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Challenges in investigating patients with isolated decreased serum IgM: The SIMcal study

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Abstract

The clinical consequences of isolated decreased serum immunoglobulin (Ig)M are not sufficiently known. Therefore, it is difficult to determine the clinical policy following such a finding. Only few reported IgM-deficient patients fulfil the European Society for Immunodeficiencies (ESID) diagnostic criteria for selective IgM deficiency (true sIgMdef), or their diagnosis is uncertain due to insufficient laboratory data (possible sIgMdef). Decreased serum IgM is often incidentally found in asymptomatic adults. The objective of our study was to further characterize true sIgMdef and to compare the European data collected through the ESID Registry community (tertiary centres) to our previously published Dutch cohort (secondary centre). Fifteen centres (12 countries) participated with 98 patients. Patients were excluded if serum IgM was only determined once (n = 14), had normalized (n = 8), or if they also had other immunological abnormalities (n = 15). Ten patients (5 adults) completely fulfilled the ESID criteria for true sIgMdef. Age-matched cut-off values varied widely between centres; when using the ESID diagnostic protocol reference values, only six patients (five adults) had true sIgMdef. Because of these small numbers, further analyses were performed in patients with true or possible sIgMdef (13 adults, 48 children). Respiratory infections were commonly reported at presentation (adults 54%, children 60%). Symptomatic adults had lower serum IgM levels (mean 0.27 g/L, 95% CI 0.22-0.31) than those without symptoms (mean 0.33 g/L, 95% CI 0.30-0.36; $P = 0.02$). To be able to explore the clinical consequences of *true* sIgMdef, we should fully analyse and accurately describe those patients in whom a decreased serum IgM is found.

1 | INTRODUCTION

The clinical consequences of isolated decreased serum immunoglobulin (Ig)M levels are not sufficiently known. Clinicians struggle with what they should do with such a finding. IgM deficiency has mainly been studied in tertiary centre cohorts, where a variety of clinical manifestations have been linked with decreased serum IgM levels, including severe or recurrent infections, atopy, autoimmunity and malignancy.[1] Only small cohorts of IgM-deficient patients have been described

*The SIMcal consortium members shown in Appendix 1.

so far.[2,3] In 2006, the largest study to date was published, reporting data from 36 patients.[14] The reported patients are almost always symptomatic and most of them presented with infections.[1] We recently showed in a secondary centre population that decreased serum IgM levels can often incidentally be found in asymptomatic adults.[15] The determination of the clinical significance of sIgMdef is not only challenged by the rarity and highly variable phenotype of this primary immunodeficiency, but also by the different criteria for "selective IgM deficiency" that are used in the literature.[5,6,14,16] ESID has defined primary selective immunoglobulin(Ig)M deficiency (sIgMdef) as a decreased serum IgM level (repeatedly ≥ 2 SD below the mean for age) with normal levels of serum IgA, IgG and IgG subclasses, normal vaccination responses, absence of T cell defects and absence of causative external factors (http://www.esid.org). When these criteria are completely fulfilled, we refer to this condition as "truly selective primary IgM deficiency" (*true* sIgMdef), albeit we consider the absence of *clinical* signs suggesting a T cell defect a sufficient criterion. Only six of 261 (2%) patients described in the literature with "IgM deficiency" completely fulfil the defined criteria for true sIgMdef.[15] For many reported patients, the diagnosis is either uncertain, which means that the ESID criteria are not fulfilled completely because data on IgG subclasses and/or vaccination responses are lacking (we refer to the latter as "*possible* sIgMdef"),[15] or their IgM deficiency is not selective, because other antibody abnormalities are present; these cases fit the ESID classification "unclassified primary antibody deficiency" (*unPAD*).[3,6,17]

A larger cohort of *true* sIgMdef patients is needed to further explore the clinical consequences. Therefore, we initiated this multi-centre observational cohort study using the ESID online database. We also compared these European data (tertiary centres) to our previously published Dutch cohort (secondary centre).[15]

2 | MATERIALS AND METHODS

2.1 | Patient identification and recruitment

Email messages with the proposal to participate in the SIMcal study were sent out to all members of ESID to identify as many patients known to ESID members as possible with sIgMdef. Fifteen centres agreed to participate. Of these, 11 centres had registered their patients in the ESID online database.[18] The four centres not connected to the ESID online database also joined the SIMcal study. All patients documented by the participating centres to have sIgMdef were eligible for analysis. Only the patients with possible and true primary sIgMdef were analysed in detail (for definitions, see introduction). In all cases, patients had given informed consent for analysis of their data. The Medical Ethical Committee Brabant approved the SIMcal study.

