

Clinical and Immunological Features in IgM Deficiency

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Key Words

IgM deficiency · Immunodeficiency · Atopy ·
Pneumococcal antibody response · Intravenous
immunoglobulin

Abstract

Background: IgM deficiency is a dysgammaglobulinemia characterized by isolated low levels of serum IgM. Patients with IgM deficiency may exhibit various clinical manifestations. However, IgM deficiency still remains to be explored with regard to diagnosis and treatment. **Methods:** Through a retrospective chart review, we investigated the clinical and immunological features of 15 symptomatic adult IgM-deficient patients who were referred to our immunology clinics over a 4-year period. **Results:** The patients were comprised of 6 males and 9 females, with a mean age of 57.2 years. On initial evaluation, 12 patients (80%) presented with susceptibility to infections, 5 (33%) had atopic manifestations such as asthma and allergic rhinitis, 3 (20%) had both infections and atopy, 4 patients (28%) had fibromyalgia-like symptoms, 3 (20%) had autoimmune manifestations, and 1 patient had lymphoma. The mean serum IgM level was 27.4 mg/dl (range 14–39). Impaired specific antibody response to pneumococcal antigens in 5 out of 11 studied patients (45%) appeared to be a notable association. Subtle abnormalities in IgG subclasses, lymphocyte subsets and in vitro proliferative lym-

phocyte responses were observed. Five patients who were treated with intravenous immunoglobulin responded very well. **Conclusion:** We propose that a thorough immunological evaluation including specific antibody responses be undertaken in patients with IgM deficiency. IgM-deficient patients who present with recurrent/severe infections may benefit from immunoglobulin treatment particularly in the presence of impaired pneumococcal antibody responses.

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Introduction

The prevalence of IgM deficiency has been reported to be 0.03–1% in a limited number of screening studies [1, 2]. Clinical and laboratory features of IgM deficiency are poorly defined. Although this immunodeficiency has been associated with some clinical disorders including recurrent infections [3–9], atopy [3, 10, 11], Bloom's syndrome [12, 13], celiac disease [9], systemic lupus erythematosus [14] and malignancy [15], it may also occur in asymptomatic individuals [16]. Therefore, IgM deficiency remains a diagnostic and therapeutic dilemma. The specific causative mechanism of IgM deficiency is also unclear. Various mechanisms have been proposed, such as an increase in suppressor T-cell functions [8, 15, 17, 18], defective helper T-cell functions [9], impaired terminal

differentiation of B lymphocytes into IgM-secreting cells [19] and failure of secreted μ mRNA synthesis [13]. Chromosomal anomalies, e.g. deletions of chromosomes 1, 18 and 22, have been reported in few cases of IgM deficiency [20]. In this study, we retrospectively investigated the clinical and immunological features of 15 adult patients with IgM deficiency. This is one of the largest symptomatic IgM-deficient patient series reported to date, allowing for a greater understanding of this immunodeficiency.

Material and Methods

We performed a retrospective chart review of 374 patients evaluated in the University of California-Irvine Immunology Clinics over a 4-year period from 2003 to 2007. Patients who repeatedly (at least twice) had a serum IgM level <2 standard deviations of the lower limit for adults [2] were included in the study. Patients with low IgG and IgA serum levels were excluded. In addition, the presence of any other well-defined immunodeficiency, e.g. common variable immunodeficiency, was considered an exclusion criterion. A total of 15 patients met the criteria for IgM deficiency. We reviewed each patient's chart regarding demographic data, clinical manifestations, immunological findings and treatment.

For the immunological evaluation of each patient, we noted the following parameters: complete blood count with differential, serum IgG, IgA and IgE levels by nephelometric method, T- and B-lymphocyte subsets as well as natural killer cell proportion and numbers measured by flow cytometry compared with those of healthy, age-matched control subjects, pre- and postvaccination pneumococcal and tetanus antibody titers determined by enzyme-linked immunosorbent assay (ELISA), and lymphocyte mitogen and antigen proliferation assays which involved stimulation of peripheral blood mononuclear cells with mitogens (phytohemagglutinin, concanavalin A, pokeweed mitogen) and with antigens (purified protein derivative, mumps antigen, tetanus toxoid, *Candida albicans*), as well as the assessment of DNA synthesis by means of measuring ^3H -thymidine incorporation. The normal ranges for the lymphocyte proliferation assays were derived from healthy adult male and female control subjects. We also noted skin prick tests and/or radioallergosorbent testing with allergens to determine the atopy status. Skin prick testing was performed with environmental allergens including trees, grasses, weeds, molds, dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and cat dander, along with a positive histamine and negative saline control. Radioallergosorbent testing was done using corresponding antigens.

