J Clin Immunol (2017) 37:559–574
DOI 10.1007/s10875-017-0420-8

ORIGINAL ARTICLE

Selective IgM Deficiency: Clinical and Laboratory Features of 17 Patients and a Review of the Literature

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Received: 8 March 2017 / Accepted: 6 July 2017 / Published online: 21 July 2017

Abstract
Purpose Primary selective IgM deficiency (sIgMD) is a primary immunodeficiency with unclear pathogenesis and a low number of published cases.
Methods We reviewed clinical and laboratory manifestations of 17 sIgMD patients. Serum IgM, IgG, and its subclasses, IgA, IgE, antibodies against tetanus toxoid, pneumococcal polysaccharides and *Haemophilus influenzae type b*, isohemagglutinins, and T and B lymphocyte subsets, expressions of IgM on B cells and B lymphocyte production of IgM were compared with previously reported case reports and a small series of patients, which included 81 subjects in total.
Results We found that some patients in our cohort (OC) and published cases (PC) had increased IgE levels (OC 7/15; PC 21/37), decreased IgG4 levels (OC 5/14), very low titers of isohemagglutinins (OC 8/8; PC 18/21), increased transitional B cell counts (OC 8/9), decreased marginal zone B cell counts (OC 8/9), and increased 21^{low} B cell counts (OC 7/9). Compared with the PC (20/20), only two of five OC patients showed very low or undetectable production of IgM after stimulation. A majority of the patients had normal antibody production to protein and polysaccharide antigens, basic lymphocyte subset counts, and expression of surface IgM molecules on B cells.
Conclusions Low IgM levels are associated with various immunopathological disorders; however, pathogenic mechanisms leading to decreased IgM serum level in selective IgM deficiency remain unclear. Moreover, it is difficult to elucidate how strong these associations are and if these immunopathological conditions are primary or secondary.

Keywords Selective IgM deficiency · primary immunodeficiency · infections · autoimmunity · allergy

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Introduction

Immunoglobulin M (IgM) is the first immunoglobulin isotype expressed on the cell surface of immature B cells during B lymphocyte lineage differentiation and represents the first antibody that is produced during an immune response after initial antigen encounter [1]. Circulating human polyclonal IgM is present in plasma at a concentration between approximately 0.5 and 2.0 g/l in healthy adults, with a half-life of about 5 days [2]. Polyreactivity, antimicrobial activity, and housekeeping functions, such as the capacity to promote the removal of apoptotic cells, belong among the key properties of IgM [3, 4].

Primary selective IgM deficiency (sIgMD) is thought to be a rare primary immunodeficiency disease (PID). The prevalence ranges from 0.03 to 3.80% in various studies [5–10]. It is characterized by low serum level of IgM (<0.20 g/l or <2 standard deviations below the age-adjusted mean) and normal IgG and IgA levels; however, the IgE levels can be increased [11]. The definition of sIgMD based on IgM levels remains

problematic compared to selective IgA deficiency (sIgAD), in which immeasurable level of IgA (<0.07 g/l) is a criterion for the diagnosis. In some previously published cases of patients with sIgMD, the IgM levels are just slightly below IgM reference ranges. This could explain the discrepancies in clinical and laboratory parameters reported among studies. No genetic or molecular defects have been established yet. The clinical features of these patients are variable. Although upper respiratory tract infections, e.g., rhinitis, otitis media, and sinusitis, were among the most common clinical symptoms found in sIgMD patients, they also presented with various other manifestations (e.g., sepsis, meningitis, and anaphylaxis). Nevertheless, some of the patients are asymptomatic [11].

Goldstein et al. described the clinical features of adult and pediatric patients with sIgMD in two review studies [6, 12]. Upper respiratory tract infections were among the most common clinical symptoms accompanied with autoimmune diseases and allergies. The course of the disease was asymptomatic in only 3% of sIgMD patients [6, 12]. On the other hand, only a few series that are primarily focused on the laboratory parameters of sIgMD patients have been published to date. In our study, we focused on previously reported cases of patients with sIgMD that contained their laboratory parameters, and we present the clinical and laboratory data of our cohort of 17 adult patients with sIgMD.

Methods

We examined the clinical and immunological features of 17 adult patients with sIgMD (referred to the Department of Clinical Immunology and Allergy of St. Anne's University Hospital in Brno and the Institute of Clinical Immunology and Allergy of Charles University Hospital in Hradec Kralove from 1995 to 2015).

In a PubMed literature search using the keywords "*IgM deficiency*" and "*Selective IgM deficiency*," 32 papers containing laboratory data of the included patients were identified.

The study was approved by the institutional ethics committee of St. Anne's University Hospital in Brno and University Hospital of Charles University in Hradec Kralove. Informed consents were obtained from the sIgMD patients for anonymous publication of their data.

Patient Characteristics

The study group consisted of 17 patients, 9 males aged between 22 and 70 years with a mean age of 43.8 years at the time of diagnosis and 8 females aged between 36 and 66 years with a mean age of 52.6 years at the time of diagnosis. All patients met the diagnostic criteria for primary sIgMD [5]. The presence of any other well-defined primary or secondary immunodeficiencies that are accompanied by decreased levels of IgM was considered an exclusion criterion.

Patient's charts were analyzed regarding clinical manifestations, and laboratory data was retrieved and evaluated for serum levels of IgG, IgG subclasses, IgA, IgM, and IgE immunoglobulins, antibody titers against tetanus toxoid (anti-TET), pneumococcal polysaccharides (anti-PPS) and *Haemophilus influenzae type b* (anti-HIB), isohemagglutinin (IH) levels, T and B cell lymphocyte subsets, expression of IgM on B cell surfaces and B lymphocyte production of IgM.

Laboratory Investigation

The serum immunoglobulin concentrations were measured by nephelometry. Autoantibody concentrations against extractable nuclear antigen, tissue transglutaminase, cardiolipin, double-stranded DNA, thyroglobulin, thyroid peroxidase, and rheumatoid factor were determined with enzyme-linked immunosorbent assay (ELISA). Autoantibodies against gastric parietal cells, smooth muscle, neutrophil cytoplasm, mitochondria, endomysium, basal glomerular membrane, and double-stranded DNA and antinuclear antibodies were determined by indirect immunofluorescence. Nephelometry was used to evaluate rheumatoid factor. Anti-TET, anti-PPS, and anti-HIB antibodies were measured with ELISA assays (*VaccZyme™ Immunoassay Kits*, *the Binding Site Group Ltd.*, *Birmingham*, UK).

Plasma anti-A and anti-B isohemagglutinins were investigated with a saline agglutination tube test with incubation to demonstrate IgM activity. Red blood cells, which possess the corresponding antigen A1 and/or B, were used for reactivity strength grading.

Immunophenotyping of lymphocyte subpopulations was performed with the Cytomix FC500 five-color cytometer (*Beckman Coulter Miami*, *FL*, *USA*). Lymphocyte subsets, including T lymphocytes ($CD3^+$), helper T lymphocytes (Th; $CD3^+CD4^+$), cytotoxic T lymphocytes (Tc; $CD3^+CD8^+$), B lymphocytes ($CD19^+$), and natural killer cells (NK; $CD16^+/CD56^+$), were identified using the following monoclonal antibodies (mAbs): fluorescein isothiocyanate (FITC) anti-CD45, phycoerythrin (PE) anti-CD4, phycoerythrin-Texas red X (ECD) anti-CD8, r-phycoerythrin-cyanine 5 (PC5) anti-CD3, PE-anti-CD56, ECD-anti-CD19 (*Cyto-Stat tetraCHROME*, Beckman Coulter, Miami, FL, USA) and PE-anti-CD16 (*Immunotech*, *Marseille*, *France*).