2.2 | Data collection

The development, ongoing management and technical database structure of the ESID online database were described previously.[18] All participating centres entered their data in the study questionnaire, providing available demographic and clinical data (gender, date of birth, country of residence, age at diagnosis, date of diagnosis, presenting history, conditions during follow-up, pathogens, familial cases, consanguinity), as well as laboratory test results (serum IgM, IgG, IgA and IgE levels, IgG subclasses, T cell subsets and function, antibody responses to vaccinations, isohemagglutinin levels, anti-nuclear antibodies (ANA) and specific IgE directed against inhalant allergens), treatment (antibiotics, immunoglobulin substitution) and follow-up period (date of the first serum sample with decreased IgM until the date of data extraction). The answers to the questionnaires were encrypted and saved on a protected server using Research Manager software developed by Cloud9 Health Solutions (Deventer, the Netherlands). For interpretation of serum immunoglobulin levels, centre-specific age-matched reference values were used. Almost all centres used immunonephelometric or immunoturbidimetric techniques (14 out of 15); in one centre, radial immunodiffusion was used (Egypt). The method of data collection for the 42 adults with true or possible sIgMdef from the secondary centre has been described before.[15]

2.3 | Statistical analysis

Frequency data were analysed with chi-square analysis, and the Fisher exact test when expected cell values were lower than 5. Measurement data were expressed as means with standard deviations (SD) and confidence intervals (CI). Differences in measurements were tested with t test (Welch's t test when the variances are unequal) and ANOVA. The statistical software package used was IBM SPSS statistics version 24.

3 | RESULTS

Data from 98 patients were reported from 15 centres in 12 different countries. Thirty-seven patients (37%) were excluded: 14 because serum IgM level was only determined once, 8 because serum IgM level had normalized, and 15 because other immunological abnmalities were also present (these patients fulfilled the criteria for unPAD).

Of the remaining 61 patients, only 10 fulfilled the ESID criteria for true sIgMdef (5 adults, 5 children), and 51 had possible sIgMdef (8 adults, 43 children) when using the age-matched cut-off values for serum IgM used by the reporting centre. In those with possible sIgMdef, the following

immunological laboratory investigations were not determined: pneumococcal vaccination responses (0 adults and 20 children), IgG subclasses (1 adult, 0 children) or both (7 adults and 23 children). Cut-off values varied widely between centres (Figure 1). When ESID diagnostic protocol cut-off values for serum IgM were used,[19] only 6 patients (5 adults, 1 child) had true sIgMdef, and 8 had possible sIgMdef (6 adults and 2 children).

3.1 | Children

Analyses were done for the total group of children with possible or true primary sIgMdef (n = 48). Most children were reported from Turkey (n = 24), followed by Italy (n = 11), Tunisia (n = 4), Belgium (n = 3), Iran (n = 3), the Netherlands (n = 1) and Spain (n = 2). The mean age at the date of the first serum sample with decreased serum IgM in this possible/true sIgMdef cohort was 7 years (range 0-17 years). Mean follow-up time was 54 months (range 0-162 months). Boys predominated (79%), but there was a significant association between country and gender (Fisher's exact test, two-sided, $P = 0.002$). The numbers of children in the various countries were too small to draw reliable conclusions from the gender data (Figure 2). Consanguinity was present in six patients (13%, n = 2 male), absent in 39 (81%, n = 35 male) and not reported in three (6%, n = 1 male). These patients from consanguineous families were reported by Iran (2 out of 3), Italy (2 out of 11) and Turkey (2 out of 24). Familial cases were present in three patients (6%; 2 from Iran, 1 from Italy), absent in 42 (81%) and not reported in three (6%).