Pre- and postvaccination pneumococcal antibody titers, 4 weeks following vaccination with 23-valent polysaccharide pneumococcal vaccine (Pneumovax®; Merck, Whitehouse Station, N.J., USA), were measured. The ELISA assays were performed by the ARUP Specialty Laboratories, Salt Lake City, Utah, USA. The postvaccination response was interpreted as positive for the particular serotype if there was a 4-fold or greater increase in the postvaccination antibody titer compared with the prevaccination

concentration. Overall, the pneumococcal antibody response was considered normal if there were positive responses in at least 50% of the tested serotypes, i.e. in more than 7 out of the 14 tested antigen serotypes (1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F, 23F). A baseline antibody titer of $\geq 1.3 \mu\text{g/ml}$ to any pneumococcal serotype, in the absence of vaccination, was interpreted as an adequate response to that particular serotype which was most likely encountered by means of natural infection [21].

Tetanus antibody (IgG) was considered positive if the concentration was $>0.10 \text{ IU/ml}$.

Results

Demographic Data

The study group consisted of 15 patients, 6 males and 9 females (male/female: 0.7). The mean age of the patients was 57.2 ± 14.3 years (range 39–79). The total follow-up period was 228 patient-months.

Clinical Findings

The clinical manifestations of each patient are summarized in table 1. The most common manifestation was increased susceptibility to infections. It was observed in 12 patients (80%; patients 2, 4, 5 and 7–15). Most of them contracted infections involving the respiratory tract. Sinus and pulmonary infections were confirmed by X-rays and CT scans. Patients were evaluated for possible underlying anatomical defects by means of imaging studies and/or bronchoscopy.

The second most common manifestation was atopic conditions. Five patients (33%; patients 2, 3, 6, 7 and 9) presented with asthma and/or allergic rhinitis. One of the atopic patients (patient 3) had an elevated serum IgE level (402 IU/ml). One patient (patient 9) was on maintenance immunotherapy to pollens, animal dander and mold by an allergist.

A constellation of long-lasting fatigue, myalgia and arthralgia resembling fibromyalgia was observed in 4 patients (28%; patients 2, 4, 6 and 14), who did not have any autoantibodies including ANA, anti-SSA, anti-SSB, anti-SM, anti-SM/RNP, anti-Scl-70 and anti-Jo-1.

Three patients (20%; patients 9, 10 and 13) had an autoimmune disorder: hypothyroidism, Hashimoto's thyroiditis and rheumatoid arthritis. Patient 10 was on oral thyroid hormone replacement, and she had a negative autoantibody against double-stranded DNA, a negative antinuclear antibody and a negative rheumatoid factor.

One patient (patient 1) who presented with angioedema was found to have an acquired C1 inhibitor (C1-INH) deficiency with low CH50 of $<10 \text{ U/ml}$ (normal range

Table 1. Clinical features of patients with IgM deficiency

Pa-tient	Age years/ gender	Manifestations
1	75/F	angioedema, C1 inhibitor deficiency, lymphoma
2	41/F	recurrent otitis and sinusitis since childhood, recurrent pneumonia as an adult, AR, asthma, fatigue, arthralgia
3	69/M	asthma, rhinorrhea
4	53/F	fatigue, myalgia, recurrent UTI and URI
5	44/F	chronic sinusitis
6	79/M	asthma, fatigue, myalgia
7	44/F	recurrent sinus infections, AR, rash
8	63/M	skin abscesses on the neck with <i>S. aureus</i> (MRSA), history of gout and psoriasis
9	39/F	recurrent sinus and ear infections, AR, asthma, hypothyroidism, fibromyalgia
10	50/F	recurrent sinus infections and three pulmonary infections since adolescence, history of sinus surgery, fatigue, Hashimoto's thyroiditis
11	76/M	recurrent URI
12	75/F	recurrent URI, <i>Haemophilus influenzae</i> and <i>Aspergillus fumigatus</i> pneumonia complicated with bronchiectasis, asthma
13	46/F	recurrent URI, rheumatoid arthritis
14	55/M	recurrent shingles, fatigue, arthralgia, myalgia
15	49/M	pneumococcal sepsis, purpura fulminans, invasive <i>A. fumigatus</i> sinusitis, <i>Varicella zoster</i> infection

AR = Allergic rhinitis; UTI = urinary tract infection; URI = upper respiratory tract infection; MRSA = methicillin-resistant *S. aureus*.

