Selective Immunoglobulin M Deficiency - an underestimated immunodeficiency

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To the Editor,

Selective Immunoglobulin M Deficiency (sIgMD) is a subtype of Inborn Error of Immunity (IEI) defined by the European Society for Immunodeficiencies (ESID) as an isolated decrease in serum immunoglobulin (Ig)M concentration greater than 2 standard deviations from normal, while the remaining immunoglobulins, as well as T-lymphocytes and antibody response to vaccinations are normal, in the absence of external factors(1-3). Janssen et al. classified sIgMD as 'true' if all ESID criteria were met, 'possible' when ESID criteria are not fulfilled completely, because data on IgG subclasses and/or vaccination responses are lacking, or 'unclassified primary antibody deficiency' when other abnormalities in antibodies are also present, i.e., IgG-subclass deficiency, below-normal levels of IgG or IgA and/or impaired vaccination responses (1-2). A prevalence

of 0.07-2.1% in Immunology and Immunodeficiency clinics has been reported (6). Clinically, sIgMD associates with increased susceptibility to infections, allergic diseases, autoimmune disorders and malignancies (2-7). However, low IgM has been incidentally observed in asymptomatic patients (6, 7). The therapeutic approach aims to manage and prevent infections, address associated conditions and provide supportive care (8, 9). Only small cohorts sIgMD patients have been described (5) and the knowledge about this entity is limited. We performed a retrospective characterization of selective IgM deficiency patients followed in our Allergy and Clinical Immunology department from 2015 to 2020. We included 13 patients with an average age at diagnosis of 41 years. Seven patients had IgM serum levels <0.17g/L, while the remaining patients had levels between 0.22-0.31g/L. None of the patients presented T cells defects (number and phenotypes). CD19+ B cells numbers were normal in 5 out of 9 patients, a lower proportion than those observed by Castagnoli et al. (10) in a pediatric cohort and Lucuab-Fergurur et al. (8) in an adult cohort. The response to pneumococcal and tetanus vaccination were evaluated in 3 patients and were normal in all. Therefore, three patients fully met the ESID criteria for sIgMD and ten patients had 'possible' sIgMD, namely due to lack of evaluation of the vaccination response. Table I summarizes the demographic characteristics and the referral reasons. None of the patients had a family history of IEI. The most frequent clinical manifestations were infections (in 12 patients), mainly respiratory, usually successfully treated with conventional courses of antibiotics, although an 86-year-old patient developed severe fatal pneumonia with sepsis. Seven patients presented with atopic diseases, 4 with autoimmune manifestations, and 2 with serological autoimmune markers without clinical expression. Over a median follow-up period of 7.5 years, three patients developed neoplastic or premalignant conditions. None of the patients progressed to another IEI. The infectious and non-infectious manifestations are shown in table II. No

patient was treated with replacement human immunoglobulin. Recognizing the significance of this frequently overlooked IEI is crucial, prompting clinicians to maintain heightened vigilance and conduct thorough follow-ups for potential complications. Our findings support other international studies in which most patients with sIgDM mostly present with recurrent respiratory tract infections and a significant proportion of patients develop also autoimmune and allergic diseases (5-7, 11). Previous reports observed that about a quarter of the patients with sIgMD progress to another IEI (3) but we did not found progression in any of our patients over the course of 7.5 years average follow-up. Additionally, it is worth noting that none of the more than 50 patients with antibody deficiencies (mostly CVID) followed in our department progressed from an initial state of sIgMD (unpublished data). In contrast to the 25% of asymptomatic patients reported in another series (3), 92% of our patients had symptoms that are probably related to sIgMD. This is the first series of sIgMD Portuguese patients published. The knowledge of this often-undervalued immunodeficiency is critical and additional multicenter studies and/or national registry are necessary for a better phenotypic characterization and the identification of prognostic factors of this immunological entity to help guide management decisions.

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Conflict of interests

The authors declare that they have no conflict of interests.

Contributions

IFCF - Investigation, Data curation, Methodology, Writing - original draft, Conceptualization, Visualization

ACDP – Resources; Writing - review & editing

FECSR - Resources; Methodology; Writing - review & editing

AMPTBFC - Supervision

EMAGF - Conceptualization, Resources, Writing - review & editing, Supervision

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Table I | Demographic characteristics and reasons for referral of patients with selective IgM deficiency.

