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Truly selective primary IgM deficiency is probably very rare

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SUMMARY

Isolated decreased serum-immunoglobulin (Ig)M has been associated with severe and/or recurrent infections, atopy and autoimmunity. However, the reported high prevalence of clinical problems in IgM-deficient patients may reflect the skewed tertiary centre population studied so far. Also, many papers on IgM deficiency have included patients with more abnormalities than simply IgM-deficiency. We studied truly selective primary IgM deficiency according to the diagnostic criteria of the European Society for Immunodeficiencies (ESID) (true sIgMdef) by reviewing the literature (261 patients with primary decreased serum-IgM in 46 papers) and analysing retrospectively all patients with decreased serum-IgM in a large teaching hospital in 's-Hertogenbosch, the Netherlands [1 July 2005–23 March 2016; n = 8049 IgM < 0·4 g/l; n = 2064 solitary (IgG+IgA normal/IgM < age-matched reference)]. A total of 359 of 2064 (17%) cases from our cohort had primary isolated decreased serum-IgM, proven persistent in 45 of 359 (13%) cases; their medical charts were reviewed. Our main finding is that true sIgMdef is probably very rare. Only six of 261 (2%) literature cases and three of 45 (7%) cases from our cohort fulfilled the ESID criteria completely; 63 of 261 (24%) literature cases also had other immunological abnormalities and fulfilled the criteria for unclassified antibody deficiencies (*unPAD*) instead. The diagnosis was often uncertain (possible sIgMdef): data on IgG subclasses and/or vaccination responses were lacking in 192 of 261 (74%) literature cases and 42 of 45 (93%) cases from our cohort. Our results also illustrate the clinical challenge of determining the relevance of a serum sample with decreased IgM; a larger cohort of true sIgMdef patients is needed to explore fully its clinical consequences. The ESID online Registry would be a useful tool for this.

Keywords: IgM deficiency, immunodeficiency, primary immunodeficiency, primary selective IgM deficiency, unclassified antibody deficiency

Introduction

Immunoglobulin (Ig)M deficiency is, on one hand, reported to be associated with a wide range of clinical presentations, including severe or recurrent infections, atopy, autoimmunity and malignancy [1]. On the other hand, there are doubts about its clinical significance [2]; studies in healthy populations have shown that genetic polymorphisms as well as environmental factors may influence serum IgM levels [2,3]. Previous studies on the clinical significance of IgM deficiency have been affected by selection bias towards 'disease', as mostly symptomatic patients from tertiary centre cohorts have been described [4–6].

The European Society for Immunodeficiencies (ESID) Registry defines primary selective IgM deficiency (sIgMdef) as a serum IgM level repeatedly below 2 standard deviations (s.d.) of normal 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). Many previously published papers that report on 'IgM deficiency' do not fulfil these criteria [7,8].

To facilitate a clear discussion, we define three categories in our study: (i) truly selective primary IgM deficiency (true sIgMdef) – the ESID criteria are completely fulfilled, which means that serum IgM levels are decreased repeatedly and IgG, IgA, IgG-subclasses and vaccination responses have been determined and were normal for age; we consider the absence of clinical signs suggesting a T cell defect sufficient; (ii) possible selective primary IgM deficiency (possible sIgMdef) – the diagnosis of true sIgMdef is uncertain, which means that the ESID criteria are not fulfilled completely, because data on IgG subclasses and/or vaccination responses are lacking; and (iii) unclassified primary antibody deficiency (unPAD) – other abnormalities in antibodies are also present: IgG-subclass deficiency, below-normal levels of IgG or IgA and/or impaired vaccination responses.

The aim of our study was to learn more about the clinical significance of true sIgMdef. Therefore, we first conducted a scoping review to identify all previously published patients with decreased serum IgM. Secondly, we analysed decreased serum IgM identified through the laboratory files of the Jeroen Bosch Hospital in 's-Hertogenbosch, the Netherlands, a large teaching hospital (secondary centre). Finally, we analysed whether these fulfilled the criteria for true sIgMdef.

