

Primary Selective IgM Deficiency: An Ignored Immunodeficiency

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Abstract Immunoglobulin M (IgM) provides the initial response to foreign antigen and plays a regulatory role in subsequent immune response development, accelerating the production of high-affinity IgG. Though selective IgM deficiency was described more than 45 years ago in children with fulminant meningococcal septicemia, it has been largely an ignored primary immunodeficiency. It appears to be more common than originally realized. Selective IgM deficiency is observed in both children and adults with no gender bias. The most common clinical manifestation of selective IgM deficiency is infections with extracellular and intracellular bacteria, viruses, and fungi. Allergic diatheses are the second commonest presentation of selective IgM deficiency. There is an increased prevalence of autoimmune diseases, which in both humans and mice appear to be secondary to selective IgM deficiency rather than IgM deficiency secondary to autoimmune diseases. Selective IgM deficiency, in some cases, is associated with 22q11.2 chromosome deletion and few familial cases of selective IgM deficiency have been reported. Innate immunity is relatively intact. T cells, T cell subsets, and T cell functions are normal. However, several patients with selective IgM deficiency and T cell and NK cell defects with *Mycobacterium avium intracellulare* infections have been reported. In a subset of patients with selective IgM deficiency circulating IgM⁺ B cells are decreased or completely lacking. Specific IgG antibody responses against pneumococcus polysaccharides are impaired in a subset of patients with selective IgM

deficiency. The pathogenesis of selective IgM deficiency is unclear; decreased T helper activity, increased isotype-specific suppressor T cell activity, and intrinsic B cell defects have been reported. Patients with selective IgM deficiency and impaired pneumococcal antibody responses appear to respond to immunoglobulin therapy.

Keywords IgM deficiency · Autoimmunity · Malignancy · Specific antibody deficiency

Introduction

During B cell development, the pre-B cell is the first cell that synthesizes immunoglobulin peptide. The rearranged Ig heavy chain gene is transcribed to produce a primary transcript that includes rearranged VDJ complex and proximal (μ and δ) C genes. Subsequent processing of RNA leads to splicing out the intervening sequences between VDJ complex and C μ gene, resulting in a functional mRNA for μ heavy chain, which is then transcribed to produce a μ chain protein in Pre-B cells. This is a membrane form of μ chain; however, most of it remains within the cytoplasm because chaperone proteins associated with newly synthesized μ chain, restrict their movement out of the cell. Most of the cytoplasmic μ chain in the pre-B cell is degraded and only a small amount is expressed on the cell surface in association with a surrogate light chain to form the pre-B cell receptor. During next stage of maturation, each developing cell also rearranges κ or λ light chain, which associates with μ heavy chain to produce a complete IgM protein, which is expressed on the surface of immature B cells. During the next stage of development to the mature B cell, the cells co-express μ and δ heavy chain in association with κ or γ light chain, thereby producing both membrane IgM and IgD. Both surface Igs have same V region, and therefore, the same specificity. Mature naïve B cells are antigen

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responsive, and respond to both protein and non-protein antigens to undergo proliferation, and a few of these cell differentiate into Ig secreting cells. IgM is the first Ig produced and is the immunoglobulin that is predominantly produced in response to T-independent antigens such as polysaccharides and lipid. Activated T cells secrete cytokines and express CD40L. A small progeny of activated IgM+IgD+ B cells upon engagement of CD40 and cytokines undergo the process of heavy chain isotype (class) switching resulting in the production of antibodies of different isotypes such as IgG, IgA, and IgE [1]. Class switch occurs in peripheral lymph nodes. In the germinal center of lymph nodes, Ig V genes undergo point mutation (somatic hypermutation) leading high affinity antibody producing B cells [1, 2]. The importance of “antigen-induced” IgM antibody in protection against infection and autoimmune diseases has been established in mice deficient in IgM secretion [3, 4]. In addition to “antigen-induced” IgM antibodies, serum IgM in healthy individuals is also comprised of a majority of “natural” autoantibodies that exhibit self reactivity [5]. These antibodies appear to arise naturally without actual antigen stimulation as they are present in human cord blood and in mice housed in germ-free conditions. Natural autoantibodies are unmutated and typically polyreactive. These natural autoantibodies provide early defense against pathogens [6] and play an important role in immune homeostasis and modulation of innate and adaptive immune responses, and clearance of apoptotic cells (self antigens), thereby conferring protection from autoimmune and inflammatory injuries [7]

