Received: 27 April 2023 | Revised: 1 August 2023 | Accepted: 14 August 2023

DOI: 10.1111/pai.14015

ORIGINAL ARTICLE

WILEY

Clinical and immunological phenotypes of selective IgM deficiency in children: Results from a multicenter study

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Editor: Fabio Candotti

Abstract

Background: A few studies assessed the clinical and immunological features of selective IgM deficiency (SIgMD), especially in the pediatric age. We aimed to characterize the clinical and immunological phenotypes of a cohort of pediatric patients with SIgMD according to the different diagnostic criteria available.

Methods: In this multicenter study, we evaluated pediatric SIgMD patients diagnosed at the Pediatric Clinic in Pavia, Italy, or through the Italian Primary Immunodeficiency NETwork (IPINET) and monitored changes in their diagnosis over a time frame that ranges from several months to several years.

Results: Forty-eight patients with SIgMD were included (mean serum IgM: 33 mg/dL). The most common clinical manifestations were recurrent infections (67%) and allergies (48%). Subgroup analysis according to SIgMD definition criteria of the European Society for Immunodeficiencies (ESID) showed no significant difference in clinical manifestations, also considering the group with additional immunological abnormalities. Sixteen patients had long-term follow-up, during which 87% preserved their SIgMD diagnosis, while two patients showed a reduction in IgA in addition to low IgM.

Conclusions: Our data suggest that the identification of a reduction in serum IgM in children should lead to a complete immunological work-up to obtain a comprehensive clinical and immunological characterization of the patient. The follow-up of these patients is fundamental to define the disease evolution and appropriate management.

KEYWORDS
antibody deficiency, atopy, clinical phenotype, inborn errors of immunity, primary immunodeficiency, recurrent infections, selective IgM deficiency

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See Appendix 1 for the Italian Primary Immunodeficiency NETwork (IPINET).

1 | INTRODUCTION

Selective immunoglobulin M deficiency (SIgMD) is a form of hypogammaglobulinemia characterized by absent or reduced serum immunoglobulin M (IgM) levels (<2 standard deviations [SD] or <10% of the values obtained from healthy controls of the same age or an absolute value <20 mg/dL in pediatric age), without other immunoglobulin isotype deficiency (IgG and IgA).[1–3] Moreover, SIgMD is diagnosed after excluding any other specific inborn error of immunity (IEI). Although SIgMD was first described in 1967 by Hobbs et al. in children presenting with meningococcal meningitis,[4] it was largely ignored as an IEI.[5]

The major comorbidities described for SIgMD are recurrent infections and increased frequency of allergic and autoimmune diseases.[6] Recurrent infections represent the presenting manifestation in more than 80% of patients with SIgMD.[6] Although upper respiratory tract infections, including rhinitis, otitis media, and sinusitis, are among the most common clinical symptoms in SIgMD patients, serious life-threatening infections – bacterial meningitis and sepsis – have been reported.[7,8] Substantial evidence supports the association between atopic diseases and SIgMD.[9–12] Allergic manifestations are displayed by almost 40% of patients with SIgM, and the frequency of asthma and allergic rhinitis in SIgMD ranged from 30% to 45%.[6] In addition, similar to other primary antibody deficiency disorders, autoimmune diseases are more common in patients with SIgMD than in the general population. The pathogenesis of SIgMD remains elusive, and no definitive genetic etiology has been established as a cause of SIgMD. However, some reports identified IgM deficiency, often in association with additional syndromic features, in different chromosomal abnormalities, including the 22q11.2 deletion syndrome.[13,14] No conclusive data are available on the correct therapeutic management and the prognosis of SIgMD. In particular, the disease natural history and the possible evolution of SIgMD to Common Variable Immunodeficiency (CVID) have not been fully investigated.

Notably, most evidence derives from adult patients with SIgMD,[13,15,16] and only a few studies included SIgMD children.[17] Moreover, it is fundamental to highlight that several studies on IgM deficiency have included patients with more abnormalities than isolated deficiency of IgM, often with another definitive IEI diagnosis. In addition, the diagnostic criteria to define SIgMD varies in the different studies.

Although in 2017 it was included in the IUIS (International Union of Immunological Societies) classification of IEI,[1–3] SIgMD remains a diagnostic and therapeutic dilemma, especially in the pediatric age. The aim of the study is the clinical and immunological characterization of pediatric patients with SIgMD, allowing for a better understanding of this condition.