B cell subpopulations, including $CD21^{low}$ B cells (21low; $CD21^{low}CD38^{low}$), naïve B cells (NA; IgM^+CD27^-), marginal zone B cells (MZ; IgM^+CD27^+), switched memory B cells (SM; IgM^-CD27^+), and plasmablasts (PB; $CD27^{+++}CD38^{+++}$), were identified using the following mAbs: Krome Orange (KO) anti-CD45, PE-anti-CD24, r-phycoerythrin-cyanine 7 (PC7) anti-CD19, allophycocyanin

(APC) Alexa Fluor 750-conjugated anti-CD38 (*Beckman Coulter, Marseille, France*), brilliant violet 421 (BV421) anti-CD27, FITC-anti-IgD, peridinin chlorophyll (PerCP) Cy5.5 anti-IgM (*Biolegend*, *San Diego*, *USA*), and APC-anti-CD21 (*BD Pharmingen*, *San Jose*, *CA*, *USA*). The reference values published by Morbach et al. [13] were used.

T cell subpopulations, including naïve (CD45RA) and memory (CD45RO) $CD4^+$ and $CD8^+$ T cells, were identified using the following mAbs: KO-anti-CD45, PC7-anti-CD3, APC Alexa Fluor A700-conjugated anti-CD8, PE-anti-CD45RA, ECD-anti-CD45RO (*Beckman Coulter, Marseille, France*), and pacific blue (PB) anti-CD4 (*Exbio*, *Prague*, *Czech Republic*).

IgM production was measured with an ELISA assay after a 10-day incubation of peripheral blood mononuclear cells (10^6 PBMCs/well) with pokeweed mitogen (PWM) at three concentrations (2.0, 0.2, and 0.02 μg/ml) and *Staphylococcus aureus* Cowan I (SAC) at a concentration 1:1000 and 1:10,000. The reference ranges used in this article are the reference ranges of a local laboratory.

Statistical Analysis

The two-sided Mann–Whitney *U* test was applied, and *p*-values ≤0.05 were considered as statistically significant. If not otherwise indicated, the results are expressed as the mean ± SD.

Results

Our sIgMD Patient Cohort

Clinical Findings

Age at Time of Diagnosis The mean age at the time of sIgMD diagnosis was 47.9 ± 15.3 years (Table 1). The onset time could not be precisely determined because more than one third of the patients were asymptomatic with respect to infections (6/17). The low IgM level findings in these patients were incidental (Table 1).

Clinical Course of the Disease Increased susceptibility to infections, especially involving recurrent upper respiratory tract infections (i.e., ≥3 per year; 9/17; 53%) [14], pneumonia (3/17; 18%), urinary tract infections (3/17; 18%), sinusitis (2/17; 12%), otitis media (2/17; 12%), meningitis (2/17; 12%), recurrent colpitis (2/17; 12%), and furunculosis (2/17; 12%), was the most common clinical manifestation in our patients. Other infectious complications in individual patients included typhoid, erysipelas, and hepatitis B. Except two episodes of meningitis, no life-threatening infections were observed. No increased incidence of infections was recorded in one third of the patients (6/17; 35%) (Table 1).

Allergic disorders included allergic rhinitis (8/17; 47%), drug allergy (5/17; 29%), bronchial asthma (3/17; 18%), atopic dermatitis (2/17; 12%), urticaria (2/17; 12%), and bee sting allergy (1/17; 6%). No clinical symptoms related to allergic disorders were registered in three patients (3/17; 18%). Autoimmune manifestations included Sjögren's syndrome (3/17; 18%), systemic lupus erythematosus (2/17; 12%), thyreopathy (1/17; 6%), and alopecia (1/17; 6%). One patient suffered from rectal adenocarcinoma, one patient from basalioma and melanoma, and patient no. 9 developed thymoma and Good's syndrome 8 years after the sIgMD diagnosis was established (Table 1).

Treatment No prophylactic antibiotic treatment or immunoglobulin substitution was required in our patients except for patient no. 9 in whom immunoglobulin replacement therapy (IVIG) was initiated because of the transition of sIgMD into Good's syndrome. The treatment of all allergic disorders of the patients did not diverge from standard approaches.

Clinical Outcome and Mortality Two of our patients died during the observation period; one aged 71 years of rectal carcinoma, and the second one aged 76 years of undetermined reason.

In a female patient no. 9, sIgMD was diagnosed at the age of 51 years. Remarkably, a gradual decrease in IgG and IgA was observed at age of 54 years. Finally, her IgA dropped to 0.14 g/l, and her IgG dropped to 1.99 g/l, which led to the IVIG administration initiation. At the age of 59 years, Good's syndrome was diagnosed due to the discovery of thymoma.

Laboratory Findings

Serum Immunoglobulin Levels Within our 17 sIgMD patients, 6 had undetectable levels of serum IgM (<0.05 g/l) and 11 had IgM levels that ranged from 0.05 to 0.19 g/l. The serum levels of IgG and IgA were 11.89 ± 5.04 and 2.97 ± 1.93 g/l, respectively. Nearly half of the patients (7/15) had increased levels of IgE (122–2110 IU/ml). The IgG subclass concentrations (IgG_1–IgG_4) were evaluated in 14 of 17 sIgMD patients; half of the patients had normal levels (Table 2). One patient had reduced IgG_1 levels; one patient had reduced IgG_2 levels, and one patient had reduced IgG_1 and IgG_4 levels. Five patients had reduced or unmeasurable levels of IgG_4 (Table 2).

Antibody Levels The anti-TET, anti-PPS, and anti-HIB IgG antibody levels were evaluated in 11 of 17 patients. All of them had protective levels of antibodies except patient no. 5, who had decreased anti-PPS IgG antibody levels (8.1, >15.5 mg/l).