Prevalence

The true prevalence of primary selective IgM deficiency is unknown. The prevalence of complete primary selective IgM deficiency in children in a community-based survey was reported in 1970s to be 0.03 % [8]. The prevalence of deficient but detectable levels of IgM was reported to be 0.1 % to 3.8 % in hospitalized patients [9–12], 1.68 % in unselected community health screening [4], and 0.07 % in an Allergy and Clinical Immunology clinic [13]. In a more recent study of long-term follow-up [14], two of 421 children with primary immunodeficiency had persistent selective IgM deficiency (0.5 %). Ozen et al. [15] reported 3 children with selective IgM deficiency among 131 children with primary immunodeficiency (2.1 %). In our Primary Immunodeficiency clinic, among 451 patients with primary immunodeficiency, we are currently following 25 adult symptomatic patients with persistent primary selective IgM deficiency (6 %); 15 were previously reported [16]. The selective IgM deficiency appears to be equally distributed among male and female.

Genetics

No definitive inheritance pattern has been reported in patients with selective IgM deficiency. However, only a few family studies have been reported. Since some of these patients are asymptomatic, and therefore, serum immunoglobulins have not been performed on family members. Few familial cases, however, have been reported. Yocum et al. [17] reported selective IgM deficiency in three generation of males in one family. We have a mother and daughter with selective IgM deficiency and specific antibody deficiency who presented with recurrent infections (unpublished data). Selective IgM deficiency has also been reported with a genetic disorder Russell–Silver syndrome, a growth disorder, which possibly involving hypomethylation of H19 and IGF2 [18]. A number of chromosomal abnormalities, including of chromosome 1, 18, and 22q11.2 have also been reported in patients with selective IgM deficiency [19–21]. Kung et al. [21] described selective IgM deficiency in two patients with 22q11.2 deletion syndrome, a 6-year-old boy who presented with chronic rhinitis and recurrent sinusitis and pneumonia, and a 14-year-old girl who presented with failure to thrive and mucopurulent discharge from nostrils. No cardiac, pulmonary, or neurological abnormalities were present. Al-Herz et al. [22] also reported selective IgM deficiency in a 15-year-old girl with 22q11.2 deletion syndrome. Others have also reported selective IgM deficiency with 22q11.2 deletion syndrome [23, 24]. Gennery et al. [23] reported low IgM levels in 3 of 32 patients with 22q11.2. However, through careful analysis of these cases, it appears that two of these cases are likely to be of common variable immunodeficiency and only one case is of selective IgM deficiency. It has been proposed that since the genetic sites of the V, J, and C regions of λ light chain are in 22q11.2 region, it may be responsible for decreased immunoglobulin synthesis [22]; however, it cannot explain selective IgM deficiency with normal IgG and IgA. Nevertheless, it would be of interest to examine a large cohort of 22q11.2 patients for selective IgM deficiency.