Recurrent respiratory infections were the most commonly reported manifestation (n = 29; 60%). Other infectious manifestations included mycobacterial adenitis, skin infections and bilateral pneumonia with an abscess. Atopic manifestations occurred in 11 children (21%), including eczema, food allergy and asthma. An autoimmune manifestation occurred in 1 child (2%), more specific information was not available in the database. The first serum IgM level ranged from 0.12 to 0.62 g/L (mean 0.35 g/L). In the majority of the children, IgM levels were not decreased according to the ESID diagnostic protocol values; none had undetectable levels of serum IgM (Figure 3A). Analysis of variance showed a significant effect for differences in serum IgM levels between countries ($F = 5.858$, $P = 0.001$, partial $\eta^2 = 0.417$, Figure 3B). Especially in Belgium, serum IgM values were higher and in Tunisia and Iran lower, but due to the low number of patients reported by these countries, it is difficult to interpret these results. Mean serum IgM levels were higher in males than in females (mean 0.37 versus 0.26 g/L; $t(12.208) = 2.697$, $P = 0.02$), but when the variation between countries was taken into account, this difference was no longer significant (two-way ANOVA; $F(1,37) = 2.038$, $P = 0.1$). Serum IgE levels were determined in 25 children (mean 184 U/mL, range 3-1225); they were elevated (>90 U/mL) in 11 children (44%). Specific IgE to ≥1 inhalant allergen were positive in 8/16 children (50%). Isohemagglutinin titres (anti-A and anti-B antibodies in the IgM class) were determined in 23 children, and low in two. Lymphocyte subsets were performed in 30 children (Table 1A). Three children (6%) were treated

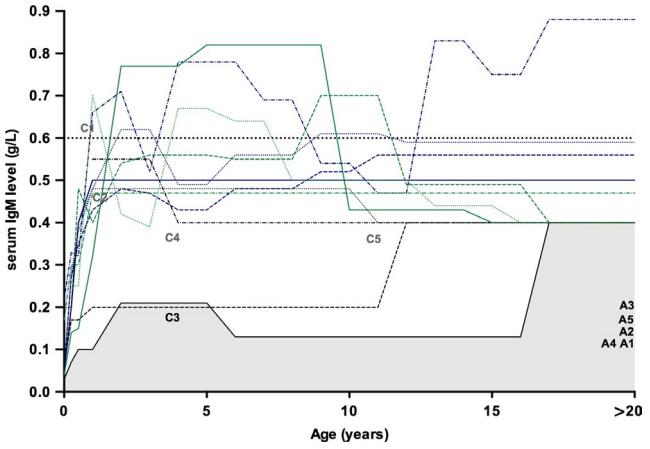

FIGURE 1 Centre-specific age-matched cut-off values of serum IgM (g/L). Each line represents the lower limit of normal for serum IgM used by a centre. The grey area represents serum IgM levels which are decreased according to the ESID diagnostic protocol values.[19] The first serum IgM levels of the ten patients with true sIgMdef according to centre-specific cut-off values are plotted (C1,2,4 from Belgium; C3 from Iran; C5, A3 from the Netherlands; A1,2,4,5 from the Czech Republic). Of these, four patients were excluded when ESID diagnostic protocol values were used (shown in grey). ESID, European Society for Immunodeficiencies; sIgMdef, selective IgM deficiency

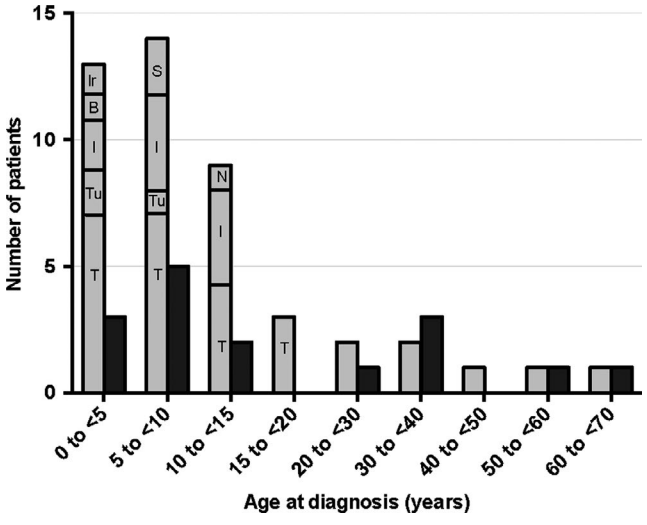

FIGURE 2 Gender distribution per age group in the patients with possible and true sIgMdef. Light grey, male; dark grey, female. The number of children reported per country is shown for the male children. T, Turkey; Tu, Tunisia; I, Italy; B, Belgium; Ir, Iran; S, Spain; N, The Netherlands