22–60), a decreased C1-INH level of 5 mg/dl (normal value >11) and a decreased C4 of <3 mg/dl (normal range 14–53). She was not taking any angiotensin-converting enzyme inhibitors, and the autoantibodies were negative as well as the skin prick tests to inhalant allergens. One year later, she was found to have a B-cell lymphoma. She clinically responded well to chemotherapy including anti-CD20 antibody; however, the serum IgM level has so far remained low.

There was no family history of any type of immunodeficiency in any of the patients with IgM deficiency.

Table 2. Serum immunoglobulin and IgG subclass levels in patients with IgM deficiency

Pa-tient	IgM mg/dl	IgA mg/dl	IgG mg/dl	IgE IU/ml	IgG1 mg/l	IgG2 mg/l	IgG3 mg/l	IgG4 mg/l
1	14	69	1,080	NA	6,970	1,960	1,150	39
2	26	192	863	41	5,580	2,850	199	131
3	39	328	1,190	402	NA	NA	NA	NA
4	35	273	697	10	4,040	1,620	359	60
5	27	71	1,190	59	6,150	6,100	224	166
6	18	114	940	37	7,120	3,170	966	117
7	28	153	1,160	37	NA	NA	NA	NA
8	16	136	1,240	NA	5,310	4,230	350	50
9	16	118	729	NA	4,340	2,350	726	154
10	34	105	921	6	5,080	3,290	448	314
11	30	185	780	20	NA	NA	NA	NA
12	32	369	1,020	14	5,410	3,590	750	340
13	39	160	985	NA	5,770	3,080	907	251
14	39	86	1,160	NA	6,600	2,790	438	294
15	18	180	1,060	124	6,600	2,190	282	967

NA = Not available. Borderline low levels are shown in italics. Normal ranges for serum immunoglobulin levels: IgM 65–263 mg/dl; IgA 68–378 mg/dl; IgG 694–1,618 mg/dl; IgE 10–150 IU/ml; IgG1 3,422–11,178 mg/l; IgG2 1,476–5,246 mg/l; IgG3 211–1,142 mg/l; IgG4 69–888 mg/l.