Key Message

Infections and allergies represented the main clinical manifestations of children with SIgMD. Follow-up analysis on pediatric patients showed that SIgMD usually persists over time, and additional immunological abnormalities may develop. Children with SIgMD should receive a complete clinical and immunological characterization; follow-up is fundamental to monitor the evolution of the condition. Further studies are required to increase our understanding of the genetic and molecular pathogenetic mechanisms underlying SIgMD.

2 | METHODS

To study children with SIgMD, we performed an observational study on pediatric patients evaluated in the Pediatric Immunology and Allergology Unit of the San Matteo Hospital, Pavia, Italy. Patients who performed an immunological evaluation and repeatedly (at least twice, evaluated at least 6 weeks apart) presented a serum IgM level <2 standard deviations of the lower limit compared with those of healthy, age-matched control subjects and normal serum IgG and IgA levels were included in the study. Any other classified inborn error of immunity and secondary hypogammaglobulinemia (caused by infections, genetic syndromes, chromosomal abnormalities, drugs, lymphomas, protein-losing enteropathy, nephrotic syndrome, and thymoma) were considered exclusion criteria. Of note, in agreement with Gupta and Gupta[18] we used an inclusive definition for SIgMD, with the aim of better characterizing the different clinical and immunological phenotypes that may be included under the diagnostic umbrella term "SIgMD." From a clinical perspective, and according to Jeffrey Modell Foundation's "Four stages of testing,"[19] patients usually undergo quantitative IgG, IgM, and IgA level dosage as the first step in the immunological work-up. For this reason, we included in our cohort all the patients with confirmed low IgM levels and normal IgG and IgA. However, we also performed a subgroup analysis differentiating "truly" (repeatedly decreased serum IgM levels; normal levels of serum IgG, IgA, IgG-subclasses and normal vaccination responses and exclusion of T-cell defect, also through the absence of clinical signs suggesting a T-cell defect) and "possible" (data on IgG subclasses, and/or vaccination responses are lacking) SIgMD patients according to European Society for Immunodeficiencies (ESID) criteria[20] as reported by Janssen et al.[21,22] versus the ones with other immunological abnormalities identified during the immunological work-up.

SIgMD cases were evaluated for presenting clinical symptoms, concurrent conditions, medications, vaccinations, and clinical courses. Family history was considered focusing on recurrent infections, defined immunodeficiencies, and a history of allergy and/or autoimmune diseases.

The blood tests included complete blood count with differential, immunoglobulin levels (IgG, IgM, IgA, IgE, and IgG subclasses), autoantibody serologic test results including antinuclear antibodies

(ANA), extractable nuclear antigen (ENA), thyroid autoimmunity, and celiac disease screening. Moreover, immune response to vaccine protein and polysaccharide antigens were analyzed by dosing tetanus and pneumococcal antibody titers (VaccZyme™ Tetanus toxoid IgG Kit and VaccZyme™ Anti PCP-IgG Enzyme Immunoassay Kit, The Binding Site). In addition, the following immunological data were included: T- and B-lymphocyte subsets proportion and numbers measured by flow cytometry compared with those of healthy, age-matched control subjects[23,24]; lymphocyte mitogen and antigen proliferation assays which involved stimulation of peripheral blood mononuclear cells with mitogens (phytohemagglutinin, PHA) and with antigens (purified protein derivative, tetanus toxoid, *Candida albicans*); in vitro immunoglobulin production assay as described in Marconi et al.[25]; isohemagglutinin levels. We performed skin prick tests and/or serum allergen-specific IgE levels to determine the atopy status.

To collect data on SIgMD from other pediatric immunology units in Italy, the study involved immunology centers from IPINET (Italian Pediatric Immunodeficiency NETwork). IPINET includes Italian centers highly specialized in the diagnosis and treatment of IEI. The total number of patients evaluated by the different centers and which center evaluated every specific patient are reported in Appendix S1.

Prospective data have been collected for a subgroup of patients who presented at the follow-up visits and underwent a complete clinical and immunological re-evaluation, allowing for longitudinal data analysis.

The study has been approved by the San Matteo Hospital Institutional Review Board as part of the protocol "Retrospective-prospective observational study on subjects enrolled in AIEOP (Italian Society of Pediatric Hemato-Oncology) and IPINET (Italian Primary Immunodeficiency Network)," shared by all the IPINET centers.

3 | RESULTS

3.1 | Demographics

A total of 48 patients were included in the study. Among them, 40 were male (83%), and eight were female (17%). The average age for SIgMD diagnosis was 8.9 years (range: 1.1–18.9 years), and the average age of onset of symptoms was 4.9 years (range: from immediately after birth to 14 years). Of note, the average delay in diagnosis was 3.8 years.