Clinical Features

Although selective immunodeficiency has been associated with various infections (Table 1) including upper and lower respiratory tract infection such as recurrent otitis media, chronic sinusitis, bronchitis, bronchiectasis, pneumonia, deep tissue and liver abscess, cellulitis, meningitis, sepsis, diarrhea, cholangitis, hepatitis, chronic moniliasis, and allergic rhinitis/asthma or anaphylaxis [9, 11–13, 16, 17, 24–33], it may also occur in asymptomatic individuals [12]. In children with selective IgM deficiency, infectious manifestations are more common and allergic and autoimmune diseases and malignancies are infrequent [34],

Table 1 Clinical presentations in selective IgM deficiency

Upper respiratory tract infections
Otitis media
Sinusitis
Bronchitis
Pneumonia
Allergic rhinitis
Allergic asthma
Atopic dermatitis
Anaphylaxis
Diarrhea
Liver abscess
Cholangitis
Chronic moniliasis
Sepsis
Meningitis
Vaccinia
Fibromyalgia
Varicella zoster infection
Cellulitis
Recurrent impetigo
Pyelonephritis

Table 2 Infections in primary selective IgM deficiency

<i>Staphylococcus aureus</i>
<i>Pseudomonas aeruginosa</i>
<i>Sterptococcus pneumoniae</i>
<i>Neisseria Meningitides</i>
<i>Hemophilus influenza</i>
<i>Mycobacterium tuberculosis</i>
<i>Mycobacterium avium complex</i> (MAC)
<i>Listeria monocytogenes</i>
<i>Brucella abortus</i>
<i>Giardia lamblia</i>
<i>Aspergillus fumigates</i>
<i>Pneumocystis carinii</i>
<i>Varicella zoster</i>
<i>Cytomegalovirus</i>
<i>Molluscum contagiosum</i>

whereas in adults with selective IgM deficiency, though recurrent upper and lower respiratory tract infections are common, allergic and autoimmune diseases are also frequently present [13, 16]. Patients with selective IgM deficiency may present with a variety of dermatological manifestations including deep skin abscesses, recurrent impetigo, pyoderma, disseminated molluscum contagiosum, CD34+ cutaneous lymphoproliferative disorder, and epidermaldysplasia verruciformis [13, 29, 35–38]. A number of autoimmune diseases and malignancies have also been reported in association with selective IgM deficiency,

Infections More than 80 % of patients present with recurrent infections [13, 16]. Infections may be caused by a variety of extracellular and intracellular bacteria, protozoan, viruses, and fungi (Table 2); some of these bacterial infections resulting in meningitis and sepsis could be life-threatening. Infection with *Aspergillus* species is intriguing [16]. Kutukchular and Gulez [14] reported a long-term follow-up (34.1 ± 22 months) of 37 children (mean age 51.5 ± 25.8 months) with symptomatic hypogammaglobulinemia among 421 children who were diagnosed with primary immunodeficiency. The commonest clinical presentations included upper and lower respiratory tract infections, urinary tract infections, and gastroenteritis. In several of these patients, spontaneous correction of various immunoglobulin deficiencies (IgG, IgA, and IgM) was observed. However, two children remained selective IgM deficient. Therefore, a

diagnosis of selective IgM in children should be established after a follow-up of their immunoglobulin levels.

These observations support that IgM is an important component of host defense against various microorganisms. It also appears that normal serum levels of IgG, i.e., secondary antibody response, cannot compensate for the defective IgM response at least under certain circumstances. However, one cannot conclude a cause–effect relationship between low IgM levels and recurrent infections. Despite normal IgG levels, specific antibody response to polysaccharide antigens may be defective. This association is shown as impaired antibody response to pneumococcal polysaccharide antigens in 45 % of 11 tested patients [16]. All of those patients presented with recurrent or severe, life-threatening infections. Nevertheless, our data do not support the opinion that the specific antibody defect in patients with IgM deficiency per se would be the cause of susceptibility to infections, since 5 out of 6 patients whose specific antibody production appeared to be intact experienced recurrent infections as well. Therefore, susceptibility to infections in IgM deficiency is probably due to a number of contributing factors of which specific antibody deficiency appears to be important factor.

Naïve B cells from mutant mice deficient in IgM secretion, following antigen stimulation, undergo Ig isotype switching to other immunoglobulin isotypes; however, these animals are unable to control viral, bacterial, and fungal infections due to lack of serum IgM and inefficient induction of a protective IgG antibody response [3, 39, 40], which is analogous to patients with selective IgM deficiency.