Materials and methods

Literature search

The PubMed database was searched for papers concerning 'IgM deficiency' published until 10 May 2017 (no starting date). The search query was defined as {selective OR isolated} AND {IgM OR Immunoglobulin M} AND {deficiency OR low} AND {immunodeficiency syndromes}. We also screened the reference lists of papers identified by our search strategy and added those papers that reported about decreased serum IgM (snowball method). Our search strategy is described in detail in Supporting information, Fig. S1. We considered decreased serum IgM to be secondary in combination with the use of immunosuppressive agents, malignancy (e.g. clear cell sarcoma, promyelocytic leukaemia, multiple myeloma) or gastrointestinal loss (e.g. enteropathy through Crohn's or coeliac disease). Only papers that (also) contained patients with primary decreased serum IgM were included into the study. We analysed whether these patients fulfilled the criteria for true sIgMdef.

Our cohort

Patient selection. All serum immunoglobulin levels determined between 1 July 2005 and 23 March 2016, in the Jeroen Bosch Hospital (JBZ) in 's-Hertogenbosch, the Netherlands (encatchment area 350 000; 500 000 out-patient visits and 32 000 admissions per year), were obtained [n = 38 149; 5342 (14%) samples from children and 32 509 (85%) samples from adults, missing age values in 298 samples]. Of these, all samples with serum IgM values $< 0{\cdot}4$ g/l were selected (n = 8049, details in Supporting information, Fig. S2). Samples were excluded if serum IgM levels were normal according to age-matched reference values (these were all young children) [9]. To identify all patients with isolated decreased serum IgM, samples with decreased age-matched IgA and/or IgG values as well as follow-up samples of serum IgM were excluded. The medical charts were screened regarding patient history and medication use to exclude the samples from those patients in whom decreased serum IgM could be secondary (caused by external factors; for definition, see literature review above). Patients with cystic fibrosis (n = 3) were excluded because their clinical symptoms would be difficult to interpret. Laboratory data of all primary cases were analysed to identify patients in whom serum IgM level was determined only once and in whom serum IgM level was determined repeatedly, but had normalized. Only the medical charts of patients with persistent decreased serum IgM levels were reviewed in detail; this patient group comprises both possible and true primary sIgMdef (for definitions, see Introduction). The Medical Ethical Committee Brabant approved the study.

Data collection. Data on demographics, clinical features, laboratory results and treatment, conclusions written by medical specialists and ICD-10 codes were derived from our electronic patient system. For clinical evaluation, we collected the type of medical specialist who discovered the decreased serum IgM, reason(s) for determining serum IgM and clinical problems that could be related to antibody deficiency. We considered the following clinical problems to be possibly related to antibody deficiency: infections, atopic and/or autoimmune manifestations, inflammation of the gastrointestinal tract, long-lasting fatigue, depression and malignancies. Pneumonia required confirmation by thoracic X-ray. Allergic diseases (allergic rhinoconjunctivitis, food allergy, allergic urticaria, allergic anaphylaxis) required confirmation by skin-prick testing or radioallergosorbent test (RAST). For immunological evaluation, we collected data on serum IgM, IgG and IgA levels and, if determined, data on IgG subclasses, T cell subsets and function, antibody responses to vaccinations, isohaemagglutinin levels, anti-nuclear antibodies (ANA) and specific serum IgE directed against inhalant allergens. For interpretation of serum immunoglobulins and lymphocyte subpopulations, age-matched reference values were used [10]. Because our laboratory cut-off for serum IgM levels is 0·2 g/l, a value of $< 0{\cdot}2$ g/l was replaced by 0·1 g/l for calculating mean serum IgM level (n = 4). For interpretation of pneumococcal antibody responses, laboratory specific reference values were used [11]. The follow-up period was