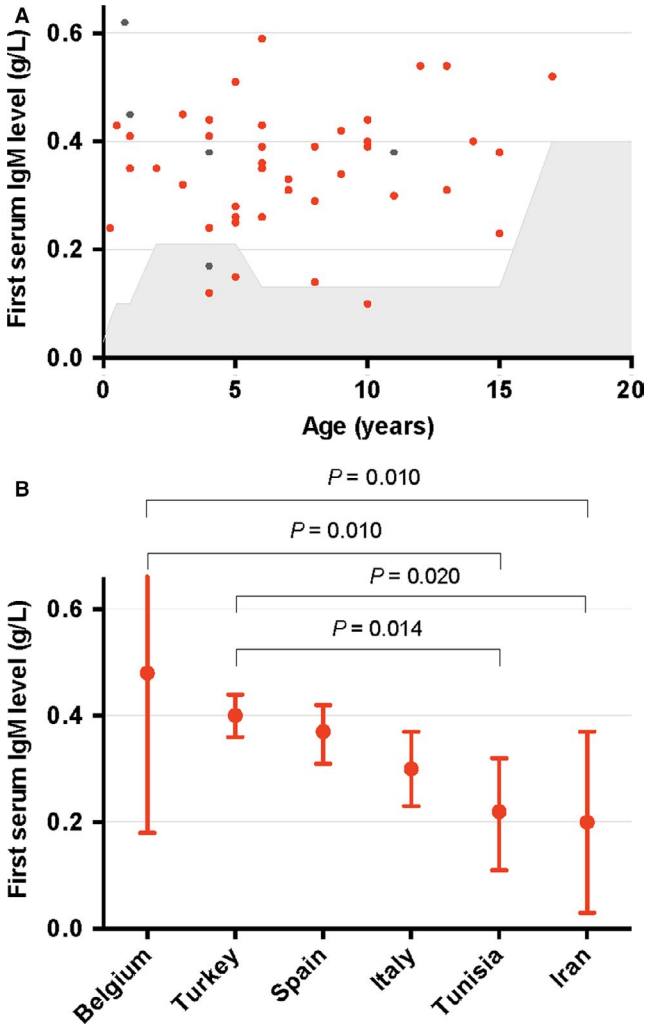

FIGURE 3 First serum IgM levels in the children from the tertiary centre cohort. A. The first serum IgM levels (y-axis) and age at the date of the first serum sample (x-axis). The grey dots represent the five children with true sIgMdef, and the red dots the 43 children with possible sIgMdef. The grey area in the graph represents decreased IgM levels according to the ESID diagnostic protocol values [18]. B. Mean first serum IgM levels + 95% CI in the different countries. sIgMdef, selective IgM deficiency

with intravenous immunoglobulins (IVIG), and 10 (21%) with prophylactic antibiotics.

Clinical manifestations of the children with true sIgMdef are described separately in Table 1B (see Table S1 for more details on all the children, and Table S2 for a comparison between the Turkish children (largest group) and the children from the other countries).

3.2 | Adults

Thirteen adults (7 males) with true or possible sIgMdef were reported from Turkey (n = 4), Czech Republic (n = 4), the Netherlands (n = 3) and the United Kingdom (n = 2). The mean age at the date of the first serum sample with decreased IgM was 40 years (range 21-63 years). Mean follow-up time was 64 months (range 4-144 months). None of the adults had a family history of immunodeficiency (unknown in one) or consanguinity.

Clinical manifestations of the adults with true sIgMdef are described in Table 2A (for details on all the adults, see Table S1). Increased susceptibility to infections, especially involving the respiratory tract, occurred most often (n = 7). Other reported infectious manifestations included hepatitis B, meningococcal sepsis and recurrent herpes simplex virus (HSV) encephalitis. Atopic manifestations occurred in two adults, including atopic dermatitis and allergic rhinitis. Autoimmune manifestations occurred in three (Sjögren's disease, alopecia, coeliac disease). The first serum IgM level ranged from 0.10 to 0.62 g/L (mean 0.27 g/L). Serum IgE levels were determined in five adults (mean 109 U/mL, range 4-410); they were elevated (>90 U/mL) in two. Isohemagglutinin titres were determined in four adults, and low in one. Lymphocyte subsets were performed in nine patients (Table 2B), all fell within the normal range. None of the adults were treated with IVIG, and three (23%) were treated with prophylactic antibiotics.

