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RESEARCH ARTICLE

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The epidemiology and clinical features of selective immunoglobulin M deficiency: A single-center study in China

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Abstract

Background: Selective immunoglobulin M deficiency (SIgMD) is a rare primary immunodeficiency that is frequently reported in Western countries. However, large epidemiological and clinical studies of SIgMD in China are still lacking. Herein, we describe a cohort of SIgMD subjects in a large tertiary university hospital in China.

Methods: A cross-sectional study included 139 668 participants at First Affiliated Hospital of Wenzhou Medical University from January 2014 to October 2018 was conducted. Individuals with a serum IgM level less than 0.3 g/L with normal levels of serum IgA and IgG were defined as having SIgMD.

Result: A total of 63 subjects met the criteria for SIgMD(63/139668, 0.045%), with a male-to-female ratio of 0.85, aged from 19 to 99 years. The most common clinical manifestation was autoimmune disorders (38/63, 60.32%), while the second most common manifestation was infections (21/63, 33.33%). Neither allergies nor tumors were found among these 63 SIgMD subjects. Most importantly, there were 30 patients with systemic lupus erythematosus among these 63 SIgMD subjects, accounting for 47.62% of all SIgMD subjects.

Conclusion: To our knowledge, we describe here the first large single-center cohort of adult patients affected by SIgMD in China. The most common clinical manifestation was autoimmune disorders, specifically systemic lupus erythematosus.

KEYWORDS

autoimmune disease, infection, selective IgM deficiency, systemic lupus erythematosus

1 | INTRODUCTION

Immunoglobulin M (IgM) is the first immunoglobulin isotype expressed on immature B cells and the first antibody that is produced when foreign antigens are encountered.[1,2] IgM is mainly distributed in serum and exists in pentamer form, comprising 5%-10% of the total serum Ig. Bactericidal, complement activation and agglutination effects are the key functions of IgM.[3]

Selective IgM deficiency (SIgMD) has been reported in Western countries and is often associated with severe or recurrent infections, autoimmunity, allergies, and malignancies; SIgMD appears to be more common than originally realized.[4]

Ni and Zhang contribute equally.

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The European Society for Immunodeficiencies (ESID) registry defines primary SIgMD as a serum IgM level repeatedly below 2 standard deviations(SDs) from the mean level for age with normal levels of the serum IgA, IgG, and IgG subclasses; the absence of T-cell defects; normal vaccination responses; and the absence of causative external factors.[5] When these criteria are completely fulfilled, this condition is referred to as "truly selective primary IgM deficiency" (true SIgMD). Importantly, Janssen reported that only 6 of 261 (2%) subjects described in the literature (261 subjects with primary decreased serum IgM in 46 papers) completely met the criteria for true SIgMD.[6] Therefore, the current definition of SIgMD should be modified to be more inclusive rather than exclusive[7]; more simply, subjects with IgM levels less than 30 mg/dL should be regarded as IgM-deficient subjects.[8]

The clinical features of SIgMD subjects have been described in previous review studies.[1,9] Among them, respiratory tract infections were the most common clinical symptoms, including upper and lower respiratory tract infections, such as chronic sinusitis, bronchitis, pneumonia, bronchiectasis, and recurrent otitis media.[10] In adults with SIgMD, autoimmune diseases and allergies are also common manifestations.

To date, only two SIgMD cases have been reported in China,[11] and no large studies have reported on the prevalence and clinical manifestations of SIgMD in Chinese populations. Therefore, we initiated this cross-sectional cohort study in a large tertiary university hospital in China by analyzing the laboratory and hospital information system databases.

2 | PATIENTS AND METHODS

This study was a retrospective investigation of 139 668 patients for whom immunoglobulin tests had been ordered in the First Affiliated Hospital of Wenzhou Medical University from January 2014 to October 2018; during that time, the Wenzhou district of Zhejiang Province had a population of 8.2 million people. The concentrations of IgA, IgM, and IgG were measured by nephelometry(Siemens BN II and Beckman Coulter IMMAGE 800). Briefly, patients who repeatedly (at least twice) had IgM levels less than 0.3 g/L were regarded as IgM-deficient subjects.[8] Patients with low or high IgG and IgA serum levels were excluded. The presence of any other well-defined primary or secondary immunodeficiencies accompanied by decreased levels of IgM was considered a criterion for exclusion. Only the clinical manifestations of patients with persistent decreased serum IgM levels were reviewed in detail.[6] This study was approved by the First Affiliated Hospital of Wenzhou Medical University Ethics Committee.

