11.8	25.9	416
P8	*AICDA*	A	M	Yes	15	1 year	8 years	100	0	500	63.2	16	41.0	23.9	–
P9	No mutation	A	M	Yes	32	7 years	25 years	100	70	650	84	33	46	11	–
P10	No mutation	A	M	No	23	2 years	14 years	30	0	700	N/A	N/A	N/A	7.5	–
P11	No mutation	A	F	Yes	21	4 years	17 years	100	10	402	79	34	50	7	–
P12	No mutation	D	M	No	4	6 months	3 years	90	2	200	62	27	35	19	310
P13	No mutation	A	M	Yes	4	8 months	2 years	240	10	106	74	45	24	N/A	700
P14	No mutation	A	M	Yes	17	1 year	15 years	320	3	383	71.7	36.1	24.7	N/A	–
P15	N/A	A	M	No	9	1 year	3 years	112	48	230	N/A	N/A	N/A	N/A	–
P16	N/A	A	F	No	9	1 year	4 years	250	20	450	43	20	52	8.9	–
P17	N/A	D	F	No	18	9 years	17 years	310	10	400	N/A	N/A	N/A	N/A	–
P18	N/A	A	M	No	6	3 years	6 years	232	3	190	60	21.3	25	30	–
P19	N/A	A	M	No	18	1 year	12 years	100	10	385	65.2	18.4	41.8	5.8	–
P20	N/A	D	M	Yes	6	1 year	5 years	150	10	400	69.5	28.4	30.9	5.8	350
P21	N/A	D	M	No	15	2 years	7 years	44	0	470	48	22	16	18.7	472
P22	N/A	D	F	Yes	8	1 year	5 years	80	10	400	36.5	20.4	15.6	5.4	–
P23	N/A	D	M	No	3	6 months	2 years	100	65	320	84.4	41.5	45.7	6.4	–

A alive, *D* dead, *F* female, *M* male, N/A not assessed; ANC: absolute neutrophil count

Table II Clinical Manifestation of the Patients with Hyper IgM Syndromes

Number	Pneumonia	Otitis media	Sinusitis	Diarrhea	Oral ulcer	Lymphoreticular system involvement	Autoimmune disease and other manifestations
P1	3	10	–	5	2	Atrophic tonsils, hepatosplenomegaly	ITP, CAH
P2	2	1	11	1		Atrophic tonsils	BCGiosis
P3	4	–	2	10	–	Atrophic tonsils	ITP
P4	–	2	5	1	–	Atrophic tonsils	–
P5	3	3	–	–	–	–	Arthritis
P6	2	–	2	–	1	–	–
P7	–	–	–	–	–	Atrophic tonsils	Arthritis
P8	3	5	10	–	–	Hypertrophic tonsils, LAP	–
P9	4	3	12	6	–	–	–
P10	2	2	–	2	–	–	Growth hormone deficiency
P11	2	2	–	–	–	–	–
P12	3	4	5	–	1	–	–
P13	5	–	–	2	2	Atrophic tonsils, hepatosplenomegaly	–
P14	2	–	–	2	–	–	–
P15	2	–	–	–	–	–	Arthritis
P16	–	12	–	6	–	Hepatosplenomegaly	Ulcerative colitis
P17	2	3	6	6	–	Hepatosplenomegaly	AIHA, ITP
P18	6	–	8	–	–	Hepatosplenomegaly	Sclerosing cholangitis
P19	6	4	3	–	–	Hypertrophic tonsils, LAP	–
P20	–	–	6	4	2	–	–
P21	–	–	8	–	3	–	–
P22	4	–	–	4	2	–	–
P23	2	2	10	–	–	–	Arthritis
Total	18/23	13/23	13/23	12/23	7/23		–

ITP immune thrombocytopenic purpura, *CAH* chronic active hepatitis, *LAP* lymphadenopathy, *AIHA* autoimmune hemolytic anemia

gen in one patient (P3). In another patient (P4), severe protracted diarrhea was caused by *Giardia lamblia*.

Tonsils were atrophic in six patients, while tonsilar hypertrophy was observed in two patients (Table II).