Allergic Diseases In our experience of adult patients with selective IgM deficiency, approximately 25 % of patients have allergic rhinitis/asthma [16]. In our series, the second most common manifestation was allergic disorders (33 %);

this is in parallel with the results of Goldstein et al. [13] in adults who found the frequency of asthma and allergic rhinitis to be 47 % and 36 %, respectively. The association of IgM deficiency and atopy was described previously in 10 patients with asthma by Kaufman and Hobbs [41]. Some other reports have also noted an association between atopic diseases and selective IgM deficiency [25]. However, it is not easy to explain the mechanism of this association since it is not clear why and how a low IgM would cause a shift from Th1 towards a Th2 response, which is the basic mechanism in allergic disorders. In addition, not all of these atopic patients had elevated serum IgE levels and/or eosinophilia. It is also important to keep in mind that the prevalence of atopic disorders can be as high as 20–25 % in the general population.

Autoimmune Diseases A number of autoimmune diseases (Table 3) have been described in association with selective IgM deficiency [42–51]. Though selective IgM deficiency has been considered secondary to autoimmune disorders, there is no evidence to support this notion. A possibility should be entertained that autoimmune disorders associated with selective IgM deficiency are secondary to primary selective IgM deficiency because patients with other primary immunodeficiency diseases also have higher incidence and prevalence of autoimmune diseases [52]. There are no large long-term follow-up studies of patients with selective IgM deficiency. In long-term follow-up of our patients, we have observed development of autoimmune diseases in 2 of 25 patients with selective IgM deficiency a few years following the diagnosis of selective IgM deficiency (unpublished data). Antar et al. [46] described an adult patient with selective IgM deficiency and recurrent infections who later developed autoimmune glomerulonephritis. These observations suggest that autoimmune diseases may be secondary manifestations of primary selective IgM deficiency. A role of both “natural” and “antigen-induced” IgM in protection against autoimmunity and autoimmune diseases is well established in mice deficient

in secreted IgM [3, 53]. Autoimmune pathology associated with IgG autoantibodies is exacerbated in mutant mice with deficient secreted IgM, possibly because of impaired clearance of autoantigen expressing apoptotic cells [4, 46]. Ehrenstein et al. [54] demonstrated that mice deficient in serum IgM have an increased propensity to spontaneous autoimmunity as evidenced by the development of serum IgG anti-DNA antibodies and the renal deposition of IgG and complement. These mice exhibit increased anti-DNA IgG production on exposure to lipopolysaccharide. More recently, several investigators have demonstrated that effector functions of IgM with regard to enhancement of antibody responses and suppression of autoimmunity are mediated via interaction of IgM with Fcμ receptor. Ochida et al. [55] reported that phenotype of FcμR-deficient mice is similar to but not as severe as CD19-deficient mice [56] in terms of decreased marginal zone B cells, impaired germinal center formation, and reduced antibody production to T-independent and T-dependent antigen, and impaired memory response. In addition, they observed that these mice, both male and female, produced elevated levels of IgG autoantibodies (anti-dsDNA, rheumatoid factor, and antinuclear antibodies) as they aged. It is interesting to note that autoimmune diseases are more common in adult patients with selective IgM deficiency than children with selective IgM deficiency. Although the precise mechanism of IgM-mediated suppression of autoimmunity is unclear, one of the possibilities that have been entertained is that the IgM–autoantigen complex may cross-link FcμR and BCR on autoreactive B cells and trigger their deletion/anergy. The phenotype of FcμR-deficient mice resembles that of mice lacking secreted IgM with regard to reduced specific antibody responses and development of autoantibody production [3, 53, 57]. Thus, deficiency in serum IgM may explain a paradox of diminished responsiveness to foreign antigens (therefore, increased susceptibility to infections) and increased responsiveness to self-antigen resulting in autoimmunity and autoimmune diseases in patients with selective IgM deficiency.

