Review

Selective IgM immunodeficiency: retrospective analysis of 36 adult patients with review of the literature

Marc F. Goldstein, MD*; Alex L. Goldstein, BS†; Eliot H. Dunsky, MD*; Donald J. Dvorin, MD*; George A. Belecanech, MD*; and Kfir Shamir, MD‡

Objective: To review and compare previously reported cases of selective IgM immunodeficiency (SIgMID) with the largest adult cohort obtained from a retrospective analysis of an allergy and immunology practice.

Data Sources: Publications were selected from the English-only PubMed database (1966–2005) using the following keywords: *IgM immunodeficiency* alone and in combination with *celiac disease, autoimmune disease, malignancy,* and *infection*. Bibliographic references of relevant articles were used.

Study Selection: Reported adult SIgMID cases were reviewed and included in a comparative database against our cohort.

Results: Previously described patients with SIgMID include 155 adults and 157 patients of unspecified age. Thirty-six adult patients were identified with SIgMID from a database of 13,700 active adult patients (0.26%, 1:385). The mean ± SD serum IgM level was 29.74 ± 8.68 mg/dL (1 SD). The mean ± SD age at the time of diagnosis of SIgMID was 55 ± 13.5 years. Frequency of presenting symptoms included the following: recurrent upper respiratory tract infections, 77%; asthma, 47%; allergic rhinitis, 36%; vasomotor rhinitis, 19%; angioedema, 14%; and anaphylaxis, 11%. Serologically, 13% of patients had positive antinuclear antibodies (ANAs), 5% had serologic evidence of celiac disease, and nearly all had non-AB blood type. Patients also had low levels of IgM isohemagglutinins. No patients developed lymphoproliferative disease or panhypogammaglobulinemia, and none died of life-threatening infections, malignancy, or fulminant autoimmune-mediated diseases during a mean follow-up period of 3.7 years.

Conclusions: The prevalence of SIgMID in our adult population was 0.26% and may be more common than previously thought. Non–life-threatening respiratory disorders were common comorbid conditions.

Ann Allergy Asthma Immunol. 2006;97:717–730.

INTRODUCTION

In humans, IgM is the first immunoglobulin to be synthesized and can be detected as early as 9 weeks of gestation. IgM does not cross the placenta; however, small amounts of pentameric IgM exist neonatally. In cases of in utero infection, IgM levels may be elevated. Functionally, IgM is the first antibody formed after primary immunization (new antigen exposure) and also appears first in the bloodstream during infection. IgM is primarily confined to the bloodstream and appears to give the host early protection against bloodborne pathogens. Ten percent of total serum immunoglobulins is IgM (IgA is 15%; IgG is 75%).[1] The half-life of IgM in the blood is 5 to 10 days. IgM is unique among the immunoglobulin isotypes in that its peak serum concentration occurs between the ages of 20 and 40 years and it reaches a lower plateau after the age of 50 years.[2] For any given age, normal serum IgM levels are usually higher in females than males.[3] Naturally occurring isohemagglutinins (anti-A and anti-B antibodies), which tend to form at approximately 6 months of age, are primarily IgM. Mucosal production of IgM occurs in physiologically significant levels. Secretory component transport of mucosally produced IgM can carry IgM across epithelial layers to the surface. The importance of mucosal IgM production in healthy individuals is still unknown. However, in patients with selective IgA immunodeficiency (SIgAID), mucosal IgM may replace IgA as the primary mucosal antibody.[4,5]

IgM exists both as a 70-kDa molecular-weight monomer and a pentamer in which 5 IgM monomers are linked together through disulfide bonds by J chains, 15-kDa polypeptides that stabilize the pentamer. The monomeric form (molecular weight, 70 kDa) of IgM is found on the surface of B cells and functions as the earliest surface marker in B-cell ontogeny and a transmembranous antigen receptor, capable of activating B cells when bound to antigen.[6] The IgM pentamer consists of 5 immunoglobulin molecules (molecular weight, 900 kDa) tethered together at their Fc domains. Pentameric IgM molecules readily

