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Original Article

Autoimmunity in Patients with Hyper IgM Syndrome

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Abstract

Introduction: hyper-IgM (HIGM) syndrome is characterized by normal to increased serum IgM, as well as very low or undetectable IgG, IgA, and IgE. HIGM (also known as class-switch recombination (CSR) defects) patients indicate different clinical manifestations such as autoimmune disorders. The present study aimed to evaluate demographic data, clinical manifestation, and immunological findings in HIGM patients.

Methods: Clinical features and immunological data were collected from medical records belonged to the 79 Iranian HIGM patients diagnosed in Children's Medical Center in Iran. To compare clinical records and laboratory data, all HIGM patients were classified into two different groups as follows: patients with autoimmune disease and patients without autoimmune diseases.

Results: A total of 79 patients (60 male and 19 female) with median (IQR) age of 12 years old at the time of the study were enrolled (6-22.45). Autoimmunity diseases were seen in 19 patients (23.75%, 3 females and 16 males). Among the noninfectious manifestations, the hepatomegaly and spelenomegaly were significantly higher in the patients with autoimmunity ($p= 0.006$), compared to the patients without autoimmunity (p=0.006). The most common autoimmune presentations among HIGM patients were ITP (32%), juvenile rheumatoid arthritis (16%), autoimmune hemolytic anemia (11%), Sclerosing cholangitis (11%), Gullain-Barré syndrome, Evans syndrome, diabetes mellitus, and chrohn's disease.

Conclusions: The relationship between HIGM syndrome and autoimmunity disorders could lead to sever clinical complications. Therefore, we suggested that immunologists should be aware of this complications.

Keywords Hyper IgM Syndrome, Autoimmunity, Immune trobocytopenia purpura.

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Introduction

Hyper-immunoglobulin M (HIGM) syndrome or class switch recombination defect (CSRD) is a rare inherited type of primary immunodeficiencies (PIDs), which is characterized by normal or elevated serum concentration of IgM, as well as absent or decreased IgG, IgE, and IgA serum levels (1-3). Defects in class switch recombination, B cell signaling, and somatic hyper mutations (SHM) processes could be associated with HIGM. Several genes mutations have been identified to be implicated to the HiGM phenotype, including cluster of differentiation 40 ligand (*CD40L*), nuclear Factor-Kappa-B essential modulator (*NEMO/IKKγ*), *CD40*, activation-induced cytidine deaminase (*AICDA*), *uracil-DNA glycosylase (UNG), inhibitor of kappa light chain gene enhancer in B cells, alpha (IκBα),* nuclear factor kappa-B subunit 1 (NKFB1), ataxia telangiectasia mutated (ATM), post meiotic segregation increased 2 (PMS2), MutS Homolog 6 (MSH6), MutS Homolog 2 (MSH2), and INO80 (4). HIGM syndrome can be inherited either as X-linked (X-HIGM) or as autosomal trait. CD40L and NEMO defects are manifested in the form of X-HIGM, while AICDA, UNG, and CD40 deficiencies have an autosomal inheritance pattern (5, 6). The most common and severe form of HIGM is related to CD40L deficiency, which accounts for up to 70% of the disease cases and can affect both humoral and cellular immune mechanisms (2, 7, 8).

Based on the genetic mutations, patietns with HIGM phenotype indicate a broad spectrum of clinical manifestations such as recurrent and opportunistic infections, gastrointestinal (GI) problems, pulmonary complications, neutropenia, autoimmune and inflammatory disease, and malignancy (4, 9). Immunoglobulin replacement therapy is a functional treatment in reducing infections; however, hematopoietic stem cell transplantation (HSCT) can be prescribed in patients suffering from combined immunodeficiencies (10). Due to immune dysregulation, HIGM patients (especially XHIGM) are vulnerable to autoimmune diseases (11). Autoimmune diseases are different in subgroups of patients with HIGM phenotypes. Some types of autoimmune diseases such as diabetes mellitus, polyarthritis, autoimmune hepatitis, autoimmune hemolytic anemia, chronic uveitis, Crohn's disease, and immune thrombocytopenia are observed in AICDA-deficient patients (12, 13). Patients with CD40/CD40L deficiency may experience autoimmune hepatitis, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), hypothyroidism and discoid lupus erythematosus (14-17), and coombs positive hemolytic anemia and nephritis (18). NEMO deficient individuals have shown predisposition to autoimmune hemolytic anemia, IBD, and arthritis (11). Accordingly, this study was conducted to assess demographic records, clinical presentations, and laboratory data of HIGM syndrome patients

with autoimmune diseases or without it.

