**Immunology and Genetics Journal**

Original Article

Received: 13 July 2020
Accepted: 28 August 2020
Published online: 22 September 2020
Doi:10.22034/igj.2020.247400.1048

# Comparison of the Familial and Sporadic Forms of Hyper IgM Syndrome in the Iranian Patients

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**Abstract**

**Background:** Hyper IgM (HIGM) syndrome or immunoglobulin class-switch recombination deficiency (Ig-CSR) is a group of primary immunodeficiencies (PIDs) where B cells are unable to undergo the process of immunoglobulin class -switching recombination (CSR), a process in which B-cells modify their DNA to switch from production of IgM to other immunoglobulins. Hence, the affected patients exhibit normal to high levels of serum IgM and low or absence of other immunoglobulin isotypes relative to mean values of age. Therefore, the present study was conducted to assess the demographic data, clinical manifestation, and immunological findings in the sporadic and familial types of HIGM.

**Method:** Demographic data, laboratory findings, and clinical presentations of 79 Iranian patients diagnosed with HIgM syndrome were collected. All the patients were classified into two different groups: sporadic and familial types of HIGM.

**Results:** Male to female ratio was significantly higher in the familial group compared to the sporadic group so that, 94.7% of the patients were male in the familial group, while only 70% of the sporadic patients were male (P=0.032). It was also found that the familial group had a significantly higher consanguinity rate (P=0.047) and a significantly lower delay of diagnosis compared to the sporadic group (P=0.006). The lower respiratory infection (42%) followed by upper respiratory infection (26%) and diarrhea (15%) were the most frequent initial presentations. It was shown that diarrhea, as an initial presentation was about three times more common among the familial group (31.6%) compared to the sporadic group (10%, P=0.028). Otitis was also found to be more prevalent in the sporadic group (P=0.042).

**Conclusion:** Our findings could be explained by more careful screenings and more vigilant and informative parents in the families with another affected member.

**Keywords:** Hyper IgM, Primary Immunodeficiency, Sporadic HIGM, Familial HIGM

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## Introduction

Hyper IgM (HIGM) syndrome or immunoglobulin class-switch recombination deficiency (Ig-CSR) is a group of primary immunodeficiencies (PIDs) where B cells are unable to undergo the process of immunoglobulin class -switching recombination (CSR) ,a process in which B-cells modify their DNA to switch from production of IgM to other immunoglobulins hence , the affected patients exhibit normal to high levels of serum IgM and low or absence of other immunoglobulin isotypes relative to mean values of age (1). So far, several genetic defects have been identified to contribute to HIGM syndrome. Mutation in the *CD40L* gene is responsible for development of up to 70 % of all the HIGM cases, and defects in this molecule result in the combined immunodeficiency (2, 3). In contrast, mutations in *CD40, AID, UNG* genes lead to the antibody deficiency (4). Furthermore, defect in the molecules associated with DNA repair defects including PIK3CD, PIK3R1, BTK, NEMO/IKKγ, PMS2, MSH2, MSH6, INO80, ATM, and NBS1/NBN could also manifest the HIGM-like pattern (5-7).

Patients with HIGM manifest various infectious and non-infectious clinical manifestations including severe recurrent common and opportunistic infections, respiratory complications, gastrointestinal problems ,such as oral ulcers, protracted diarrhea, sclerosing cholangitis, and liver cirrhosis, autoimmune and inflammatory diseases, neutropenia, lymphoproliferatve disorder ,and cancers (8). The complications can occur as early as the first year of life (1, 9). Early diagnosis and appropriate management are beneficial in these patients. Intravenous immunoglobulin (IVIG) is an effective treatment for reducing the chronic infections in the patients however, in the patients with the combined immunodeficiency, hematopoietic stem cell transplantation (HSCT) should be considered (10).