3.3 | Comparison between the tertiary and secondary centre cohorts of adult patients

We first compared the 13 adults with true or possible sIgMdef from this tertiary centre cohort with the 42 adults with true or possible sIgMdef from the secondary centre cohort we previously published.[15] These two cohorts differ in the type of population from which the data were collected (general hospital versus specialised medical centres) and in the way of collecting the data (analysing all laboratory data with decreased serum IgM vs only analysing patients reported as diagnosed with IgM deficiency by an immunologist). Given this different patient selection process, further immunological analyses were as expected more often performed in the tertiary centre cohort: repeated measurements of serum IgM in 86% vs 14% (Fisher's exact test, $P < 0.001$), measurements of IgG subclasses in 92% vs 14% (Fisher's exact test, $P < 0.001$) and pneumococcal vaccination responses in 42% vs 7% (Fisher's exact test, $P = 0.003$). Not only in the previously described secondary centre cohort, but also in this tertiary centre cohort, few patients can be classified as *true* sIgMdef (Figure 4). In contrast to the tertiary centre cohort, adults in the secondary centre cohort were often asymptomatic. The first serum IgM levels were significantly higher in the secondary centre cohort (mean 0.30 g/L, 95% CI 0.28-0.33) compared to the tertiary centre cohort (mean 0.27 g/L, 95% CI 0.17-0.37, $P = 0.01$; Figure 5A).

Second, comparisons were made between three groups: (a) symptomatic adults from the tertiary centres (n = 13), (b) symptomatic adults from the secondary centre (n = 18)

TABLE 1 Children. A, Lymphocyte subsets in children with true (n = 5) or possible sIgMdef (n = 25). B, Clinical manifestations of the children with true sIgMdef (n = 5)

Patient	Age[a] (years)	CD3 + T cells ×10[e]9/L	%	CD4 + T cells ×10[e]9/L	%	CD8 + T cells ×10[e]9/L	%	CD19 + B cells ×10[e]9/L	%	CD3- CD16 + CD56+ NK cells ×10[e]9/L	%
A											
True sIgMdef											
C1	0[b]	2.5		1.2		1.2		0.7		0.2	
C2	1	3.8		2.4		1.3		2		0.4	
C3	4		45		33		11		33		17
C4	4	1.8		0.9		0.8		0.7		0.24	
C5	11	1.6		0.8		0.6		NA		NA	
Possible sIgMdef											
C6	0[c]		70		***25***		42		24		7
C7	0[d]		64		36		24		28		8
C9	1		67		39		25		21		7
C10	2		58		28		22		21		15
C13	4	1.9		1.0		0.8		0.2		0.2	
C17	5		75		53		21		15		9
C18	5		72		47		23		22		5
C20	5		63		38		21		16		16
C22	5		90		52		38		***3***		11
C23	5		81		49		26		13		6
C26	6		75		30		34		13		10
C28	6		75		31		38		14		7
C29	7	1.9		1.0		0.7		0.5		0.36	
C31	8		78		58		17		9		12
C32	8		73		36		34		15		10
C33	8		79		39		34		11		9
C34	9		57		35		12		13		24
C36	10		80		51		25		12		8
C37	10		58		26		30		16		18
C38	10		73		43		27		15		12
C39	10		68		43		23		16		14
C40	11		73		31		29		17		10
C41	11		73		38		17		7		16
C47	15		76		30		43		9		15
C48	17		77		39		29		7		15

Patient	Age[a] (years)/ gender	Clinical manifestations	Familial cases	First and last serum IgM (g/L)	Treatment	Follow-up period (months)
B						
C1	0/M	Recurrent pneumonia	No	0.62[e], 0.39	IVIG + AB	105
C2	1/M	Recurrent ENT infections	n.r	0.45, 0.22	AB	30

(Continues)

TABLE 1 (Continued)

Patient	Age[a] (years)/ gender	Clinical manifestations	Familial cases	First and last serum IgM (g/L)	Treatment	Follow-up period (months)
C3	4/F	Complicated atypical mycobacterial adenitis, recurrent respiratory infections	Yes	0.17, 0.10	AB	42
C4	4/F	Atopic dermatitis, eczema, food allergy, asthma, warts	No	0.38, 0.38	IVIG	n.r
C5	11/F	Severe eczema	n.r	n.r, 0.38	none	162

Reference ranges from: Schatorjé et al Scand J Immunol 2011;74(5):502-10.[35]

AB, prophylactic antibiotics; C, child; ENT, ear-nose-throat; F, female; IgM, immunoglobulin M; IVIG, intravenous immunoglobulins; M, male; n.r, not reported; sIgMdef, selective IgM deficiency.

[a]Age at first sample collection.

[b]8 months.

[c]6 months.