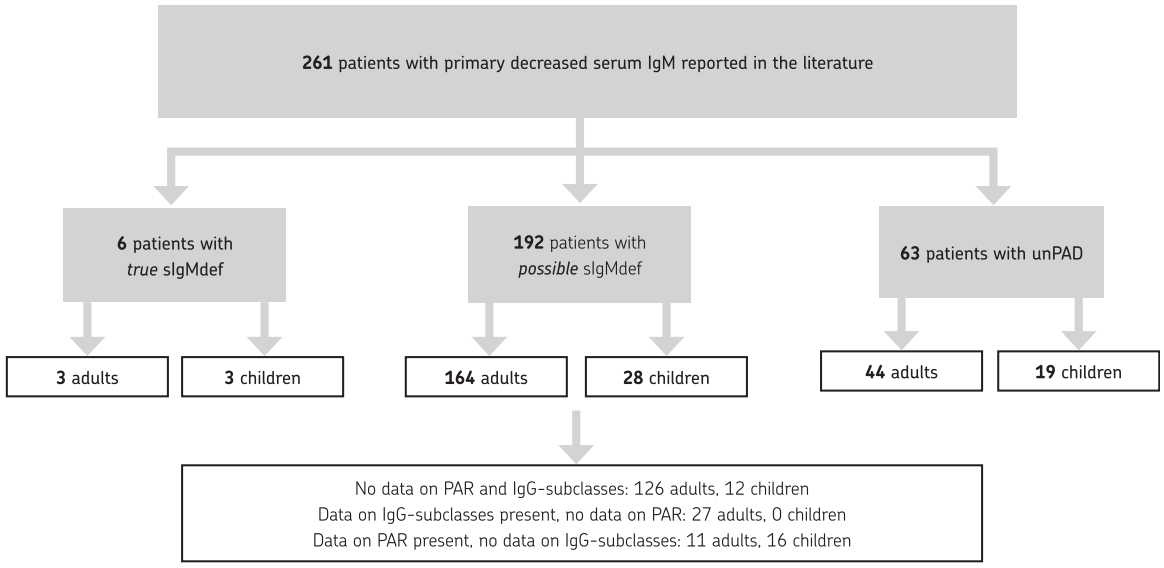

Fig. 1. Patients with truly selective primary immunoglobulin (Ig)M deficiency in the literature [according to the European Society for Immunodeficiencies (ESID) Registry clinical diagnosis criteria]. PAR = pneumococcal antibody response; sIgMdef = selective IgM deficiency; unPAD = unclassified primary antibody deficiency.

defined as the date of the first serum sample with decreased IgM until the date of data extraction. All patient data were encrypted and saved on a protected server using Research Manager software developed by Cloud9 Health Solutions (Deventer, the Netherlands).

Statistical analysis. Statistical analysis was performed using SPSS for Windows, version 21. Descriptive statistics were used to compute frequencies of categorical variables and mean (with s.d.) or median [with interquartile range (IQR)] of continuous variables, depending on the distribution.

Results

Literature search

Supporting information, Table S1 provides an overview of the identified relevant literature. A total of 261 patients with primary decreased serum IgM were described in 46 papers; eight patients (two adults and six children) fulfilled the criteria for combined immunodeficiency and these were excluded. Only six of 261 patients (2·3%, three adults and three children) fulfilled the ESID criteria completely for true sIgMdef; 63 of 261 (24·1%; 44 adults and 19 children) fulfilled the criteria for unclassified antibody deficiency. In 192 of 261 patients (73·6%, 164 adults and 28 children) the diagnosis was uncertain (possible sIgMdef), due to incomplete laboratory data (Fig. 1).

Clinical and laboratory features of the published adult and paediatric cases with true or possible sIgMdef are summarized in Tables 1 and 2. More than two-thirds of both adults and children were male (57 of 85 adults, 67% *versus* 23 of 31 children, 74%). Many patients presented with infectious problems (30 of 62 adults, 48% *versus* 14 of 15 children, 93%). In three of 62 (5%) of the reported adults, decreased IgM was identified 'by accident' as part of laboratory evaluation for ischaemic heart disease, hypertension and visual disturbance. Thirteen of 62 (21%) of the reported adults and one of 15 (7%) children were asymptomatic; this boy was detected during family screening. Serum IgM values were reported in 86 adults and 14 children (mean 0·23 g/l, range 0·004–0·45 g/l for adults *versus* mean 0·18 g/l, range 0·00–0·36 g/l for children). Undetectable serum IgM levels were reported in two children [12,13] and four adults [14]. Three adults and one baby were treated with intravenous immunoglobulin substitution (IVIG).

