Morbidity and Mortality of Iranian Patients with Hyper IgM Syndrome: a Clinical Analysis

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ABSTRACT

Background: Defects in B cell class switch recombination (CSR) are a heterogeneous and yet very uncommon group of disorders which all have a genetic basis uniformly leading to hyper IgM (HIgM) syndrome. Due to the rare frequency of these conditions, a very small number of case series have been conducted on the affected patients. **Objective:** To shed some light on the morbidity and mortality regarding a relatively large cohort of diagnosed CSR defective Iranian patients. **Methods:** This study was performed using demographic information, laboratory findings and clinical data obtained from an observation of 33 Iranian patients of different ethnicities referred from all medical centers of Iran to the Children's Medical Center Hospital, pediatrics center of excellence, Tehran, Iran; of which 28 were males and 5 were females. **Results:** Our patients mean age at the onset of symptoms was 1.8 ± 0.2 years; they were diagnosed with a mean delay of 4.4 ± 3.3 years and followed for a mean time of 5.7 ± 4.8 years. The most prominent clinical features observed were multi-organ infections, affecting mostly the respiratory system, followed by lymphoproliferative and autoimmune disorders, the latter being of much higher frequency (44%) in our study than the reported frequency in previous reports. The three year survival rate for our enrolled patients was 67.9%. **Conclusions:** Based on our findings, the most common cause of death in HIgM patients is respiratory failure. The molecular mechanism behind the nature of the CSR defective patients in Iran is more compatible with autosomal recessive mutations rather than X-linked HIgM syndrome which is in contrast with other large cohorts of patients with CSR defect.

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INTRODUCTION

Hyper immunoglobulin M (HIgM) syndrome is a heterogeneous group of disorders, either caused by primary genetic mutations or is secondary to different acquired conditions. Acquired HIgM might be secondary to congenital rubella syndrome, T cell leukemia, lymphomas, use of phenytoin and other anti-epileptic drugs, and pregnancy (1,2). Genetic mutations resulting in HIgM include those which definitely characterized by B cell class switch recombination (CSR) defect and thus reduced serum class switched immunoglobulin with usually increased level of IgM (3-5). Defects in expression of several genes are causative of CSR defects; which have mostly been discussed and studied in great detail in previous studies (6-9).

CSR defects in some cases have been accompanied by impaired B cell somatic hypermutation (SHM) and thus poor antibody response, defect in B cell memory generation, cell mediated adaptive immunity, and the last of which frequently involves such cells as macrophages and dendritic cells (12-14). Therefore, genetic abnormalities leading to HIgM have been categorized into two groups, those affecting only B cell events, including CSR (e.g. AID, UNG), and causing isolated B cell problems and those leading to defects in functions of other immune cell types, including dendritic cells, macrophages and monocytes, including antigen presenting-T cells interactions in addition to B cell defects (e.g. CD40 Lignad, CD40 and NEMO) (11-12).

Both types of HIgM with CSR defect are categorized as a primary immunodeficiency (PID). A study of 7430 PID patients by Gathmann *et al*. (13) demonstrated that 3.08% of Europeans with PID enrolled had CSR defects, the most prevalent being CD40Ligand (CD40L) deficiency with a frequency of 1.16%. Another study, performed in the United states, also reported the most frequent CSR defect to be being *CD40L* gene mutation, with a prevalence of 1:500,000 males in total population (2).

Various other types of PID with complicated problems in DNA repair mechanisms and non homologous end joining proteins, though very rare, might also lead to immunologic manifestations resembling those of HIgM (14), probably due to subsequent faults in immunoglobulin gene recombination by expression of RAG1 and RAG2 deficiency, in ataxia telangiectasia syndrome (15), Nijmegen breakage syndrome (16) and PMS2 deficiency (postmeiotic segregation increased 2) (9). Also some other PIDs causing forms of antibody deficiency (including XLA and CVID) might have laboratory findings suggesting a HIgM syndrome, including low serum IgG and IgA and elevated IgM, resulting in misdiagnosis (17,18).