[d]7 months.

[e]This serum IgM level is decreased according to the age-matched reference values used by this centre.

TABLE 2 Adults. A, Clinical manifestations of the adults with true sIgMdef (n = 5). B, Lymphocyte subsets in adults with true (n = 5) or possible sIgMdef (n = 4)

Patient	Age[a] (years)/ gender	Clinical manifestations	Familial cases	First and last serum IgM (g/l)	Treatment	Follow-up period (months)
A						
A1	36/F	Atopic dermatitis, allergic rhinitis, sinusitis	No	0.10, 0.10	None	38
A2	38/F	Bronchitis, nasopharyngitis, chronic hepatitis B	No	0.14, 0.12	None	70
A3	50/F	Bronchiectasis, coeliac disease, fatigue, recurrent respiratory infections	No	0.20, 0.37	AB	67
A4	55/M	Vertebral pain syndrome	No	0.10, 0.10	None	39
A5	63/F	Sjögren's syndrome, alopecia, multiple lung cysts, fatigue	No	0.16, 0.14	None	101

Patient	$CD3^+$T cells $\times10^e9$/L	%	$CD4^+$T cells $\times10^e9$/L	%	$CD8^+$T cells $\times10^e9$/L	%	$CD19^+$B cells $\times10^e9$/L	%	CD3-$CD16^+CD56^+$ NK cells $\times10^e9$/L	%
B										
True sIgMdef										
A1	0.9		0.6		0.3		0.2		0.12	
A2	1.3		0.9		0.4		0.4		0.68	
A3	2.0		1.5		0.6		0.1		0.20	
A4	1.7		1.0		0.6		0.6		0.22	
A5	0.8		0.5		0.3		0.3		0.19	
Possible sIgMdef										
A7		70		39		27		13		13
A10	2.0		0.9		1.0		0.2		0.10	
A12		79		47		29		10		10
A13	1.3		0.9		0.4		0.1		0.12	

Reference ranges from: Schatorjé et al Scand J Immunol 2011;74(5):502-10.[35]

A, adult; AB, prophylactic antibiotics; F, female; IgM, immunoglobulin M; M, male; sIgMdef, selective IgM deficiency.

[a]Age at first sample collection.

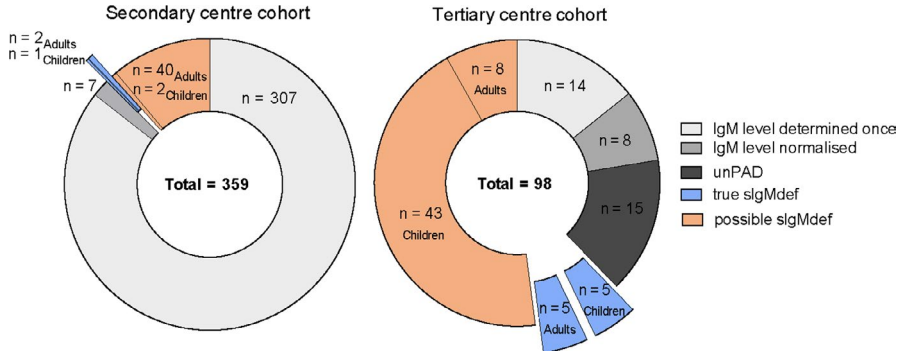

FIGURE 4 Classification of patients with decreased serum IgM in the tertiary (n = 98) and secondary (n = 359) centre cohorts. Abbreviations: sIgMdef, selective IgM deficiency; unPAD, unclassified primary antibody deficiency

and (c) asymptomatic adults from the secondary centre (n = 24) (Table 3). The mean age at diagnosis was significantly higher in patients without symptoms that could be related to antibody deficiency (mean 65 years, 95% CI 60-70) compared to those with symptoms from the secondary centre (mean 56 years, 95% CI 49-64) and tertiary centres (mean 40 years, 95% CI 31-49; $P < 0.01$). We evaluated the mean first serum IgM levels in the different clinical manifestations (Figure 5B). Two symptoms, autoimmunity and fatigue, showed a significant difference, the patients with the symptoms having lower IgM levels (autoimmunity n = 6, mean 0.21 g/L, 95% CI 0.09-0.33; no autoimmunity n = 49, mean 0.30 g/L, 95% CI 0.27-0.33; $t(53) = -2.137$, $P = 0.037$; fatigue n = 9, mean 0.22 g/L, 95% CI 0.16-0.29; no fatigue n = 46, mean 0.31 g/L, 95% CI 0.27-0.34; $t(53) = -2.265$, $P = 0.03$). When combining all symptoms that could be related to antibody deficiency, adults with these symptoms (n = 31) had significantly lower IgM levels compared to adults without these symptoms (n = 24) (mean 0.27 g/L, 95% CI 0.22-0.31 vs mean 0.33 g/L, 95% CI 0.30-0.36; $t(47.094) = 2.353$, $P = 0.02$, Figure 5C).

