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Hematologic Problems in Hyper-IgM Patients

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Abstract

Background/objectives: HIGM syndrome is a rare kind of primary Immunodeficiency disease (PID) characterized by normal to the increased serum IgM and very low or undetectable IgG, IgA, and IgE. Broad spectrum of clinical manifestations and laboratory findings are observed in the HIGM patients including hematologic problem and malignancy. This study was conducted to assess demographic data, clinical manifestation, and immunological findings in the HIGM patients.

Methods: Lab findings and clinical presentations data of 79 Iranian patients diagnosed with HIgM syndrome were collected. All the patients were classified into two different groups including the patients with hematological problems and those without hematological problems.

Results: Hematologic problems were observed in 34 patients (43%, 23 males and 11 females). The most common hematologic problems types were anemia and leukemia (33 and 25%, respectively). Also, 19 patients (24.1%) had a family history of PID. Significant data that were higher in the patients with hematologic problems, were the oral ulcer (p=0.037), failure to thrive (p=0.022), recurrent diarrhoea (p=0.021), chronic diarrhoea (p=0.022), urinary tract infections (p=0.037), anemia (p=0.000), neutropenia (p=0.000), thrombocytopenia (p=0.001), gastrointestinal problem (p=0.011), neurologic problem (p=0.000), multiple site problem (p=0.000), platelet count (p=0.005), and IgG level (p=0.048).

Conclusions: The association between HIgM syndrome and hematologic problems could lead to severe clinical disorders. Therefore, it is necessary for immunologists to be aware of these situations.
Keywords: hyper IgM, hematologic problems, primary immunodeficiency disorders, malignancy

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Introduction

Hyper-Immunoglobulin M (HIGM) syndrome is a kind of primary immunodeficiency disorder (PID), which is also known as class switch recombination defect (CSRD) and immunoglobulin class switch recombination (Ig- CSR) deficiencies. HIGM syndrome was firstly described in 1961, and then characterized by normal or elevated serum level of IgM, decreased or absent serum concentrations of IgA, IgG, and IgE (1-4). Several genes mutations have been identified for the HIGM pathogenesis including cluster of differentiation 40 ligand (CD40L), nuclear Factor-Kappa-B essential modulator (NEMO/IKKγ), CD40, and 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), postmeiotic segregation increased 2 (PMS2), MutS Homolog 6 (MSH6), phosphatidylinositol 3-kinase catalytic delta (PIK-3CD), MutS Homolog 2 (MSH2), and INO80, which result in some Defects in class switch recombination, B cell signalling, and somatic hypermutations (SHM) (5). Most of the HIGM cases are X-linked (XHIGM), which is CD40 and NEMO mutation, and are responsible for 65-70% of all cases (2, 6). The HIGM patients are susceptible to recurrent and opportunistic infections, Gastrointestinal complications, autoimmunity, and hematologic problems (5, 7). Although Immunoglobulin replacement therapy is an effective choice for chronic infections in the HIGM patients, hematopoietic stem cell therapy (HSCT) should be also considered for the patients with the combined immunodeficiency (CID) (5, 8).

Recent investigations have identified that, some of the above-mentioned genes mutations can result in hematologic problems. Hematologic complications including anemia, leukopenia, thrombocytopenia, lineage cytopenia, pancytopenia, autoimmune hemolytic anemia (AIHA), and lymphomas were observed in 10% of the affected patients. These hematologic problems must be considered to clinicians during the HIGM patients' management process (9, 10).

Hence, the aim of the present study was to evaluate demographic data, clinical manifestation, and immunological findings in the HIGM patients with and without hematologic problems.

Materials and methods

Study population

The present study was conducted on 79 patients who were referred to Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) between 1999 and 2019, and the informed consents were obtained from all the patients.

In terms of the European Society criteria for Immunodeficiencies diagnostic (ESID), HIGM diagnosis was followed by normal or elevated serum IgM, low IgG serum level (2SD below age-related normal values in at least twice measurements), increased vulnerability to infections, immune dysregulation, cytopenia, the affected family member, and malignancy without any profound T-cell abnormalities (https://esid.org/Working- Parties/Registry-Working-Party/Diagnosis-criteria). Other types of the PID patients were excluded from the study.