3.2 | Clinical manifestations

The main clinical manifestations found in our cohort were infectious diseases, seen in 32 (67%) patients, mainly bronchitis (15; 31%), pharyngitis (13; 27%), and otitis (13; 27%) (Figure 1 and Appendix S1). SIgMD patients also presented with pneumonia (6; 13%) and gastroenteritis (4; 8%). Seven patients (15%) showed other infectious manifestations, as seen in Table 1A. Of note, 15 (31%) patients presented with multiple infections.

The second main clinical features were allergic manifestations seen in 23 patients (48%), primarily atopic dermatitis (13; 27%) and allergic rhinitis (12; 25%), followed by asthma (4; 8%), cow's milk protein allergy (4; 8%) and urticaria (3; 6%) (Figure 1 and Appendix S1). Five patients (10%) presented with other allergic manifestations, as seen in Table 1B. Eleven (23%) patients showed more than one allergic manifestation.

Ten patients (21%) presented with both infectious and allergic manifestations.

Five patients presented with autoimmune manifestations, namely autoimmune thyroiditis (two patients, 4%), psoriasis, alopecia, and Schoenlein-Henoch purpura (one patient, 2%, respectively). No patients had neoplastic disease. Five patients (10%) showed growth retardation. Four patients (8%) had a positive familial history of immunodeficiency, 13 (27%) of autoimmune disease, and 17 (35%) of allergies.

The first clinical manifestation in our cohort is mainly represented by respiratory infections (eight patients [17%] with recurrent respiratory infections) followed by dermatitis (Table 2).

3.3 | Immunological characterization

Serum IgM levels ranged from 5 to 52 mg/dL (mean IgM: 33 mg/dL). According to the inclusion criteria, serum IgG and IgA were normal. Twenty-eight (58%) patients had IgG subclasses evaluated, and 36 (75%) patients had their IgE concentration measured. Only one patient presented IgG2 reduction and one IgG3 reduction. An increase in serum IgE was found in 10 patients (21%).

One patient (2%) had lowered percentage of $CD3^+$ T-lymphocytes (absolute count: 977/mm^3), seven (14%) patients had a reduced percentage of $CD4^+$ T-lymphocytes (absolute count available for four patients and reduced for three patients; mean absolute count: 437/mm^3), seven (14%) patients had reduced percentage of $CD8^+$ T-lymphocytes (absolute count available for six patients and reduced for three patients; mean absolute count: 417/mm^3) and eight (16%) patients had reduced percentage of $CD19^+$ B-lymphocytes (all above 2%, absolute count available for five patients and reduced for all five patients; mean absolute count: 176/mm^3).

Evaluation of lymphocyte proliferation following stimulation with mitogens (PHA) was performed in 23 patients (47%). Among them, three patients (13%) showed a partial reduction in response to mitogens. The response to antigens (*C. albicans*) was performed in 15 patients (31%), and of these, two patients (13%) showed a reduced response.

Considering the B-cell subsets, 10 (21%) patients and six (12%) patients showed a reduction and an elevation in the B-naïve cell percentage, respectively. Four (8%) and nine (18%) presented with a decrease or an elevation in the percentage of non-switched B-memory

