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LETTER TO EDITOR

Defining Primary Selective IgM Deficiency

Sudhir Gupta[1] · Ankmalika Gupta[2]

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To The Editor:

Selective IgM deficiency (also previously known as type V dysgammaglobulinemia) was described more than 50 years ago in two children with meningococcus meningitis [1]. This disease was largely ignored because primary IgM deficiency was considered very rare and often thought to be secondary to other associated disorders [2]. As a result, selective IgM deficiency was not included in the IUIS Classification of Primary Immunodeficiency Diseases until 2017 [3]. Selective IgG deficiency has since been reviewed [4]. It is defined as serum IgM levels 2 standard deviations below the mean for healthy controls and the presence of normal serum IgG and IgA. However, recently, the European Society for Immunodeficiencies (ESID) registry has arbitrarily defined selective IgM deficiency as serum IgM level repeatedly below 2 standard deviations of normal with normal levels of serum IgA and IgG and IgG subclasses, normal vaccine responses, absence of T cell defects, and absence of causative external factors. Unfortunately, this ESID registry definition subsequently led Janssen at al [5] to classify selective IgM deficiency as follows: [a] "true" Selective IgM Deficiency who met ESID registry criteria, [b] "possible" Selective IgM deficiency where ESID registry criteria were not fulfilled completely because data on IgG subclasses and/or vaccination response were not available, and [c] unclassified primary antibody deficiency since other abnormalities of antibodies, IgG subclass deficiency, and/or impaired response to vaccine were present. The same group in their more recent publication classified selective IgM deficiency in a similar manner and assigned the definition as "ESID Criteria"; there are no "ESID criteria for selective IgM deficiency" [6]. Notably, no other primary immunodeficiency has been classified in this manner. More importantly, the ESID registry definition of selective IgM deficiency is not evidence based, and it has largely ignored published data in humans and in IgM deficient mice.

The following is a discussion of each component of the ESID registry definition of selective IgM deficiency.

According to ESID registry criteria, selective IgM deficiency must have normal IgG subclasses. A number of investigators have reported IgG subclass deficiency in a subset of patients with selective IgM deficiency [7–11]. Chovancova et al. [11] observed IgG subclass deficiency in 6 of 14 patients (42%). Goldstein et al. [10] reported IgG subclass deficiency in 9 of 36 adults with selective IgM deficiency (25%). Similarly, IgG subclass deficiency has been reported in patients with selective IgA deficiency [12]. We, however, do not exclude such patients from the diagnosis of selective IgA deficiency.

Another ESID registry criteria for this disorder is an absence of T cell defects. Although the majority of patients with selective IgM deficiency do have normal quantitative T cells and T cell subsets and normal T cell functions [2, 4], alterations in T cell subsets and impaired T cell responses to mitogens have been reported in patients with selective IgM deficiency [13, 14]. La Concha et al., [14] described lack of delayed cutaneous hypersensitivity response to all three tested antigens (Candida, PPD, and streptokinase) in two patients with severe selective IgM deficiency (IgM <4 mg/dl). Hong and Gupta [15] reported impaired proliferative response to mumps, *Candida albicans*, and tetanus toxoid in a patient with selective IgM deficiency and *Streptococcus pneumoniae* sepsis and invasive aspergillosis. Raziuddin and associate [13] described alterations in T cell subsets and T cell functional defects in four patients with severe selective IgM deficiency with undetectable levels of serum IgM. Three patients had low CD4 and all four had increased CD8+ T cells. All four patients had impaired proliferative response to PHA and to Con A, and all four had impaired IL-2 production in response to both PHA and Con A. According to ESID Registry definition, these patients would not qualify for the diagnosis of selective IgM

✉ Sudhir Gupta
sgupta@uci.edu

[1] Division of Basic and Clinical Immunology, University of California, Irvine, CA 92697, USA

[2] Hoag Medical Group, Hoag Hospital, Newport Beach, CA, USA

deficiency even though they have a complete lack of serum IgM.