Data collection

A comprehensive questionnaire was designed to obtain some data as follows: (a) demographical data (including the onset age, the diagnosis age, delay in diagnosis, and consanguinity), (b) clinical presentations (such as pulmonary infections, GI complications, allergy, enteropathy, lymphoproliferative disorder, presences of autoimmune diseases, and malignancy), (c) lab findings (including IgG, IgM, And IgA serum concentration, complete blood count (CBC) along with differentiation, and lymphocyte

subsets evaluation). Also, the enzyme-linked immunosorbent assay (ELISA) was performed to investigate the antibody response against polysaccharide (unconjugated pneumococcal vaccines) and protein (tetanus and diphtheria vaccines) (13). The whole diagnosis process was performed under the supervision of a clinical immunologist. To compare the clinical records and laboratory data, all the HIGM patients were classified into two different groups as (a) the patients with hematologic problems, (b) the patients without hematologic problems.

Statistical analysis

SPSS software, version 22 (SPSS Inc., Chicago, IL, USA) was used for performing the statistical analysis of this retroactive cohort study. To estimate whether the data were normally distributed, we performed the Kolmogorov- Smirnov test, and also data was analysed based on the parametric or nonparametric values. For 2 × 2 categorical variable comparisons, Chi- square test in addition to Fisher's exact test were utilized. The numerical variables were compared by Mann-Whitney U and Kruskal- Wallis H tests and the parametric equivalent of the categorical comparisons.

Results

Our study population were 79 HIgM patients (60 males and 19 females; with mean age of diagnosis, 53 months old). Demographic data of the HIgM patients with and without hematologic problems are shown in (**Table 1**). Respiratory tract infections were the most common clinical manifestations in the HIgM patients (78.5%) (**Table 2**). Pneumonia and otitis were the most common and the first presentations among all the HIgM patients (28% and 14%, respectively) (**Figure 1**).

Our data showed that, the patients with hematologic problems were from 23 consanguineous families (67.6%), similarly those patients without hematologic problems were from 24 consanguineous families (53.3%), and it was not significantly differed (p=0.199). Also, there was no significant relationship between the existence of family history and hematologic problems in the HIgM patients (p=0.662).