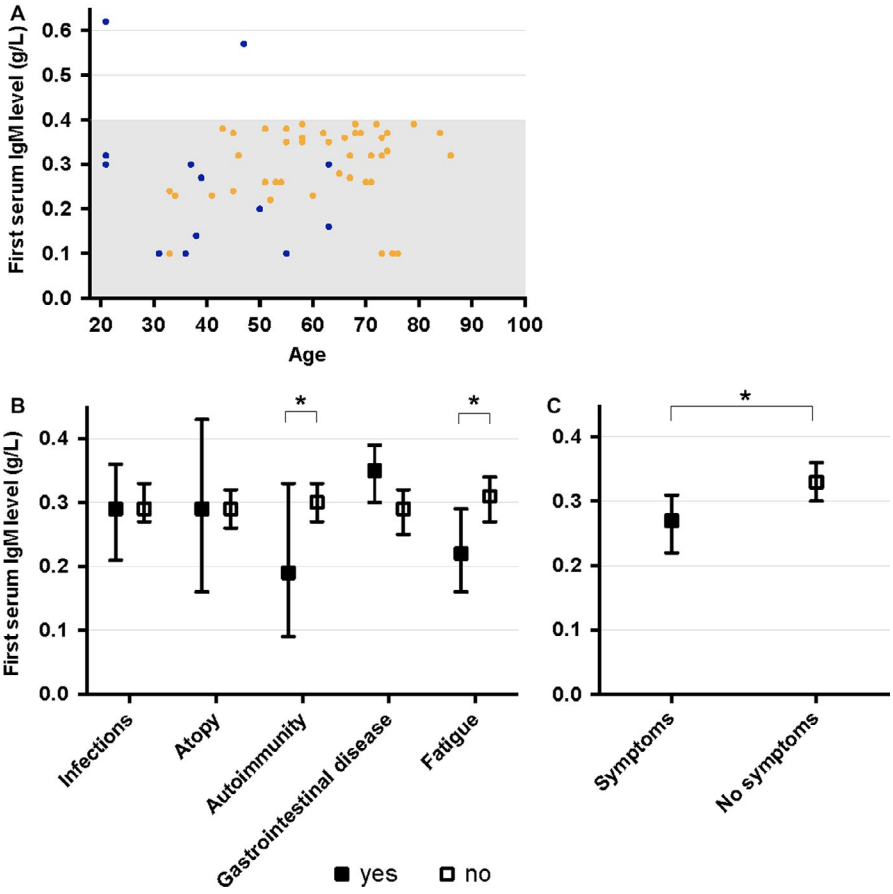

FIGURE 5 First serum IgM levels in the adults from the tertiary and secondary centre cohorts. Tertiary centre cohort n = 13, blue; secondary centre cohort n = 42, yellow. The first serum IgM levels (y-axis) and age at the date of first serum sample (x-axis) (A). The grey area in the graph represents decreased IgM levels according to the ESID diagnostic protocol values [18]. Mean first serum IgM levels + 95% CI (g/L) in the different clinical manifestations of adults from both tertiary and secondary centres (B), and in those with (n = 30) and without (n = 25) symptoms that could be related to antibody deficiency (C). *Two-sided *t* test; $P < 0.05$

TABLE 3 Clinical and laboratory features of the adults with true or possible sIgMdef