Immunological Findings

Serum Immunoglobulin Levels

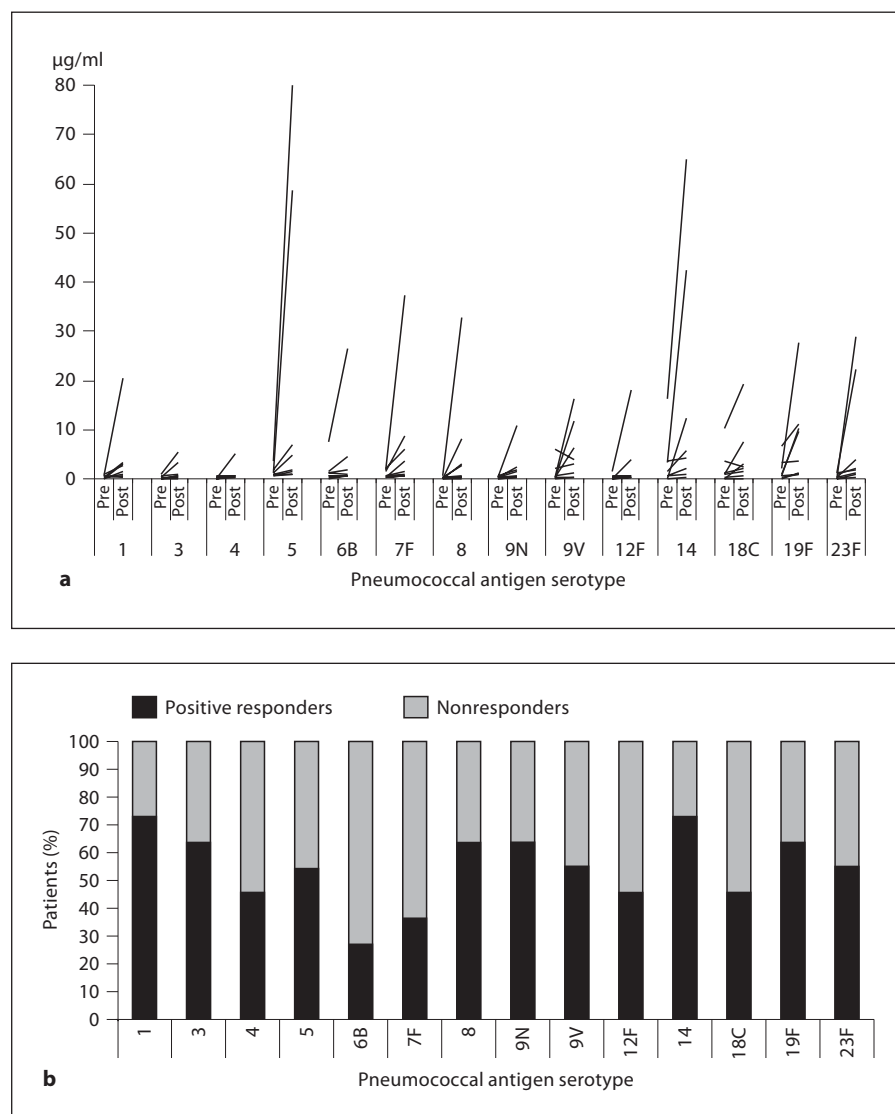
The serum IgM level ranged from 14 to 39 mg/dl (mean 27.4 ± 9.1) (table 2). In accordance with the inclusion criteria, the mean serum levels of IgG and IgA were normal (IgG $1,001 \pm 176$ mg/dl and IgA 169 ± 100 mg/dl). The mean serum IgG subclass levels were normal: 5,748 $\pm$ 985, 3,102 $\pm$ 1,191, 567 $\pm$ 320 and 240 $\pm$ 252 mg/l for IgG1, IgG2, IgG3 and IgG4, respectively (table 2), although 3 patients (patients 2, 4 and 8) had borderline IgG3 and IgG4 levels at one point.

Specific Antibody Responses

Tetanus antibody titers were measured in 10 patients, and all of them had protective levels (a tetanus IgG level >0.10 IU/ml).

A total of 11 patients were evaluated for antibody response to pneumococcal antigens. Three patients (patients 4, 5 and 6), 2 of whom (patients 4 and 5) had recurrent infections, had adequate pneumococcal antibody response at baseline without vaccination. Figure 1a shows the pre- and postvaccination pneumococcal antibody titers in the remaining 8 patients. Of those, 3 patients (patients 7, 9 and 14) had a positive response to Pneumovax.

Fig. 1. Pneumococcal polysaccharide antibody responses. **a** Antibody titers in 8 patients in whom both pre- and postvaccination titers were measured. Fourteen pneumococcal antigen serotypes (1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F and 23F) are shown on the x-axis. Pneumococcal antibody titers ($\mu\text{g/ml}$) for each serotype are shown on the y-axis. **b** Percentage of positive responders and nonresponders to pneumococcal polysaccharide antigens in 11 patients who were evaluated for pneumococcal antibody responses. Positive responders either had an adequate response ($\geq 1.3 \mu\text{g/ml}$) at the baseline without vaccination (3 patients) or a 4-fold or greater increase in the postvaccination titer compared with the prevaccination titer for each individual serotype. Nonresponders had less than a 4-fold increase in the postvaccination titer. Pneumococcal antigen serotypes are shown on the x-axis.