In addition, to effector function of IgM in self tolerance, other mechanisms of autoimmunity in patients with selective IgM deficiency may be explored. A possibility of lost tolerance either at the level of bone marrow (receptor editing) and/or in the periphery secondary to a deficiency of isotype-specific regulatory T cells may be entertained. In addition, selective IgM deficiency might also have decreased or absence of natural IgM autoantibodies, resulting in impaired clearance of apoptotic cells (self antigens) leading to the development of autoimmune diseases. These possibilities are currently under investigation in our laboratories.

Malignancies There are only few cases of malignancy with selective IgM deficiency that have been reported [38, 58–60]. These include clear cell sarcoma, multiple

Table 3 Autoimmune diseases associated with selective IgM deficiency

Systemic lupus erythematosus
Rheumatoid arthritis
Hashimoto's thyroiditis
Autoimmune hemolytic anemia
Crohn's disease
Celiac disease
Vitiligo
Polymyositis
Autoimmune glomerulonephritis
Chronic idiopathic thrombocytopenic purpura

myeloma, non-Hodgkin's lymphoma, primary cutaneous anaplastic large cell CD30+ lymphoma, promyelocytic leukemia, hepatocellular carcinoma, and stomach Leiomyoma. Any cause and effect relationship remains unclear. These malignancies may be just coincidental findings, or secondary to B cell defects (in B cell malignancies), or due to an increased susceptibility to malignancies as in other primary Immunodeficiency diseases. One patient with selective IgM deficiency and angioedema developed non-Hodgkin's lymphoma one year after the diagnosis of selective IgM deficiency [16]. It is still possible that it might have been a low grade lymphoma therefore explaining the delay in the diagnosis of lymphoma, and the selective IgM deficiency being secondary to lymphoma. In a patient with clear cell carcinoma, co-culture of mononuclear cells in vitro suppressed IgM secretion by normal B cells, suggesting increased suppressor cell activity may be responsible for selective IgM deficiency [58].

Immune Response in Selective IgM Deficiency

Various abnormalities in T and B cell numbers and functions have been reported in selective IgM deficiency [16, 17, 35, 36, 61–66]. In contrast, innate immune responses appear to be preserved, including a number of polymorphonuclear leucocytes, natural killer cells, and monocytes [65]. Neutrophil functions, including chemotaxis, phagocytosis, bactericidal killing, and levels of complement components are normal [36, 63, 65].

Lymphocyte Phenotype

In the majority of patients with selective IgM deficiency, surface IgM+ B cells (sIgM+), CD19+ B cells, and CD20+ B cells are normal (16, 17, 64). However, low to complete lack of sIgM+ or CD19+ or CD20+ B cells has been reported [16, 64, 65]. We observed decreased number of peripheral blood CD19+ B cells in 2 of 15 subjects and complete lack of CD19+ B cells in one of 15 patients with selective IgM deficiency [16]. Inoue et al. [61] reported three patients with decreased B cells; however, two of them also had decreased expression of sIgM, sIgG, and sIgA. In only one patient, selective sIgM+ expression was decreased. Ideura et al. [65] reported decreased number of memory B cells in a single patient with selective IgM deficiency who presented with bronchial polyp. Belgemen et al. [36] observed decreased class-switched memory B cells in a patient with selective IgM deficiency. In IgM-deficient mice as well as FcμR mutant mice, there is an impaired germinal center formation and decreased memory cells [55].