* Allergic Disease Associates, PC/The Asthma Center, Philadelphia, Pennsylvania.
† Wharton Undergraduate Division, University of Pennsylvania, Philadelphia, Pennsylvania.
‡ Hahnemann University Hospital, Philadelphia, Pennsylvania.
Received for publication March 28, 2006.
Accepted for publication in revised form June 16, 2006.

activate complement (more efficiently than IgG because of its higher valence) and serve as opsonizers and agglutinators to assist the phagocytic system in eliminating a variety of microorganisms. In the presence of complement and IgM, whole microbial cells may be lysed and killed. Other clinically relevant IgM antibodies include cold agglutinins, heterophil antibody, Wassermann antibodies, and rheumatoid factor.[7]

Selective IgM immunodeficiency (SIgMID) is defined as a dysgammaglobulinemia differentiated by an isolated low level of serum IgM (<20 mg/dL in infants and children or <2 SDs below age-adjusted means in children and adults).[3,7] The levels of other immunoglobulin isotypes are typically normal, although IgE may be increased. It is said to be a rare primary immunodeficiency, with the prevalence of completely deficient IgM patients reported as approximately 0.03% in a community-based study.[3] The prevalence of those with deficient but detectable levels of IgM has been reported as 0.1% to 3.8% in hospitalized patients,[4,9–13] 1.68% in an unselected community health screening,[3] and 0.07% in an allergy and immunology clinic[14] (Table 1). There is a slightly higher penetration of SIgMID in males (1.97%) vs females (1.42%).[3]

Table 1. Comparison of SIgAID and SIgMID

Variable	SIgAID	SIgMID*
Comorbid conditions		
Recurrent respiratory tract infections	Up to 50%[76]	11%[4]
Allergies and asthma	Up to 13%[76]	Up to 22%[4]
Autoimmune disease	Up to 28%[76]	Up to 3%[4]
Meningitis and sepsis	Rare[54]	Up to 11%[4]
Gastrointestinal disease	3%[76]	14%[4]
Celiac disease	2/30 (7%)[22] 2/75 (3%)[21] 2/110 (2%)[61]	11/30 (37%)[22] 10/51 (21%)[61] 8/19 (42%)[62] 28/75 (37%) adults[21] 5/5 (100%) children[21]
Malignancy	Double the risk compared with general population[77]	Up to 7%[4]
Asymptomatic	7/127 (6%)[76]	Up to 19%[4]
Undetectable IgA or IgM, respectively	0.097%[3]	0.03%[3]
IgG subclass deficiencies	Low IgG_2 in 8% of patients[76] Low IgG_3 in 29% of patients[76] Low IgG_4 in 2% of patients[76]	2 cases of qualitative nonspecific subclass IgG deficiency[68]
Transformation into Pan hypogammaglobulinemia	Rare[5,55]	None
Prevalence		
General population	1.93%[3] 1/700 (0.14%)[78]	1.68%[3]
Hospitalized population	24/11,000 (0.22%)[13] 1:418 (0.23%)[77]	23/11,000 (0.2%)[21] 3%[10] 29/3,000 (0.96%)[9] 0.1%[4] 0.1%[11] 12/315 (3.8%)[12]
Incidence in atopic population	29/641 (4.5%)[34]	10/641 (1.56%)[34] 22%[4]
Allergy/immunology clinic	13/3,000 (0.43%)[14] 0.65% (our adult population)	2/3,000 (0.07%)[14] 1:385 (0.26%) (our adult cohort)
Drug-induced cases	Yes[54,55]	None
F:M ratio	Higher in males[5]	1.4[4] 1.77 female to male (our cohort)
Familial inheritance	25% of cases[79] 20%[55]	Rare[9,24]
Anti-IgA or anti-IgM antibodies	20%–40% with anti-IgA 60% in patients with IgAID and IgG subclass deficiency[79]	None[39,67]
Molecular defect	Mutations in TNP RS + 13B[53]	None reported
Chromosomal abnormality	Rare reports[76]	Rare reports[8,15,16]
IVIG	Sometimes used[54]	2 reports[27,56]

Abbreviations: IVIG, intravenous gammaglobulin; SIgAID, selective IgA immunodeficiency; and SIgMID, selective IgM immunodeficiency.
* Combination of reported pediatric and adult cases and our cohort.