Table 1 Clinical manifestations and characteristics of sIgMD patients

No.	Sex	Age at time of			Reason for the first immunological investigation	Clinical manifestation	URTI	P	S	O	M	Other infections	Allergy	Autoimmunity	Malignancy or benign tumors
		S	D	M											
1	M	35	22	20	Cough, breathlessness (referred from GP)	Increased frequency of URTI	R	1	×	1	×	×	AR, AB, DA	×	×
2	M	76[a]	65	65	Generalized candidiasis (referred from GP)	Increased frequency of URTI, generalized candidiasis	R	×	×	×	×	UTI, VZV, TS, ERY	DA	×	×
3	M	71[a]	41	38	Recurrent furunculosis (referred from GP)	Recurrent furunculosis	NF	×	×	×	×	Furunculosis	DA	×	Rectal adenocarcinoma
4	M	33	26	21	Tiredness, subfebrile temperature (referred from GP)	Increased frequency of URTI	R	×	×	R	×	×	AR, AD	×	×
5	F	59	49	48	Cold urticaria (referred from GP)	Increased frequency of URTI	R	×	×	×	×	*H. pylori*	Cold urticaria	×	×
6	F	73	65	65	Allergic symptoms (referred from GP)	Asymptomatic	NF	×	×	×	×	×	Urticaria	SLE	×
7	F	77	66	63	Incidental finding of low IgM (referred from rheumatology)	Increased frequency of URTI	R	×	×	×	×	UTI	AR, DA	SLE, SS	×
8	F	78	63	63	Increased IgG and FW, leucopoenia (referred from hematology)	Increased frequency of URTI	R	1	×	×	×	UTI, RC	AR	SS	×
9	F	68	51	51	Incidental finding of low IgM (referred from hematology)	Increased frequency of URTI	R	×	R	×	1	RC	AR, AB, DA	×	Thymoma
10	M	57	65	65	Tiredness (referred from GP)	Asymptomatic	NF	×	×	×	×	×	×	Hypothyreosis	×
11	M	36	31	31	Incidental finding of low IgM (referred from reproduction clinic)	Asymptomatic	NF	×	×	×	×	×	×	×	×
12	M	39	32	32	Incidental finding of low IgM (referred from reproduction clinic)	Asymptomatic	NF	×	×	×	1	×	AR	×	×
13	F	42	38	38	Increased frequency of URTI (referred from GP)	Increased frequency of URTI	R	1	×	×	×	Hepatitis B	AR, AB	×	×
14	M	44	42	34	Recurrent furunculosis (referred from GP)	Recurrent furunculosis	NF	×	×	×	×	Furunculosis	AR	×	×
15	F	71	53	50	Suspicion of Sjögren's syndrome (referred from GP)	Asymptomatic	NF	×	×	×	×	×	×	SS, Alopecia	×
16	M	79	70	69	Recurrent skin carcinoma (referred from GP)	Asymptomatic	NF	×	×	×	×	×	Bee sting allergy	×	Basalioma melanoma
17	F	38	36	10	Incidental finding of low IgM (referred from allergy clinic)	Increased frequency of URTI	R	×	R	×	×	×	AD	×	×

S study, *D* diagnosis, *M* manifestation, *GP* general practitioner), *R* recurrent, *NF* normal frequency, *URTI* upper respiratory tract infections, *P* pneumonia, *S* sinusitis, *O* otitis media, *M* meningitis, *UTI* urinary tract infections, *RC* recurrent colpitis, *VZV* varicella zoster virus, *TA* typhus abdominalis, *ERY* erysipelas, *AR* allergic rhinitis, *AB* asthma bronchiale, *DA* drug allergy, *SLE* systemic lupus erythematosus, *SS* Sjögren's syndrome

[a] Year of death

After excluding the patients with proven autoimmune disease (patient nos. 6, 7, 8, and 15), positive antinuclear autoantibodies were observed in 5 of remaining 14 patients (Table 2). No other autoantibodies were detected during the follow-up period.

We performed ABO blood group testing by measuring isohemagglutinin titers (anti-A and anti-B antibodies in IgM class) in nine patients. One patient had the AB blood group; the remaining patients had low but detectable titers of the corresponding isohemagglutinins in the IgM class. In three patients, the IgM anti-A isohemagglutinin titer value was 2 (reference ranges: anti-A ≥ 32). In six patients, the IgM anti-B isohemagglutinin titer value ranged from 2 to 16 (reference ranges: anti-B ≥ 8) (Table 3).

Lymphocyte Subsets The lymphocyte subsets were determined in 11 patients. The absolute numbers and frequencies of the total T cells, Th and Tc cells, NK cells, and B cells were within the reference ranges in all investigated patients, except patient no. 9, who had a decreased Th cell percentage, patient no. 8, who had a decreased B cell percentage, and three patients (nos. 3, 7, and 8), who had decreased absolute B cell numbers. Moreover, patient no. 8 had a decreased absolute B cell count and B cell frequency (data not shown).

B lymphocyte subpopulations were analyzed in nine patients (Fig. 1). We found that eight out of nine patients had increased transitional B cell frequencies and absolute counts compared with the reference range [13].

The patients had variable naïve B cell counts; two patients had increased frequencies as well as absolute counts; three patients had normal frequencies but decreased absolute counts; two patients had normal frequencies and increased absolute counts, and two patients had increased frequencies but decreased absolute counts. Regarding marginal zone B cells, out of nine patients, six had decreased absolute numbers and percentages, two had decreased percentages but normal absolute counts, and one had both increased absolute counts and frequency. Regarding 21^{low} B cells, out of nine patients, seven had increased and two had normal percentages; out of seven patients, three had increased and one had decreased absolute counts. The numbers of switched memory B cells and plasmablasts were variable (Fig. 1a, b).

The T lymphocyte differentiation stages were analyzed in nine patients (Fig. 2). The absolute numbers and percentages of $CD4^+$ naïve T cells (Fig. 2a, b) were comparable with the reference range in healthy population [15]. Most of the patients had decreased absolute numbers of $CD4^+$ memory T cells; nevertheless, the frequency of these cells was normal in nearly all of the investigated patients

Table 2 Immunoglobulin concentrations and autoantibody presence in our sIgMD patient cohort

N/S/A	IgM (g/l)	IgG (g/l)	IgG_1 (g/l)	IgG_2 (g/l)	IgG_3 (g/l)	IgG_4 (g/l)	IgA (g/l)	IgE (g/l)	Autoantibodies
1/M/35	<0.05	9.41	9.00	2.23	0.77	0.30	2.29	157	ANA
2/M/76	0.17	11.34	7.32	2.45	0.31	0.52	2.73	32	Negative
3/M/71	0.05	8.03	5.23	3.06	1.29	0.32	2.52	157	Negative
4/M/33	<0.05	13.40	8.90	3.66	0.92	0.62	3.59	393	ANA
5/F/59	<0.05	8.13	5.41	1.02	0.30	0.17	8.13	2110	Negative
6/F/73	0.12	11.80	6.26	3.10	0.30	<0.07	6.33	171	ANA, Sm/RNP
7/F/77	0.18	11.20	6.81	2.61	0.20	0.25	5.21	<20	ANA
8/F/78	<0.05	30.30	27.94	1.60	0.70	0.07	1.77	41	ANA, RF, anti-SSA, anti-SSB, anti-GPC
9/F/68	<0.05	8.08	3.54	1.88	1.04	<0.08	0.63	<35	Negative
10/M/57	<0.05	13.50	8.80	5.70	0.71	<0.07	3.30	26	Negative
11/M/36	0.16	10.00	n.d.	n.d.	n.d.	n.d.	1.18	n.d.	ANA
12/M/39	0.17	9.59	n.d.	n.d.	n.d.	n.d.	1.45	n.d.	Negative
13/F/42	0.14	9.50	n.d.	n.d.	n.d.	n.d.	2.53	100	ANA
14/M/44	0.19	13.30	9.10	2.42	0.24	2.02	3.07	1121	Negative
15/F/71	0.16	15.00	12.00	2.67	0.20	<0.07	3.27	4	ANA, anti-SSA, anti-U1RNP, anti-TG
16/M/79	0.19	8.50	3.40	5.04	0.45	0.26	1.72	18	Negative
17/F/38	0.07	11.10	7.00	3.32	0.46	0.43	0.82	122	ANA

Reference ranges: IgM (0.46–3.04), IgG (7.51–15.6 g/l), IgG_1 (4.90–11.40 g/l), IgG_2 (1.50–6.40 g/l), IgG_3 (0.20–1.10 g/l), IgG_4 (0.08–1.40 g/l), IgA (0.82–4.53 g/l), IgA_1 (0.58–2.63 g/l), IgA_2 (0.12–1.41 g/l), IgE (0–100 IU/ml)