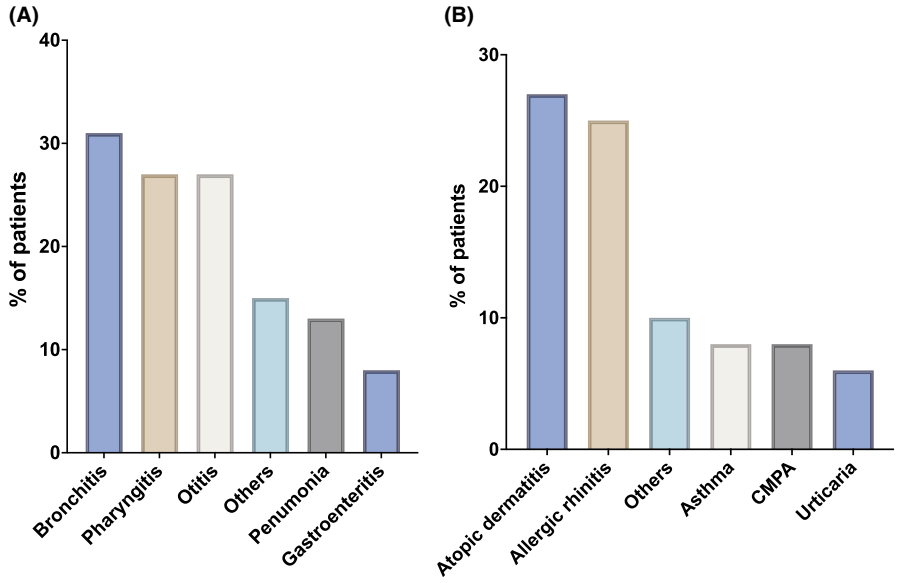

FIGURE 1 Main clinical manifestations. Panel A: Main infectious manifestations. Panel B: Main allergic manifestations. CMPA, cow's milk protein allergy.

cells. Moreover, a reduction in B class-switched memory cells percentage was reported in 10 (20%) patients.

The in vitro Ig production test was performed in 17 (35%) out of 48 patients. Of note, in vitro IgM production is partially preserved in most of the patients (14; 82%), while IgG and IgA production were respectively impaired in only one (6%) and three patients (18%), with reduced production in all immunoglobulin isotypes in one patient and reduced production in IgA and IgM in two patients. Of note, the patient with reduced in vitro IgG, IgA, and IgM production is the one with IgG3 deficiency.

The antibody response to protein antigens (tetanus) has been checked in 33 patients, four (12%) of them had reduced response after tetanus vaccination. The antibody response to polysaccharide antigens has been checked in four patients, and among them, two patients (50%) had reduced response after pneumococcal polysaccharide vaccination (PPSV23).

All the immunological data for every patient are available in Appendix S1.

TABLE 1 Other clinical manifestations. (A) Other infectious manifestations reported in SIgMD patients ($n=7$, 15%). (B) Other allergic manifestations reported in SIgMD patients ($n=5$, 10%).

	Number of Patients (*n*)	Percentage
A		
Herpetic gingivostomatitis	2	4%
Aphthous stomatitis	3	6%
Candida infections	1	2%
Gastrointestinal parasitic infection	1	2%
Skin infections	1	2%
	Number of Patients (*n*)	**Percentage**
B		
Recurrent wheezing	2	4%
Food allergy	1	2%
Hymenoptera venom allergy	1	2%
Drug allergy	1	2%

3.4 | Therapeutic interventions

Two patients (4%) were on prophylactic antibiotic treatment (one with azithromycin three times a week and one with trimethoprim/sulfamethoxazole three times a week). One patient underwent intravenous immunoglobulin replacement therapy, and one (2%) was treated with acyclovir. Moreover, 12 patients (25%) were on medications for allergic manifestations (in particular, antihistamine drugs and corticosteroid inhalers).

3.5 | Long-term follow-up

Sixteen of 48 patients had a long-term follow-up (mean duration: 4 years). The results are presented in Table 3 below. Of note, two patients developed a reduction also in IgA in addition to IgM deficiency.

3.6 | Subgroup analysis according to ESID criteria

To further characterize our patients' cohort, we performed a subgroup analysis dividing patients into two groups. The first group ($n=27$) included all the patients with "truly" and "possible" SIgMD diagnosis according to ESID criteria as reported by Janssen et al.[21] The second group ($n=21$) included the remaining patients who showed additional immunological abnormalities during the immunological work-up. Table 4 shows the two-group comparison.

TABLE 2 Presenting clinical manifestations.

	Number of Patients (*n*)	Percentage		Number of Patients (*n*)	Percentage
Bronchitis	9	19%	Chronic cough	3	6%
Bronchospasm	8	17%	Urticaria	2	4%
Recurrent airways infections	8	17%	Laryngospasm	2	4%
Dermatitis	8	17%	Aphthous stomatitis	2	4%
Incidental (asymptomatic)	7	15%	Growth retardation	2	4%
Otitis	6	13%	Recurrent skin infections	1	2%
Pneumonia	4	8%	Autoimmune thyroiditis	1	2%
Allergic rhinitis	4	8%	Glomerulonephritis	1	2%