Neutropenia (absolute neutrophil count of less than 1,000/mm^3) was observed in ten patients; seven of them had concomitant oral ulcers. Moreover, three patients (P1, P3, and P17) developed an episode of immune thrombocytopenic purpura during the course of disease; one of them (P17) also experienced episodes of hemolytic anemia (Table II). Growth hormone deficiency was detected in one patient (P10), with a history of malignancy in several members of his family [17].

Follow-Up and Survival

The patients were followed up after diagnosis for a median period of 6.5 years (range, 2–15 years); six subjects (26%) died during this period. The oldest survivor to date is 32 year-old man (P9), who is under regular intravenous immunoglobulin therapy. Respiratory infections were incriminated as the cause of death in four patients. The other causes of death were chronic hepatitis and pyogenic pericarditis. The survival curve for all patients is shown in Fig. 1. Post-diagnosis survival was estimated to be 80% for the first 3 years, which remains the same up to 8 years after diagnosis.

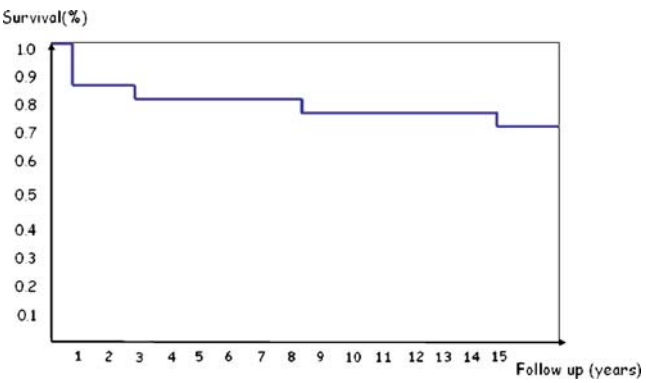

Fig. 1 Estimated probability of survival after diagnosis of HIGM

Laboratory Findings

Quantitative levels of serum immunoglobulins were measured at the time of diagnosis in which the median values for IgG, IgA, and IgM were 100 (range, 0–320) mg/dl, 10 (range, 0–270) mg/dl and 371.5 (range, 27–850) mg/dl, respectively.

Mutation Analysis

Mutation analysis was undertaken in 14 of 23 patients (13 families), in which seven patients showed a mutation in the *CD40L* gene and one patient had a novel mutation in *AICDA*. Table III summarizes the mutations, identified in individual patients. In the remaining six patients (P9–P14), we did not find any mutation in *CD40L*, *AICDA*, *UNG*, and *CD40* genes.

Among seven *CD40L* mutations, six were novel. Four patients (P2, P3, P4, and P7) showed missense mutations in the tumor necrosis factor homology (TNFH) domain. In the P2, c.817C>T created an amino acid change (T254M). P3 and P7 showed novel missense mutation c.499G>C (G167R) similar to the P4 who showed c.482 T>C (L161P).

P5 and P6 had deletions resulting in frame shift and premature stop codons, c.83delT (T29fsX36) and c.180-196 del 17 (D62fsX79), affecting the intracellular (IC) and TNFH domains, respectively [18, 19]. The remaining patient (P1) showed a splice site mutation (IVS1+2T>C) in intron1.

One patient (P9) showed an amino acid substitution in the TNFH domain (G219R), which has been suggested previously as a polymorphic variant in the *CD40L* gene [20].

The G219R variant was found in three out of the 244 controls, two female and one male, whereas the L161P, G167R, and T254M were not found in any of the controls.

In P8, we found novel nonsense mutation c.364G>T (E122X) in the Apobec-like domain of the *AICDA* gene.

Discussion

This study describes the clinical, immunological, and molecular features of patients with HIGM in Iran. Initial diagnosis was made based on elevated serum IgM levels and decreased levels of IgG and IgA. However, two patients (P1 and P6) had high IgA levels, and one patient (P7), who was a nephew of a confirmed HIGM patient, had low IgM level. There are some reports indicating that a number of HIGM patients with *CD40L* mutations had elevated IgA or IgE, which may suggest involvement of additional molecular mechanisms other than CD40L in the process of isotype switching [2, 21].

Mutation analysis was performed in 14 of 23 investigated patients, and underlying mutations were found in eight subjects. X-HIGM is the most common type of HIGM caused by mutations in *CD40L* [9, 21, 22]. In our study, seven patients had *CD40L* mutations.