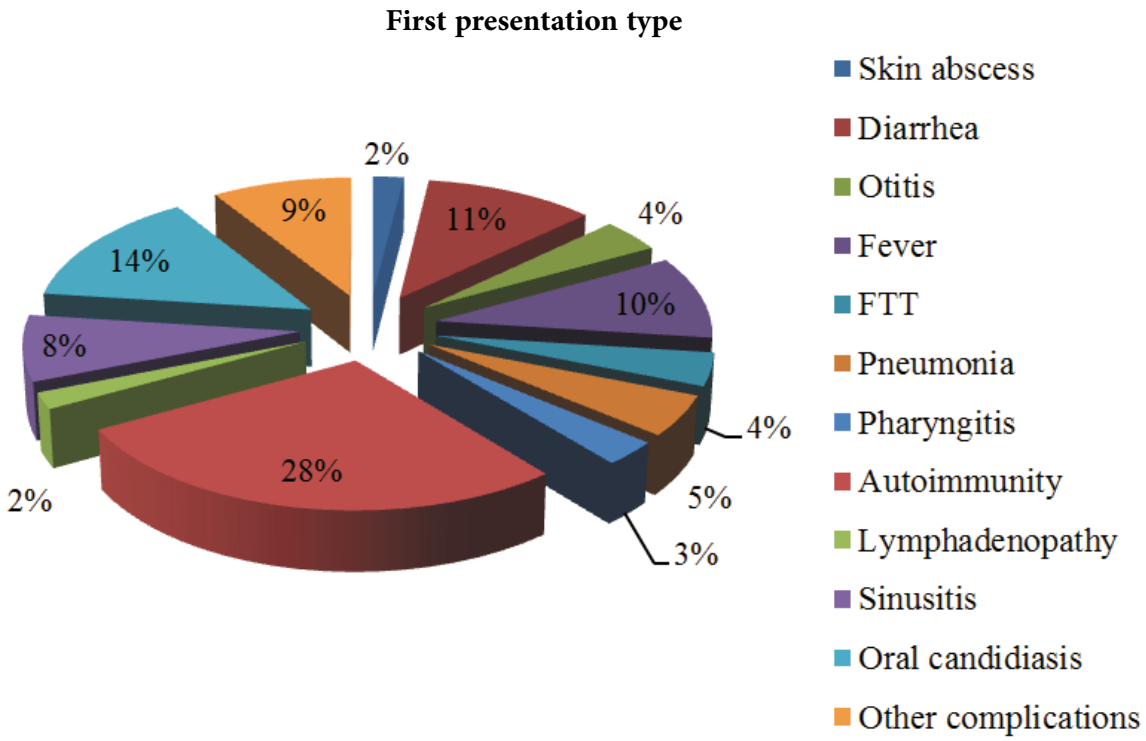

Figure 1. First presentation type in HIgM patients. FTT, Failure to thrive

There were hematologic problems in 34 cases (43%) (67.6% males and 32.4% females) (**Table 1**). Almost, the mean age at the study time was similar in the patients with and without hematologic problems and it was not significantly important (138 vs. 135 months) (p=0.690). Hematologic problems frequency in the HIgM patients are shown in **Figure2**. Anemia and leukemia were the most common hematologic problems in the HIgM patients (33% and 25%, respectively). There were some significantly important data in clinical manifestations (p<0.05). The rates of oral ulcer, FTT, and recurrent and chronic diarrhoea were significantly higher in the HIgM patients with hematologic problems than the HIgM patients without hematologic problems (26.5% vs. 8.9%; p=0.037, 38.2% vs. 15.6%; p=0.022, 44.1% vs. 20%; p=0.021, 38.2% vs. 15.6%; p=0.022, respectively).

Also, the rates of anemia, neutropenia, and thrombocytopenia were significantly higher in the HIgM patients with hematologic problems than the HIgM patients without hematologic problems (76.5% vs. 8.9%; p=0.000, 55.9% vs. 6.7%; p=0.000, 29.4% vs. 2.2%; p=0.001, respectively). Likewise, the rates of urinary tract, gastrointestinal, neurologic, and multiple sites problems were significantly higher in the HIgM patients with hematologic problems than the HIgM patients without hematologic problems (26.5% vs. 8.9%; p=0.037, 44.1% vs. 24.7%; p=0.011, 41.2% vs. 6.7%; p=0.000, 97.1% vs. 61.4%; p=0.000, respectively). Other clinical data are presented in **Table 2**.

The mean of Platelet count was significantly lower in the patients with hematologic problems in comparison with the patients without hematologic problems (2385000 vs. 333000 cell/μL; p=0.005).

Also, the mean level of IgG was significantly lower in the patients with hematologic problems than the patients without hematologic problems (90 vs. 124.5 mg/dl; p=0.048). Other laboratory data are shown in **Table 3**.

Some data of 34 HIgM patients with and without hematologic problems are shown in **Table 4**.

Table 1. Demographic data of HIgM patients with and without hematologic problems

Parameter	Total patients (n=79)	With hematologic problems (n=34)	Without hematologic problems (n=45)	p-value
Age at the study time, m (IQR)	135 (72-255)	138 (72–291)	135 (72-219.75)	0.690
Age at onset of disease, m (IQR)	12 (6-36)	12 (6–48)	9 (6–35)	0.763
Age at diagnosis, m (IQR)	53 (19.5-80)	60 (19-76)	49 (19.25-84)	0.763
Delay diagnosis, m (IQR)	18 (5-48)	16.5 (6.5-48)	18 (5-36)	0.578
Sex, N (%) Male	60(75.9)	23 (67.6)	37 (82.2)	0.133
Female	19 (24.1)	11 (32.4)	8 (17.8)	
Consanguinity, N (%)	47 (59.5)	23 (67.6)	24 (53.3)	0.199
Family history, N (%)	19(24.1)	9 (26.5)	10 (22.2)	0.662
Mortality, N (%)				0.321
Alive	49 (62)	19 (55.8)	30 (66.6)	
Dead	19 (24)	11 (32.3)	8 (17.7)	
Unknown	11 (13.9)	4 (11.7)	7 (15.5)	