The origin of SIgMID is unclear. No genetic or molecular basis has been established as a cause of SIgMID. Chromosomal anomalies have been reported in a limited number of cases of SIgMID (partial deletion of chromosome 18, chromosome 1 deletions, and chromosome 22q11.2 deletion).[8,15,16] Some cases of SIgMID have been reported in the context of congenital disorders: Wiskott-Aldrich syndrome,[17] Bloom syndrome,[18,19] and Russell-Silver syndrome.[20] Transient SIgMID has been reported as associated with celiac disease, with improvement in IgM levels noted with gluten-free diets,[4,21,22] and with Hashimoto thyroiditis, with improvement noted with thyroid replacement therapy.[23] It has been suggested that in the latter case thyroid hormones may have stimulated IgM-producing B cells to produce normal IgM levels.[23] Unlike selective IgG immunodeficiency or SIgAID, there have been no reported cases of drug-induced SIgMID.

A variety of bacterial and viral infections have been linked to SIgMID in the pediatric and adult population.[9,12,24–31] These organisms account for recurrent infections, resulting in dermatitis, diarrhea, meningitis, upper and lower respiratory tract infections, skin infections, and, in some cases, death.[10,29,32–36] SIgMID has also been associated with a broad array of noninfectious diseases, in particular, autoimmune diseases and malignancies.[4,21,22,33,37–46] In many of these cases, SIgMID was identified in the investigation and reporting of the associated conditions. Treatment of the underlying disorders led to recovery of normal IgM levels in some cases,[4,21] whereas others showed no change in IgM levels after treatment of the underlying process.[45,46] In the latter case, it would appear that SIgMID is unlikely induced by the primary process.

SIgMID has also been reported as an inherited condition. Clustered familial cases have been associated with meningitis and recurrent viral illnesses or have been asymptomatic.[9,12,29–31,35,47]

We present a retrospective analysis of 36 adult patients with SIgMID. This is the largest series of adult cases. The relative frequencies of various clinical, immunological, and demographic features, associations, and complications are reported in our series. These findings are compared and contrasted to adult cases previously reported.

METHODS

We undertook a retrospective medical record review of 20,000 patients seen in our allergy and immunology practice during a 4-year period (January 2002 to December 2005). Of these, 13,700 patients were adults (≥18 years of age). Medical records were identified with a diagnosis of SIgMID, SIgAID, common variable hypogammaglobulinemia (CVID), idiopathic anaphylaxis, and idiopathic angioedema. Cases of SIgMID were reviewed for immunoglobulin levels (IgG, IgM, IgA, IgE, and IgG subclasses), isohemagglutinin levels, autoantibody serologic test results, presenting clinical symptoms, concurrent conditions, and clinical course. Patients diagnosed as having SIgMID were routinely screened serologically for celiac disease, autoimmune thyroid disease, and autoimmune collagen vascular disease. A literature search using the keywords *IgM immunodeficiency* alone and in combination with *celiac disease, autoimmune disease, malignancy,* and *infection* was conducted of reported cases of SIgMID in the English literature through PubMed from 1966 to 2005 and from the bibliographies of related articles. Informed consent was obtained from SIgMID patients for anonymous publication of their cases in this article. Comparative analysis was made of our clinical, laboratory, and demographic data to adult cases of SIgMID previously reported in the literature. We were able to identify 155 reported cases of adult SIgMID and 157 cases of age unspecified.