Their infections slightly improved after the first evaluation when pneumococcal vaccine was administered. Figure 1b shows the percentage of positive responders and nonresponders to each individual pneumococcal antigen serotype. Antigen serotypes 1 and 14 elicited the greatest number of positive responses (in 73%, 8 out of 11 patients) followed by serotypes 3, 8, 9N and 14 (in 64%, 7 out of 11 patients). Serotypes 6B and 7F elicited the lowest numbers of positive responses: 27 and 36% of patients, respectively. Overall, 5 (45%) out of 11 patients (patients 2, 8, 10, 12 and 15), who all presented with recurrent/severe infections, had decreased pneumococcal antibody responses. Figure 2 shows the fold increase in postvaccination titers compared with prevaccination titers for each individual

serotype in patients 2, 8, 10 and 12. Data on patient 15 were reported previously [22].

Lymphocyte Subsets and in vitro Proliferative Responses

Lymphocyte subsets were performed in 13 patients (table 3). Two patients (patients 5 and 8) had a decreased number and percentage of CD19+ B lymphocytes. Patient 14 had decreased CD8+ T lymphocytes (208 cells/mm^3) with an increased CD4+ T-cell/CD8+ T-cell ratio of 2.69. He also had decreased T-cell responses to tetanus toxoid and *Candida*.

There were 9 patients in whom lymphocyte proliferation assays to mitogens and antigens were performed (ta-

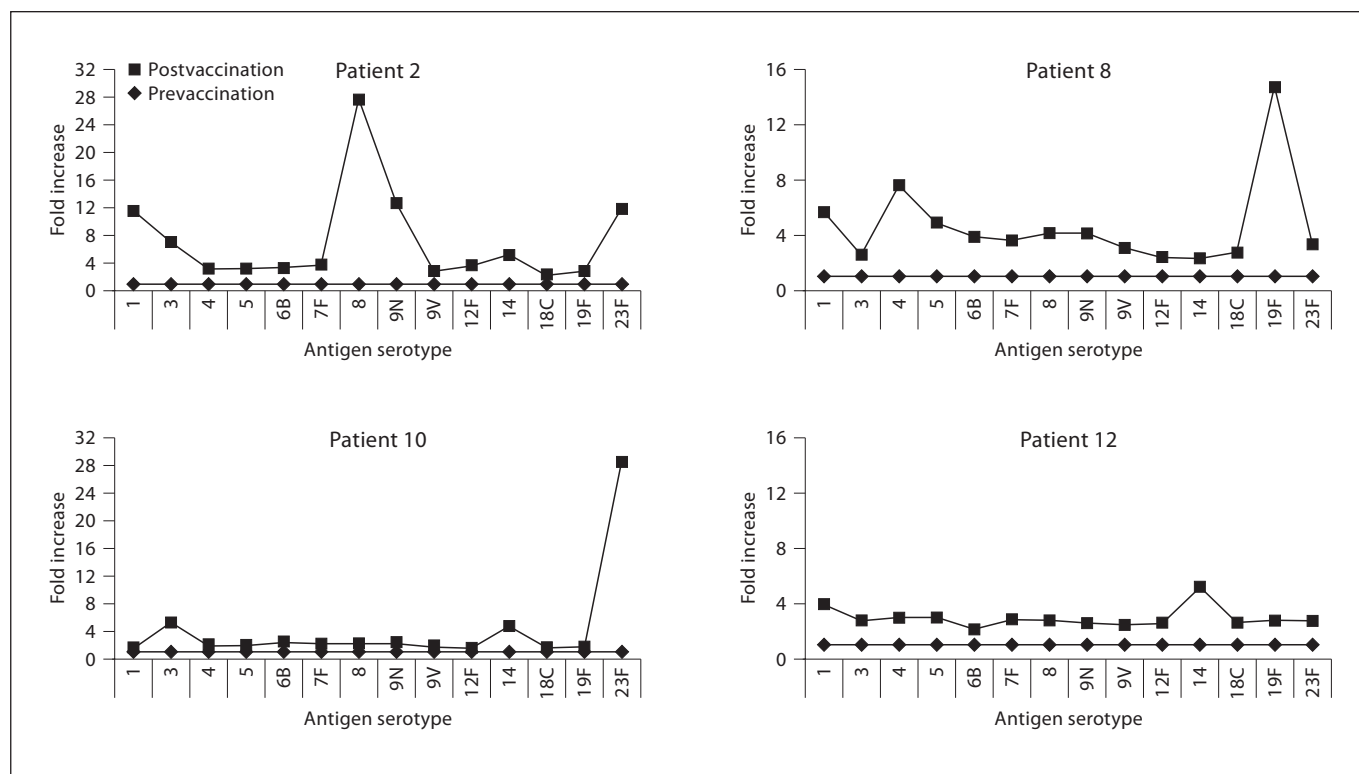


Fig. 2. Impaired polysaccharide antibody responses in patients 2, 8, 10 and 12. Fourteen pneumococcal antigen serotypes (1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F and 23F) are shown on the x-axis. The y-axis depicts the fold increase in antibody response to each serotype calculated as postvaccination antibody titer divided by prevaccination antibody titer. The postvaccination response