Materials and methods

Patients

This study was carried out on the recorded data of 166 HIGM patients who were referred to Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) during 1999-2019. HIGM diagnosis was accomplished based on European society criteria for immunodeficiencies diagnostic, including low serum IgG (2 SD below age-related normal values in at least twice measurement) and normal or elevated serum IgM, no evidence of profound T-cell deficiency 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). Individuals with immunodeficiencies resulted from other causes and imperfect diagnosis were excluded from the present study. All patients were enrolled in this study via informed consent.

Methods

To obtaine medical records of each patient, a comprehensive questionnaire was designed and some data such as (a) demographical data (including the onset age, the diagnosis age, delay in diagnosis, and consanguinity), (b) clinical manifestations (such as pulmonary infections, GI complications, allergy, enteropathy, lymphoproliferative disorder, and presences of autoimmune diseases), (c) lab tests results (including IgG, IgM, and IgA serum concentration, complete blood count (CBC), along with differentiation, and lymphocyte subsets evaluation) were exrtacted. The enzyme-linked immunosorbent assay (ELISA) was carried out to investigate the antibody response against polysaccharide (unconjugated pneumococcal vaccines) and protein (tetanus and diphtheria vaccines) (19). The autoimmune diseases were precisely diagnosed in HIGM patients regarding their clinical presentations (such as colonoscopy, endoscopy, and biopsy), laboratory data (including anti-double-stranded DNA (anti-dsDNA), anti-nuclear antibody (ANA), fluorescent anti-nuclear antibody (FANA), and using direct coombs test along with other para-clinical supplementary tests such as radiology investigation. The whole diagnosis process was performed under the supervision of a clinical immunologist. To compare clinical records and laboratory data, all HIGM patients were classified into two different groups as follows: (a) patients with autoimmune disease, (b) patients without autoimmune diseases.

Statistical analysis

SPSS software, version 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of this retroactive cohort study. To estimate the normal distribution of data, we conducted the Kolmogorov-Smirnov test, and data was also analyzed based on parametric or nonparametric values. For 2×2 categorical variable comparisons, Chi-square test was utilized as well as Fisher's exact test. The

numerical variables were compared by Mann-Whitney U, Kruskal-Wallis H test, and the parametric equivalent of the categorical comparisons.

Results

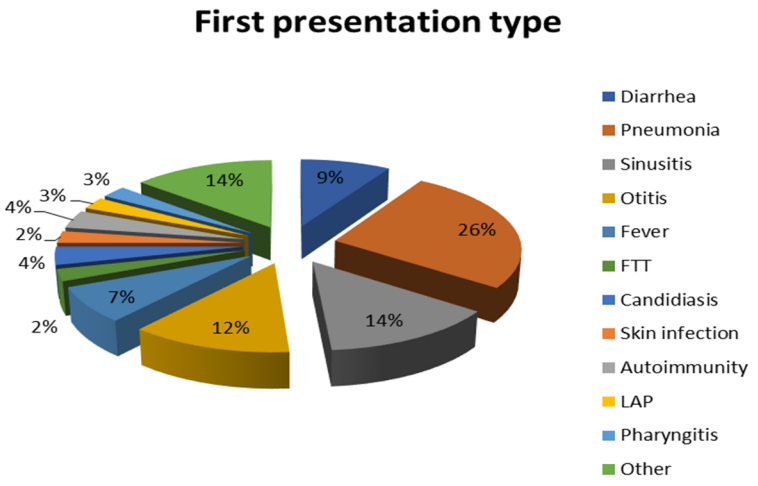
A total of 79 patients (60 male and 19 female) with median (IQR) age of 12 years old at the time of the study (6-22.45) were included in the present study. Median (IQR) date of diagnosis and delay in diagnosis were 53 (19.5-80) and 24 (7-53) months, respectively. Forty seven (59.5%) of the patients were born in consanguineous families. The positive family history of primary immunodeficiency was observed in 19 (24.1%) patients. Demographic characteristics of all HIGM patients are shown in **Table 1**. The most common clinical manifestation among HIGM patients was respiratory tract infectins (78.5%).