The group mean with 1 SD was calculated for serum IgM, IgA, IgG, and IgE levels and age of presentation for previously reported adult cases and our cohort. The mean follow-up period with 1 SD for our adult cohort was calculated. Descriptive statistics were used to denote frequencies of occurrence of presenting and comorbid conditions. Joint probability calculations and χ^2 analyses were performed, looking at certain disease associations with SIgMID. Statistical analyses were performed with a commercially available software package (JMP-IN statistical software package, SAS Institute Inc, Cary, NC) and Microsoft Excel (Microsoft Corporation, Redmond, WA).

RESULTS

Previously Reported Adult Cases

One hundred fifty-five previously reported cases of SIgMID involved adult patients, ranging in age from 18 to 87 years with a mean ± SD age at time of diagnosis of 45.6 ± 17.4 years (Table 2). The most common presenting conditions were respiratory infections, including upper respiratory tract infections (6%), bronchitis (3%), nonspecific bacterial respiratory infections (8%), pneumonia or lower respiratory tract infections (6%), and pulmonary tuberculosis (1%) (Table 2 and Table 3). Frequencies of other presenting illnesses included the following: autoimmune disease, 14%; asthma, 6%; skin disease, 6%; and gastrointestinal disease, 5% (Table 3). Associated comorbidities were observed with the following frequencies: asthma, 7%; autoimmune disease, 14%; nonrespiratory infections, 6%; and malignancies, 3% (Table 4). Six asymptomatic cases (4%) were reported.

The mean ± SD serum IgM level was 23.7 ± 14.9 mg/dL (Table 2). The mean serum IgA and IgG levels were normal in all cases. The mean ± SD serum IgE level was elevated at 559.9 ± 771.5 IU/mL. No patients died from fulminant infection, malignancy, or severe autoimmune disease. Six cases were associated with familial SIgMID. Poor IgM responses to antigen challenge were reported in 3 cases. One patient was reported to have an atypical infectious organism.

Previously Reported Unspecified Age

One hundred fifty-seven patients were identified without specific age indications[4,7,12,14,21,22,40,61,62] or exact IgM levels (Table

Table 2. Characteristics of Adults Previously Reported as Having SIgMID*

Age/sex	Presenting history	IgM, mg/dL	IgG, mg/dL	IgA, mg/dL	IgE, IU/mL, or AST results	Comment	Reference
4 Adults	Asymptomatic	<25	WNL	WNL		Family member with SIgMID	9
Adult/F	NA	NA	WNL	WNL			9
Adult/M	NA	NA	WNL	WNL			9
Adult/M	Asymptomatic	40	1,300	320		Relative with SIgMID	9
Adult/M	Asymptomatic	40	1,100	125		Relative with SIgMID	9
Adult/unknown	Asymptomatic	45	1,600	125		Relative with SIgMID	9
Adult/M	Asymptomatic	40	640	480		Relative with SIgMID	9
28 Adults/unknown	Untreated celiac disease	31.4	NA	NA	NA	IgM increased on gluten free diet in most patients to mean level of 73.6	21
39/F	Recurrent OM	33	1,236	896		Allergic rhinitis	47
23/M	Celiac disease	48	2,100	420	NA		22
75/M	Celiac disease	48	1,200	320	NA		22
Adult/M		30	800	146		Son with SIgMID	27
20/M	Asthma and bacterial infections	36	NA	NA	Positive AST results		34
23/M	Allergic rhinitis	41	NA	NA	Positive AST results		34
28/M	Asthma and bacterial infections	42	NA	NA	Positive AST results		34
30/F	Asthma, AD, and bacterial infections	41	NA	NA	Positive AST results		34
31/M	Asthma and bacterial infections	35	NA	NA	Negative AST results		34
33/M	AD and bacterial infections	24	NA	NA	Negative AST results		34
48/F	Asthma	41	NA	NA	Positive AST results		34
50/F	Asthma	43	NA	NA	Negative AST results		34
56/F	Asthma	41	NA	NA	Negative AST results		34
75/M	Asthma and bacterial infections	35	NA	NA	Negative AST results		34
18/F	Sclerosing cholangitis, recurrent bronchitis, asthma, AD, meningitis	<10	3,200	67		Low isohemagglutinin titers	60
22/M	CMV hepatitis	28–40	NA	NA	NA		35
20/M	Psittacosis	33–50	NA	NA	NA		35
56/F	NA	1	580	57			3
20 F patients >17 y	NA	<23	WNL	WNL	NA		3
23 M patients >16 y	NA	<23	WNL	WNL	NA		3
65/M	Ulcerative colitis	5	997	249		Diabetes mellitus, no isohemagglutinin, pulmonary TB	10
72/M	Ischemic heart disease, diarrhea	15	703	403			10
60/M	TB pneumonia	4	983	551			10