It has been demonstrated that the family members of the patients with common variable immunodeficiency (CVID) are at the greater risk of other immune-related disorders, particularly malignancy and autoimmunity (11, 12). Evaluation of the family history has been considered in some of PIDs including CVID, IgA deficiency (SIgAD), and IgG subclass deficiency. Based on the literature review, no study has been conducted on the evaluation of the clinical and immunologic phenotypes in the familial and sporadic forms of HIGM. So, in the present study, the demographic data, clinical manifestations, and laboratory findings of two HIGM groups including familial and sporadic were analyzed and compared with each other.

## Materials and Methods

### Patients

The present retrospective cohort study was conducted on 79 patients with HIGM registered in the Iranian primary immunodeficiency disorders (PIDs) registry network. The diagnosis of these patients was based on the inclusion criteria defined by the European society of immune deficiencies (ESID). These criteria include a positive family history or clinical symptoms of HIGM syndrome, along with a significant decrease in the serum IgG with normal or increased levels of serum IgM and no evidence of T-cell deficiency, such as ataxia telangiectasia and other known causes of hypogammaglobulinemia (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria). The diagnosed population was subsequently classified into familial and sporadic groups. The familial group was defined as the patients having at least one first- or second-degree family member diagnosed with HIGM, while the sporadic group was defined as the patients without any family history of HIGM or stillbirth. The patients with incomplete family history and pedigree data were excluded from the study. An informed written consent was obtained from the patients or their parents, and the study procedure was approved by the Ethics Committee of Tehran University of Medical Sciences.

### Data Collection

In the present study, a questionnaire was designed to collect the patients' detailed demographic information (age, sex, consanguinity, age at the time of diagnosis, delay of diagnosis, and family history of PID), clinical manifestations (initial presentations, infectious and non-infectious complications, findings of physical examination, response and reaction to the vaccinations, and cause of death), and laboratory findings (CBC-diff, lymphocyte subtyping, and immunoglobulin profile). Diagnostic delay was defined as the period between the onset of symptoms and the time of clinical diagnosis of HIGM. Assessment of lymphocytes including $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cells was performed by the flow cytometry. Levels of IgG, IgM, IgA, and IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were measured at the first clinical visit using the nephelometric technique.

### Statistical Analysis

Statistical analysis was performed by the SPSS (version 24) software (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine the normal distribution of the data. Parametric and non-parametric analyses were done using the findings of this evaluation, and analytical studies were performed based on this issue. For variables with skewed distribution, median and interquartile range (IQR) were considered as the index of data dispersion. A P-value of <0.05 was considered as statistically significant.

## Results

### Demographic Data

Seventy-nine cases of HIGM (60 sporadic and 19 familial cases) were included in this analysis. Overall, the patients were predominantly male (75.9%) and had a consanguinity rate of 58%, which was higher than the average population. The median age at the time of onset of symptoms was about one year old, although the first symptoms could have manifested as soon as 6 months up to 3.5 years of age. The median age at the time of diagnosis was about 4.4 years old, which showed a median delay of diagnosis of about 2 years.

Male to female ratio was significantly higher in the familial group compared to the sporadic group so that, in the familial group, 94.7% of the patients were male, while only 70% of the sporadic patients were male ($P$=0.032). It was also found that the familial group had a significantly higher consanguinity rate ($P$=0.047) and a significantly lower delay of diagnosis compared to the sporadic group ($P$=0.006). **Table 1** shows the demographic data in detail.

**Table 1.** Demographical Data of HIGM patients

| Variable | Total (N=79) | Sporadic (N=60) | Familial (N=19) | *P value* |
|---|---|---|---|---|
| Sex(M/F) | 60/19 | 42/18 | 18/1 | 0.032* |
| Dead/alive, n (Unknown) | 19/49 (11) | 15/34 (11) | 4/15 (0) | 0.431 |
| Positive parental consanguinity, n (%) | 47 (58.8) | 32 (53.3) | 15 (78.9) | 0.047* |
| Median age at onset, months (IQR) | 12 (6-36) | 12 (6-36) | 10 (5.5-41.7) | 0.830 |
| Median age at diagnosis, months (IQR) | 53 (19.5-80) | 59 (23-105) | 43 (12.7-61.5) | 0.104 |
| Median delay of diagnosis, months (IQR) | 24 (7-53) | 35 (8.5-70) | 11 (1.5-24) | 0.006* |