Table 1. Demographic data of HIGM patients with and without autoimmunity

Parameters	**Total patients (n=79)**	**AID (n=19)**	No AID (n=60)	***p*-value**
Age at the study time, m (IQR)	12 (6-22.45)	14.5 (9.08-25.25)	11 (6-22)	0.185
Age at diagnosis,m (IQR)	53 (19.5-80)	60(30.5-135)	49 (19.25-72)	0.317
Delay diagnosis, m(IQR)	24 (7-53)	33 (9-75)	24 (5.75-48)	0.302
Sex, N (%)				0.539
Male	60 (75.9)	16 (84.2)	44 (73.3)	
Female	19 (24.1)	3 (15.8)	16 (26.7)	
Consanguinity, N (%)	47 (59.5)	7 (46.7)	50 (40)	0.484
Family history, N (%)	19 (24.1)	4 (21.1)	15 (25)	1.0
Mortality, N(%)				0.078
Alive	49 (62)	10 (52.6)	39 (65)	
Dead	19(24.1)	8 (42.1)	11(18.3)	
Unknown	11 (13.9)	1 (5.3)	10 (16.7)	

*p-value <0.05 have been regarded as significant.Abbreviations: AID; autoimmune disease, WBC; white blood cells, Hb; Hemoglobin, Ig; Immunoglobulins, CD; Cluster of Differentiation, Y; year.Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.

Figure 1. First presentation type in HIGM patients



FTT; Failure to thrive, LAP: Lymphadenopathy

Table 2. Clinical manifestations and organ involvements of HIGM patients with and without autoimmunity

Parameter	Total patients (n=79)	AID (n=19)	No AID (n=60)	*p*-value
First presentation with Upper Resp , N(%)	16 (20.3)	2 (10.5)	14 (23.3)	0.332
First presentation with Lower Resp , N(%)	19 (24.1)	6 (31.6)	13 (21.7)	0.374
First pressntation Infection , N(%)	33 (41.8)	7 (36.8)	26 (43.3)	0.617
First pressntation (non resp) , N(%)	27 (34.2)	10 (52.6)	17 (28.3)	0.052
Pneumonia, N (%)	47 (59.5)	2 (12.5)	49 (32.7)	0.148
Sinusitis, N (%)	23 (29.1)	5 (31.3)	38 (25.3)	0.758
Bronchiectasis, N (%)	7 (9)	0 (0)	5 (3.3)	1.0
Clubbing, N (%)	10 (12.8)	0 (0)	2 (1.3)	0.057
URI, N (%)	44 (55.7)	12 (63.2)	32 (53.3)	0.452
LRI,N(%)	46(58.2)	13 (68.4)	33 (55)	0.301
Oral ulcer, N (%)	13 (16.5)	8 (42.1)	16 (26.7)	1.0
FTT, N (%)	20 (25.3)	2 (10.5)	18 (30)	0.131
Recurrent diarrhea, N (%)	24 (30.4)	8(42.1)	16 (26.7)	0.202
Chronic diarrhea, N (%)	20 (25.3)	6 (31.6)	14 (23.3)	0.548
Recurrent infection, N (%)	46 (58.2)	12 (63.2)	34 (56.7)	0.617
Otitis, N (%)	41 (51.9)	11 (57.9)	30 (50)	0.548
Allergy, N (%)	7 (9)	2 (10.5)	5 (8.5)	1.0
Splenomegally, N (%)	22 (27.8)	10 (52.6)	12 (20)	0.006
Hepatomegally, N (%)	15 (19)	8 (42.1)	7 (11.7)	0.006
LAP, N (%)	31 (39.2)	11 (57.9)	20 (33.3)	0.056
Malignancy, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0
BCGosis, N (%)	2 (2.5)	0 (0)	2 (3.3)	1.0
Respiratory tract infectin, N (%)	62 (78.5)	8 (50)	71 (47.3)	0.539
Urinary tract problem, N (%)	13 (16.5)	4(21.1)	9 (15)	0.501
Entropathy , N (%)	7 (8.9)	3 (15.8)	4 (6.7)	0.350
Eyes Problem , N (%)	6 (7.6)	1 (5.3)	5 (8.3)	1.0
Heart problem, N (%)	5 (6.4)	3 (15.8)	2 (3.4)	0.090
Hematologic problem, N (%)	34 (43)	10 (52.6)	24 (40)	0.332
Anemia, N (%)	30 (38)	9 (47.4)	21 (35)	0.333
Neutropenia, N (%)	22 (27.8)	8 (42.1)	14 (23.3)	0.112
Adenopathy , N (%)	10 (12.8)	1 (5.3)	9 (15.3)	0.436
Tonsil Hypoplasia , N (%)	5 (6.3)	2 (10.5)	3 (5)	0.589
Conjectivitis , N (%)	4 (5.1)	1 (5.3)	3 (5)	1.0
Leukopenia, N (%)	2 (2.5)	1 (5.3)	1 (1.7)	0.426
Thrombocytopenia, N (%)	11 (13.9)	7 (36.8)	4 (6.7)	0.003
Gastrointestinal problem, N (%)	23 (29.1)	9 (47.4)	14 (23.3)	0.044
Rheumatoid problem, N (%)	12 (15.2)	5 (26.3)	7 (11.7)	0.148
Skeletal problem, N (%)	6 (7.6)	2 (10.5)	4 (6.7)	0.627
Neurologic problem, N (%)	17 (21.5)	3 (15.8)	14 (23.3)	0.749
Dermatologic problem, N (%)	26 (39.2)	9 (47.4)	17 (28.3)	0.124
Liver problem, N (%)	15 (19)	8 (42.1)	7 (11.7)	0.006
Endocrine problem, N (%)	7 (8.9)	3 (15.8)	4 (6.7)	0.350
Multiple sites problem, N (%)	60 (76.9)	17 (89.5)	43 (72.9)	0.211
Facial Problem , N (%)	5 (6.3)	3 (15.8)	2 (3.3)	0.087