It is important to note, that although patients with true defects in CSR would seemingly result in an elevated IgM at diagnosis, IgM level at diagnosis is normal or even decreased in reportedly about half of the patients (19).

Therefore, distinguishing specific burden of HIgM syndromes with CSR defect through morbidity and mortality is essential to compare with other PID diseases. In this article we sought to report laboratory and clinical findings and survival rate regarding registered HIgM patients with CSR defect, in an attempt to help better clarify prognosis of this very rare condition in Iranian patients.

MATERIALS AND METHODS

Patients. This research was conducted in form of a case series study. The environment of this study was the Children's Medical Center, Pediatrics Center of Excellence; Tehran, Iran affiliated to Tehran University of Medical Sciences. Patients population consisted of those with definite clinical HIgM diagnosis with immunodeficiency and CSR defect according the classification of international Union of Immunological Societies (IUIS) (20). Those patients whose clinical and immunologic data was not recorded completely were removed from this study. The genetic analysis has been performed to confirm the diagnosis of all of studied patients (manuscript in preparation) according to the methods that previously were described (21-27). Approval for this study was obtained from the institutional ethical review boards of the Tehran University of Medical Sciences and informed consents were obtained from the adult patients and children's parent(s).

Methods. At the beginning of the study and by surveying medical documents, patients' general information including age, sex, age at the onset of symptoms, family history of the immunodeficiency and clinical manifestations (both in outpatient visits and admissions) of patients were evaluated and recorded in a questionnaire devised for this purpose. By reviewing the laboratory data of the patients, their immunologic tests at the time of diagnosis was registered in the aforementioned questionnaire. Complete blood count was evaluated by the cell counter and Westergren method, using anticoagulated whole blood, respectively. Serum levels of IgG, IgA and IgM were measured by turbidimetry (Behring Nephelometer, Behringwerke, Marburg, Germany), and lymphocyte subpopulations of CD3, CD4, CD8 and CD19 were counted by flow cytometry (Partec PAS, Münster, Germany) at the time of the study. Immunoglobulin E levels were measured, using an enzyme-linked immunosorbent assay (ELISA, Neuss, Germany). Also the files of the expired patients or the unavailable ones were reviewed and the reasons for the exit of the unavailable patients from the follow up or the causes of death of those patients expired as a result of HIgM were noted.

Statistical Analysis. The results for the continuous numerical variables were summarized and expressed in form of mean ± SD and for the categorical ones in form of percent. Statistical analysis for drawing Kaplan-Meier survival table was performed using a commercially available software package (SPSS Statistics 17.0, SPSS, Chicago, Illinois).

RESULTS

General Information. A total of 33 patients (28 males and 5 females) with a mean ± SD age of 11.5 ± 7.8 were enrolled in the study. Mean ± SD age of the patients at the onset of their symptoms was 1.8 ± 0.2 years, their mean ± SD age at the time of diagnosis was 6.3 ± 6.0 years and their calculated mean ± SD delay in diagnosis time was 4.4 ± 3.3 years accordingly. Also patients were followed up for a mean ± SD time of 5.7 ± 4.8 years. Moreover the genetic analysis of studied patients has been performed to confirm the definite diagnosis of HIgM (manuscript in preparation).

Family History. A family history of defined PID was observed in 6 (18.2%) of the patients. A family history of recurrent infections and of early age of death was observed in 3 (9.1%) and 9 (27.3%) of the patients, respectively. No family history of malignancy

was observed in the study population. A family history of autoimmunity was observed in only one (3.0%) of the patients. Also, 6.1% (n=2) of the patients reported a family history of allergy.

Clinical Complications. Multi-organ infections were observed in 66.7% of the patients, being the most frequent clinical manifestation in our study population. Autoimmune and lymphoproliferative disorders were observed in 42.4% and 63.6% of them, respectively; while enteropathy occurred in 3 cases (9.1%) and malignancy in only one patient (3.0%; Table 1).

Table 1. Frequency of different clinical manifestations of the 33 patients with CSR defect.