Of note, no major significant difference in clinical manifestations (infections, allergies, and autoimmune diseases) was found. In addition, we found that patients with additional immunological abnormalities were diagnosed at a younger age (years, median, 6 vs. 10). Considering the two patients with herpetic gingivostomatitis (patient ID 10 and 42), both patients had a normal lymphocyte count, while patient 42 presented a reduction in the absolute count and percentage of $CD8^+$ T-lymphocyte. Also, the single patient with *Candida* infection had a normal lymphocyte count, but he presented a reduction in B-naïve cells ($sIgM^+/sIgD^+$, $CD27^-$) and in B-non switched memory cells (IgM^+/IgD^+, $CD27^+$). Considering the immunological findings in the B-cell compartment (a variable not included in the SIgMD ESID criteria), we found no significant differences between the two groups. Still, interestingly, we found that IgM and IgA in vitro production were reduced more often in patients with additional immunological abnormalities other than low IgM levels (Table 5). The two patients who received prophylactic antibiotic treatment and the one who received intravenous immunoglobulin (IVIG) replacement therapy belong to the group with additional immunological abnormalities.

Regarding the two patients who developed a reduction in IgA in addition to low IgM through the follow-up period, one belongs to the first group and one to the second group.

4 | DISCUSSION

SIgMD has been recently classified as an inborn error of immunity.[1–3] However, as recently reported by the US National Institutes of Health (https://rarediseases.info.nih.gov/diseases/12547/selective-igm-deficiency), this condition needs further understanding.

Our observational study reported a cohort of 48 pediatric SIgMD patients.

The mean age of diagnosis of SIgMD was 8.9 years, consistent with the results presented by Caka et al.[13] and slightly higher than the mean age of diagnosis (6 years) reported by Goldstein et al.[17]

The average delay in SIgMD diagnosis since initiation of symptoms was 3.8 years, consistent with the study of Caka et al.[13] The ratio of male to female patients in our cohort was 5:1. It differs from male to female ratio seen in Goldstein et al.[17] study which is 7:5 but is similar to Hobbs[26] and Caka et al.[13] ratios. These data are consistent with the PedPAD study that showed a boy predominance in the hypogammaglobulinemia registry of the ESID online database.[27]

The main clinical manifestations in our cohort were infections, with respiratory infections being the most frequent, followed by allergic manifestations. This result confirms the previous reports from Goldstein et al.[17] and Caka et al.,[13] although a lower rate of patients presented allergies in these studies. None of our pediatric patients had a neoplastic disease, as reported by Goldstein et al.,[17] while Caka et al.[13] and Lucuab-Fegurgur and Gupta[16] reported neoplastic diseases in adult cohorts.

Regarding the immunological characterization, in agreement with Gupta et al. (and consistent with the recent US National Institutes of Health definition; https://rarediseases.info.nih.gov/diseases/12547/selective-igm-deficiency), SIgMD should be defined without exclusion of IgG subclass deficiency, alterations in T-cell and T-cell subset numbers and functions, and impaired response to vaccines.[18] This inclusive approach will allow for a better understanding of the different clinical and immunological phenotypes that may be included under the diagnostic umbrella term "SIgMD."

Of note, the complete immunological evaluation did not show additional abnormalities other than reduced serum IgM for most of the patients included in our study. However, performing an extensive immunological characterization of these patients is always recommended to identify other associated immunological changes.

In our cohort, two patients (4%) had reproducibly low IgG subclasses. Indeed, several investigators have reported IgG subclass deficiency in a subset of SIgMD patients. Goldstein et al.,[9] in their retrospective study of 36 adult SIgMD patients, observed IgG subclass deficiency in 25%. Chovancova et al.[28] observed IgG subclass deficiency in 6 of 14 patients (42%).

T-cell number and function are normal in most SIgMD patients.[10,15,29] However, alterations in subgroups of patients have been reported.[30,31] In the presented cohort, the lymphocyte subsets data were available for 44 patients (92%). Most patients had normal T-cell numbers, while only one showed a reduced T-lymphocyte population. In our cohort, a significant number of patients (14%) had a reduced T helper ($CD4^+$) lymphocyte population. Similar results have been reported by Lucuab-Fergurur et al. in adult populations.[16] Cytotoxic T lymphocytes ($CD8^+$) were decreased in 14% of patients, while in the adult cohort of Lucuab-Fergurur et al., only one patient (1.6%) had low $CD8^+$ T cells.

TABLE 3 Immunological findings at follow-up.