N/S/A number/sex/age, *M* male, *F* female, *ANA* antinuclear antibodies, *RF* rheumatoid factor, *anti-GPC* antibodies against gastric parietal cells, *anti-TG* anti-thyroglobulin antibodies, *Sm/RNP* antibodies against Smith antigen/ribonucleoprotein, *anti-U1 RNP* antibodies against U1 ribonucleoprotein

Table 3 Isohemagglutinin levels in our sIgMD patient cohort

N/S/A	Blood group	Anti-A IgM	Anti-B IgM
1/M/35	A	×	1
3/M/71	A	×	2
4/M/33	B	2	×
6/F/73	B	2	×
7/F/77	A	×	2
8/F/78	AB	×	×
9/F/68	0	2	8
13/F/42	A	×	4
15/F/71	A	×	16

Reference ranges: anti-A ≥ 32, anti-B ≥ 8

N/S/A number/sex/age, *M* male, *F* female, *IH* isohemagglutinins, *n.d.* not done, × not applicable

(Fig. 2a, b). Majority of the patients had normal absolute $CD8^+$ naïve T cell counts and increased absolute $CD8^+$ memory T cell counts while displaying increased percentage of both naïve and memory $CD8^+$ T cells (Fig. 2c, d) [16].

IgM Surface Expression IgM surface expression was measured in 10 patients and compared with 24 healthy donors (HDs). We found no significant difference in the B cell surface IgM expression between the patients and HDs (Fig. 3). The range of B cells bearing IgM on their surface was 70.8 ± 8.4% in the HD group and 80.2 ± 9.5% in the patient group. Additionally, we did not observe any significant difference in the median fluorescence intensity (MdFI) of the IgM expression on the transitional, naïve, marginal zone, IgM only ($CD27^+IgM^+IgD^-$), switched memory, $CD21^{low}$ B cells, and plasmablasts (data not shown).

IgM Production Testing of B lymphocyte IgM production was performed in five patients (nos. 1, 3, 7, 8, and 9) (Table 4). After stimulation with PWM and SAC, the IgM production was comparable to the HDs in three patients (nos. 1, 3, and 7) and decreased in two patients (nos. 8 and 9).

Previously Reported sIgMD Patients

A cohort of 81 sIgMD patients was derived from relevant articles. Serum IgM concentrations were available for 65 of

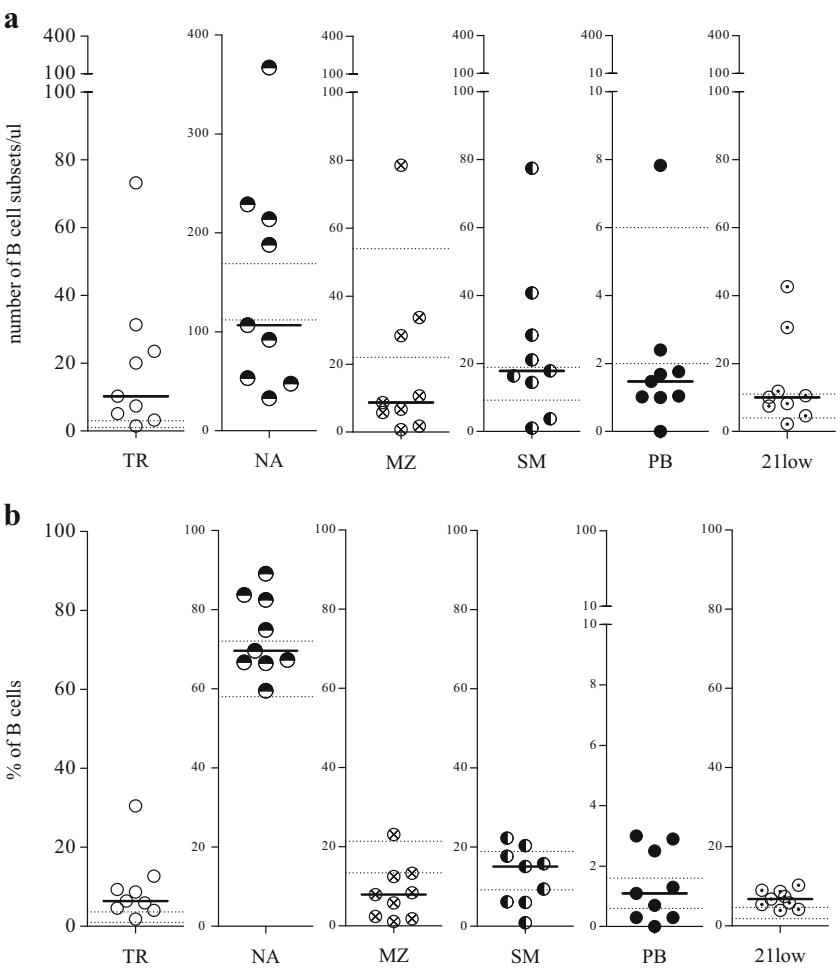


Fig. 1 Absolute counts (**a**) and percentages (**b**) of B cell subpopulations. *TR* ($CD24^{++}CD38^{++}$ transitional B cells), *NA* ($CD27^-IgM^+$ naïve B cells), *MZ* ($CD27^+IgM^+$ marginal zone B cells), *SM* ($CD27^+IgM^-$ switched memory B cells), *PB* ($CD27^{+++}CD38^{+++}$ plasmablasts), 21^{low} ($CD21^{low}CD38^{low}$ $CD21^{low}$ B cells). *Dotted lines* in the graph represent reference ranges: *TR* (1.0–3.6 %; 1–3/μl of blood), *NA* (58.0–72.1 %; 112–169/μl of blood), *MZ* (13.4–21.4 %; 22–54 /μl of blood), SM (9.2–18.9 %; 18–40 /μl of blood), PB (0.6–1.6 %; 2–6/μl of blood), 21^{low} (1.8–4.7 %; 4–11 μl of blood) [13]. The relative numbers of B cell subpopulations are shown as the mean ± SD.