Our cross-sectional retrospective cohort

A total of 2064 patients with isolated decreased serum IgM were identified in the laboratory system of the JBZ (1 July 2005–23 March 2016): 2034 adults and 17 children aged 6–18 years (13 children < 6 years were excluded because the age-matched reference value was lower than the cut-off value of the test). The patient selection process is shown in detail in Supporting information, Fig. S2; 1685 of 2034 adults (83%) and seven of 17 (41%) children had secondary isolated decreased serum IgM; 349 of 2034 (17%) adults and 10 of 17 (59%) children had a primary form; of these, serum IgM levels were determined more than once in only 49 of 349 (14%) adults and three of 10 (30%) children. In seven of 49 (14%) of the adults the serum IgM level normalized, yielding persistent isolated decreased

Table 1. Adult patients from the literature

Year	Reference	Reported patients*	Age (years/ gender)	Clinical manifestation(s) that could be related to antibody deficiency†	Familial cases	Serum IgM level (g/l)	IVIG (yes/no)
ESID criteria completely fulfilled (true sIgMdef)							
2009	[4]	3	79/M	Asthma, myalgia, fatigue	No	0·18	No
			39/F	Recurrent respiratory infections, allergic rhinitis, asthma, myalgia	No	0·16	No
			55/M	Recurrent shingles, myalgia, arthralgia, fatigue	No	0·39	No
ESID criteria not completely fulfilled: data on IgG subclasses and/or pneumococcal antibody responses lacking (possible sIgMdef)							
1967	[22]	5	Adult/M	Asymptomatic	Yes	0·40	No
			Adult/M	Asymptomatic	Yes	0·40	No
			Adult/M	Asymptomatic	Yes	0·45	No
			Adult/M	Asymptomatic	Yes	0·30	No
			Adult/F	Asymptomatic	Yes	0·30	No
1970	[24]	10	20/M	Bacterial infections, asthma	n.r.	0·36	No
			23/M	Allergic rhinitis	n.r.	0·41	No
			28/M	Bacterial infections, asthma	n.r.	0·42	No
			30/M	Bacterial infections, asthma, atopic dermatitis	n.r.	0·41	No
			31/M	Bacterial infections, asthma	n.r.	0·35	No
			33/M	Bacterial infections, atopic dermatitis	n.r.	0·24	No
			48/M	Asthma	n.r.	0·41	No
			50/M	Asthma	n.r.	0·43	No
			56/M	Asthma	n.r.	0·41	No
			75/M	Bacterial infections, asthma	n.r.	0·35	No
1973	[25]	2	22/M	CMV hepatitis	Yes	0·28	No
			20/M	Psittacosis	Yes	0·33	No
1975	[17]	70	n.r.‡	Recurrent respiratory infections(59%), asymptomatic (19%)	n.r.	n.r.	No
1976	[26]	2	72/M	No	No	0·15	No
			60/M	Tuberculosis pneumonia	No	0·04	No
1978	[27]	1	48/M	Pneumonia, sepsis, rheumatic heart disease	n.r.	0·21	No
1981	[28]	1	21/M	Smallpox, pneumonia, died from infection	No	0·20	No
1981	[29]	1	85/M	No	n.r.	0·17	No
1982	[30]	1	65/M	No	n.r.	0·01	No
1984	[31]	1	66/M	Stomach leiomyoma	n.r.	0·08	No
1986	[32]	7	58/M	Urinary tract infection, pulmonary tuberculosis	n.r.	0·20	No
			73/F	Urinary tract infection, respiratory infection	n.r.	0·14	No
			71/F	Urinary tract infection, pneumonia	n.r.	0·11	No
			53/F	Urinary tract infection, rheumatoid arthritis	n.r.	0·17	No
			29/F	Urinary tract infection, respiratory infection, SLE	n.r.	0·25	No
			30/M	Urinary tract infection, SLE	n.r.	0·06	No
			48/M	Pneumonia	n.r.	0·10	No
1987	[33]	4	44/F	SLE-like	n.r.	0·26	No
			62/F	Asthma	n.r.	0·23	No
			60/F	Lymphoma	n.r.	0·08	No
			51/F	SLE	n.r.	0·10	No
1992	[34]	6	50/M	Liver abscess, cholangitis, dermatitis	No	0·18	No
			57/M	Diabetes mellitus	No	0·06	No
			22/M	Streptococcal infection	No	0·32	No
			34/M	Chronic tonsillitis, bronchitis, psoriasis pustulosa	No	0·01	No
			57/M	Diabetes mellitus, polyarthritis	No	0·004	No
			37/F	Asymptomatic	No	0·34	No
2004	[35]	1	23/M	Recurrent respiratory infections, allergic rhinitis, asthma	No	0·28	Yes
2006	[5]	23	Unknown§	n.a.	No	0·32	No
2009	[4]	5	69/M	Asthma, rhinorrhoea	No	0·39	No
			44/F	Chronic sinusitis	No	0·27	Yes
			44/F	Recurrent sinus infections, allergic rhinitis, rash	No	0·28	No
			76/M	Recurrent respiratory infections	No	0·30	No
			46/F	Recurrent respiratory infections, rheumatoid arthritis	No	0·39	No