Type of manifestation	Frequency (percent)	Type of manifestation	Frequency (percent)
Autoimmune disorders		**Bacterial infection**	
ITP	5 (15.2)	Pneumonia	18 (54.5)
AIHA	4 (12.1)	Otitis media	17 (51.5)
JRA	4 (12.1)	Bacterial gastroenteritis	16 (48.5)
Neutropenia	3 (9.0)	Sinusitis	15 (45.5)
Thyroiditis	1 (3.0)	URTI	9 (27.3)
Ulcerative colitis	1 (3.0)	Conjunctivitis	6 (18.2)
Uveitis	1 (3.0)	Osteomyelitis	2 (6.1)
Primary sclerosing cholangitis	1 (3.0)	Septic arthritis	2 (6.1)
Secondary sclerosing cholangitis	1 (3.0)	Cutaneous abscess	2 (6.1)
Lymphoproliferative Syndromes		Cystitis	1 (3.0)
Lymphadenopathy	12 (36.4)	Cellulitis	1 (3.0)
Splenomegaly	12 (36.4)	Empyema	1 (3.0)
Hepatosplenomegaly	9 (27.3)	Lymphadenitis	1 (3.0)
		Orkitis	1 (3.0)
Malabsorption	2 (6.1)	Pyelonephritis	1 (3.0)
Unspecific gastroenteritis	1 (3.0)		
Clubbing	5 (15.2)	**Viral infection**	1 (3.0)
Failure to thrive	6 (18.2)	Measles	1 (3.0)
Bronchiectasis	3 (9.1)	Pneumonia	1 (3.0)
Hearing impairment	3 (9.1)	**Other infections**	
Ascites	1 (3.0)	Candidiasis	9 (27.3)
Liver cirrhosis	1 (3.0)	PCP	6 (18.2)
Growth hormone secretion defect	1 (3.0)	Giardiasis	2 (6.1)

AIHA: Autoimmune hemolytic anemia , ITP: Idiopathic thrombocytopenic purpura, JRA: Juvenile rheumatoid arthritis, PCP: *Pneumocystis jiroveci* pneumonia, URTI: Upper respiratory tract infection

Respiratory system were the most commonly involved organ with infections (87.9%), followed by gastrointestinal (48.5%), cutaneous (45.5%), urinary tract (21.2%) systems and infections of the bones and joints (15.2%). Nervous system infections were not observed in any of the patients (Figure 1).

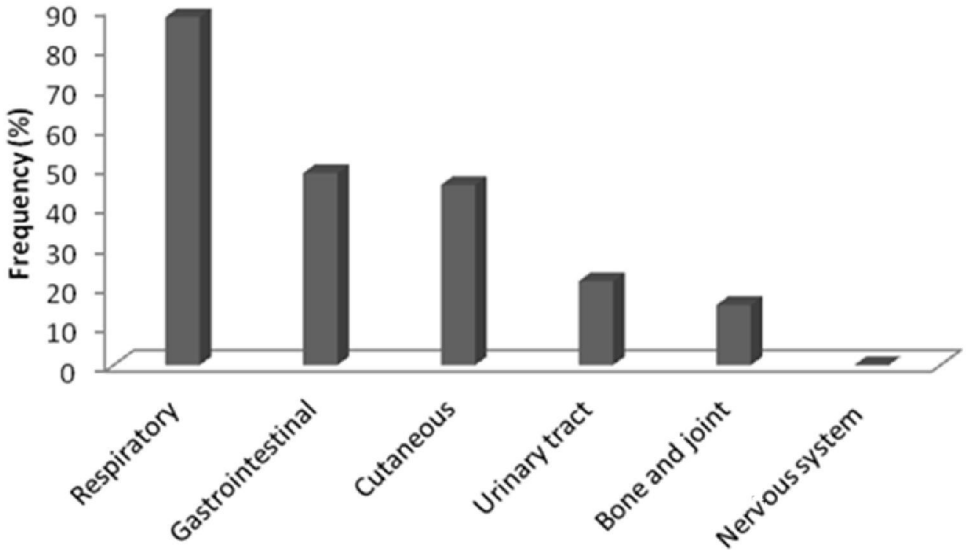

Figure 1. Frequency of observed infections of different systems in 33 patients with CSR defect.