IQR, interquartile range 25-75%
*P-value is statically significant <0.5

**Table 2. Clinical Data of HIGM Patients**

| Variable | Total (N=79) | Sporadic (N=60) | Familial (N=19) | *P*-value |
|---|---|---|---|---|
| First presentation | | | | |
| Upper respiratory infection (%) | 21 (26) | 15 (25) | 6 (31.6) | 0.556 |
| Lower respiratory infection (%) | 34 (42) | 25 (42) | 9 (48) | 0.568 |
| Respiratory tract infection (%) | 48 (60.7) | 35 (58.3) | 13 (68.4) | 0.361 |
| Diarrhea (%) | 12 (15) | 6 (10) | 6 (31.6) | 0.028* |
| Skin infection (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| Urinary tract infection (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| Failure to thrive (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| Lymphadenopathy (%) | 4 (5.1) | 4 (6.7) | 0 | 0.568 |
| Oral candidiasis (%) | 3 (3.8) | 3 (5.1) | 0 | 1 |
| Allergy (%) | 1 (1.3) | 0 | 1 (5.3) | 0.234 |
| Arthritis (%) | 2 (2.5) | 1 (1.7) | 1 (5.3) | 0.415 |
| Organomegaly (%) | 3 (3.8) | 3 (5.1) | 0 | 1 |
| Immune thrombocytopenic purpura (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| History of Bronchiectasis (%) | 7 (8.8) | 6 (10) | 1 (5.3) | 1 |
| Clubbing (%) | 10 (12.5) | 9 (15) | 1 (5.3) | 0.438 |
| History of skin infection (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| History of Splenomegaly (%) | 22 (27.8) | 19 (31.6) | 3 (15.7) | 0.178 |
| History of Hepatomegaly (%) | 15 (19) | 13 (21.6) | 2 (10.5) | 0.281 |
| History of lymphoproliferative disorders (%) | 31 (39.2) | 25 (41.6) | 6 (31.6) | 0.433 |
| History of allergy (%) | 7 (8.8) | 5 (8.3) | 2 (10.5) | 1 |
| History of Autoimmunity (%) | 19 (23.8) | 15 (25) | 4 (21) | 1 |
| Immune thrombocytopenic purpura (%) | 4 (5.1) | 3 (5.1) | 1 (5.3) | 1 |
| Primary sclerosing cholangitis (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| Autoimmune arthritis | 5 (6.3) | 4 (6.6) | 1 (5.3) | 1 |
| Guillain barre syndrome | 2 (2.5) | 1 (1.6) | 1 (5.3) | 0.426 |
| Type 1 Diabetes mellitus | 1 (1.3) | 1 (1.6) | 0 | 1 |
| Autoimmune hemolytic anemia | 5 (6.3) | 5 (8.3) | 0 | 0.329 |
| Unspecified autoimmune disorder | 4 (5.1) | 3 (5.1) | 1 (5.3) | 1 |
| History of enteropathy | 8 (10.1) | 4 (6.6) | 4 (21) | 0.09 |
| History of failure to thrive (%) | 21 (26.5) | 15 (25) | 6 (31.6) | 0.572 |
| History of oral ulcer (%) | 14 (17.7) | 10 (16.6) | 4 (21) | 0.733 |
| History of recurrent diarrhea (%) | 24 (30.4) | 16 (26.6) | 8 (42.1) | 0.202 |
| History of chronic diarrhea (%) | 20 (25) | 14 (23.3) | 6 (31.6) | 0.471 |
| History of BCGosis (%) | 2 (2.5) | 2 (3.3) | 0 | 1 |
| History of conjunctivitis (%) | 4 (5.1) | 2 (3.3) | 2 (10.5) | 0.213 |
| History of tonsillar hypoplasia (%) | 5 (6.3) | 2 (3.3) | 3 (15.7) | 0.087 |
| History of adenopathy (%) | 10 (12.8) | 7 (11.6) | 3 (15.7) | 0.699 |
| History of respiratory tract infection | 65 (84.4) | 51 (87.9) | 14 (73.7) | 0.157 |
| History of pneumonia (%) | 53 (67.1) | 42 (70) | 11(57.9) | 0.328 |
| History of sinusitis (%) | 23 (29.1) | 17 (28.3) | 6 (31.6) | 0.786 |
| History of otitis (%) | 41 (51.9) | 35 (58) | 6 (31.6) | 0.042* |