		Immunoglobulin				IgG subclasses				Lymphocyte subsets				B-lymphocyte subsets				
Patient ID (IPINET Center)	Age at follow-up	IgG [mg/dL]	IgA [mg/dL]	IgM [mg/dL]	IgE [kU/L]	IgG1 [mg/dL]	IgG2 [mg/dL]	IgG3 [mg/dL]	IgG4 [mg/dL]	$CD3^+$ [%]	$CD4^+$ [%]	$CD8^+$ [%]	$CD19^+$ [%]	Naive [%]	Class-switched Memory [%]	Non-switched Memory [%]	Antibody response to protein antigens (tetanus)	Antibody response to polysaccharide antigens (pneumococcus)
1 (PV)	7	990	90.8	28.8[a]	>5000[b]	8279[b]	1140	416	789	56	14	22	28	84[b]	5	NA	NA	NA
	9	1020	104	25.6[a]	4414[b]	8643[b]	1368	369	1903[b]	72	35	30	12	84[b]	6	NA	NA	NA
2 (PV)	6	842	75.1	32.9[a]	NA	7013	1125	601	99	NA	NA	NA	NA	NA	NA	NA	NA	NA
	8	751	89.7	28.2[a]	NA	6533	967	437	117	NA	NA	NA	NA	NA	NA	NA	NA	NA
	9	779	81	32.2[a]	NA	6243	1115	365	118	NA	NA	NA	NA	NA	NA	NA	NA	NA
3 (PV)	6	951	63.5	54.1[a]	NA	8215[b]	1339[b]	182	199[b]	NA	NA	NA	NA	NA	NA	NA	NA	NA
5 (PV)	14	867	72.9	57.6[a]	NA	6743[b]	1402[b]	346[b]	100	NA	NA	NA	NA	NA	NA	NA	Normal	NA
6 (PV)	13	679	114	28.8[a]	29.5	5510[b]	1433[b]	439[b]	106[b]	71	40	26	15	NA	NA	NA	Normal	NA
7 (PV)	24	869	141	31[a]	2933[b]	619	181	22[a]	72	75	43	30	14	NA	NA	NA	NA	NA
14 (PV)	6	1160	48.2	45.7[a]	NA	NA	NA	NA	NA	81	41	25	10	NA	NA	NA	NA	NA
	7	1090	38.5[a]	33.8[a]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
22 (MI)	14	1100	155	35.7[a]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
23 (PV)	16	1290	209	33.3[a]	74.4	9733[b]	3115[b]	193	18	NA	NA	NA	NA	NA	NA	NA	NA	NA
35 (Rome 1)	12	809	107	52.1[a]	NA	6149[b]	1402[b]	286[b]	18	NA	NA	NA	NA	NA	NA	NA	NA	NA
36[c] (PV)	11	791	115	20.80[a]	NA	6168[b]	1100[b]	389[b]	433[b]	72	23[a]	39[b]	20	85	6	NA	NA	NA
	12	1110	141	48.6[a]	67.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
38 (PV)	13	1060	113	49.5[a]	NA	8177[b]	1335[b]	225[b]	982[b]	NA	NA	NA	NA	NA	NA	NA	NA	NA
39 (PV)	14	680	122	36[a]	7	401	107	70	60	NA	NA	NA	NA	NA	NA	NA	NA	NA
40[c] (CT)	14	994	131	30[a]	327[b]	530	240	60	120	70	40	18	20	86	6.5	NA	NA	NA
41[c] (FI)	15	726	58.5[a]	31[a]	124	NA	NA	NA	NA	71	43	22	14	91[b]	3.6	NA	NA	NA
47[c] (Rome 2)	23	792	176	<10[a]	NA	NA	NA	NA	NA	97[b]	32	33	4[a]	NA	NA	NA	NA	NA

Note: IPINET center: PV = Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. MI = Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, Milan, Italy. Rome 1 = Pediatric Immunopathology and Allergology Unit, Policlinico Tor Vergata, University of Tor Vergata, Rome, Italy. Rome 2 = Department of System Medicine, University of Tor Vergata, Rome, Italy; Research Unit of Primary Immunodeficiency, IRCCS Bambin Gesù Children Hospital, Rome, Italy. CT = Hematology Unit, Pediatric Oncology, Catania, Italy. FI = Immunology and Molecular Microbiology Unit, Department of Health Sciences, Meyer Children's University Hospital, University of Florence, Florence, Italy.

Abbreviation: NA, not available.

[a]Values abnormally reduced.

[b]Values abnormally increased.

[c]ESID Criteria Fulfilled for "truly" or "possible" SIgMD according to Janssen et al.[21]

TABLE 4 Subgroup analysis according to ESID criteria.