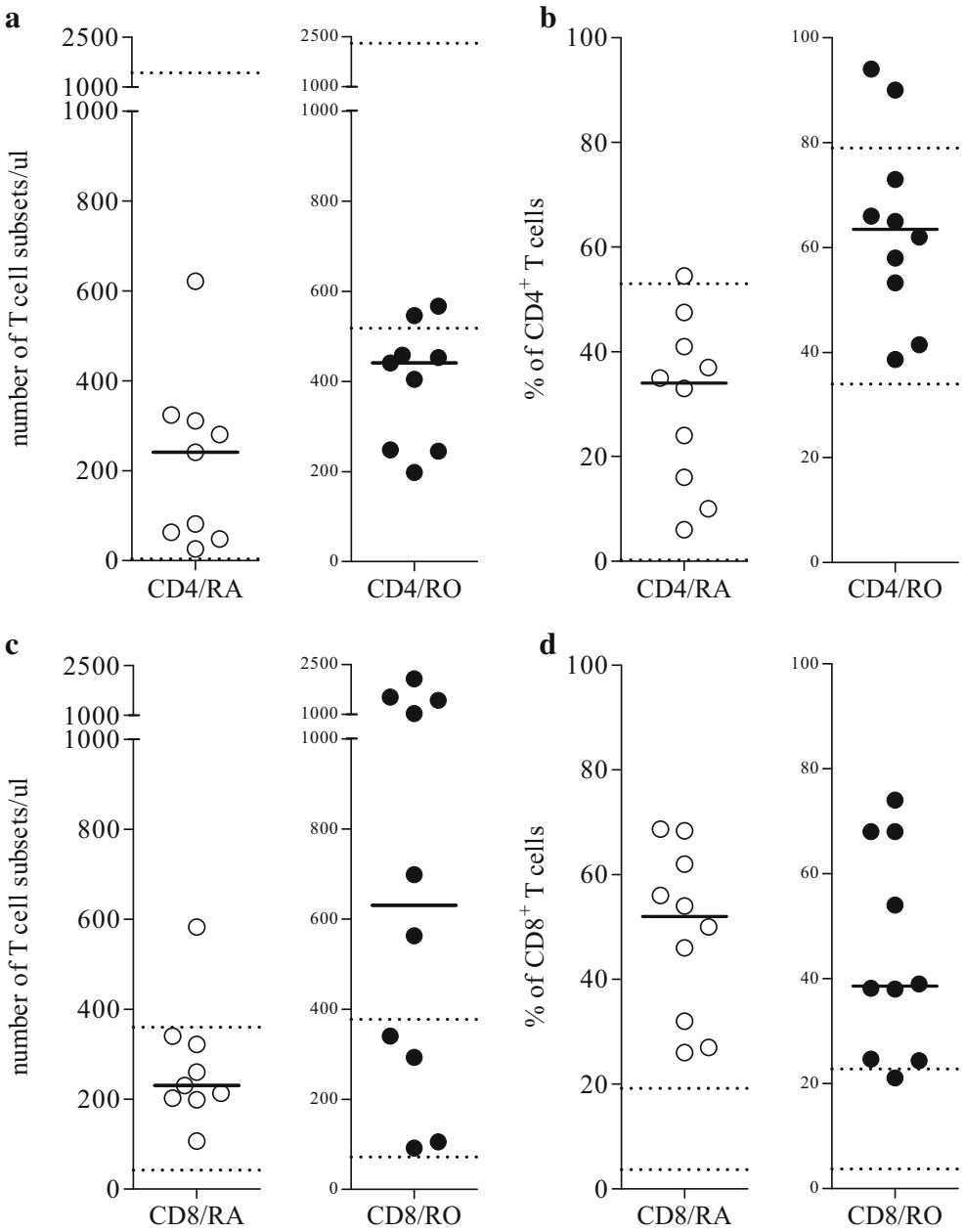


Fig. 2 Absolute counts and percentages of naïve and memory $CD4^+$ and $CD8^+$ T cells. *CD4/RA* (naïve T lymphocytes), *CD4/RO* (memory T lymphocytes), *CD8/RA* (naïve $CD8^+$ T lymphocytes), *CD8/RO* (memory $CD8^+$ T lymphocytes). *Dotted lines* in the graph represent reference ranges: *CD4/RA* (0.23–53 %; 4–1424/μl of blood), *CD4/RO* (34–79 %; 518–2300/μl of blood) [15]; *CD8/RA* (3.68–19.23 %; 42–360/μl of blood), *CD8/RO* (3.78–22.80 %; 72–377/μl of blood) [16]

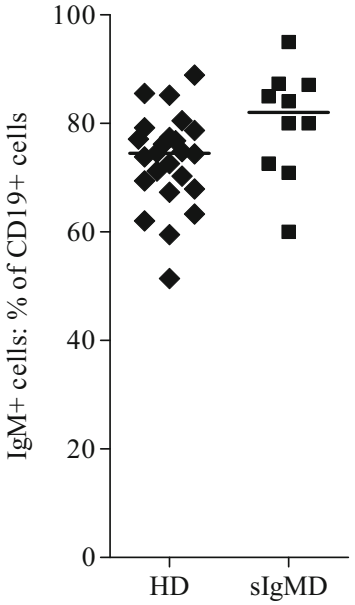
these patients; 15 had undetectable IgM levels (<0.05 g/l); 29 had IgM levels between 0.05 and 0.20 g/l; 21 had IgM levels between 0.21 and 0.39 g/l. IgE concentration data were available for 37 of these patients; 21 patients had increased IgE levels (124–8900 IU/ml) [8, 17–42].

The level of antibodies against protein and polysaccharide antigens was available for 20 out of 81 patients. Protective levels against TET, PPS, and diphtheria toxoid were observed in 11/14, 4/7, and 5/9 patients, respectively. The responses to other vaccine against bacterial or viral antigens are shown in Table 5.

Isohemagglutinin titers were determined in 21 out of 81 patients. Low but detectable anti-A or anti-B antibody titers were observed in 18/21 patients. Specifically, the anti-A and anti-B isohemagglutinin titer range was 1–32 in 15/18 patients, and 3/18 had natural isohemagglutinins present without a detailed specification (Table 6).

The lymphocyte populations were reviewed for 47 previously reported patients. Not all the subsets were measured for all the patients; nevertheless, the sIgMD patients had normal percentages of $CD3^+$ T cells (mean 74.7 ± 9.5%; 60–85%), $CD4^+$ cells (40.8 ± 14.3%; 28–57%), $CD8^+$ cells (31.1 ± 13.6%; 10–39%), NK cells (9.8 ± 5.2%; 7–31%), and B cells (12.6 ± 6.8%; 6–19%) [8, 17–19, 22, 25, 26, 28, 29, 32, 33, 35, 37, 38, 40–42].

B lymphocyte subpopulations were analyzed individually in three patients [10, 26, 38] and in cohorts of 16, 29, and 20 sIgMD patients [43–45]. The cell numbers were variable.



HD (healthy donors), sIgMD (patients with sIgMD)

Fig. 3 IgM surface expression on $CD19^+$ B cells

Belgemen et al. observed normal naïve and marginal zone B cell frequencies but a decreased frequency of switched memory B cells [38]. Low levels of switched memory B cells were also described in a patient in a study conducted by Saini et al., along with a decreased frequency of marginal zone B cells [10]. A patient in a case report by Ideura et al. had an increased frequency of naïve B cells, decreased frequency of marginal zone B cells, and normal frequency of switched memory B cells [26]. Çipe et al. also observed decreased marginal zone B cell levels in a cohort of 16 patients [43]. Recently, in a cohort of 29 patients, Mensen et al. described that these patients had significantly increased transitional B cells ($CD38^{hi}CD24^{hi}$) and decreased IgM only ($CD27^+IgM^+IgD^-$) and switched ($CD27^+IgM^-IgD^-$) and non-switched ($CD27^+IgM^+IgD^+$) memory B cells [44]. Additionally, in a cohort of 20 patients, Louis et al. described significant increase of $CD21^{low}$, IgM memory B cells, Breg cells, and CD8 Treg cells and significant decrease of germinal center B cells, $CXCR3^+$ naïve, and memory B cells [45].

Cell proliferation after mitogen stimulation (PWM, phytohemagglutinin or concanavalin A) was measured in 23 out of 81 patients. T lymphocytes proliferated normally after mitogen stimulation in 17/23 patients, but the proliferative response was impaired or diminished in 6/23 patients (Table 7). B cell mitogen stimulation by SAC was performed in 6/23 patients resulting in low response in all of them (Table 7).