	Tertiary centre symptomatic (n = 13)	Secondary centre symptomatic (n = 18)	Secondary centre asymptomatic[a](n = 24)	*P* value
Age[b], years (95% CI)	40 (31-49)	56 (49-64)	65 (60-70)	**<0.01**[*]
Males, n (%)	7 (54)	11 (61)	12 (50)	0.79[#]
Follow-up period, months (95% CI)	64 (36-92)	68 (52-84)	80 (65-95)	0.41[*]
Clinical manifestation(s), n (%)				
Infectious manifestations	7 (54)	9 (50)	0 (0)	**<0.01**[#]
Atopic manifestations	2 (15)	5 (28)	0 (0)	**0.02**[#]
Autoimmune manifestation	3 (23)	1 (6)	0 (0)	**0.05**[#]
Gastrointestinal disease	2 (15)	2 (11)	3 (12)	1.00[#]
Long-lasting fatigue	3 (23)	5 (28)	1 (4)	0.09[#]
First IG levels, g/L (95% CI)				
Serum IgM	0.27 (0.17 - 0.37)	0.27 (0.22-0.31)	0.33 (0.30-0.36)	0.11[*]
Serum IgG	12.1 (11.5-13.6)	10.5 (9.5-11.4)	10.7 (9.9-11.5)	0.09[*]
Serum IgA	2.4 (1.8-3.0)	2.7 (1.9-3.5)	2.9 (2.2-3.6)	0.63[*]
Treatment, n (%)[c]				
Prophylactic antibiotics	3 (23)	0 (0)	0 (0)	**0.01**[#]

Tertiary centre cohort (n = 13), and symptomatic (n = 18) and asymptomatic (n = 24) secondary centre cohort.
CI, confidence interval; IG, immunoglobulin.
[a]This means no symptoms potentially related to antibody deficiency were present.
[b]Age at first sample collection.
[c]None of the adults were treated with immunoglobulins.
*ANOVA.
[#]Fisher's exact test.

4 | DISCUSSION

When isolated decreased serum IgM levels are repeatedly found in a patient, clinicians are confronted with a dilemma. To date, it is not clear what the clinical consequences of such a finding are, and whether and if so how such patients should be treated. The results of our study underline these challenges. Not only in our previously published secondary centre cohort,[15] but also in this tertiary centre cohort as well as in other cohorts in the literature,[5-7,14] only few patients with decreased serum IgM levels have *true* sIgMdef. This condition is probably very rare.

However, the adults with more severely decreased serum IgM levels were more likely to be younger and to be symptomatic. This information can help in interpreting the clinical significance when an isolated decreased serum IgM level is discovered. While just below normal values tend to have little clinical meaning, we suggest that lower cut-off values than the current "two standard deviations (SD) below the mean" probably distinguish the clinically relevant category of patients. We propose to develop a classification for sIgMdef similar to the one previously developed for selective IgA deficiency. This classification distinguishes selective IgA deficiency (serum IgA < 0.07 g/L) from the often clinically irrelevant partial IgA deficiency (serum IgA > 0.07 g/L but 2 SD below normal age-adjusted means).[20,21] For selective IgM deficiency, such a cut-off value will have to be determined in future studies.

Our study has several limitations. First, our results are based on a still relatively small cohort including not only true but also possible sIgMdef. This group contained a high number of children, which is in contrast to few children reported in the literature.[5] This is probably bias resulting from the type of centres that decided to participate in the study. Second, it is possible that mildly affected patients with a known genetic defect are "hidden" in the sIgMdef population and fulfil the criteria for syndromic immunodeficiencies instead.[22,23] This can only be revealed by genetic testing in such cases. Third, age-matched cut-off values varied widely between the centres; when using the ESID diagnostic protocol values, even fewer patients had true sIgMdef (1 child, 5 adults). This cannot only be explained by variations in technique or in genetic, ethnic or geographical differences, which have also been shown to influence serum IgM levels.[26,27] Almost all centres (14 out of 15) used immunonephelometric or immunoturbidimetric techniques, which have been demonstrated to be reliable and to have good comparability.[33,34] Although interlaboratory variability in the current methodologies can make

unification of reference values challenging, investigating opportunities for achieving this would be worthwhile.

In conclusion, even this multi-centre study could not solve the dilemma. Even enlarging the study to global proportions will probably not answer our questions. To be able to explore the clinical consequences of *true* sIgMdef, full analysis and accurate description of all patients in whom a decreased serum IgM is found would be more effective, leaving no patients with *possible* sIgMdef to dilute the results.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the cresponding author on reasonable request.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest relative to this project.

AUTHOR CONTRIBUTIONS

LMAJ and EdV designed the study and wrote the manuscript. LMAJ acquired the data and carried out descriptive statistical analyses. EdV supervised and critically reviewed all data collection. RWNMvH carried out statistical analyses. All authors approved the final manuscript as submitted. The SIMcal constium members supplied the patient data and critically reviewed the manuscript; all members approved the final manuscript as submitted.

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SUPPORTING INFORMATION

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

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APPENDIX 1

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