Table 2. (Continued)

Age/sex	Presenting history	IgM, mg/dL	IgG, mg/dL	IgA, mg/dL	IgE, IU/mL, or AST results	Comment	Reference
52/M	Subcutaneous staphylococcus abscesses	17	1,100	265	50	No IgM response to *Salmonella* O antigen, no IgM hemagglutinins antibody response to meningococcal group C polysaccharide	29
41/M	Subcutaneous staphylococcus abscesses	0	1,900	480	2,000	No IgM hemagglutinins antibody response to meningococcal group C polysaccharide	29
48/M	Pneumonia	21	790	228	NA	*Achromobacter xylosoxidans* pneumonia and sepsis rheumatic heart disease	36
85/M	Hypertension	17	1,165	289			66
21/M	Smallpox	20	2,210	188		Death from infection	32
65/M	Visual disturbance	1	843	217		Diffuse atherosclerosis	67
58/F	Cellulitis	10	2,540	150		Clear cell sarcoma, IDDM, hypertension, pneumonia, death	44
47/M	Prolymphocytic leukemia	40	1,520	437	<25		46
66/M	Stomach leiomyoma	8	850	253			45
58/M	UTI, pulmonary TB	20	972	93	208		33
73/F	UTI, lower RTI	14	1,248	206	30		33
71/F	UTI, pneumonia	11	1,726	412	130		33
53/F	UTI, RA	17	2,159	612	244		33
29/F	UTI, lower RTI, SLE	25	1,597	203	840		33
30/M	UTI, SLE	6	936	221	175		33
48/M	Pneumonia	10	1,641	243	154		33
44/F	SLE-like	26	2,504	410			42
62/F	Asthma	23	1,091	182			42
60/F	Lymphoma	8	1,707	326			42
51/F	SLE	10	2,340	312			42
43/F	SLE	5	1,426	389			41
37/F	SLE	15	1,506	508			41
33/F	SLE	17	1,532	340			41
47/F	SLE	23	1,567	298			41
41/F	SLE	25	1,900	522			41
42/F	SLE	28	1,316	280			41
36/M	SLE	30	1,267	443			41
59/F	SLE	32	2,546	352			41
30/F	SLE	37	1,109	240			41
63/F	SLE	43	1,319	300			41
36/F	SLE	44	1,226	443			41
55/F	SLE	44	1,441	221			41
60/F	NA	18	WNL	WNL		No IgM response to pneumococcal vaccine	50
29	Bronchitis, sinusitis	4	726	174	115	Allergic rhinitis	68/25
52	Bronchitis, sinusitis	4	885	352	368	Asthma	68/25
21/M	Bloom syndrome	28	1,166	233			18
19/F	Bloom syndrome	48	1,036	212			18
50/M	Cholangitis, liver abscess, dermatitis	18	1,534	283	2,000		49

Table 2. (Continued)