IQR, interquartile range 25-75%

**P*-value is statically significant <0.5

Table 3. Laboratory Findings of HIGM Patients

| Variable | Total (N=79) | Sporadic (N=60) | Familial (N=19) | *P*-value |
|---|---|---|---|---|
| White blood count /ml, median (SD) | 8785 | 8600 | 10200 | 0.313 |
| Lymphocytes, % | 51 | 53 | 41 | 0.218 |
| Neutrophil ,% | 40 | 37 | 43 | 0.486 |
| CD3 T cells ,% | 68.5 | 69 | 63 | 0.808 |
| Patients with low helper T cell,% | | | | |
| CD4+ T cells ,% | 30 | 28.7 | 32 | 0.520 |
| CD8+ T cells ,% | 30 | 30 | 31 | 0.686 |
| Patients with high cytotoxic T cell,% | | | | |
| CD19+ cells ,% | 16 | 13.5 | 18 | 0.072 |
| Patients with low B cell,% | | | | |
| IgG, mg/dl (SD) | 112 | 150 | 42 | 0.006* |
| IgA, mg/dl (SD) | 9 | 13 | 8 | 0.266 |
| IgM, mg/dl (SD) | 235.5 | 241 | 164 | 0.606 |
| IgE, mg/dl (SD) | 3 | 4 | 1 | 0.178 |

**P*-value is statically significant <0.5

### Clinical Presentations

The lower respiratory infection (42%) was the most frequent initial presentation followed by the upper respiratory infection (26%) and diarrhea (15%). It was found that diarrhea, as an initial presentation was about three times more common among the familial group (31.6%) compared to sporadic group (10%, *P*=0.028). Results also showed that otitis was more prevalent in the sporadic group (*P*=0.042). At the same time, tonsillar hyperplasia was more common in the familial group, though the latter finding was not statistically significant (*P*=0.087). The lower respiratory infection, upper respiratory infection, and diarrhea were the most common initial presentations of both groups. In general, gastrointestinal complications were more common in the familial patients. Diarrhea, as an initial presentation was significantly more prevalent in the familial patients (*P*=0.024), they also had a higher chance of manifesting the chronic and recurrent diarrhea during their disease. Moreover, enteropathy was three times more common in the familial group (*P*=0.09). **Table 2** summarizes the complete clinical data**.**

### Laboratory Data

Complete blood cell count (CBC) and proportions of each cell type along quantitative levels of serum immunoglobulins were measured at the time of diagnosis. Our analysis showed that despite having a relatively higher proportion of the lymphocytes, such as $CD19^{+}$ (*P*=0.072), the familial group had significantly lower IgG levels compared to the sporadic group (*P*=0.006). **Table 3** presents the comprehensive laboratory data**.**

## Discussion

HIGM syndrome, a type of PID is also known as the class -switch recombination defect (CSRD). This disease, which is first described in 1961, is characterized by normal or elevated IgM serum level, decreased level or absence of IgA, IgG, and IgE. Patients with HIGM are vulnerable to the opportunistic infections, gastrointestinal complications, autoimmunity, and hematological problems (13-18). As mentioned earlier, no study has been carried out regarding evaluation of the family history in the patients with HIGM hence herein, it was attempted to compare 60 sporadic cases with 19 familial cases of HIGM considering the duration of the disease.