Serum Immunoglobulins and Specific Antibody Responses

Serum Immunoglobulins

Serum IgM levels in selective IgM deficiency ranged from undetectable (complete absence) to levels below 2 SD of the mean (partial deficiency). IgM deficiency was first described by Hobbs et al. [11] in 1967, when 2 male children with fulminant meningococcal septicemia were found to have low levels of IgM. In our 15 cases, IgM levels ranged between 14 and 39 mg/dl [20]. Since this publication, we have an additional ten patients with selective IgM deficiency in whom serum IgM levels ranged from 3 to 47 mg/dl (unpublished data). IgG and IgA levels are normal. However, a few cases of associated low IgG subclasses have been reported [16, 65], a condition very similar to selective IgA deficiency, which is also occasionally associated with IgG subclass deficiency. We reported one of 15 patients with primary selective IgM deficiency with IgG3 subclass deficiency [16]. Ideura et al. [65] reported IgG4 subclass deficiency in a patient with selective IgM deficiency who presented with fibroepithelial bronchial polyp and possibly drug-induced exanthema. The clinical significance of associated IgG subclass deficiency with selective IgM deficiency is unclear since these patients did not have any difference clinical course than those who had no IgG subclass deficiency. Interestingly, elevated serum IgE levels have been observed more frequently than deficiency of IgG subclasses in patients with selective IgM deficiency [16, 17, 63, 66, 67]. Yamasaki [66] observed elevated IgE in 2 of 7 patients with selective IgM deficiency. Yel et al. [16] had one of 10 patients with elevated IgE. Inoue et al. [61, 67] reported 2 of 7 patients with elevated IgE. Though atopic manifestations are the second most common presentation in patients with selective IgM deficiency, there is no correlation between elevated IgE levels and presence or absence of atopic diseases or positivity of skin tests to allergens, and no correlation was observed between elevated IgE levels and deep skin abscesses or pneumonia, which are commonly observed in hyperimmunoglobulinemia E syndrome.

Specific Antibody Responses

Natural isohemagglutinin (IgM) are diminished in a subset of patients with selective IgM deficiency [22, 25]. We reported normal protective levels of tetanus IgG antibody titers in all 10 patients with selective IgM Deficiency [16]. Kung et al. [21] also reported protective specific antibody titers against tetanus and diphtheria in 2 children with selective IgM reported. In contrast, they observed that these patients had impaired protective antibody titers against pneumococcus polysaccharides 7/12 and 4/12 serotypes. Yel et al. [16] reported specific antibody response to pneumococcal

polycassharides in 11 adults with selective IgM deficiency following Pneumovax-23 vaccination. Three patients, two of whom had recurrent infections, had adequate pneumococcal antibody response at baseline and therefore, no Pneumovax-23 vaccination was administered. Five (45 %) of 8 remaining patients, who all presented with recurrent/severe infections, had impaired pneumococcal antibody responses following Pneumovax-23 administration, which demonstrates a specific antibody deficiency.

Lymphocyte Proliferative Response

The lymphocyte transformation in response to mitogens phytohemagglutinin, concanavalin A, and pokeweed mitogen, recall antigens, *Candida albicans*, mumps, and tetanus toxoid, and alloantigens appear to be intact in selective IgM deficiency [16, 17, 66].

Pathogenesis of Primary Selective IgM Deficiency

It is possible that IgM deficiency represents a heterogeneous disorder as evident by complete absence to partial deficiency of serum IgM, normal to complete absence of circulating B cells, normal to severely impaired specific antibody responses against pneumococcal polysaccharides, and chromosomal association.

The pathogenesis of selective IgM remains to be defined. De la Concha et al. [63] observed that the IgM-deficient patients' B cells produced normal amounts of IgM in vitro when co-cultured with normal T cells, whereas the patients' T cells demonstrated a decreased helper activity for IgM, IgG, and IgA production. They proposed that a defect in T-helper cell function was the most likely cause of decreased IgM production. On the other hand, Matsushita et al. [67] and Endoh et al. [68] hypothesized that in IgM deficiency, terminal differentiation of B lymphocytes into IgM-secreting cells in vitro was impaired, as observed in patients with selective IgA deficiency. They demonstrated presence of isotype-specific increased suppressor activity in IgM-deficient patients. These findings were also reproduced in 2 other studies, with a significant number of patients having decreased CD4/CD8 ratios [61, 62]. Raziuddin et al. [69] also observed increased IgM-specific T suppressor activity in in vitro immunoglobulin synthesis assay. Yamasaki et al. [66] and Karsh et al. [64] did not observe any defect in T helper or T suppressor activity, suggesting an intrinsic B cell defect. Kondo et al. [70] reported reduced secreted μ mRNA transcript in selective IgM deficiency associated with Bloom syndrome. However, it is unlikely that decreased μ chain transcript is responsible for selective IgM deficiency since other immunoglobulins are normal in patients with selective IgM deficiency.