Table 1. *Continued*

Year	Reference	Reported patients*	Age (years/ gender)	Clinical manifestation(s) that could be related to antibody deficiency†	Familial cases	Serum IgM level (g/l)	IVIG (yes/no)
2009	[36]	2	n.r.	n.r.	n.r.	n.r.	n.r.
2015	[37]	1	52/M	CEP, pericarditis, allergic rhinitis, asthma, coeliac disease	No	0·32	No
2016	[2]	11	57/M	Asymptomatic	No	0·19	No
			45/M	Urinary tract infection (×2)	No	0·29	No
			48/M	Atopic dermatitis, allergic rhinitis, food allergy	No	0·27	No
			50/F	Atopic dermatitis, allergic rhinitis	No	0·25	No
			32/M	Atopic dermatitis	No	0·27	No
			55/F	Asymptomatic	No	0·23	No
			63/M	Asymptomatic	No	0·27	No
			57/M	Asymptomatic	No	0·19	No
			48/M	Asymptomatic	No	0·29	No
			50/M	Asymptomatic	No	0·16	No
			30/M	Asymptomatic	No	0·26	No
2016	[14]	10	Unkown¶	n.r.	n.r.	Unknown	n.r.

The three adults with true and 164 adults with possible selective primary immunoglobulin (Ig)M deficiency from the literature (definition of true selective IgM deficiency (sIgMdef) according to the European Society for Immunodeficiencies (ESID) registry clinical diagnosis criteria). *Only reported patients fulfilling the criteria for reported true or possible primary sIgMdef are described in this table. †The difference between 'asymptomatic' and 'no' is that 'no' refers to patients who were screened for problems not related to antibody deficiency in contrast to asymptomatic patients, who had no clinical problems at all. ‡Seventy patients were reported without specific age indications or exact IgM levels in this paper. §Clinical manifestations of patients were not described separately in this paper. Mean age at diagnosis of the whole group was 54 years; 11 males, 12 females. One patient was treated with intravenous Ig (IVIG) because of refractory asthma. ¶Patient data were not described separately in this paper. Of the 20 described patients, 50% had also specific anti-polysaccharide antibody deficiency and fulfilled the criteria for 'unclassified antibody deficiency'. Therefore, these 10 patients were not included in this table. Age range of the whole group: 24–56 years, F : M ratio 1.1 : 1.0, serum IgM range: 0·04 g/l to 0·32 g/l. CEP = chronic eosinophilic pneumonia; CMV = cytomegalovirus; F = female; M = male; n.a. = not applicable; n.r. = not reported; SLE = systemic lupus erythematosus.

serum IgM (possible or true sIgMdef cases) in 42 adults and three children.

More than half the adults (54.8%) and all the children were male. Mean age at the date of the first serum sample with decreased IgM was 61 (range 33–86) years in the adults and 16 (range 16–17) years in the children. Mean follow-up time was 74·8 (range 20–133) months in the adults and 102·7 (range 82–119) months in the children.

Clinical and laboratory features are described in Tables 2 (three children) and 3 (42 adults). The onset and duration of symptoms could not be determined accurately in the medical files; 24% of the adults and two of the three children were analysed for suspected potential immunodeficiency. The others were detected during analysis for other problems; however, 22% of these adults and one child had a history of symptoms that could be related to antibody deficiency (mainly infections). The majority (72%) of adults without such symptoms remained asymptomatic during follow-up; 28% developed symptoms that could be related to antibody deficiency. In none of the patients was a family history of immunodeficiency found in the medical charts. Only 7% (two adults and one child) fulfilled the ESID criteria completely for true sIgMdef.