*p-value <0.05 have been regarded as significant.
Abbreviations: AID; autoimmune disease, No AID; no autoimmune disease, FTT; failure to thrive.
Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.

The most common autoimmune presentations among HIGM patients were ITP (32%), juvenile rheumatoid arthritis (16%), autoimmune hemolytic anemia (11%), Sclerosing cholangitis (11%), Gullain-Barré syndrome, Evans syndrome, diabetes mellitus, and chrohn's disease (Figure 2).

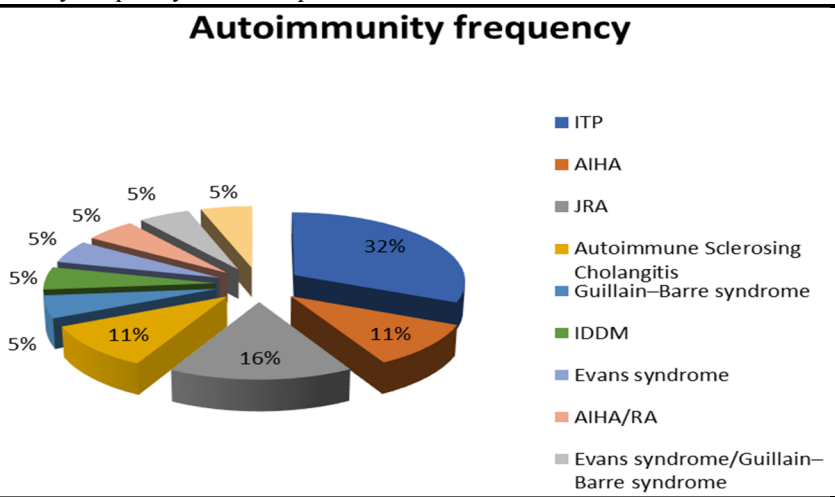
Based on laboratory data, there was no significant difference between patients with autoimmunity and without immunity (p>0.05). Laboratory features of the HIGM patients are shown in Table 3. Some of demographic data, clinical manifestations, and laboratory data of 19 HIGM patients with autoimmunity disease are presented in **table 4.**