The most frequent bacterial infections observed were pneumonia (in 54.5% of patients), otitis media (in 51.1%), bacterial gastroenteritis (especially with toxoplasmosis and Cryptococcus cytomegaloviruses in 48.5%) and sinusitis (in 45.5%). Other infections were comparatively much less frequent. Disseminated viral infections were observed in only two patients (one case of generalized measles and another of varicella pneumonia). From among fungal infections, candidiasis and opportunistic fungal infections (especially due to *Pneumocystis jiroveci*) were recorded in 9 (27.3%) and 6 (18.2%) of the patients, respectively, and finally, parasitic infection observed was giardiasis in only 2 patients.

The most frequent autoimmune manifestation in our study population was idiopathic thrombocytopenic purpura (ITP), which occurred in 15.2% of cases, followed by autoimmune hemolytic anemia (AIHA) and juvenile rheumatoid arthritis (JRA) that occurred in 12.1% of our patients.

Drug reactions to antibiotics were reported in 3 patients (9.1%), and urticaria, eczema and food allergy were each reported in only one patient.

The most frequent lymphoproliferative syndromes were lymphadenopathy and splenomegaly observed each in 36.4% of the patients, followed by hepatomegaly (27.3%) and malabsorption and non-specific gastroenteritis each in two cases (6.1%).

Only one patient had an occurrence of malignancy in the form of Hodgkin's lymphoma. Among other manifestations related to the HIgM, fever of unknown origin was commonly observed in a third of the patients (11 cases), 5 had a finger clubbing manifestation on physical examination and 6 suffered from failure to thrive (FTT).

Some other, less commonly observed manifestations include ascites, liver cirrhosis and defect in growth hormone secretion each in one (3%) of the patients, bronchiectasis and hearing impairment each in three (9.1%) of the patients. All of patients' recorded for laboratory findings also are summarized in Table 2. According to the finding of complete blood count, neutropenia was recorded in 3 cases (9.4%). Patients serum IgA levels were decreased, but more mildly so than serum IgG levels, with an average of 35.0 mg/dl which is not much lower than normal. In fact, 3 patients had a completely normal IgA level and 2 had elevated titers.

Table 2. Mean values of certain immunologic data in 33 patients with CSR defect. All values presented as mean ± Standard deviation.

Blood cell count & CD marker levels	CSR patients Mean ± SD	Normal range
White blood cells (cell/ml)	9784.1±7286.1	4300-11400
Neutrophil (%)	51.01±20.02	40-65
Lymphocyte (%)	37.48±20.76	28-67
CD3 (%)	15.10 ± 65.55	58-82
CD4 (%)	13.56 ± 33.22	26-48
CD8 (%)	11.84 ± 28.42	16-32
CD16 (%)	7.16 ± 9.38	0.69-2.53
CD19 (%)	7.88 ± 13.75	10-30
CD20 (%)	17.20 ± 20.90	10-30
CD56 (%)	3.54 ± 7.50	0.69-2.53
IgG (mg/dl)	142.4 ±134.1	600-1500
IgM (mg/dl)	638.8±387.4	80-380
IgA (mg/dl)	35.0±19.8	50-370
IgE (IU/ml)	3.7±3.2	0-10
IgG1 (mg/dl)	34.8±16.0	450 - 900
IgG2 (mg/dl)	74.3±46.3	180 - 530

Follow up and Survival Rate. Despite administration of regular intravenous immunoglobulin for all cases, our patients had a mean hospital admission time after diagnosis of 73.0 ± 33.1 days (range: 4 to 92 days), and their mean number of hospitalization was 6.6 ± 3.3 times (range: 3 to 15 times). A total of 8 patients died

during 12 years of follow up, according to our patients survival calculation, studied patients one year survival rate was 82.4%, their two year survival rate was 75.5% and their three year survival rate was 67.9% (Figure 2). The most prevalent cause of death was respiratory failure (75%).