Another ESID Registry criteria is normal response to vaccines. A number of investigators have reported impaired response to both protein (T cell-dependent) and polysaccharide (T-independent) vaccines in selective IgM deficiency [7, 9, 15–17]. Guill et al. [16] reported decreased specific antibody response to tetanus toxoid and *Streptococcus pneumoniae*. Yocum et al. [17] reported impaired specific antibody response to vaccines in two patients with selective IgM deficiency, one with a complete absence of serum IgM. Both patients failed to produce hemagglutinin antibodies to KLH immunization. One patient failed to developed typhoid antibodies to "H" of "O" antigens despite two booster injections. Hong and Gupta [15] reported complete lack of response to Pneumovax-23 (unprotective titers of all 14 serotypes tested) and unprotected titers against tetanus toxoid in a patient with selective IgM deficiency that presented with *Streptococcus pneumoniae* sepsis. La Concha et al. [15] described two patients with serum IgM levels less than 4 mg/dl in which no IgG antibodies to *E. coli* were present, and there was no specific secondary IgG antibody response even after four repeated vaccinations with tetanus toxoid. Yel et al. [7] reported impaired specific antibody response to pneumococcal vaccine in 8 of 11 cases. Goldstein et al. [9] reported lack of protective or no response to pneumococcal vaccine in two patients with selective IgM deficiency; one of them had serum IgM level of 1 mg/dl. These data of impaired specific antibody responses along with clinical response to immunoglobulin treatment [7, 15, 18] strongly argue for the presence of significant specific IgG antibody deficiency in a subset of patients with selective IgM deficiency.

Similar to humans, mice lacking secreted IgM have similar phenotype as humans. This includes (A) increased susceptibility to bacterial and fungal infections, (B) development of autoimmunity as mice age (adults patients with selective IgM deficiency have higher frequency of autoimmunity than children [4]), (C) normal numbers of IgM expressing B cells, (D) impaired response to vaccine, and (E) deficiency of germinal center and germinal center cells. Ehrenstein et al. [19] observed impaired IgG response to T-dependent antigens NP-KLH and NP-CG in selective IgM deficient mice generated by targeted gene disruption. Boes et al. [20] reported impaired IgG antibody responses to suboptimal doses of a T cell-dependent antigen NP-KLH, in newly constructed mutant mice in which B cells do not secrete IgM but still express surface IgM. Both groups of investigator observed impaired antibody affinity maturation. These mice have decreased splenic germinal centers. Patients with selective IgM deficiency also display decreased germinal center B cells [21].

In summary, primary selective IgM deficiency is a heterogeneous disorder in which a subset of patients demonstrates abnormalities in T cell subsets, T cell functions, IgG subclass deficiency, and impaired response to vaccines. Current ESID registry definition would exclude a sizeable number of patients, including those with complete absence of serum IgM from the diagnosis of selective IgM deficiency. Therefore, selective IgM deficiency should be defined without exclusion of IgG subclass deficiency, alterations in T cell and T cell subset numbers and functions, and impaired response to vaccine. Furthermore, terminology of "true," "possible," and "unclassified" selective IgM deficiency should not be used. As far as what levels of serum IgM should be considered as selective IgM deficiency could be argued and will be a topic of further ongoing discussions. Given the variability of different levels of IgM in children (of various ages), and in adults, and different inter-laboratory reference ranges, currently, it is difficult to establish serum levels for the diagnosis of selective IgM deficiency. There should be further studies stratifying phenotypic data with different serum IgM levels before a definitive serum IgM levels could be established as a diagnostic criteria. Therefore, the current definition of selective IgM deficiency may remain inclusive rather than exclusive as "reproducible serum IgM levels 2 standard deviations below the mean for controls and normal levels of total IgG and IgA, and secondary causes of selective IgM have been excluded". Serum IgM levels should be repeated at regular intervals for any recovery to exclude secondary cause(s) or for progression to common variable immunodeficiency.

Compliance with Ethical Standards

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

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