was interpreted as negative for the particular serotype if there was less than a 4-fold increase. Overall, the pneumococcal antibody response was considered impaired if the response was negative in greater than 50% of the tested serotypes, i.e. in more than 7 out of the 14 tested antigen serotypes.

ble 4). Of those, 7 patients (78%) showed subtle decreased responses to mitogens and/or antigens.

Treatment

A total of 5 patients (33%; patients 2, 5, 8, 10 and 15) who had recurrent/severe infections were treated with intravenous immunoglobulin 400 mg/kg every 3–4 weeks in addition to optimal antibiotic administration, supportive measures and specific interventions. All of them responded to intravenous immunoglobulin remarkably well.

Discussion

Our series of 15 symptomatic adult IgM-deficient patients is one of the largest to explore the clinical and immunological findings in IgM deficiency. IgM deficiency

was first described by Hobbs et al. [7] in 1967, when 2 male children with fulminant meningococcal septicemia were found to have low levels of IgM. The same authors also performed a retrospective survey of 3,000 hospitalized patients and found 11 patients with low IgM levels who presented with meningitis and pyelonephritis. Although it has been a while since the first description, the clinical entity of IgM deficiency has not been clearly understood, and its significance in host response or how it reflects in a clinical setting is still a challenge.

In parallel with the initial cases of IgM deficiency, and with a more recent study by Goldstein et al. [20], the most common presentation in our series is recurrent infections. Eighty percent of patients in our series manifested with susceptibility to infections which mostly involved the respiratory tract. One patient in our study experienced skin abscesses due to *Staphylococcus aureus*. Yocum et al. [4] reported 2 cases with IgM deficiency who had recurrent

Table 3. Lymphocyte subsets in patients with IgM deficiency

Pa-tient	CD3+ T cells, %	CD4+ T cells, %	CD8+ T cells, %	CD4+/CD8+ ratio	CD19+ B cells, %	CD3–D16+CD56+ NK cells %
1	86 (771)	30 (269)	55 (493)	0.55	<1, <10	8 (72)
2	75 (1,275)	55 (935)	22 (374)	2.5	8 (136)	15 (255)
4	82 (1,804)	58 (1,276)	26 (572)	2.23	12 (264)	4 (88)
5	91 (890)	53 (522)	29 (285)	1.83	2 (20)	7 (69)
6	48 (1,152)	32 (768)	16 (384)	2	33 (792)	14 (336)
7	71 (959)	56 (756)	17 (216)	3.5	19 (323)	12 (204)
8	84 (924)	46 (506)	37 (407)	1.24	3 (33)	15 (165)
9	80 (1,120)	49 (686)	31 (434)	1.58	8 (112)	13 (182)
10	74 (1,110)	22 (330)	42 (630)	0.52	8 (120)	12 (180)
12	76 (1,368)	45 (810)	32 (576)	1.41	10 (180)	5 (90)
13	78 (2,340)	52 (1,560)	27 (810)	1.93	14 (420)	6 (180)
14	61 (793)	43 (559)	16 (208)	2.69	16 (208)	22 (286)
15	81 (1,265)	68 (1,062)	10 (158)	6.81	14 (219)	4 (62)

Figures in parentheses are absolute numbers given in mm³. NK cells = Natural killer cells. Borderline low numbers are shown in italics. Normal ranges: CD3+ T cells 65–80%, 844–2,395 mm³; CD4+ T cells 31–56%, 437–1,597 mm³; CD8+ T cells 17–34%, 281–1,125 mm³; CD4+/CD8+ ratio 0.78–2.21; CD19+ B cells 4–17%, 132–399 mm³; CD3–D16+CD56+ NK cells 4–16%, 102–424 mm³.