s: N, Count; m, month. Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles].
*p-value <0.05 have been regarded as significant.

Table 2. Clinical manifestations and organ involvements of HIgM patients with and without hematologic problems

Parameter	Total patients (n=79)	With hematologic problems (n=34)	Without hematologic problems (n=45)	*p*-value
Pneumonia, N (%)	47 (59.5)	22 (64.7)	25 (55.6)	0.412
Sinusitis, N (%)	23 (29.1)	10 (29.4)	13 (28.9)	0.960
Bronchiectasis, N (%)	7 (9)	3 (8.8)	4 (9.1)	1.000
Clubbing, N (%)	10 (12.8)	6 (17.6)	4 (9.1)	0.317
Respiratory tract infections, N (%)	62 (78.5)	30 (88.2)	32 (71.1)	0.067
Oral ulcer, N (%)	13 (16.5)	9 (26.5)	4 (8.9)	0.037*
FTT, N (%)	20 (25.3)	13 (38.2)	7 (15.6)	0.022*
Recurrent diarrhea, N (%)	24 (30.4)	15 (44.1)	9 (20)	0.021*
Chronic diarrhea, N (%)	20 (25.3)	13 (38.2)	7 (15.6)	0.022*
Recurrent infection, N (%)	46 (58.2)	24 (70.6)	22 (48.9)	0.053
Allergy, N (%)	7 (9)	4 (11.8)	3 (6.8)	0.693
Splenomegaly, N (%)	22 (27.8)	13 (38.2)	9 (20)	0.073
Hepatomegally, N (%)	15 (19)	7 (20.6)	8 (17.8)	0.752
LAP, N (%)	31 (39.2)	16 (47.1)	15 (33.3)	0.216
Malignancy, N (%)	0 (0)	0 (0)	0 (0)	-
BCGosis, N (%)	2 (2.5)	0 (0)	2 (4.4)	0.503
Urinary tract infections, N (%)	13 (16.5)	9 (26.5)	4 (8.9)	0.037*
Heart problem, N (%)	5 (6.4)	4 (12.1)	1 (2.2)	0.156
Hematologic problem, N (%)	34 (43)	34 (100)	0 (0)	-
Anemia, N (%)	30 (38)	26 (76.5)	4 (8.9)	0.000*
Neutropenia, N (%)	22 (27.8)	19 (55.9)	3 (6.7)	0.000*
Leukopenia, N (%)	2 (2.5)	2 (5.9)	0 (0)	0.182
Thrombocytopenia, N (%)	11 (13.9)	10 (29.4)	1 (2.2)	0.001*
Gastrointestinal problem, N (%)	23 (29.1)	15 (44.1)	37 (24.7)	0.011*
Rheumatoid problem, N (%)	12 (15.2)	3 (18.8)	8 (17.8)	0.917
Skeletal problem, N (%)	6 (7.6)	5 (14.7)	1 (2.2)	0.079
Neurologic problem, N (%)	17 (21.5)	14 (41.2)	3 (6.7)	0.000*
Dermatologic problem, N (%)	26 (39.2)	14 (41.2)	12 (26.7)	0.174
Liver problem, N (%)	15 (19)	7 (20.6)	8 (17.8)	0.752
Endocrine problem, N (%)	7 (8.9)	3 (8.8)	4 (8.9)	1.000
Multiple sites problem, N (%)	60 (76.9)	33 (97.1)	27 (61.4)	0.000*

Abbreviations: N, Count; LAP; Lymphadenopathy, FTT; failure to thrive.
Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles].
*p-value <0.05 have been regarded as significant.