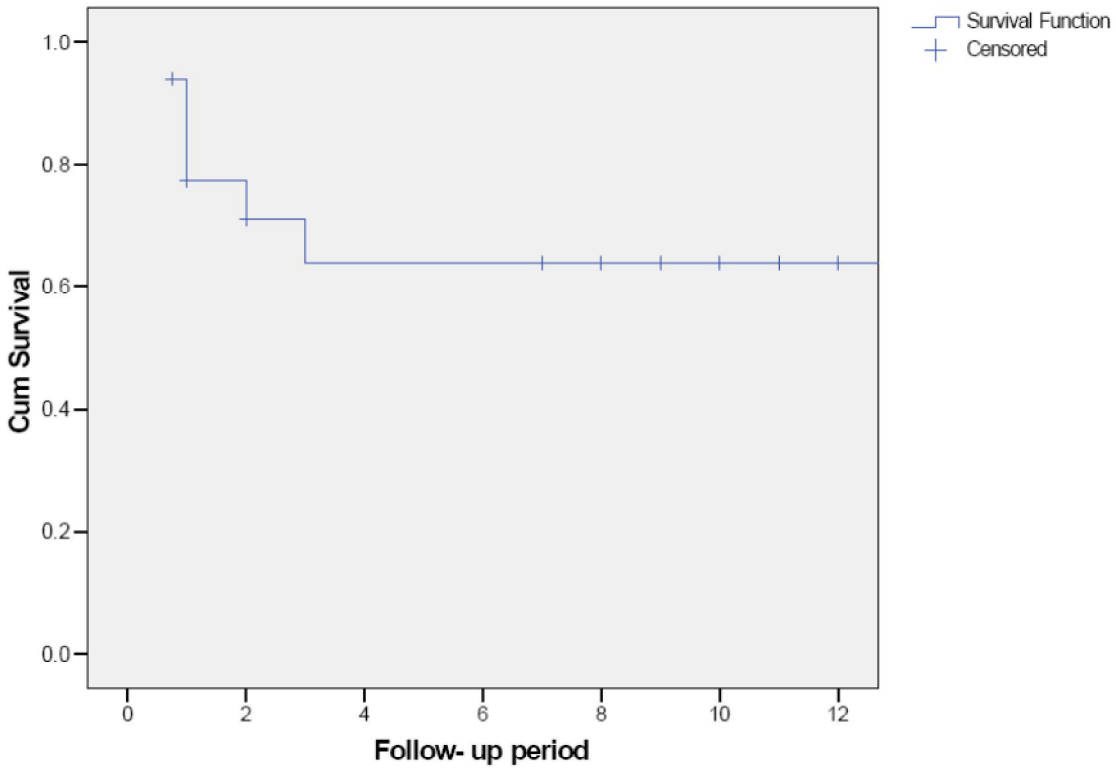

Figure 2. Survival rate of the studied 33 patients with CSR defect.

DISCUSSION

This study was conducted with the purpose of evaluating clinical features of PID patients with CSR defect, including their manifestations, together with their laboratory findings and prognosis.

Firstly, mean age of the patients at the onset of symptoms in our study was 1.8 years, which is significantly higher than the age reported by Winkelstein *et al*., although two of their patients had manifestations at the ages of 13 and 16 (2), and unlike their study in which almost all patients had developed symptoms by the age of 4, 15.1% of our patients had a later onset, the oldest being 7 at the start of manifestations. However, these results were compatible with the mean age of the onset reported by quartier *et al*. for AID patients, being about 2 years (28). Also in one study, a UNG deficient patient who was asymptomatic until 15 years of age, two BTK deficient brothers who were

asymptomatic until 8 and 9 years of age and two patients that were older than 14 years when their symptoms appeared were reported among 140 HIgM patients (29). It may indicate female cases and also some of our males with parental consanguinity had suffer from autosomal recessive disease of CSR defect with only B cell defects rather than CD40L disorders in other registry with both humoral and cellular defects leading to more severe or early onset disease. Our patients had a parental consanguinity rate of 51.5%, even a higher rate than that observed in a study of AID deficient patients (28).