Data regarding IgM surface expression were available for 27 out of 81 patients. Surface IgM was present on B cells in normal levels in 21/27 patients, and the expression was decreased in 6 patients; however, in 3 of these patients, it was normalized after a 7-day incubation with PWM (Table 7).

PWM-induced immunoglobulin production by PBMCs over a 7-day culture period was measured in 20 out of 81 patients. All of them had very low or undetectable IgM production after stimulation, although IgG and IgA immunoglobulin production was normal or nearly normal (Table 7).

Table 4 IgM concentration (μg/l) after 10-day stimulation with PWM and SAC

	No.	PWM			SAC	
		2.0 μg/ml	0.2 μg/ml	0.02 μg/ml	1:1000	1:10,000
P	1	176	1564	2023	1289	1037
P	3	280	201	18	106	3326
P	7	175	198	58	70	289
P	8	12	11	6	0	0
P	9	12	11	28	6	128
HD	1	47	234	782	3962	5333
HD	2	86	110	557	103	68
HD	3	228	151	116	176	139
HD	4	290	180	227	240	210
HD	5	383	461	554	52	404

P patient, *HD* healthy donor, *PWM* pokeweed mitogen, *SAC* *Saccharomyces cerevisiae* Cowan I

Discussion

Primary sIgMD was first described by Hobbs et al. in 1966 in two boys who suffered from fulminant meningococcal septicemia and also had very low levels of IgM [46]. Increased susceptibility to infections is indeed the most common manifestation of sIgMD [6, 8, 44]. This may be explained by the role of IgM in primary antibody responses, which cannot be completely compensated for by other immunoglobulins [47–49]. The critical role of IgM in response against bacterial or viral infections was repeatedly demonstrated. For example, soluble IgM (sIgM)-deficient mice were unable to eradicate bacterial infections caused by cecal ligation and puncture [49], and they displayed significantly reduced virus clearance ability and survival rates compared with wild-type mice [50]. Moreover, the presence of specific neutralizing IgM antibodies early in the course of Nile virus infection limited viremia and prevented dissemination into the central nervous system [51]. IgM antibodies enhanced the primary antibody response to sheep erythrocytes [52], and deficiency in secretory IgM resulted in delayed maturation of response to T cell-dependent antigens [53]. Furthermore, it was shown that IgM antibodies might attenuate the infectious consequences of a lack of other immunoglobulin isotypes in patients with hyper-IgM syndrome and polyvalent IgG replacement therapy might not

Table 5 Antibody levels against protein and polysaccharide antigens in the reviewed sIgMD patients

N/S/A	Anti-TET response (IU/ml)	Anti-PPS response (μg/ml)	Anti-DPT response (IU/ml)	Other vaccination response	Ref.
58/F/15	Adequate	1/6	Adequate	n.d.	[24]
61/M/49	Adequate	Adequate	n.d.	n.d.	[25]
64/>M/6	Adequate (6.31)	5/12	Adequate (0.740)	n.d.	[21]
65/F/14	Adequate (>3)	8/12	Adequate (>7.000)	n.d.	[21]
66/F/15	Adequate	1/6	Adequate	n.d.	[21]
68/M/58	n.d.	n.d.	Inadequate (0.065)	n.d.	[30]
71/M/11	n.d.	Inadequate	n.d.	n.d.	[32]
73/F/16	n.d.	n.d.	n.d.	Adequate response to rubella, HSV, EBV VCA (IgG, IgA but not IgM), EBV EA-DR (IgG)	[34]
74/F/59	Adequate (0.5)	n.d.	n.d.	Inadequate response to rubella (IgG < 5 IU/ml)	[35]
78/M/13	Adequate	n.d.	Adequate	Adequate response to measles, mumps, rubella, pertussis	[10]
80/M/6.5	n.d.	Adequate	n.d.	Adequate response to poliovirus	[38]
1/F/3	Inadequate	n.d.	n.d.	Inadequate response to *E. coli*	[18]
2/M/9	Inadequate	n.d.	n.d.	Inadequate response to *E. coli*	[18]
25/F/12	Adequate	n.d.	Inadequate	Inadequate response to *S. typhi*	[42]
63/M/10	n.d.	n.d.	n.d.	Adequate response to rubella and CMV	[27]
69/M/52	Adequate	n.d.	Inadequate	n.d.	[31]
70/M/41	Adequate	n.d.	Inadequate	n.d.	[31]
75/M/65	Inadequate	n.d.	n.d.	n.d.	[36]
76/M/72	Adequate	n.d.	n.d.	n.d.	[36]
81/M/21	n.d.	n.d.	n.d.	Adequate response to vaccinia and variola	[39]
Impaired specific antibody response to pneumococcal antigens in 5 out of 11 studied patients (45%)					[8]

N/S/A number/sex/age, *anti-DPT* antibodies against diphtheria toxoid, *HSV* herpes simplex virus, *EBV* Epstein–Barr virus, *CMV* cytomegalovirus, *E. coli Escherichia coli*, *S. typhi Salmonella typhi*, *EA-DR* antigen diffused/restricted, *VCA* viral capsid antigen, n.d. not done

Table 6 Isohemagglutinin levels in the reviewed sIgMD patients

N/S/A	Blood group	Isohemagglutinins		Reference ranges	Ref.
		Anti-A	Anti-B		
1/F/3	n.d.	×	8	n.m.	[18]
2/M/9	n.d.	16	×	n.m.	[18]
10/M/65	A Rh+	0	×	n.m.	[33]
58/F/15	n.d.	Isohemagglutinins 16		4–64	[24]
60/M/3	B Rh+	1	×	>10	[17]
64/M/6	n.d.	16	8	1–64	[21]
66/F/15	n.d.	16		4–64	[21]
69/M/52	A	×	4	n.m.	[31]
70/M/41	0	16	4	n.m.	[31]
71/M/11	0	16	4	n.m.	[32]
73/F/16	0 Rh+	4	2	>32	[34]
75/M/65	B Rh−	0	×	n.m.	[36]
76/M/72	A Rh+	×	Very weak	n.m.	[36]
77/M/60	n.d.	Present	Present	n.m.	[36]
78/M/13	n.d.	Isohemagglutinins >128		n.m.	[10]
79/M/16	0 Rh+	32	2	n.m.	[37]
80/M/6.5	B Rh+	2	×	>10	[38]
81/M/21	B	16	×	n.m.	[39]
25/F/12	B Rh+	<2	×	n.m.	[42]
59/F/3.5	n.d.	2	×	>10	[20]
72/M/6	n.d.	×	1	5–640	[22]

N/S/A number/sex/age, *M* male, *F* female, *n.d.* not done, × not applicable, *n.m.* not mentioned