3 | RESULT

3.1 | Sixty-three subjects were defined as having SIgMD among the 139 668 subjects

Among the 139 668 subjects, a total of 63 subjects (63/139 668, 0.045%) met the criteria for SIgMD, including 29 males and 34 females, aged from 19 to 99 years with a mean age of 52 years at patient admission (Figure 1, Table 1).

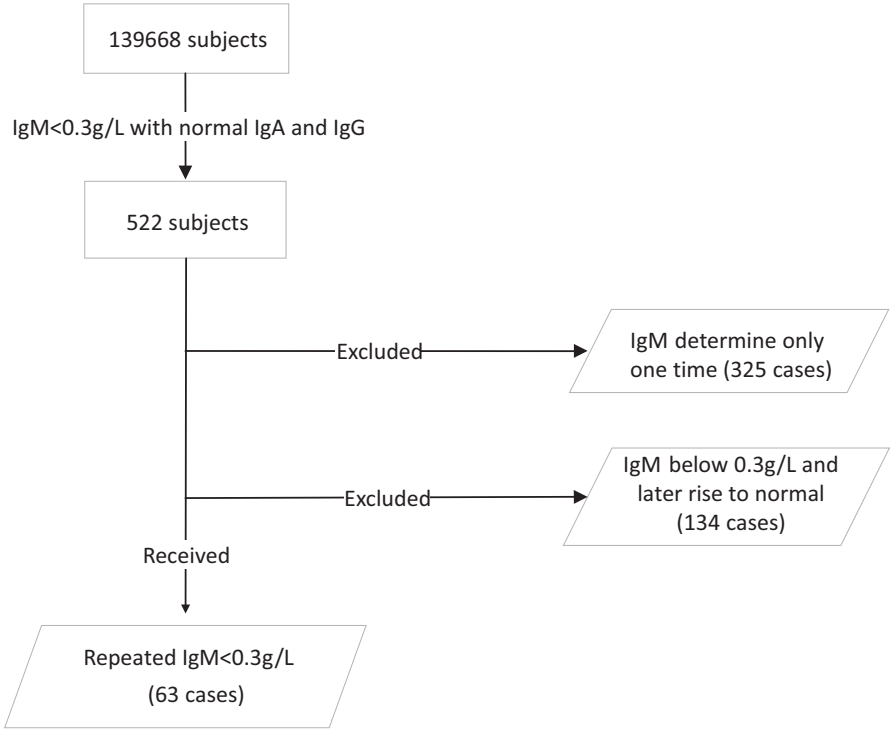

FIGURE 1 Flow chart of the selection of the selective IgM deficiency patients

TABLE 1 Patient basic information of selective IgM deficiency

Patient information	
No. of patients	63
Gender	
Male	29
Female	34
Age	52.08 ± 16.89
Prevalence(detected more than twice)	63/139 668 (0.045%)
Prevalence(detected only one)	325/139 668 (0.233%)
Prevalence(both one and more than twice)	388/139 668 (0.278%)

3.2 | Clinical manifestations of these 63 SIgMD subjects

Recurrent infections as the presenting manifestation occurred in more than 80% of the patients with SIgMD. However, in contrast to previous SIgMD studies, subjects in this cohort commonly presented with recurrent infections. In this study, the most common clinical manifestation at the time of patient admission was an autoimmune disorder (38/63, 60.32%). Most importantly, there were 30 patients with systemic lupus erythematosus (SLE) among these 63 SIgMD subjects, accounting for 47.62% of all SIgMD subjects (Table 2). Other autoimmune diseases found in the study population are listed in Table 2.

Infectious diseases occurred in 21 adults (21/63, 33.33%), and these diseases are listed in Table 2. Because many patients showed more than one clinical feature after the discharge diagnosis, other diagnoses affecting the circulatory, motor, urinary, endocrine, respiratory, digestive, and nervous systems of these SIgMD subjects are included in Table 3. These patients also had a significant presence of hypertension (15.87%), atherosclerosis (12.70%), osteoporosis (17.46%), renal cysts (7.94%), diabetes(9.52%), and brain infarction (7.94%). Of note, no tumor cases were found among these 63 SIgMD subjects.

TABLE 2 The common clinical manifestation of selective IgM deficiency[a]

	No. of patients (%)
Autoimmune disease	38 (60.32)
Systemic lupus erythematosus	30 (47.62)
Sjogren syndrome	4 (6.35)
Rheumatic heart disease	1 (1.59)
Scleroderma	1 (1.59)
Psoriasis	1 (1.59)
Rheumatoid arthritis	1 (1.59)
Infection disease	21 (33.33)
Chronic gastritis	6 (9.52)
Pulmonary infection	4 (6.35)
Herpes	3 (4.76)
Upper respiratory tract infection	2 (3.17)
Bronchial asthma	2 (3.17)
Tuberculosis	1 (1.59)
Epididymitis	1 (1.59)
Cholecystitis	1 (1.59)
Bronchiectasis with infection	1 (1.59)

[a]Many patients showed more than one clinical feature.