Age/sex	Presenting history	IgM, mg/dL	IgG, mg/dL	IgA, mg/dL	IgE, IU/mL, or AST results	Comment	Reference
57/M	Diabetes	6	1,413	288	59		49
22/M	Psoriasis, tonsillitis, bronchitis	1	1,314	168	59		49
57/M	Diabetes, polyarthritis	0.4	1,747	462	2,000		49
37/F	Asymptomatic	34	1,446	340	ND		49
70/M	Hashimoto thyroiditis	3	1,972	223		IgM normalized after thyroid replacement	23
21/F	Recurrent OM, URI	48	1,063	212	NA	Bloom syndrome	19
51/F	SLE, recurrent URI	<4.6	1,010	535	NA		39
23/M	Recurrent RTIs	28	WNL	WNL	NA	Allergic rhinitis, asthma, chronic sinusitis, nasal polyposis, fatigue	56
67/F	RA	29	WNL	WNL	NA		69
52/M	ARDS, pneumonia, postsplenectomy	26	WNL	WNL	NA		69
61/F	Recurrent sinusitis	26	WNL	WNL	NA		69
59/F	Sinusitis, pneumonias	29	WNL	WNL	NA		69
31/F	Recurrent sinusitis	39	WNL	WNL	NA		69
38/F	Autoimmune thyroiditis, vitiligo	31	WNL	WNL	NA		69
72/M	Recurrent UTIs	12	WNL	WNL	NA		69

Abbreviations: AD, atopic dermatitis; ARDS, acute respiratory distress syndrome; AST, allergy skin test; CMV, cytomegalovirus; IDDM, insulin-dependent diabetes mellitus; NA, not available; ND, not done; OM, otitis media; RA, rheumatoid arthritis; RTI, respiratory tract infection; SIgMID, selective IgM immunodeficiency; SLE, systemic lupus erythematosus; TB, tuberculosis; URI, upper respiratory tract infection; UTI, urinary tract infection; WNL, within normal limits.

* Mean ± SD values are as follows: IgM, 23.7 ± 14.7 mg/dL; IgG, 1,416.6 ± 544.7 mg/dL; IgA, 310.6 ± 151.2; and IgE, 559.9 ± 771.5 IU/mL.

Table 3. Prevalence of Presenting Conditions in Adult Patients With Selective IgM Immunodeficiency

Condition	Frequency of previously reported adult cases, % (n = 155)	Frequency of our adult cohort, % (n = 36)
Pneumonia or lower respiratory tract infection	6	3
Otitis media	1	3
Meningitis	0.6	0
Skin disease	6	0
Bronchitis	3	3
Asymptomatic	4	0
Autoimmune disease	14	0
Other infections*	2	0
Asthma	6	64
Nonspecific bacterial respiratory tract infection	8	0
Allergic rhinitis	0.6	58
Upper respiratory tract infections	6	61
Vasomotor rhinitis	0	19
Idiopathic angioedema	0	11
Idiopathic anaphylaxis	0	11
Polyps	0	8
Gastrointestinal disease	5	0

* Nonrespiratory, nonmeningitis, and nonskin infections (includes urinary tract infections).

5). In general, these reports were limited in their descriptive value. Recurrent infections occurred in 32% of cases, celiac disease in 17%, and systemic lupus erythematosus (SLE) in 13% (Tables 4 and 5). There were 19% asymptomatic cases.

Adult Cohort

Sex distribution and racial background. There were 13 men and 23 women evaluated in our cohort, with a 1.77 female-male preponderance. All were white. In general, the cause of

Table 4. Frequencies of Comorbid Diseases in Patients With Selective IgM Immunodeficiency

Disease state	Previously reported adults cases, % (n = 155)	Previously reported unspecified age, % (n = 157)	Our adult cohort, % (n = 36)
Allergic rhinitis	2	0	58
Angioedema	0	0	11
Asthma	7	0	64
Autoimmune disease	14	13	3
Gastrointestinal disease	5	17	42
Malignancy	3	0	0
Meningitis	0.6	0	0
Nasal polyps	0.6	0	19
Other infections*	2	0	0
Respiratory infections†	25	32	64
Skin disease	6	0	0
Thyroid disease	1	0	19
Vasomotor rhinitis	0	0	19
Asymptomatic	4	19	0

* Nonrespiratory, nonmeningitis, and nonskin or nonspecified infections.

† Includes otitis media, sinusitis, bronchitis, pharyngitis, and pneumonia.

illness, complications, and associated clinical findings to be discussed occurred without sex preponderance.