Id	Gender	Diagnosis age	Current Age	Referral Reasons
1	F	19	✝ 86 pneumonia	Selective IgM deficiency
2	M	28	41	Rhinorrhea
3	F	70	81	IEI suspicion
4	M	51	58	IEI suspicion
5	M	41	46	Recurrent folliculitis
6	F	51	59	Chronic rhinosinusitis
7	M	15	21	Recurrent ENT infections
8	F	67	70	Selective IgM deficiency
9	M	7	13	Recurrent infections
10	F	28	32	Urticaria
11	F	30	37	Atopic dermatitis
12	F	42	46	Asthma
13	M	47	52	Recurrent angioedema

Legend: F – female; M- male; ENT - Ear, nose and throat; IEI - Error of Immunity

Table II | Infectious and non-infectious manifestations of patients with selective IgM deficiency.

Id	Infectious manifestations	Allergic / autoimmune / malignant diseases
1	Upper respiratory infections >4/year Pneumonia with sepsis	Squamous cell carcinoma
2	Sinusitis	Bee venom anaphylaxis; Chronic rhinosinusitis; House dust mite and grass sensitization
3	Upper respiratory infections 2-3/year Pneumonia	Sweet's syndrome; Monoclonal gammopathy of undetermined significance
4	Chronic diarrhea and gastroenteritis	None
5	Cutaneous Infections	Asthma and rhinitis allergic to grasses; Psoriasis
6	Upper respiratory infections >5/year Pneumonia; Sinusitis	Weak positive ANA without clinical correlation
7	Upper respiratory infections >5/year Pneumonia; Sinusitis Folliculitis	None
8	Upper respiratory infections 1/year	Hypothiroidism Weak positive ANA without clinical relevance
9	Upper respiratory infections >4/year	Asthma and Rhinitis
10	None	Dermatographic Urticaria
11	Upper respiratory infections 2/year Pneumonia	Allergic Asthma and Rhinoconjunctivitis; Atopic Dermatitis; Hypothyroidism
12	Upper respiratory infections 1/year	Asthma, atopic dermatitis, rhinoconjunctivitis; food and drug allergy; Breast carcinoma
13	Upper respiratory infections 1/year	Recurrent angioedema

Legend: ANA – antinuclear antibodies

SUPPLEMENTS

Table 3 | Immunoglobulins levels and T and B-Cells numbers of patients with selective IgM deficiency.

Id	IgM (g/L)	IgG (g/L)	IgA (g/L)	CD3 cells/mm^3	CD4 cells/mm^3	CD8 cells/mm^3	CD19 cells/mm^3	B-lymphocyte	
								Naive cells/mm^3	Memory cells/mm^3
1	<0.17	11.6	1.67	1373	789	556	31*	23*	7
2	0.24	9.56	2.21	NA	NA	NA	NA	NA	NA
3	<0.17	15.7	1.1	975	542	431	580	NA	NA
4	<0.17	5.98	0.71	1879	1240	582	66*	40*	25
5	<0.17	13.3	1.69	1386	915	430	462	NA	NA
6	<0.17	6.2	2.34	1042	602	430	240	178	53
7	<0.17	6.89	1.5	1586	730	730	73*	53*	20
8	0.31	14.6	2.98	NA	NA	NA	NA	NA	NA
9	0.30	9.16	1.27	1440	662	648	92*	73	17
10	0.22	11.7	2.73	968	531	432	77*	NA	NA
11	0.25	14.6	3.53	NA	NA	NA	NA	NA	NA
12	0.25	11.2	2.27	1332	768	535	384	NA	NA
13	0.23	7.64	3.17	NA	NA	NA	NA	NA	NA

NA, not available; *Values abnormally reduced.

Table 4 | Laboratory Investigations for suspected selective IgM deficiency

Laboratory investigations	**Objective**
Quantification of serum immunoglobulins IgM, IgG and subclasses and IgA	Exclude other types of immunodeficiency that affect multiple classes of immunoglobulins.
Evaluation of Vaccine Response	Evaluate the capacity for specific immune response
Lymphocyte Counting and Phenotyping Total lymphocyte count Count of B cells (CD19+), T cells (CD3+), subdivided into helper T cells (CD4+) and cytotoxic T cells (CD8+)	Evaluate the distribution and proportion of the main lymphocyte populations

Memory and naive B cells	