The first serum IgM level in possible or true sIgMdef cases ranged from $< 0{\cdot}2$ to 0·39 g/l (mean $0{\cdot}30 \pm 0{\cdot}84$) in the adults and from 0·28 to 0·38 g/l (mean $0{\cdot}34 \pm 0{\cdot}05$) in the children. First serum IgA levels were increased ($> 4{\cdot}0$ g/l) in seven adults (17%). Serum IgE levels were determined in six adults and one child (mean 133 ± 182 U/ml; range 5–410 U/ml); they were elevated (> 90 U/ml) in two adults. None of the patients were treated with IVIG or prophylactic antibiotics.

Discussion

We studied true sIgMdef (according to the ESID diagnostic criteria) by reviewing the literature and by analysing decreased serum IgM in our secondary hospital population. Our main finding is that true sIgMdef is probably very rare. Unfortunately, when a decreased serum IgM level is found, it is rarely analysed fully. In most cases in our cohort serum IgM levels were determined only once (86%). When proven persistently decreased, further immunological analysis is often not performed (data on IgG subclasses and/or vaccination responses were lacking in 74% of the literature cases and 93% of the cases in our cohort). Also, different criteria for 'selective IgM deficiency' are used in the literature; in a quarter of the cases, the deficiency is not 'selective', other immunological abnormalities were present. Eight literature cases even showed clinical and/or laboratory signs fitting combined immunodeficiency; these should not be classified as a form of 'predominantly

Table 2. Paediatric patients from the literature and our cohort

Year	Reference	Reported patients	Age (years/ gender)	Clinical manifestations that could be related to antibody deficiency	Serum IgM level (g/l)	IVIG (yes/no)
ESID criteria completely fulfilled (true sIgMdef)						
Our cohort			16/M	URTI, growth retardation, verrucae vulgares, RLS	0·36	No
2008	[6]	2	10/M	Recurrent otitis media	0·21	No
			12/M	Pneumonia	0·30	No
2009	[38]	1	6/M	Multiple recurrent impetigo	0·21	No
Data on IgG subclasses present, but no data on pneumococcal antibody responses (possible sIgMdef)						
No cases						
Data on pneumococcal antibody responses present, but no data on IgG subclasses (possible sIgMdef)						
2013	[39]	16	Unknown*	n.r.	n.r.	n.r.
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)						
Our cohort			16/M	Recurrent infections, asthma, verrucae vulgares	0·28	No
Our cohort			17/M	Depression, long-lasting fatigue	0·38	No
1967	[22]	1	5/M	Meningococcal meningitis, died from infection	0·12	No
1971	[13]	1	0/M	Recurrent pseudomonas infections	0·00	No
1973	[40]	1	2/F	Recurrent otitis media, laryngitis, meningitis	0·08	No
1973	[25]	1	13/M	CMV hepatitis	0·26	No
1973	[41]	2	4/M	Meningitis	0·34	No
			1/M	Asymptomatic	0·36	No
1986	[42]	1	16/F	Disseminated molluscum contagiosum	0·04	No
1989	[12]	1	3/M	Recurrent infections	0·00	No
2001	[43]	1	10/M	Recurrent sinusitis, pneumonia, chronic staphylococci blepharitis	0·23	No
2005	[23]	1	0/M	Pseudomonas septicemia	0·12	Yes
2009	[44]	1	6/M	Chronic recurrent multi-focal osteomyelitis	0·20	No
2010	[45]	1	16/M	Refractory giardiasis	0·21	No

The three paediatric patients from our cohort and 31 paediatric patients with true or possible selective primary IgM deficiency (sIgMdef) from the literature. *Patients were not described separately in this paper. Median age at diagnosis was 4·2 years; 10 males, six females. CMV = cytomegalovirus; F = female; Ig = immunoglobulin; IVIG = intravenous immunoglobulin; M = male; n.a. = not applicable; n.r. = not reported; URTI = upper respiratory tract infection; RLS = Raynaud-like symptoms.

antibody deficiency'. Sixty-three (24%) literature cases fitted the ESID classification 'unclassified antibody deficiency'. These patients with concomitant defects in specific antibody production (SPAD) and/or IgG subclass deficiencies may be at risk of more severe and frequent infections, comparable to the increased number of lower respiratory tract infections and bronchiectasis in patients with IgA deficiency in combination with IgG subclass deficiency and/or SPAD [15]. Patients with recurrent and/or severe infections and decreased serum IgM levels in combination with SPAD have been described to benefit from immunoglobulin treatment [4,16].