Age at time of diagnosis. The mean ± SD age at the time of diagnosis of SIgMID was 55 ± 13.5 years (Table 6). The time of onset of SIgMID could not be determined or estimated accurately. It is likely that a long interval existed between onset of symptoms (recurrent infections) and time of diagnosis. The earliest age of diagnosis for our adult group (defined as ≥18 years) was 18 years, and the oldest patient at time of diagnosis was 87 years.

Observation period. The mean ± SD observation period for our patients was 44.6 ± 52.5 months, with a total of 1,584 patient-months observed. The duration of observation was determined from date of diagnosis to last follow-up observation point or death.

Immunoglobulin levels. Thirty-six patients in our adult patient population of 13,700 (incidence, 0.26%) were identified with reduced IgM levels less than 2 SDs of healthy controls with normal serum IgG and IgA levels. Asymptomatic patients may have been missed, since only symptomatic patients with recurrent infections or unusual infections were screened for immunodeficiency. Of these 36 patients, none had undetectable IgM levels. The mean ± SD serum IgM level was 30 ± 8.7 mg/dL. The range in serum IgM levels was 12 to 46 mg/dL (Table 6, Fig 1). The mean ± SD serum IgA level was 186 ± 100 mg/dL, and the mean ± SD serum IgG level was 937 ± 265 mg/dL (Table 6). IgG subclasses were evaluated in 31 patients. Most patients had normal IgG subclasses with 9 exceptions (Table 6). Four patients had reduced IgG_3 subclass, 1 patient had reduced IgG_1 subclass, 3 patients had reduced IgG_1 and IgG_3 subclasses, and 1 patient had reduced IgG_1, IgG_2, and IgG_3 subclasses.

The mean ± SD serum IgE level was 70.03 ± 25 IU/mL (n = 32) and was within normal levels (<200 IU/mL) (Table 6). Within the same database of 13,700 patients were 3 patients with CVID (incidence, 0.02%), 6 patients with SIgAID (incidence, 0.04%), 54 patients with idiopathic angioedema (0.39%), and 58 patients with idiopathic anaphylaxis (0.42%).

Serologic evaluation. Because of previous reports of autoimmune disease, thyroiditis, and celiac disease in patients with SIgMID, patients were screened for ANA, antiendomysial antibody, antigliadin antibody, antitransglutaminase antibody, and thyroid autoantibodies. A few patients had abnormal serologic findings, including 4 (12.5%) of 32 with positive low titer ANA, 3 (10%) of 31 with positive antitransglutaminase antibody, 1 (3%) of 32 with positive antiendomysial and/or antigliadin antibody, and 2 (10%) of 20 with thyroid autoantibodies.

Functional antibodies. Thirty-three patients had ABO blood group testing with isohemagglutinin assays performed. Excluding the 1 patient with AB blood type, all tested patients had detectable low titer corresponding isohemagglutinin titers with rare exceptions. The range in anti-A isohemagglutinin titer was 1:4 to 1:256, with a mean ± SD of 1:50 ± 92 (healthy control, ≥1:64). The range in anti-B isohemagglutinin titer was 1:2 to 1:64, with a mean ± SD of 1:12 ± 13 (healthy control, ≥1:64).

Clinical Manifestations

Infections. Most patients presented with a history of recurrent infections, especially involving the respiratory tract (64%) (Table 3). The frequency and severity of infections were variable, and no patients had a severe life-threatening infection in either childhood or adulthood. Since the mean ± SD age of our cohort was 55 ± 13.5 years, most patients had a history of recurrent infections beginning as an adult. Respiratory infections had the following distribution: relapsing acute or chronic rhinosinusitis, 53%; recurrent pneumonia, 17%; and recurrent otitis media, 11% (Table 4). There were 5 cases of bronchiectasis (14%). There were no cases of unusual bacterial, viral, fungal, or parasitic infections and no cases of meningitis, bacteremia, or abscess disease before or during the observation period.