	SIgMD according to ESID criteria ("truly" and "possible")[21] (*n* = 27)	SIgMD with other immunological abnormalities (*n* = 21)	*p*-Value
Sex (F/M)	7/20	1/20	0.051
Age at diagnosis, years (median [IQR])	10 (7–12)	6 (4–10)	**0.0130**
Age at symptom onset, years (median [IQR])	5 (2–9)	3.5 (1–6)	0.354
Diagnostic delay, years (median [IQR])	3 (0–9)	2 (0–5)	0.377
Serum IgM level, mg/dL (median [IQR])	33 (26–41)	36 (22–41)	0.714
Infectious diseases, *n* (%)	20 (74%)	15 (71%)	0.838
Pharyngitis	6 (22%)	7 (33%)	0.390
Otitis	4 (15%)	8 (38%)	0.065
Bronchitis	6 (22%)	9 (43%)	0.126
Pneumonia	3 (11%)	3 (14%)	0.742
Gastroenteritis	2 (7%)	2 (10%)	0.792
Others	7 (26%)	2 (10%)	0.149
Multiple diseases	6 (22%)	8 (17%)	0.230
Allergic diseases, *n* (%)	14 (52%)	9 (43%)	0.536
CMPA	3 (11%)	1 (5%)	0.430
Atopic dermatitis	8 (30%)	5 (24%)	0.653
Urticaria	0 (0%)	3 (14%)	**0.043**
Asthma	3 (11%)	1 (5%)	0.430
Allergic rhinitis	9 (33%)	3 (14%)	0.131
Others	2 (7%)	3 (14%)	0.439
Multiple diseases	8 (30%)	6 (29%)	0.936
Autoimmune manifestations, *n* (%)	3 (11%)	2 (10%)	0.858
Thyroiditis	1 (4%)	1 (5%)	0.856
Psoriasis	1 (4%)	0 (0%)	0.373
Alopecia	0 (0%)	1 (5%)	0.252
Schoenlein-Henoch purpura	1 (4%)	0 (0%)	0.373
Familial history			
History of IEI	1 (4%)	2 (10%)	0.409
History of autoimmune disease	7 (26%)	5 (24%)	0.867
History of allergies	12 (44%)	5 (24%)	0.138
Immunological features			
Lymphocyte subsets and B-cell subsets			
CD19 B-cells reduction	3 (11%)	5 (24%)	0.242
B-Naïve ($sIgM^+/sIgD^+$, CD27neg)	6 (22%)	5 (24%)	0.897
Non-switched memory (IgM^+/IgD^+, $CD27^+$)	5 (19%)	5 (24%)	0.654
Class switched memory ($IgG^+/IgA^+/IgE^+$, $CD27^+$)	1 (4%)	2 (10%)	0.409
In vitro immunoglobulin production			
Impaired IgM production	0 (0%)	3 (14%)	**0.043**
Impaired IgG production	0 (0%)	1 (5%)	0.252
Impaired IgA production	0 (0%)	3 (14%)	**0.043**
Treatment			
Antibiotics prophylaxis	0 (0%)	2 (10%)	0.101
IVIG	0 (0%)	1 (5%)	0.252
Acyclovir	1 (4%)	0 (0%)	0.373

Note: Criteria according to Janssen et al.[21]: "Truly" selective primary IgM deficiency = repeatedly decreased serum IgM levels; normal levels of serum IgG, IgA, IgG-subclasses and normal vaccination responses and exclusion of T-cell defect, also through the absence of clinical signs suggesting a T-cell defect; "possible" selective primary IgM deficiency = the diagnosis of true sIgMdef is uncertain, because data on IgG subclasses and/or vaccination responses are lacking. Chi-square test except for age and serum IgM level statistics (two-tailed Mann–Whitney *U*-test).

Abbreviations: CMPA, cow's milk protein allergy; IEI, inborn error of immunity; IQR, interquartile range.

TABLE 5 Immunological characteristics of the patients with impaired in vitro Ig production.

Patient ID	Impaired in vitro Ig production	Additional immunological features
3	IgA and IgM	↓ CD19, ↓ CD4
7	IgA, IgM, and IgG	↓IgG3, ↓ CD8, ↓ B-naïve
13	IgA and IgM	↓ CD4

$CD19^+$ B cells are normal in the majority of SIgMD patients. However, low to complete absence of B cells has been reported in a limited number of patients with SIgMD.[32,33] In our pediatric cohort, 16% of patients had a low number of $CD19^+$ B cells, similar to the data from Lucuab-Fergurur et al. in their adult cohort.[16] Considering the B-cell subset, we found that a significant percentage of our patients had a reduction in B-naïve cells and in B class-switched memory cells (20%). A reduction in naïve B-cell count can play a role in the pathogenesis of SIgMID and inappropriate clonal expansion upon antigen activation, according to Louis et al.[15] Moreover, as previously reported,[16] the antibody response to protein antigens (tetanus) and to polysaccharide antigens (pneumococcus) was reduced respectively in 12% and 50% of the tested patients.