Totally, 79 patients with HIGM selected from the Iranian registry for PIDs were studied in this research. Among these patients, 19 patients had a positive family history for HIGM and were categorized as familial HIGM cases. While, overall, the cases were predominantly male, it was found to be even more prominent amongst the familial group so that, from 19 familial cases, 18 cases were male (95%), while 42 out of 60 (70%) cases of sporadic group were male. Similar findings have also been observed in the previous studies. A study by the registry of Latin American society of immunodeficiencies (LASID) showed that 17 out of 37 (46%) of their HIGM studied cases had a positive history of infections among the male relatives. Consistently, it was found that all the familial cases were male with X-linked CD40L deficiency (8). Another report from the registry of United States immunodeficiency network (USIDNET) showed that 62 out of 127 (49%) affected patients had a positive family history for HIGM, which supported the X-linked pattern of inheritance (XHIGM) (6). A significantly higher male to female ratio in the familial group may suggest that the X-linked pattern of inheritance plays even a more substantial role in the familial forms of HIGM. While, the mutation in X-linked CD40 ligand is underlying cause of most cases of HIGM (hence called "classic HIGM") (2-4, 7), mutations in X-linked NEMO/IKKγ gene (cause of X-linked anhidrotic ectodermal dysplasia with immunodeficiency) are also known to contribute to the development of HIGM syndrome (19-21). Furthermore, X-linked humoral PIDs including mutations in the BTK gene (associated with X-linked agammaglobulinemia) and SAP/SH2D1A gene (associated with X-linked lymphoproliferative disease) have been reported to manifest the HIGM pattern in some cases (7). Thus, it is recommended to further elaborate on the evaluation of molecular underpinnings of HIGM syndrome based on its familial and sporadic forms.

Parental consanguinity is a significant risk factor for the PIDs. This risk factor is mostly observed in the Middle East countries and North Africa (MENA) region, (22). Totally, 65% of all the PID patients in Iran are born from the consanguineous marriages. This proportion is notably higher amongst those with severe forms of PIDs, specifically those with cellular immunodeficiencies and combined immunodeficiencies (76%) (23-25). Our findings showed that the total parental consanguinity of the Iranian HIGM population was about 59%; which was significantly higher in the familial cases (78%) compared to the sporadic ones. Only 4 cases of the familial group were from the non-consanguineous marriages. These findings showed even a higher prevalence of the combined immunodeficiency (as seen in CD40L -deficient XHIGM syndrome) among the familial HIGM cases. Severe forms of PIDs, particularly the combined immunodeficiencies and phagocytic dysfunctions are more common in the families with a higher rate of parental consanguinity (23, 24). Moreover, in antibody deficiency disorders, such as CVID, patients from the consanguineous families are at higher risk for earlier onset of disease, more severe clinical outcomes, and poorer prognosis (4, 25).

It has been established that the pneumonia infection is related to a severe defect in the class -switching recombination process in the subgroup of familiar patients, resulting in a higher level of IgM (26). Valizadeh et al., (27) reported that the patients with familial CVID had a higher level of IgM compared to the sporadic patients, which resulted in a higher rate of pneumonia infection in the familial subgroup. In contrast, our sporadic subgroup patients who experienced more pneumonia incidence had higher IgM serum concentration in comparison with the familial subgroup. Several overlapping mechanisms including the increased antigen exposure, immune dysfunction, and genetic predisposition lead to a higher rate of autoimmunity among the patients with CVID (as an immunoglobulin disorder). However, the rate of autoimmunity was higher in our sporadic subgroup patients compared to the familial subgroup patients, but there were no significant differences between these two groups (11).

## Conclusion

Although, no significant difference was found on the grounds of the onset of symptoms, a median of 2 years lower delay of diagnosis was evident in the familial group. This finding could be explained by more careful screenings and more vigilant and informative parents in the families with another affected member. Thus, it is suggested to monitor the male offspring of the families with a history of HIGM, especially those with positive parental consanguinity at birth.

## Conflict of Interests

All the authors declared no conflict of interest.

## Acknowledgment

This research received no grant from any financial organizations or funding agency related to the public, commercial or not-for-profit sectors.

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