Table 7 Functional cell characteristics in the reviewed sIgMD patients

	Proliferation and other functional tests	Immunoglobulin production	Surface molecule expression	Other cell information	Ref.
1/F/3	Normal thymidine uptake in response to PHA, ConA, and PWM stimulation	Very low IgM and IgA and normal IgG production in PWM-induced Ig production by PBMC during 7-day culture	Normal or high percentage of sIgM cells, normal differentiation into IgM secreting cells in vitro	n.m.	[18]
2/M/9	Reduced thymidine uptake in response to PHA, ConA, and PWM	No detectable IgM or IgA and very reduced IgG level production in PWM-induced Ig production by PBMC following 7-day culture	Normal or high percentage of sIgM cells, normal differentiation into IgM secreting cells in vitro	n.m.	
3/M/58	E-RFC normal percentage 72% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of IgM after 7-day stimulation of PBLs with PMW (10 μg/ml)	Normal smIgA, smIgM and smIgD reduced smIgG, normal surface IgG, IgA, and IgM after 7-day incubation with PWM	Co-culture of normal B cells with patients' T cells failed to synthesize normal amounts of IgM coculture of irradiated T cells from the patients with normal B cells synthesized sufficient amounts of IgM	[28]
4/F/73	E-RFC normal percentage 84% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Reduced smIgA, smIgG, smIgD, and smIgM, normal surface IgG, IgA, and IgM after 7-day incubation with PWM		
5/F/71	E-RFC normal percentage 74% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG, smIgD, and smIgM, normal surface IgG, IgA, and IgM after 7-day incubation with PWM		
6/F/53	E-RFC normal percentage 88% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Reduced smIgA, smIgG, smIgD, and smIgM normal surface IgG, IgA and IgM after 7-day incubation with PWM		
7/F/29	E-RFC normal percentage 74% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG and smIgD reduced smIgM, normal surface IgG, IgA, and IgM after 7-day incubation with PWM		
8/M/30	E-RFC normal percentage 75% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG, smIgD and smIgM normal surface IgG, IgA and IgM after 7-day incubation with PWM		
9/M/48	E-RFC normal percentage 56% (67.3 ± 4.0)	Normal levels of secreted IgG and IgA, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG and smIgM, reduced smIgD, normal surface IgG, IgA, and IgM after 7-day incubation with PWM		
10/M/65	E-RFC normal percentage 80% (67.3 ± 4.0)	Normal levels of secreted IgG, lower levels of secreted IgM after 7-day stimulation of PBL with PMW (1 μg/ml)	Normal smIgA and smIgG sIgM not present	n.m.	[33]

Table 7 (continued)

	Proliferation and other functional tests	Immunoglobulin production	Surface molecule expression	Other cell information	Ref.
11/F/44	n.d.	Almost normal levels of secreted IgG and IgA, low levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG, smIgD and smIgM	n.m.	[40]
12/F/62	n.d.	Almost normal levels of secreted IgG and IgA, low levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG, smIgD, and smIgM	n.m.	
13/F/51	n.d.	Almost normal levels of secreted IgG and IgA, low levels of secreted IgM after 7-day stimulation of PBL with PMW (10 μg/ml)	Normal smIgA, smIgG, smIgD, and smIgM	n.m.	
14/F/60	n.d.	PBL showed class non-specific hyporesponsiveness to PWM; however, the fall in IgM-ISC was greater than that of the other isotypes	Normal smIgA, smIgG, and smIgM increased smIgD	n.m.	
15/M/4	Impaired proliferation response to PHA and ConA	n.d.	IL-2 receptor-positive lymphocytes (measured by anti-CD25 moAb): 13% (normal range 0–3%)	Circulating B cell numbers in all three IgM-deficient patients were normal, as was the ability of B cells to synthesize Ig under the influence of normal T cells in response to PWM stimulation	[19]
16/F/3	Impaired proliferation response to PHA and ConA	n.d.	IL-2 receptor-positive lymphocytes (measured by anti-CD25 moAb): 0% (normal range 0–3%)		
17/F/2.5	Impaired proliferation response to PHA and ConA	n.d.	IL-2 receptor-positive lymphocytes (measured by anti-CD25 moAb): 19% (normal range 0–3%)		
18/M/3	Normal proliferation response to PHA and ConA	n.d.	IL-2 receptor-positive lymphocytes (measured by anti-CD25 moAb): 0% (normal range 0–3%)		
19/M/50	Almost normal proliferation of T cells after PHA and ConA stimulation, low proliferation of B cells to SAC	sIgMD B cells + sIgMD T cells: 1% PWM (production of one third to one tenth of the control level of IgM) sIgMD B cells + normal T cells: 1% PWM (production of one fourth to two thirds of the control level of IgM) no difference in IgG and IgA production between patient and control B cells under the same conditions IgM production by the control B cells	Normal smIgA, smIgD and smIgM decreased smIgG	n.m.	[41]
20/M/57	Almost normal proliferation of T cells after PHA and ConA stimulation, low proliferation of B cells to SAC		Normal smIgG, smIgD and smIgM increased smIgA	n.m.	
21/M/22	Almost normal proliferation of T cells after PHA and ConA stimulation, low proliferation of B cells to SAC		n.d.	n.m.	

Table 7 (continued)

	Proliferation and other functional tests	Immunoglobulin production	Surface molecule expression	Other cell information	Ref.
22/M/34	Almost normal proliferation of T cells after PHA and ConA stimulation, low proliferation of B cells to SAC	co-cultured with patient T cells was Similar to the controls	Normal smIgA, smIgG and smIgM decreased smIgD	n.m.	
23/M/57	Almost normal proliferation of T cells after PHA and ConA stimulation, low proliferation of B cells to SAC		Normal smIgA, smIgG and smIgM decreased smIgD	n.m.	
24/F/37	Almost normal proliferation of T cells after PHA and ConA stimulation, low proliferation of B cells to SAC		Normal smIgA, smIgG, smIgD and smIgM	n.m.	
25/F/12	Normal proliferation of T cells after PHA and ConA stimulation	n.d.	Normal smIgA, smIgG and smIgM	n.m.	[42]
57/M/66	n.d.	n.d.	Normal smIgM	n.m.	[23]
58/F/15	Normal lymphocyte proliferation after PHA, ConA, and PWM stimulation	n.d.	n.d.	n.m.	[24]
60/M/3	Normal lymphocyte proliferation after PHA stimulation	n.d.	n.d.	n.m.	[17]
62/F/37	Mildly excessive proliferative T cell response to PHA and ConA	n.d.	n.d.	n.m.	[26]
65/F/14	Normal lymphocyte proliferation after PHA, ConA, and PWM stimulation	n.d.	n.d.	n.m.	[21]
66/F/15	Normal lymphocyte proliferation after PHA, ConA, and PWM stimulation	n.d.	n.d.	n.m.	
67/F/64	n.d.	n.d.	Few surface IgM-positive B lymphocytes	n.m.	[29]
71/M/11	n.d.	n.d.	Normal smIgM	n.m.	[32]
73/F/16	Slightly impaired lymphocyte proliferation after PHA and ConA	n.d.	Normal smIgM	n.m.	[34]
75/M/65	Diminished lymphocyte transformation after PHA and PWM stimulation	n.d.	Normal number of IgM staining B lymphocytes in the peripheral blood	Jejunal biopsy had normal IgM plasma cell numbers, jejunal aspirate IgM nil, IgA, and IgG present secretory component present	[36]
76/M/72	Normal response to mitogen and antigen stimulation	n.d.	Normal smIgM	Bone marrow (fluorescent microscopy) IgM cells present jejunal biopsy no IgM plasma cells in jejunal aspirate	

Table 7 (continued)

	Proliferation and other functional tests	Immunoglobulin production	Surface molecule expression	Other cell information	Ref.
78/M/13	Normal	n.d.	Decreased smIgM	IgM nil, IgA and IgG present secretory component present n.m.	[10]
80/M/6.5	Normal lymphocyte proliferation after PHA and anti-CD3 stimulation	n.d.	n.d.	n.m.	[38]