Routine determination of serum IgM is advised in many medical protocols, mainly for adults; we showed in our cohort that this leads to many incidental findings of decreased serum IgM. The relatively common finding of a low serum IgM level in, immunologically speaking, asymptomatic adults (see Table 3), often not followed by further evaluation, warrants re-evaluation of these medical protocols. In our cohort, secondary decreased serum IgM was five times more prevalent in adults and 2·5 times more prevalent in children than the primary form. Hobbs [17] reported that secondary decreased IgM was 20 times more prevalent than the primary form in 1975. This may be explained by the fact that age-related reference values have changed over the years, as the sensitivity of the methods used to measure serum IgM increased (Hobbs *et al.* $< 0{\cdot}47$ g/l > 3 years, our cohort $< 0{\cdot}21$ g/l < 6 years, $< 0{\cdot}13$ g/l < 16 years and $< 0{\cdot}40$ g/l ≥ 16 years). In any case, the first reaction to finding a low IgM should be to exclude a secondary cause.

The fact that only a few incidental findings of decreased serum IgM were followed by further evaluation in our cohort suggests that the perceived medical problems were mild. Most of our incidentally diagnosed cases with true or possible sIgMdef did not have a history of symptoms related to antibody deficiency (76%), and that often remained to be the case during follow-up (72%) (conversely, 28% later developed symptoms that could be related to antibody deficiency). The higher prevalence of various associated diseases in the literature cases [1] is probably related to the fact that these patients had been referred to specialized allergy and immunology clinics [4–6].

Table 3. Adult patients from our cohort

Patient	Age (years/ gender)	Reason(s) for determining serum IgM level	Manifestation(s) during follow-up that could be related to antibody deficiency	First serum IgM level (g/l)	Last serum IgM level (g/l)
10 adults analysed for potential immunodeficiency					
ESID criteria completely fulfilled (true sIgMdef)					
1	54/F	Recurrent respiratory infections, asthma, AR	Long-lasting fatigue, keratitis	0·26	0·27
2	41/M	Recurrent respiratory infections, asthma	–	0·23	0·26
Data on IgG subclasses present, but no data on pneumococcal antibody responses (possible sIgMdef)					
3	33/M	Recurrent respiratory infections, asthma	–	0·29	0·24
4	33/F	Recurrent vaginal candidiasis, weight loss	–	0·24	0·24
5	68/F	Pneumonia	CREST syndrome, ABPA	0·37	0·30
6	73/F	Recurrent pneumonia, bronchiectasis, AR	Chronic sinusitis	0·36	0·29
Data on pneumococcal antibody responses present, but no data on IgG subclasses (possible sIgMdef)					
7*	34/M	Arthralgia	Erysipelas	<0·20	<0·20
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)					
8	53/F	Recurrent UTI, sinusitis	Inflammatory nodular hand osteoarthritis	0·26	0·24
9	71/M	Pneumonia, bronchiectasis	–	0·26	0·22
10	76/F	Non-healing ulcer on feet	Depression, bronchiectasis, UTI	<0·20	<0·20
7 adults diagnosed during analysis for other problems; history of symptoms that could be related to antibody deficiency					
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)					
Serum IgM ordered by a neurologist					
11	45/M	Migraine	–	0·24	0·25
12	79/M	Polyneuropathy	Psoriasis	0·39	0·32
Serum IgM ordered by an internist					
13	55/F	Liver test abnormalities	–	0·38	0·31
14	58/F	Liver test abnormalities	–	0·35	0·32
15	60/M	Collapsed vertebra	–	0·23	0·23
16	73/M	Renal insufficiency	Chronic Q fever	<0·20	0·21
17	51/M	Long-lasting fatigue, Q fever infection	–	0·26	0·33
25 adults diagnosed during analysis for other problems; no history of symptoms that could be related to antibody deficiency					
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)					
Serum IgM ordered by a rheumatologist					
18	68/M	Arthralgia, RLS	Cholecystitis, pharyngitis, infected hematoma	0·28	0·27
19	65/M	Arthralgia, myalgia	–	0·28	0·26
20	75/F	Raynaud-like symptoms	Basal cell carcinoma	<0·20	0·22
21	51/M	Arthritis urica	Inflammatory arthritis	0·38	0·30
Serum IgM ordered by an internist					
22	67/F	Hypoparathyroidism, hypothyroidism	Abscess in thigh, infection of right hip	0·27	0·27
23	70/M	Liver test abnormalities	–	0·26	<0·2
24	62/F	Weight loss	–	0·37	0·30
25	52/F	Micro-albuminuria, hypothyroidism	Chronic Q fever	0·22	0·27
26	43/F	Splenic infarcts, abdominal pain	–	0·38	0·23
27	55/M	Haematuria, recurrent kidney stones	UTI, respiratory infection, cervical lymphadenopathy	0·35	0·37
28	71/F	Renal insufficiency	–	0·32	0·31
29	45/M	Renal insufficiency	–	0·37	0·32
30	69/M	Renal insufficiency	–	0·37	0·32
Serum IgM ordered by a neurologist					
31	66/M	Polyneuropathy	–	0·36	0·31
32	67/F	Polyneuropathy	–	0·32	0·31
33	68/M	Polyneuropathy	Nodular basal cell carcinoma	0·39	0·37
34	72/F	Polyneuropathy	–	0·39	0·39
35	73/F	Polyneuropathy	–	0·32	0·36
36	74/F	Polyneuropathy	–	0·37	0·36
37	74/M	Polyneuropathy	–	0·33	0·37
38	58/F	Polyneuropathy	–	0·36	0·39
39	84/M	Polyneuropathy	–	0·37	0·36