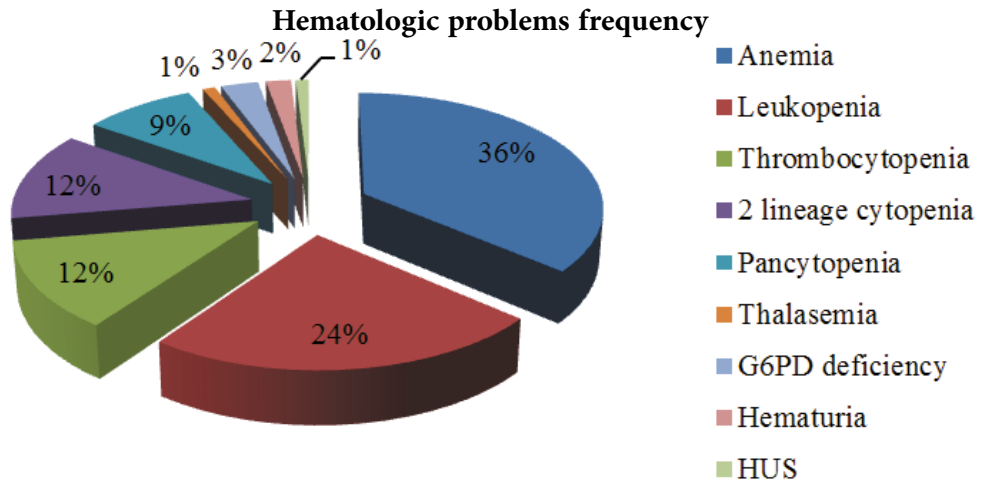

Figure 2. Hematologic problems frequency in HIgM patients. G6PD, glucose-6-phosphate dehydrogenase; HUS, uremic hemolytic syndrome

Table 3. Laboratory data of HIgM patients with and without hematologic problems

Parameter	Total patients (n=79)	With hematologic problems (n=34)	Without hematologic problems (n=45)	*p*-value
WBC, 1000/µL (IQR)	8785 (5800-13800)	9250 (4492.5-14375)	8350 (6800-12525)	0.724
Neutrophil, % of total	37 (18-56)	32.5(14-48.25)	43 (28-63)	0.051
WBC (IQR)				
Lymphocyte, % of total	52 (29- 66)	53.5(28-70)	51(29-64)	0.587
WBC (IQR)				
Hb, g/dl (IQR)	11.25 (10-12.78)	11(9.59-12)	12(10-13.8)	0.127
Platelet, cell/µL (IQR)	285000 (197250-379000)	238500(169500-353750)	333000(243250-423750)	0.005*
IgG, mg/dl (IQR)	112.5 (31.5-310)	90(15.25-242.25)	124.5(91-335.5)	0.048*
IgG1, mg/dl (IQR)	165 (16.5-313.5)		165(16.5-313.5)	
IgG2, mg/dl (IQR)	92 (51-178.75)	206 (206-206)	87 (39-135)	0.180
IgG3, mg/dl (IQR)	161.5(40-283)		161.5 (40-283)	
IgG4, mg/dl (IQR)	36 (1-71)		36 (1-71)	
IgA, mg/dl (IQR)	9 (4-27)	8 (1.5-23)	16 (4-49)	0.092
IgM, mg/dl (IQR)	241 (106- 450)	243(98.25- 678.25)	230 (106-400)	0.421
IgE, IU/ml (IQR)	3 (0.93-10)	3 (1-8)	2 (0.7-10)	0.920
CD3+ lymphocytes, cell/µL (IQR)	67.5 (57.5–75)	63 (57-79)	68 (57.5-74.5)	0.894
CD4+ lymphocytes, cell/µL (IQR)	30 (22.5–38.45)	31 (23-40)	30 (20-38.23)	0.596
CD8+ lymphocytes, cell/µL (IQR)	30 (20.25–41.6)	26 (18.25-38.75)	32.3 (25.35-42.13)	0.167