Increased susceptibility to infection is the hallmark of X-HIGM, while most patients usually develop symptoms of combined immunodeficiency in their first year of life [21]. The most common clinical manifestations observed in our patients were infections, especially in the respiratory and gastrointestinal tracts; about 86% of our X-HIGM patients experienced their first infectious manifestation during the first year of life, while one patient developed infections after 9 years.

It has been noted that more than half of patients with pneumonia are affected by opportunistic infections, with *P. jiroveci* being the most common isolated pathogen [2, 21]. However, we only found *P. jiroveci* in one patient. Opportunistic infections are also a common cause of chronic diarrhea and resulting growth failure in the HIGM patients [2, 21]. We identified *C. parvum* and *G. lamblia* as the etiologic agent of chronic diarrhea in two patients. The low number of diagnosed patients in our series may be due to the fact that other patients were not systematically evaluated for such infection.

We noted marked paucity of cervical lymph nodes and tonsilar tissues in five out of seven X-HIGM patients, while the patient with AICDA deficiency showed lymphoid hyperplasia. This clinical finding is an important clue to distinguish X-HIGM from other forms of HIGM due to intrinsic B-cell defects. Affected individuals with AICDA

Table III Mutations of HIGM Patients

Patients	Gene mutated	cDNA mutation	Type of mutation	Predicted effect on protein	Affected domain	Exon/intron	Novel or known
P1	*CD40L*	IVS1+2T>C	Splice site	–	–	Intron 1	Novel
P2	*CD40L*	c.817C>T	Missense	T254M	TNFH domain	Exon 5	Known
P3	*CD40L*	c.499G>C	Missense	G167R	TNFH domain	Exon 5	Novel
P4	*CD40L*	c.482 T>C	Missense	L161P	TNFH domain	Exon 5	Novel
P5	*CD40L*	c.83del T	Frame shift deletion	T29fsX36	IC domain	Exon 1	Novel
P6	*CD40L*	c.180–196del17	Frame shift deletion	D62fsX79	EC domain	Exon 2	Novel
P7	*CD40L*	c.499G>C	Missense	G167R	TNFH domain	Exon 5	Novel
P8	*AICDA*	c.364G>T	Nonsense	E122X	–	Exon 3	Novel

or UNG deficiency frequently develop lymphoid hyperplasia [7, 23–25]

In this study, ten patients developed neutropenia during the course of disease; among them, six had CD40L deficiency. Neutropenia is the most common hematologic manifestation and could also be the first clinical finding in X-HIGM [26–28]. It usually follows a chronic course but can also be episodic or cyclic [19, 28, 29]. It may result from autoantibodies against neutrophils, a defective myeloid differentiation causing maturational arrest or a defect in the release of mature granulocytes from the marrow to the peripheral blood [1, 19, 30].

Despite advances in the clinical management of patients with HIGM, the survival rate is still poor, with a variable mortality rate [2, 21]. In our patients, the survival rate decreased to 70%, after 15 years of follow-up. The most common cause of death was respiratory failure (probably due to opportunistic infections).

The human *CD40L* gene includes five exons with various mutations being scattered throughout [9, 16, 20]. However, most of the *CD40L* mutations are located within exon 5, which is important for CD40L–CD40 interactions. Our study revealed four of seven (57%) mutations being located in this region, which suggests that mutation screening should start within exon 5 as a time and cost-effective strategy in patients suspected to have mutations in the *CD40L* gene.

In this survey, we detected two novel missense mutations (L161P and G167R) in the *CD40L* gene. Sequence alignment showed that the L161 and G167 of the CD40L protein are conserved in several species (Fig. 2). Moreover, these two residues are among the invariant positions in the TNF superfamily members. Missense mutations have been reported in six other (W140C/G/R, Y169D/N, G226A, G227V, L231S, and G257D/S) invariant positions until now [31]. Using the Polyphen tool (http://genetics.bwh.harvard.edu/pph/), L161P and G167R changes are predicted to affect CD40L function.

Mutation analysis of P10 revealed c.655G>A, which would result in the substitution of an arginine for glycine at codon 219. This amino acid change has previously been reported in normal Caucasians [20]. We also documented this variant in 1.2% of our control subjects, although we did not analyze the functional consequences of this change, as it is predicted to be benign using Polyphen. Thus, G219R seems to be a disease-contributing rather than a disease-causing mutation.