Table 3. Laboratory data of HIGM patients with and without autoimmunity

Parameter	Total patients (n=79)	AID (n=19)	No AID (n=60)	*p*-value
WBC, 1000/µL (IQR)	8785 (5800-13800)	7000 (5800-12700)	9200 (5800-15200)	0.284
Neutrophil, % of total WBC (IQR)	37 (18-56)	42 (27.5-48.5)	35 (18-58)	0.854
Lymphocyte, % of total WBC (IQR)	52(29- 66)	50(28-66)	52.5(29.25-66.75)	0.815
Hb, g/dl (IQR)	11.25 (10-12.78)	11.1 (9.95-12.45)	12 (10-12.9)	0.353
Platelet, cell/µL (IQR)	258000 (197250-379000)	270000(173500-393000)	290000 (208500-373000)	0.705
IgG, mg/dl (IQR)	112.5(31.5-310)	155(100-310)	112 (22-310)	0.352
IgA, mg/dl (IQR)	9(2.75-27)	20 (4-33)	8 (2-25)	0.227
IgM, mg/dl (IQR)	235.5(105.75-480.25)	320 (103-400)	222 (106-500)	0.866
IgE, IU/ml (IQR)	3 (0.93-10)	6.3 (2.35-28.5)	2 (0.75-9.5)	0.141
$CD3^+$ lymphocytes %	67.5 (57.5-75)	61.5 (46.75-75.25)	69 (62-75)	0.160
$CD4^+$ lymphocytes %	30 (22.5-38.45)	27 (20-32)	32 (23-44)	0.075
$CD56^+$ lymphocytes, cell/µL (IQR)	10(3.5–15)	2 (1-16.5)	10 (5.75-15.5)	0.314
$CD16^+$ lymphocytes	7 (4.25-10.75)	8.5 (3-12)	7 (5-10.5)	0.921
$CD16^+56^+$ lymphocytes	3.5 (1.5-6)	2.5 (1.125-8.375)	5 (2-6)	0.569
$CD19^+$ lymphocytes %	16 (9-23.3)	17 (7.5-24)	16 (9.5-23)	1.0
$CD20^+$ lymphocytes, cell/µL (IQR)	14(8–24.150)	21 (12.15-25.3)	12 (7.5-19)	0.171

*p-value <0.05 have been regarded as significant.
Abbreviations: AID; autoimmune disease, WBC; white blood cells, Hb; Hemoglobin, Ig; Immunoglobulins, CD; Cluster of Differentiation, y; year, Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.

Figure 2. Autoimmunity frequency in HIGM patients



Abbreviations: ITP; Immune thrombocytopenia purpura, AIHA; Autoimmune hemolytic anemia, JIA; Juvenile idiopathic arthritis, IDDM; Insulin-Dependent Diabetes Mellitus, RA; Rheumatoid Arthritis.

Table 4. Data of 19 patients with autoimmunity

Patient	Sex	Age (M)	DOD (M)	Autoimmunity type	IgA, mg/dl	IgM, mg/dl	IgG, mg/dl
1.	M	168	60	Sclerosing cholangitis	20	400	646
2.	M	312	150	JRA	9	386	100
3.	M	180	6	JRA	92	320	100
4.	M	300	180	guillain barre / ITP / AIHA	30	383	320
5.	M	132	84	Diabetes	0	153	103
6.	F	324	45	AIHA/ITP	20	481	249
7.	F	240	204	AIHA/RA	19	480	310
8.	M	252	60	AIHA	0	2400	157
9.	M	120	120	AIHA	29	320	100
10.	M	144	12	Sclerosing cholangitis	119	327	155
11.	M	108	12	JRA	6	34	316
12.	M	420	53	ITP	0	84	0
13.	M	204	69	guillain barre	22	850	9
14.	M	96	48	ITP	0	20	240
15.	M	36	16	ITP	33	103	490
16.	M	110	72	ITP	4	80	99
17.	M	48	-	ITP	56	170	113
18.	F	108	-	ITP	20	106	32
19.	M	444	252	Crohn's	313	275	302

Discussion

In this study, we reported findings related to demographic, clinical features, and laboratory data of HIGM patients refferd to childrens medical center in Iran. Among the previously published cohort studies, this current study examined larger number of HIGM patients. HIGM syndrome has a wide variety and clinical involvement in various organs. In the present study, respiratory tract infections, especially pneumonia, was recognized as the most clinical manifestiation. In consistent with our studies, previous retrospective studies have shown that respiratory tract infection is the most common feature in almost all cases (20-23).