4 | DISCUSSION

IgM deficiency was first described in 1967, when two male children with fulminant meningococcal septicemia were found to have low levels of IgM. The same authors also found 11 patients with low IgM levels who presented with meningitis and pyelonephritis in a retrospective study of 3,000 hospitalized patients.[12] In 2006, the largest study of 36 SIgMD and 17 other SIgMD subjects was published.[1,9] Although decades have passed, the prevalence and clinical consequences of decreased serum IgM levels are not sufficiently known. To date, only small cohorts of IgM-deficient subjects have been described.[5] A variety of clinical manifestations has been associated with decreased serum IgM levels, including severe or recurrent infections, autoimmunity, allergy, and malignancy.[5] However, the exact prevalence and clinical manifestations of SIgMD still need to be investigated.

The ESID registry defines SIgMD as a serum IgM level repeatedly below 2 SDs from the mean level for age with normal levels of serum IgA, IgG, and IgG subclasses; the absence of T-cell defects; normal vaccination responses; and the absence of causative external factors. Unfortunately, this ESID registry definition subsequently led Janssen et al[6] to report that only 6 of 261 patients (261 primary decreased serum IgM patients in 46 papers) documented in the literature completely fulfilled the defined criteria for true SIgMD. Moreover, Janssen et al also classified selective IgM deficiency as follows: (a) true SIgMD when patients met the ESID registry criteria, (b) possible SIgMD when patients did not completely fulfill the ESID registry criteria because data on vaccination response or IgG subclasses were not available, and (c) unclassified primary antibody deficiency when other IgG subclass deficiencies and/or impaired responses to vaccine were present; however, this dilemma could not be solved by this multicenter study.[5,7] Therefore, SIgMD should be defined without the exclusion of IgG subclass deficiencies, alterations in the T-cell subset, or impaired responses to vaccine.[7]

Thus, in this study, patients who had IgM levels less than 0.3 g/L with normal IgG and IgA serum levels were regarded as IgM-deficient subjects as previously reported.[8] Moreover, patients in whom serum IgM was determined only once or rose to normal or patients with other secondary SIgMDs were also excluded.[5] Only patients in whom IgM was determined on repeat occasions (at least

TABLE 3 The other clinical manifestation of selective IgM deficiency[a]

	No. of patients (%)
Circulatory system	33 (52.38)
Hypertension	10 (15.87)
Atherosclerosis	8 (12.70)
Arrhythmia	3 (4.76)
Hyperlipidemia	3 (4.76)
Thrombocytopenia	2 (3.17)
Lymphocytosis	1 (1.59)
Leukopenia	1 (1.59)
Heart dysfunction	1 (1.59)
Paroxysmal ventricular tachycardia	1 (1.59)
Varicose veins of lower extremities	1 (1.59)
Abdominal aortic aneurysm	1 (1.59)
Pulmonary hypertension	1 (1.59)
Motion system	14 (22.22)
Osteoporosis	11 (17.46)
Fracture	1 (1.59)
Cervical spondylosis	1 (1.59)
Gout	1 (1.59)
Urinary system	12 (19.05)
Renal cyst	5 (7.94)
Benign prostatic hyperplasia	3 (4.76)
Kidney stones	2 (3.17)
Renal allergic purpura	1 (1.59)
Abnormal renal function	1 (1.59)
Endocrine system	10 (15.87)
Diabetes	6 (9.52)
Thyroid dysfunction	3 (4.76)
Nodular goiter	1 (1.59)
Respiratory system	9 (14.29)
Respiratory failure	4 (6.35)
Chronic obstructive pulmonary disease	3 (4.76)
Interstitial lung disease	1 (1.59)
Epistaxis	1 (1.59)
Digestive system	9 (14.29)
Oral ulcer	1 (1.59)
Duodenal ulcer	1 (1.59)
Gastrointestinal bleeding	1 (1.59)
Intestinal dysfunction	1 (1.59)
Multiple colonic polyps	1 (1.59)
Liver nodules	1 (1.59)
Hepatitis B virus	1 (1.59)
Abnormal liver function	1 (1.59)
Cholelithiasis	1 (1.59)
Nervous system	8 (12.70)
Brain infarction	5 (7.94)
Metabolic encephalopathy	1 (1.59)
Optic neuromyelitis	1 (1.59)
Parkinson's Disease	1 (1.59)
Immune system	1 (1.59)
Splenomegaly	1 (1.59)
Others	
Physical examination	6 (9.52)
Solar dermatitis	1 (1.59)
Inguinal hernia	1 (1.59)
Hand Tinea	1 (1.59)

[a]Many patients showed more than one clinical feature.

twice) were included, further supporting the accurate description of these SIgMD subjects in this study.