Table 3. *Continued*

Patient	Age (years/ gender)	Reason(s) for determining serum IgM level	Manifestation(s) during follow-up that could be related to antibody deficiency	First serum IgM level (g/l)	Last serum IgM level (g/l)
40	86/M	Polyneuropathy	–	0·32	0·36
41	46/M	Polyneuropathy	–	0·32	0·23
42	63/M	Polyneuropathy	–	0·35	0·27

The 42 adult patients with true or possible selective primary IgM deficiency (sIgMdef) from our cohort. *This patient was diagnosed during analysis for rheumatoid arthritis. He was referred to a university centre elsewhere for analysis for potential immunodeficiency when a persistent decreased IgM level was discovered. ABPA = allergic bronchopulmonal aspergillosis; AR = allergic rhinitis; CREST = calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, teleangiectasia; ESID = European Society for Immunodeficiencies; F = female; Ig = immunoglobulin; M = male; RLS = Raynaud-like symptoms; UTI = urinary tract infection.

Interestingly, possible or true sIgMdef was observed more frequently in males in our cohort. This parallels the observed male predominance in the literature. However, also among healthy controls low IgM levels are more common in males [18–21], and there are some reports of low serum IgM levels among fathers of patients [22,23]. It would be of interest to investigate this gender difference further.

The limitation of our study is, of course, its retrospective design. We collected our cohort data from the medical files, which were not collected with a research purpose in mind. Therefore, we could not correct for environmental factors and genetic polymorphisms that may influence serum IgM levels [3]. However, although very interesting on a population basis, these factors are probably not very helpful in directing decisions regarding individual patient care in the doctor's consulting room.

In conclusion, our review of the literature and retrospective secondary centre cohort study on decreased serum IgM illustrate the challenge of determining the clinical significance of a serum sample with decreased IgM. The diagnosis could rarely be made with certainty, but truly selective primary IgM deficiency is probably very rare. Our strict definitions and thorough analysis of the available information have yielded the largest cohort study so far. However, a larger cohort of true sIgMdef patients is needed to fully explore the clinical consequences; the ESID online Registry would be a useful tool for this.

Disclosure

There are no conflicts of interest.

Author contributions

L. M. A. J. and E. d. V. designed the study and wrote the paper. L. M. A. J. acquired the data and carried out statistical analyses. E. d. V. supervised and critically reviewed all data collection. T. M., M. C. W. C., J. F. M. P. and J. J. J. E. critically reviewed the results and contributed to the final version of the paper; all authors approved the final paper as submitted.

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Supporting information

Additional Supporting information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Identification of papers that report on patients with decreased serum immunoglobulin (Ig)M (date: 10 May 2017). sIgMdef = selective IgM deficiency; unPAD = unclassified primary antibody deficiency.

Fig. S2. Patient selection. CF = cystic fibrosis; Ig = immunoglobulin; pt = patient; sIgMdef = selective IgM deficiency.

Table S1. Overview of the literature