Mean diagnostic delay for our patients was 4.5 years, not much higher than previous studies (2,28), but 15.1% of our patients, mostly referred from other provinces other than Tehran, had a delay of more than 7 years, with the highest delay being 19.5 years in two patients. It has also been reported that AID deficient patients might have a diagnostic delay of one or two decades (28), though they present more frequently in our survey. This event can confirm with the rate of our female patients (15.1%), which is relatively close to the 14.2% reported in a case series study by Lee *et al*. (10), the 12.5% reported by Banatvala *et al*. (30) but higher than the registry involving mostly CD40L deficiency (2,29). This is to no surprise, as most CSR defective patients suffer from *CD40L* gene mutation which is a X-linked condition.

Although only 18% of our patients had a positive family history of PID, much less than the 30-40% (28,30) reported in previous studies, about a third of our patients reported at least one incidence of early age death in their families suggesting a higher frequency of positive family history which was undiagnosed because of lack of awareness or laboratory facilities.

The clinical outcome of our patients as a morbidity report resembles that of Wilkentein *et al*. study (2) and Bejaoui *et al*. (31) with interesting accuracy. Septic arthritis, cellulitis, osteomyelitis and more commonly central nervous system infections were observed in lesser frequency in our patients.

Opportunistic infections occurred at a rate of 21% in our patients which is considerably lower than what was reported in previous studies (19), however fungal infections, mostly by candidias, were observed to be of strikingly high frequency in our patients (42%). HIgM patients are thought to be generally more prone to fungal complications (2) but their frequency was not reported to be nearly this high.

The high incidence of lymphoproliferation in our population, is near the reportedly high frequency of this condition in AID deficient patients that have a high risk of developing lymphoid hyperplasia (8), the reported incidence being 69% (28) and 75% (29). But our observed rate is much higher than the previously reported frequencies among non-classified CSR deficient (2,32).

It had previously been discussed that the self-reactive IgM profile of HIgM patients was significantly different from healthy controls and could result in a higher risk of autoimmune complications (30) and it was postulated that CD40 interaction with its ligand might have an essential role to play in peripheral B cell tolerance(33). The frequency of autoimmune manifestations in our population was higher than the near 20% reported by Levy *et al*. (29), the 15% reported in X linked HIgM patients (2) and the reported 21% in AID deficient patients(28).

Among autoimmune manifestations, the most commonly observed in our patients were autoimmune cytopenia which were reported previously in AID deficient patients (35), but the Levy *et al.* report demonstrated a much higher rate of autoimmune enteropaty (6%) (19).

Another complication of HIgM patients is malignancy. A case of Hodgkin's lymphoma was the only malignancy we observed in this survey. Although, the incidence of lymphoma (particularly Hodgkin's disease associated with EBV infection) is increased in CD40L deficient patients (34), neuroectodermal gastrointestinal (including pancreatic and hepatic) carcinoids, biliary tract carcinomas and adenocarcinoma were previously reported to be of higher incidence in HIgM patients (29).

Some of patients in our series had normal and elevated IgA level, which was observed in previous study, in which only 76% of the patients had decreased IgA (2), but normal IgA was not reported with such a high frequency in the other study.

Neutropenia is a common laboratory finding in HIgM patients. About a fourth of our patients were found to be neutropenic, which is lower than the previously reported 30-60% (2,19,29).

These significant variations suggest underlying genetic differences in Iranian patients compared to other studied races, and further genetic analysis might lead to discovery of new mutations in the already studied genes and perhaps even lead to discovery of new genes modulating mechanisms of B cell CSR.

Of our 33 patients, 8 have died during a 12 year follow up. Our resulting annual mortality rate was 2.02%, which compared to a 1.78% (35) and a 0.86% (28) annual mortality rate was significantly higher. Unfortunately, some other large cohort did not report any mortality during follow up time (2,19).

In conclusion, according to the findings of this survey, our higher recorded mortality might be due to several underlying factors, such as different genetic background, insufficient professional expertise of Iranian physicians regarding PIDs, differences in standards of care, and relative unavailability of required curative clinical interventions like bone marrow transplantation.

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