Selective IgM Deficiency with T Cell Deficiency—A Distinct Syndrome?

Selective IgM deficiency is commonly associated with normal T cell functions. Recently, we described three adult patients with selective IgM deficiency with severe T cell lymphopenia (predominantly shared by CD4+ T cells), T cell functional defects, and Natural killer cell function deficiency [71]. All three patients had *Mycobacterium avium complex* (MAC) infections. Furthermore, severity of MAC infection correlated with severity of CD4 lymphopenia and T cell functions; disseminated MAC infection was associated with more severe CD4 lymphopenia and T cell functional deficiency as compared to those with relatively mild MAC infection. These functional defects and low serum IgM persisted even after successful treatment of MAC. However, a role of IgM deficiency (if any) in this clinical complex remains unclear. All these patients were negative for HIV infection. Does this represent a distinct syndrome remain to be determined? Raziuddin et al. [69] reported a 9-year-old girl with selective IgM deficiency (complete lack of serum IgM) with *Brucella abortus* infection who had almost complete absence of CD4 during acute phase of infection. Following 5 weeks of therapy, patients CD4+ T cells returned to normal and serum IgM was detectable; however remained low on further follow-up.

Immunoglobulin Therapy

The treatment of patients with IgM deficiency is challenging. Patients who do not have adequate response to polysaccharide pneumococcal vaccine may benefit from vaccination with the conjugated pneumococcal vaccine. In theory, immunoglobulin replacement would be ideal. However, there is no immunoglobulin product that renders IgM antibodies. Therefore, it is not easy to supplement these patients with immunoglobulin products which mainly provide immunoglobulin of the IgG isotype. Nonetheless, other constituents of the immunoglobulin preparations, such as cytokines and growth factors, may act as adjuvants to the impaired immune system. In our published series, among five IgM-deficient patients with susceptibility to infections, four with associated specific antibody deficiency, were treated with intravenous immunoglobulin [16]. The outcome in all patients was favorable in regard to frequency and severity of infections. However, no changes in serum IgM were observed, excluding the possibility that cytokines or growth factors in immunoglobulin preparations may somehow help IgM levels. Since our publication [16], we have now treated five additional symptomatic adult patients with selective IgM deficiency associated with specific antibody deficiency with intravenous immunoglobulin resulting in significant reduction in the frequency and severity of infections.

Stoelinga et al. [45] reported beneficial effect of Ig therapy in a boy with selective IgM deficiency with specific antibody deficiency. Fallon [72] also treated patient with selective IgM deficiency with immunoglobulin. Therefore, an association of specific antibody deficiency may be taken as an indication for immunoglobulin treatment in IgM deficiency.

In summary, selective IgM deficiency is more common than previously recognized. Selective IgM deficiency may be associated with often serious life-threatening infections. Interestingly, patients with common variable immunodeficiency with low serum IgM are clinically worse than those with normal IgM levels. Autoimmunity may be secondary to primary selective IgM deficiency rather than selective IgM deficiency secondary to autoimmune diseases. Patients with selective IgM deficiency should undergo a thorough immunological evaluation, particularly in the presence of recurrent/severe infections. Furthermore, immunoglobulin treatment is a beneficial therapeutic approach for patients with selective IgM deficiency who present with recurrent infections in the presence of an associated defective specific antibody response to pneumococcal and/or other antigens.

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