The exact prevalence of primary SIgMD remains unknown. A community-based survey showed that the prevalence of primary SIgMD in children was 0.03%.[13] Additionally, a prevalence of 0.07% in an allergy and clinical immunology clinic and 1.68% in an unselected community health screening was found.[14] Furthermore, a prevalence of 6% was found in primary immunodeficiency patients.[4] Recently, an Iranian blood transfusion center study showed that the prevalence of healthy blood donors was 0.37%.[8]

Importantly, SLE among all autoimmune disorders was the most common clinical manifestation in this study. However, the current study is limited. At the time of IgM measurement, they may be on the concomitant immunosuppressive medications, we cannot rule out the effect of concomitant immunosuppressive medications on the low IgM. Therefore, this may contribute to a spuriously high prevalence of SIgMD among SLE patients. Moreover, this retrospective study lacked long-term follow-up of these patients. We cannot determine the cause-effect relationship between SIgMD and these autoimmune diseases. In the literature, a statistical analysis of serum Ig levels in 54 SLE patients first reported by Saiki[15] showed a decrease in serum IgM that was closely related to the disease duration of SLE. Patients with a longer duration of SLE had more striking decreases in serum IgM levels. Fegurgur et al[16] in 62 adult SIgMD patients observed a significantly higher rate (42%) of autoimmunity and autoimmune disease with predominance of Hashimoto's thyroiditis and SLE. Chovancova et al[1] in their 17 adult patients with SIgMD reported four patients with SLE and five additional patients with positive ANA without a diagnosis of SLE. However, it is still difficult to elucidate how strong these associations are and if these immunopathological conditions are primary or secondary. Furthermore, whether the concomitant immunosuppressive agents could specifically decrease IgM without affecting the IgG and IgA in SLE patients is still need to be investigated.

Furthermore, Boes[14] revealed that compared with regular lupus-prone lymphoproliferative (lpr) mice, lpr mice that lacked secreted IgM developed increasing levels of IgG autoantibodies to double-stranded DNA and had more abundant deposits of immune complexes in the kidney. Similarly, Ehrenstein et al[17] demonstrated that mice deficient in serum IgM were prone to spontaneous autoimmunity, as evidenced by the development of anti-DNA antibodies and the renal deposition of IgG. More recently, Nguyen[18] revealed that natural IgM could prevent autoimmunity through the induction of B-cell central tolerance and highlighted that polyclonal IgM can rescue B-cell development and reduce autoantibody levels. Therefore, all these reports could partly support the strong association between the SLE and SIgMD. Due to the possible immunomodulatory effects and antimicrobial effects of IgM, highly enriched IgM preparations may be the most desirable therapeutic modality for SIgMD.[10]

Additionally, the second most frequent clinical manifestation was infectious diseases, with recurrent infections as the presenting manifestation occurring in more than 80% of patients with SIgMD. However, in contrast to previous studies in which SIgMD subjects commonly presented with recurrent infections, our study reported significantly fewer patients presenting with recurrent infections.[10] Importantly, the clinical manifestations were recorded at the time of discharge in this study, and long-term follow-up may help to determine the true incidence of recurrent infection in these SIgMD subjects. Moreover, SLE patients prone to infection were not included the analysis of infection rate, which may further contribute to the lower incidence of infectious diseases in this study.[19]

The prevalence of allergic disorders in individuals with SIgMD is estimated to be 25%-33% in Western countries.[4,20] However, only two patients with bronchial asthma were found among these 63 SIgMD subjects. In contrast to Western countries, the demand for specialists and consultants in allergy and clinical immunology in China is still lagging behind the number of patients suffering from allergies or immunodeficiency, which may contribute to this low incidence.[21] Additionally, nearly half of the SIgMD subjects in our study were 50 years of age or older, and most of them had underlying common diseases, including hypertension, atherosclerosis, osteoporosis, renal cysts, or diabetes. Whether these common diseases are associated with SIgMD still needs to be investigated. Thus, from this study, we concluded that SIgMD is likely a heterogeneous disorder. More attention should be paid to autoimmune disease, especially SLE, in these patients.

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