In P2, a recurrent mutation (T254M) has been found. This alteration is reported in several X-HIGM patients [9, 16] and assumed to be associated with a mild phenotype. However, P2 presented in early infancy and developed neutropenia in the course of disease.

P8 had a novel nonsense mutation in *AICDA* (E122X) that affects the Apobec-like domain, considered to be detrimental for CSR as well as SHM [14].

We could not find any mutation in six out of 14 (36%) HIGM patients. As we used genomic DNA for mutation analysis, it is possible that some intronic mutations could be missed from our detection. In addition, HIGM could also be caused by defects in other genes involved in class switching specific to T or B lymphocytes. Hypomorphic mutations in *NEMO* could present a phenotype characterized by HIGM and a T-cell defect [32]. Although *NEMO* mutations frequently produce ectodermal dysplasia, some patients have been reported without this feature [33].

Moreover, about half of the Ig CSR deficiencies, caused by an intrinsic B-cell defect, have an unknown molecular defect. A CSR defect located downstream from the DNA cleavage step may be responsible for this HIGM group [8, 34].

Recently, a new type of B-cell intrinsic CSR deficiency was found in patients with homozygous mutations in the gene encoding the PMS2 component of the mismatch repair machinery. It is characterized by defective occurrence of double-strand DNA breaks in switch regions and abnormal

a

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Homo sapiens              TSVLQWAEKGYYTMSNNLVTLENGKQLTVKRQGLYYIYAQVTFCSNREAS   184
Pan troglodyte            TSVLQWAEKGYYTMSNNLVTLENGKQLTVKRQGLYYIYAQVTFCSNREAS   232
Canis familiaris          ASVLRWAPKGYYTISSNLVSLENGKQLAVKRQGLYYVYAQVTFCSNRAAS   183
Bos Tauru                 TSVLQWAPKGYYTLSNNLVTLENGKQLAVKRQGFYYIYTQVTFCSNRETL   184
Mus musculus              ASVLQWAKKGYYTMKSNLVMLENGKQLTVKREGLYYVYTQVTFCSNREPS   183
Rattus norvegicus         ASVLQWAKKGYYTMKSNLVVLENGRQLTVKREGLYYVYTQVTFCSNREPL   183
Gallus gallus             VRVLKWMTTS-YAPTSSLISYHEGK-LKVEKAGLYYIYSQVSFCT—KAA    194
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b

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TNFSF5(CD40L)     GYYTMSNNLVTLENGKQLTVKRQ-------GLYYIYAQVTFCSNR------------EAS 184
TNFSF15(VEGI)     LGLAFTKNRMNYTNK-FLLIPES-------GDYFIYSQVTFRGMTSECSEIRQ--AGRPN 172
TNFSF2(TNF-α)     RANALLANGVELRDN-QLVVPSE-------GLYLIYSQVLFKGQ------------GCPS 147
TNFSF1(TNF-β)     TDRAFLQDGFSLSNN-SLLVPTS-------GIYFVYSQVVFSGKAYS--------PKATS 126
TNFSF14(CD258)    LGLAFLR-GLSYHDG-ALVVTKA-------GYYYIYSKVQLGGVG-----------CPLG 157
TNFSF11(RANKL)    RGWAKIS-NMTFSNG-KLIVNQD-------GFYYLYANICFRHHETSG--------DLAT 233
TNFSF10(TRAIL)    RSGHSFLSNLHLRNG-ELVIHEK-------GFYYIYSQTYFRFQEEIK--------ENTK 201
TNFSF18(AITRL)    ----------KVSDW-KLEILQN-------GLYLIYGQVAPNAN--------------- 106
TNFSF7(CD70)      --------GPELDKG-QLRIHRD-------GIYMVHIQVTLAICSS----------TTAS 121
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Fig. 2 **a** CD40L in human and corresponding region in six other species. The amino acids L161 (*red*) and G167 (*blue*) are conserved. **b** Alignment of the human TNF superfamily members including CD40L indicating the putative invariant L161 (*red*) and G167 (*blue*)

formation of switch junctions [15]. The three reported patients presented with lymphoid malignancies in early childhood; however, description of more cases is needed to delineate all clinical pictures of this defect.

Phenotypic description and molecular analysis of more HIGM patients could define the mechanisms underlying class switching in the near future.

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