Parameter	Total patients (n=79)	With hematologic problems (n=34)	Without hematologic problems (n=45)	*p*-value
CD16+ lymphocytes, cell/μL (IQR)	7 (4.25–10.75)	6.3 (3.9-10)	7 (5-16)	0.427
CD56+ lymphocytes, cell/μL (IQR)	10 (3.5–15)	9 (4-11)	10 (2-16)	0.480
CD19+ lymphocytes, cell/μL (IQR)	16 (9–23.3)	13(8.75-23.25)	18 (9-23.6)	0.217
CD20+ lymphocytes, cell/μL (IQR)	14 (8–24.15)	17 (12-29.25)	13.65(7.25-23.45)	0.337

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

Table 4. Data of 34 HIgM patients with and without hematologic problems

NO	Sex	Age at diagnosis, m	Hematologic problem	IgG, mg/dl	IgA, mg/dl	IgM, mg/dl	Family history of PID	Other explanations
1.	Male	53	Neutropenia, thrombocytopenia	2300	8	>400		Oral candidacies/ telangiectasia/ respiratory distress
2.	Female	45	Anemia, neutropenia, thrombocytopenia, leukopenia	0	0	84	*	Conjunctivitis/ esophageal varices grade 2 / gallbladder hydrops / facial paralysis/ mastoiditis / cholecystitis/ pneumonia by pneumocystis carinii/ osteomyelitis
3.	Female	60	Anemia	27	3	206		Large adenoid
4.	Female	204	Anemia	100	9	19		LAP/ tonsil hypertrophy
5.	Male	76	Anemia	240	10	75	*	Oral candidacies/ anal abscess/ esophagitis/ dysgenesis / infection with cryptosporidium / hypocalcaemia/ upper respiratory infection/ tonsil hypoplasia/ fistula neck
6.	Male	150	Neutropenia	90	2	201		Ataxia / Hypokalemia
7.	Male	6	Anemia, neutropenia, thrombocytopenia	350	7	956		
8.	Female	60	Anemia, neutropenia	90	0	245		Osteomyelitis
9.	Male		Thrombocytopenia	99	4	80		
10.	Female		Anemia, neutropenia, thrombocytopenia	155	119	327		Sclerosing cholangitis/ ascites/ gum infection
11.	Male	13	Anemia, neutropenia	0	0	65	*	
12.	Male	18	Anemia, neutropenia	140	8	12	*	LAP/ oral candidacies
13.	Male	12	Anemia, neutropenia	157	0	2400		Oral candidacies/ hypo pigmentation
14.	Female	204	Anemia, neutropenia	206	26	763		
15.	Male	168	Anemia	550	70	650		Perforation ear/ minor thalassemia/ G6PD deficiency / giardiasis
16.	Female	16	Anemia	4	20	1467		Neck lymphadenitis

NO	Sex	Age at diagnosis, m	Hematologic problem	IgG, mg/dl	IgA, mg/dl	IgM, mg/dl	Family history of PID	Other explanations
17.	Female		Anemia, neutropenia	0	0	2590		
18.	Male	24	Anemia	42	4	164	*	Sinopulmonary/ rise liver enzyme
19.	Male	96	Anemia	17	8	1403		Neck lymphadenitis/ upper respiratory infection
20.	Male	23	Anemia, thrombocytopenia	249	20	481		CAH/ Parotidite / esophagitis/ colitis ulcerosa
21.	Male	16	Neutropenia	490	33	103		G6PD deficiency / hematuria/ microlithiasis in both kidney
22.	Male	42	Leukopenia	17	44	192		Ataxia / telangiectasia/ hypo pigmentation
23.	Female	72	Anemia, neutropenia	9	22	850	*	Pharyngitis / gallbladder hydrops / parotidite / orchid/ enteritis/ blastosistis hominis/ lymphoid hypertrophy/ tonsil hypertrophy
24.	Female	132	Anemia	61	27	3256		Pancytopenia/ ataxia/ Evans syndrome/ Alopecia
25.	Female	23	Anemia, neutropenia, thrombocytopenia	240	0	1.8		Kidney stones / hematuria/ gastrointestinal bleeding
26.	Male	66	Anemia, neutropenia, thrombocytopenia	0	45	158	*	Uremic hemolytic syndrome / conjunctivitis/ pneumocystis carinii / septic arthritis
27.	Male	50	Anemia, neutropenia, thrombocytopenia	376	0	241		
28.	Male	16	Neutropenia	76	6	217		
29.	Male	19	Anemia, thrombocytopenia	320	30	383		Hypothyroidism / sepsis
30.	Male	252	Anemia	17	15	80	*	Oral candidacies
31.	Male	60	Anemia, neutropenia, thrombocytopenia	310	19	480		
32.	Male	72	Anemia, neutropenia	2	3	360		ADHD / pharyngitis / kidney stones/ tonsil atrophy/ fever
33.	Male	60	Neutropenia	76	6	217		Anorexia
34	Male	60	Anemia	10	0	420	*	