Table 4. Lymphocyte response to mitogens and antigens in patients with IgM deficiency

Pa-tient	PHA, cpm	Con A, cpm	PWM, cpm	Mumps, cpm	Tetanus, cpm	PPD, cpm	<i>C. albicans</i> , cpm
2	196,357	108,487	40,620	11,362	15,223	125	2,450
4	108,641	91,622	23,860	6,052	14,351	8	14,381
5	49,631	46,586	8,846	13,141	14,255	7,304	13,159
6	100,104	110,323	29,463	226	7,213	365	3,179
7	183,701	210,335	34,133	19,589	26,889	0	22,815
8	58,495	188,724	23,188	159	279	6	3,636
10	189,634	175,638	15,621	5,294	3,065	220	45,253
14	268,445	317,982	41,375	2,357	2,456	1,871	6,358
15	198,871	174,387	21,399	3,763	907	1,324	4,957

cpm = Count per minute; PHA = phytohemagglutinin; Con A = concanavalin A; PWM = pokeweed mitogen; PPD = purified protein derivative. Borderline low numbers are shown in italics. Normal ranges: PHA 123,609–193,794 cpm; Con A 131,199–252,925 cpm; PWM 23,648–90,931 cpm; mumps 2,052–26,495 cpm; tetanus 6,092–94,539 cpm; PPD 0–3,411 cpm; *C. albicans* 21,494–78,166 cpm.

staphylococcal pyoderma. These observations support that IgM, being the responsible immunoglobulin isotype in the primary antibody response, 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 with low IgM levels and recurrent infections. Despite normal IgG levels, specific antibody response to polysaccha-

ride antigens may be defective. This association is shown as impaired antibody response to pneumococcal polysaccharide antigens in 45% of 11 tested patients. 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 seemed to be intact experienced recurrent infections as well. Therefore, susceptibility to infec-

tions in IgM deficiency is probably due to a number of contributing factors of which specific antibody deficiency appears to be the most important.

In our series, the second most common manifestation was allergic disorders (33%); this is in parallel with the results of Goldstein et al. [20], 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 [10]. Some other reports have also noted an association between atopic diseases and selective IgM deficiency [3, 5, 11]. 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.

IgM deficiency has been described in nonbacteremic, nonatopic patients in whom the presenting illness does not appear to be related to low IgM levels [16], such as fatigue [5] and malignancy, specifically with clear cell sarcoma [15]. In our series, a considerable number of patients (28%) had fibromyalgia-like symptoms and chronic fatigue of an undefined etiology. Three patients had an autoimmune disorder, and interestingly, 1 patient who presented with angioedema was found to have an acquired C1-INH deficiency probably secondary to lymphoma. These individuals may have developed IgM deficiency due to their presenting disorder.

It is possible that IgM deficiency represents a heterogeneous spectrum of genetic defects. In our series, the patients with IgM deficiency showed associated immunological abnormalities such as borderline low IgG4 levels, low numbers of B cells, altered CD4+ and CD8+ T-cell numbers and slightly decreased T-cell responses to mitogens and/or antigens. The significance of those in IgM deficiency remains controversial at this point. Endoh et al. [19] 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. De la Concha et al. [9] observed that the IgM-deficient patients' B cells produced normal amounts of IgM in vitro when cocultured 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. [17] observed an increased suppressor activity in an IgM-deficient patient. This finding was reproduced in 2 other studies, with a significant number of patients having decreased CD4/CD8 ratios [8, 18]. In our study, we did not attempt to determine the causative mechanism in selective IgM deficiency. However, the subtle abnormalities in T-cell number and functions in our series may be supportive of the above observations which imply that the defect(s) in selective IgM deficiency may reside in T cells or in cross-talk between B and T cells.

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 series, 5 IgM-deficient patients with susceptibility to infections, 4 of whom also with specific antibody deficiency, were treated with intravenous immunoglobulin. The outcome in all patients was favorable. Therefore, an association of specific antibody deficiency may be taken as an indication for immunoglobulin treatment in IgM deficiency.

In summary, we believe that patients with IgM deficiency should undergo a thorough immunological evaluation, particularly in the presence of recurrent/severe infections, and immunoglobulin treatment is a beneficial therapeutic approach in the presence of an associated defective antibody response to pneumococcal antigens.

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