PHA phytohemagglutinin, *ConA* concanavalin A, *PWM* pokeweed mitogen, *PBL* peripheral blood lymphocytes, *PBMC* peripheral blood mononuclear cells, *E-RFC* E rosette-forming cells, *ISC* immunoglobulin secreting cells, *sIgM* surface IgM, *moAb* monoclonal antibodies, *smIgG* peripheral blood lymphocytes with surface IgG, *smIgA* peripheral blood lymphocytes with surface IgA, *smIgM* peripheral blood lymphocytes with surface IgM, *smIgD* peripheral blood lymphocytes with surface IgD, *n.d.* not done, *n.m.* not mentioned

fully compensate for IgM deficiency [54]. On the other hand, while prevalence of bronchiectasis was higher in patients with low levels of IgA (<0.8 g/l) and IgM (<0.5 g/l) in addition to IgG deficiency (<5.0 g/l), the difference in bronchiectasis prevalence between patients with normal IgA or IgM and patients with normal IgA and IgM was not statistically significant [55]. In addition, low IgG and IgA but not IgM were shown to be associated with increased risk of pneumonia and bronchiectasis in a long-term follow-up of large cohort of patients with common variable immunodeficiency [56].

An increased frequency of autoimmune diseases is markedly associated with sIgMD [57]; however, this association remains unclear. Recently, secreted polyclonal IgM was shown to prevent autoantibody formation by facilitating normal B cell development and enforcing negative selection of autoreactive B cells [58]. Moreover, secreted IgM (including IgM autoantibodies) may lessen the severity of the autoimmune pathology associated with IgG autoantibodies [59]. sIgM/antigen immunocomplexes promote a negative feedback loop for B cell activation via CD22 receptor in glycan ligand-dependent manner, which may contribute to B cell tolerance [60]. In contrast, increased IgM levels can also be associated with autoimmunity [61, 62]. In human PIDs characterized by elevated IgM levels and impaired B lymphocytes switching to IgG-producing cells, autoimmune disorders may develop [48]. Mice with activation-induced cytidine deaminase defects, that prevent class switch recombination, develop hyper-IgM-like syndromes associated with autoimmune diseases [63, 64]. Nevertheless, the role of IgM in association with autoimmune diseases remains unclear [65–68]. An association between sIgMD and atopic disorders is prominent; however, the mechanism through which the low IgM levels would cause Th1 to Th2 response shift remains unclear. In addition, since the pathogenesis of sIgMD is obscure, it may be even possible that the low IgM levels are secondary to atopy rather than the reverse.

The available data on lymphocyte subpopulations in larger sIgMD cohorts is insufficient and often contradictory. Regarding marginal zone B cells, reduced numbers [10, 26, 38, 43, 44], normal numbers [44, 45], as well as the expansion of the marginal zone B cell compartment in mice deficient for secreted IgM were described [69]. Gupta et al. recently described that adults with sIgMD displayed significantly increased $CD21^{low}$, IgM memory B cell, B regulatory, and CD8 regulatory T cell levels and a significant decrease in germinal center B cells and $CXCR3^{+}$ naïve and memory B cells [45]. Our results confirmed the increased 21^{low} B cell levels, which is a feature typical for some other PIDs and autoimmune conditions [70]. The plasmablast numbers were normal [45], which corresponds to the normal IgG and IgA levels in sIgMD patients. The increase of transitional B cells described in the Mensen et al. cohort was confirmed in our study [44]. We observed variable levels of switched memory

B cells; however, previous publications predominantly report a decrease in this population [26, 38, 43–45]. Overall, the results concerning B cell levels in patients with sIgMD are ambiguous. Larger studies might clarify association with certain B cell subpopulation abnormalities, such as in CVID [71]; however, the real clinical value is probably limited.

Naïve B cells, transitional B cells, marginal zone B cells, IgM only B cells, and IgM^+ plasmablasts belong to a group of membrane IgM-expressing cells. It seems that the frequency of IgM-expressing B cells within the total B cell population is not diminished in patients with sIgMD compared with HDs [18, 23, 28, 34, 36, 40–42, 44] although a few studies described decreased surface IgM expression [10, 29, 33]. The loss of serum IgM was not accompanied by diminution in membrane IgM expression in mouse models [53]. In contrast to Mensen et al. observations of significantly decreased membrane IgM expression on IgM-expressing B cells, IgM only memory B cells, marginal zone-like B cells, and $IgM^+CD27^-IgD^-$ memory B cells [44], we found no statistically significant change compared with HDs. The presence of normal circulating B cell numbers with surface IgM suggests a defect in the terminal differentiation of immature B lymphocytes into IgM-secreting plasma cells [18, 23, 36, 72–74].

A small number of studies showed a failure of B and T cell cooperation in IgM production. Functional studies showed that co-cultivation of patient B and T cells in the presence of PWM led to absent or markedly decreased IgM production [18, 23, 28, 34, 41]. Concurrently, the IgG and IgA production was normal [23, 28, 41] or impaired [18, 34] under the same conditions described previously. Some studies showed normal production of IgM when the patient T cells were co-cultured with normal B cells [28, 34, 41], while others showed impaired IgM production [18, 23]. When patient B cells were co-cultured with normal T cells, the IgM production increased or reached normal levels [18, 41]. When irradiated patient T cells were added to patient B cells, IgM production was sufficient [23, 28]. Furthermore, Inoue et al. observed that increased T cell numbers in culture led to increased IgG and IgA but not IgM production [28]. Moreover, when patient B cells were stimulated with SAC and IL-6, they produced a significant amount of IgG and IgA under the same conditions. Recently, Mensen et al. showed a decrease in numbers of IgM-producing antibody-secreting B cells in two out of six patients [44]. Moreover, significantly decreased numbers of IgM-secreting and IgG-secreting cells were found in patients compared with healthy controls due to the low B cell expansion rate in majority of the patients [44]. Interestingly, patient B cells were able to undergo isotype switching and produce immunoglobulins of all other classes, resulting in normal [10, 27, 34, 38, 39] or impaired [18, 21, 24, 32, 36] specific antibody production. IgG and IgM isohemagglutinin production remained at lower levels compared with healthy populations [10, 18, 21, 24, 31, 32, 34, 36, 37, 39]. This suggests the presence of a selective defect in patient B cells during B cell maturation into IgM-producing cells. Overall, our understanding of T or B cells' function in patients with sIgMD is limited by low number of studies based on small number of patients. In vitro studies have not produced consistent results, which might be attributed to variable pathogenesis of sIgMD and/or differences in in vivo and in vitro conditions of IgM production. Although B cells or T cells' intrinsic defects were suggested to play role in pathogenesis of sIgMD [18, 23, 28, 33, 40, 41, 74, 75], the key problem may be within IgM secretory process because patients produce normal amounts of other immunoglobulin isotypes and majority of them have normal surface IgM expression.

Conclusions

In summary, the underlying mechanism of sIgMD remains elusive. The clinical presentation and laboratory parameters range from asymptomatic individuals to patients affected with severe infections, suggesting that the cause of low or undetectable production of IgM may vary among patients. The treatment is only symptomatic; prophylactic antibiotic treatment is usually not necessary. We advocate that all sIgMD patients should undergo regular immunological evaluation to limit the risk of unrecognized transformation into other, more severe primary immunodeficiency.

Acknowledgements This work was supported by grant 15-28541A from the Czech Ministry of Health.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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