Abbreviations: M, month; Ig, Immunoglobulins; PID, Primary immunodeficiency; LAP, Lymphadenopathy; G6PD, glucose- 6-phosphate dehydrogenase; CAH, congenital adrenal hyperplasia; ADHD, attention-deficit/ hyperactivity disorder.

Discussion

This present cohort study was conducted on 79 patients diagnosed with HIgM who were registered in the Research Centre for Immunodeficiencies at the children's medical Centre from 1999 to 2019. We determined and focused on 34 (43%) HIgM patients with hematologic problems.

Some recent studies have been identified hematologic problems in the HIgM patients. In this regard, some important mutations in HIgM syndrome had direct relationship with hematologic problems. For example, mutation in PIK3CD gene, which was diagnosed in HIgM syndrome is associated with hematologic malignancies (12, 13). PIK3CD gene encodes a catalytic subunit of phosphoinositide 3-kinase δ, which its name is p110δ protein. Activated phosphoinositide 3-kinase δ syndrome (APDS) is an autosomal dominant disorder caused by heterozygous and gain of function mutation in PIK3CD gene (14). Unlike other HIgM mutations, PIK3CD mutation is associated with severe hematologic malignancies, especially with chronic lymphoproliferation disorders (15). A large international cohort on 53 HIgM patients with APDS mutation, showed 13% incidence of lymphoma between the age of 18 months and 27 years old in their patients (9). Zhang et al. have been identified diffuse large B-cell lymphomas in the HIgM patients with PIK3CD mutation (16). Another study showed that, PIK3CD mutation was mostly associated with Epstein–Barr virus (EBV) and Cytomegalovirus (CMV) virus infections (15).

Moreover, in another study, it was shown that, some acute myeloid leukemia (AML) progenitors can be treated with a combination of mitogen-extracellular activated protein kinase (MEK) and PI3K p110δ inhibitors (17). Also, in another study, it was described that, PI3K p110δ inhibitors can be considered as an important treatment for chronic lymphocytic leukemia and follicular lymphoma (18). In a case report in 2006, a female with HIgM syndrome was reported to have large granular lymphocyte leukemia (LGL) and autoimmune hemolytic anemia (AIHA) (10).

Generally, the frequency of hematologic problems in the HIgM patients is more than 10%, based on the recent studies (8). Our HIgM patients had 33% anemia, 25% leukopenia, 13% thrombocytopenia and 2 lineage cytopenia, 9% pancytopenia, 3% G6PD deficiency and hematuria, and 1% thalassemia and uremic hemolytic syndrome (HUS), which indicated that, anemia was the most common type of hematologic problems in our patients. Also a recent study, in the field of autoimmunity, reported a HIgM case with AIHA (9). In our study, the rate of anemia was significantly higher in the patients with hematologic problems than the patients without hematologic problems. AIHA, especially Coombs positive, has been frequently seen in the X-linked HIgM patients (CD40L mutation) (19-21). It is because of, specific auto antibody IgM against different cells like anti-erythrocyte and anti-erythropoietin (20-22,24). In a study by Ouadani et al., it was reported that, 10 of 16 HIgM patients had anemia, which 2 of them had AIHA (25). In another study with 79 HIgM patients, 15% anemia were found (26). Sometimes, in the HIgM patients with parvovirus B19, red cell aplastic anemia may be observed that can be treated by IVIG therapy (27). Anemia was also reported in the HIgM patients with NEMO mutation. Also in a study, it was found that, one patient from 13 NEMO patients had AIHA (28).