We aimed to follow-up on SIgMD pediatric patients to understand the disease course better. We wanted to evaluate the evolution of SIgMD in children (persistent or transitory) and identify the possible progression to common variable immunodeficiency (CVID) or other well-defined immunodeficiencies. Over an average follow-up period of 4 years, we have seen that for most patients, SIgMD persists. Two patients had IgA deficiency added to their diagnosis, making them now patients at risk of developing CVID according to the ESID criteria.[20] Of note, CVID mainly develops in young adults, more specifically between 20 and 40 years of age. SIgMD in these two patients might have been the first sign of possible CVID development, further highlighting the importance of a complete clinical and immunological follow-up in these patients.[34]

Consistent with the results from Goldstein et al.,[17] only a limited number of SIgMD in our cohort received specific treatment for their immunodeficiency condition, in contrast with adult patients that received more frequently antibiotic prophylaxis and/or IVIG.[13,16]

The comparison analysis between "truly"/"possible" SIgMD patients according to ESID criteria and those with other immunological abnormalities showed no significant clinical difference, making the two groups impossible to distinguish according to the clinical manifestations. This aspect further highlights the importance of performing a complete immunological work-up in children with confirmed low serum IgM levels.

Considering the indistinguishable clinical phenotypes, the earlier diagnosis in the group with additional immunological abnormalities may be explained by a different approach of the caring physicians who earlier defined the SIgMD diagnosis in patients with low IgM plus other immunological abnormalities.

Moreover, the two groups were indistinguishable according to the B-cells subset composition and disease evolution. Impaired in vitro Ig production appears more frequent in the group with additional immunological abnormalities. Still, this finding is based on a limited number of patients, as it is for the differences observed in the need for antibiotic prophylaxis and IVIG.

Our study presented some limitations. First of all, the cohort included patients referred to Immunology Units, making it possible that SIgMD is more frequent, particularly in asymptomatic patients. Second, some immunological tests have been performed on a limited number of patients. Third, the long-term follow-up analysis included only some of the patient cohort. Fourth, no genetic testing has been performed on our patients, limiting our understanding of the etiopathogenetic hypothesis of SIgMD.

Nonetheless, this multicentric study involving several Immunology Units in Italy may help to broaden our knowledge of SIgMD. In particular, this is the first observational study on SIgMD that includes a long-term follow-up analysis starting from the pediatric age.

From our and previous data, it is now clear that children with SIgMD should receive a complete clinical and immunological characterization, and follow-up is fundamental to monitor the evolution of the condition. Further studies are required to increase our understanding of the genetic and molecular pathogenetic mechanisms underlying SIgMD.

AUTHOR CONTRIBUTIONS

Riccardo Castagnoli: Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; formal analysis; project administration; data curation; resources; visualization; supervision. **Ivan Taietti:** Writing – original draft; methodology; writing – review and editing; formal analysis; data curation. **Martina Votto:** Writing – review and editing; validation; data curation; supervision. **Matteo Naso:** Writing – review and editing; methodology; data curation; formal analysis. **Maria De Filippo:** Writing – review and editing; formal analysis; data curation; methodology. **Alessia Marseglia:** Writing – review and editing; methodology; formal analysis; data curation. **Lorenza Montagna:** Methodology; validation; formal analysis; data curation. **Mara De Amici:** Methodology; validation; formal analysis; data curation. **Maria Antonietta Avanzini:** Methodology; validation; formal analysis; data curation. **Daniela Montagna:** Conceptualization; investigation; supervision; data curation. **Gian Luigi Marseglia:** Conceptualization; investigation; writing – review and editing; supervision. **Amelia Licari:** Conceptualization; investigation; writing – review and editing; methodology; validation; formal analysis; supervision; data curation.

ACKNOWLEDGMENTS

The authors would like to thank Alberto Vivaldo, Elena Santori, and Yonat Ofir, medical students at the University of Pavia, Italy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.14015.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Castagnoli R, Taietti I, Votto M, et al. Clinical and immunological phenotypes of selective IgM deficiency in children: Results from a multicenter study. *Pediatr Allergy Immunol*. 2023;34:e14015. doi:10.1111/pai.14015

APPENDIX 1

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