Primary antibody deficiencies (PADs) are characterised by recurrent and frequent infections (24-27), however, some of PADs manifest autoimmue disorders. In the present study, we have shown that out of all patients, 19of them manifested autoimmunity diseases (23.75%). Autoimmune disorders were observed in all HIGM patients with genetic defects, especially in the patients with AID (25%), NEMO (23%), and CD40L (20%) mutations (28). Autoimmune disorders, including autoimmune haemolytic anaemia, thrombo-cytopenia purpura, hepatitis, and arthritis have been formerly demonestrated in approximately 21% of HIGM patients with AICDA deficiency (29). Durandy et al. reported that due to AID deficiency, 25% of HIGM patients have autoimmune diseses such as hemolytic anemia, thrombocytopenia, and autoimmune hepatitis (30). However, this high rate of autoimmunity has not been seen in other studies by Minegishi et al. (31) and Revy et al. (32). Moreover, Autoimmuity has been observerd in HIGM patients with CD40L mutations. Yazdani *et al.* reported in a large cohort that

19.0% of HIGM patients with CD40L mutations presented autoimmune disorders (33). These reports demonstrated that HIGM patients with different genetic mutations copuld manifest autoimmune disorders; however, the rates are different among them.

Different forms of autoimmune disorders are observed in HIGM patients including autoimmune hemolytic anemia, juvenile rheumatoid arthritis, sclerosing cholangitis, gullain-barré syndrome, evans syndrome, diabetes mellitus, and chrohn's disease. The most common autoimmune presentations among our HIGM patients were ITP (32%), juvenile rheumatoid arthritis (16%), autoimmune hemolytic anemia (11%), sclerosing cholangitis (11%), gullain-barré syndrome, evans syndrome, diabetes mellitus, and chrohn's disease. High rate of idiopatic thrombocytopenia purpura in our HIGM patients is similar to the findings of Azizi et al. (28). However, in a study by Adriana et al., inflammatory bowel disease (IBD) was considered as the most common type of autoimmunity in HIGM patients (34, 35). Orange et al. (24) described 13 NEMO patients presenting autoimmune manifestations, including inflammatory bowel disease in 10, arthritis in 2 and autoimmune hemolytic anemia in only one of them (36). IBD disease has been also observed in a study performed by Levy et al., as they reported 6 patients with IBD (35). Difference rates of types of autoimmunity could be resulted from diferent genetic mutations in HIGM patients, thus it is suggetsted to investigate the prevalence of autoimmunity types in further cohort of HIGM patients. Accordingly, Thakker et al. showed that important causes of death in HIGM patients were due to liver failure caused by spondylitis cholangitis (37), thus, it seems that autoimmunity occurs in all types of HIGM disease with variable manifestations (34).

Autoimmune disorders as the second common firs presentation are considered as interesting point in our study. Among the noninfectious manifestations, the hepatomegaly and spelenomegaly were significantly higher in the patients with autoimmunity, compared to the patients without autoimmunity. This rate of autoimmunity in HIGM patients could be caused by the presence of IgM autoantibodies, impaired development of regulatory T cells, decreased peripheral control of B lymphocytes, and activation of autoreactive T cells that are considered as potential mechanisms for the autoimmune process in HIGM patients (34, 40, 41). Autoimmunity disorders has been identified with the symptoms and clinical course of many primary immunodeficiency disease. However, the pathogenesis of autoimmune diseases in PID patients are still unclear, the use of novel approaches such as whole exom sequencing, can help attaining higher understanding of autoimmune complications. In some patients with PID, autoimmune diseases, specially ITP and AIHA, may be the first or only clinical signs of the disease. The management of HIGM patients with autoimmunity is more complex than patients without autoimmunity because of different reasons, and clinical symptoms may overlap with the

underlying symptoms of immunodeficiency. The response to treatment in patients with autoimminy complication is often weaker compared to patients without autoimmunity; therefore, evaluating the level of antibodies, following positive results due to immunodeficiency, should be considered for the diagnosis of autoimmune disease in PID, and we suggested to investigate special tests for autoimmunity along with performing imonological examinations (42).

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

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