The rates of neutropenia and thrombocytopenia were significantly higher in our patients with hematologic problems than the patients without hematologic problems. Neutropenia was seen in HIgM, CVID, and XLA. In this study, more than 1/3 HIgM patients had neutropenia (29).

Previously, the high frequency of neutropenia (68%) was reported by ESID in a population of 56 HIgM patients (20). Neutropenia may occur in PID, as a result of an infection or autoimmunity (30, 31). In another study on 79 HIgM patients, 60% neutropenia and 4% thrombocytopenia were found (26).

Also, the HIgM patients were prone to get immune thrombocytopenia, and it was shown that, the tolerance was not correctly done in this patients (19). Specially, in the HIgM patients with AID deficiency, thrombocytopenia was described (22, 25). In these studies, the reason of thrombocytopenia was found because of the existence of auto antibody of IgM isotype like antiplatelets (25).

The rate of oral ulcer, failure to thrive (FTT), recurrent and chronic diarrhoea, and gastrointestinal problems were significantly higher in our patients with hematologic problems than the patients without hematologic problems. In agreement with our data, recurrent oral ulcers usually with neutropenia, FTT and gastrointestinal infection with encapsulated bacteria were observed in 50% of the X-linked and AID deficient HIgM patients (20-22, 24). Also, a recent study showed that, some of the most common infections in primary antibody deficiency were diarrhoea from Giardia lamblia or Cryptosporidium parvum and oral ulcer (66.7% and 33.3% in HIgM, respectively) (29). A high rate of gastrointestinal and oral problems were reported as the first presentation of HIgM (32). In a case report study, an infant with an autosomal recessive form of HIgM caused by CD40 deficiency had FTT (33).

Some studies discussed that, oral ulcer and FTT are resulted from chronic neutropenia, and the examination of oral and growth situation is critical to imply a significant neutropenia (34, 35).

Other significant data that were higher in our HIgM patients with hematologic problems were urinary tract infections (UTI), neurologic, and multiple site problems. In a recent study on 13 HIgM patients, 2 patients had UTI with P. mirabilis and P. aeruginosa infections (25). In a study by Nabavi et al., UTI was reported in the HIgM patients (36). Also, in another study, the rate of UTI, neurologic, and multiple site problems in the HIgM patients were 9.3%, 0%, and 68.8%, respectively (37). Interestingly, in recent reports about ataxia telangiectasia (AT), the AT patients with class switching defect (CSD) and elevated IgM level had neurologic problems (38, 39). Also, in 2007, a X-linked HIgM patient was reported with multifocal leukoencephalopathy (40). However, there is no link between hematologic problems and UTI, and neurologic and multiple site problems in the HIgM patients, and we could not compare our data with the recent studies' data; therefore, performing further studies is recommended.

Regarding laboratory data, we found that, the mean level of IgG was significantly lower in our patients with hematologic problems than the patients without hematologic problems; however, there is no study to relate the low level of IgG to hematologic problems in the HIgM patients. We suggest further studies to investigate the relationship between these two issues in HIgM syndrome.

Conclusions

Hematologic problems could be observed in the HIgM patients, thus knowing the hematologic problems in these patients is important. Based on the relationship between the HIgM syndrome and hematologic problems, and the evidence of the presence of anti-IgM antibody against red blood cell and platelet; receiving blood for some the HIgM patients should be done with care due to the existence of autoantibodies. The HIgM patients with hematologic problems should be followed up longer than the patients without hematologic problems.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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