Gastrointestinal abnormalities. Gastrointestinal diseases were commonly reported (42%) by our patients. Most patients had gastrointestinal reflux disease. There were 2 cases presenting with biopsy-proven celiac disease. IgM levels did not increase after gluten avoidance in these cases. One case of ulcerative colitis was observed. No cases of malabsorption, steatorrhea, or giardiasis were observed.

Autoimmune disease. There were no cases of rheumatoid arthritis or SLE noted in our cohort. One patient had ankylosing spondylitis. Low titer ANA of unclear clinical significance was seen in 12.5% of patients. During the follow-up

Table 5. Characteristics of Previously Reported Cases of Selective IgM Immunodeficiency in Patients of Unspecified Age (Serum IgM Level, <2 SDs)

Source	No. of cases	IgM level, mg/dL	Presenting symptoms
Gilbert and Hong[7]	2 cases (men)	<60 (<2 SDs)	
Hobbs et al[21]	27	<2 SDs	17 asymptomatic, 9 with recurrent infections
Asquith et al[61]	10	<47 (<2 SDs)	Celiac disease
Blecher et al[22]	9	<50 (<2 SDs)	Celiac disease
Brown et al[62]	8	<50 (<2 SDs)	Celiac disease
Kelly et al[12]	2	<2 SDs	Meningitis
Kelly et al[12]	7	<2 SDs	NA
Hobbs[4]	70	<2 SDs	Asymptomatic (19%), recurrent infections (59%)
Senaldi et al[40]	20 (adults)	<2 SDs	SLE
Palma-Carlos et al[14]	2	<2 SDs	NA

Abbreviations: NA, not available; SLE, systemic lupus erythematosus.

period, these patients did not develop clinically significant autoimmune disease.

Thyroid disease. Seven patients had thyroid disease (6 with hypothyroidism and 1 with euthyroid benign nodule). Two of 19 patients with autoimmune thyroiditis (positive thyroid autoantibodies) developed hypothyroidism.

Other respiratory conditions. Upper respiratory tract allergies confirmed by skin testing were present in 61% of patients, although only 1 of these patients had an elevated IgE level (Table 6). The group mean ± SD serum IgE level was 70 ± 85 IU/mL. Other noninfectious respiratory conditions seen included asthma (64%), nasal polyps (19%), vasomotor rhinitis (14%), 1 case of idiopathic interstitial pneumonitis, and 1 case of allergic fungal sinusitis.

Miscellaneous abnormalities. Idiopathic angioedema was diagnosed in 5 patients (14%), and idiopathic anaphylaxis was noted in 4 patients (11%). One patient had both conditions. During the follow-up period of observation after the diagnosis of SIgMID, no patients developed CVID. There was 1 malignancy diagnosed (a plasmacytoma in a 62-year-old man). There were single cases of patients with benign monoclonal gammopathy and Guillain-Barré syndrome.

Mortality

No patients died of serious infections in our series. Two patients died during the observation period: one 20 years after the diagnosis of SIgMID and the other 2 years after the diagnosis of SIgMID. Autopsies were not performed, and the causes of death appeared to be cardiovascular in the first patient and intraoperative cardiopulmonary arrest during a biopsy procedure on a plasmacytoma in the second patient.

Family History of Patients

There were no family histories of infantile death, increased susceptibility to infections, or primary immunodeficiencies among immediate relatives. Screening for immunodeficiencies in parents and siblings was routinely recommended, but compliance was inconsistent. Where tested, no parent, sibling, or offspring was identified with an immunoglobulin deficiency.

Therapy

Patients were not treated with intravenous gammaglobulin (IVIG) therapy for SIgMID. One patient with SIgMID was treated with IVIG (2 g/kg every month) because of refractory asthma, with notable improvement in asthma along with reduced oral steroid use and less relapsing acute sinusitis and acute bronchitis. In general, infections were successfully treated with conventional courses of antibiotics in most patients. Five patients with medically refractory sinusitis eventually required endoscopic sinus surgery.

DISCUSSION

Dysregulation of IgM leading to elevated or reduced serum levels has been reported in a number of conditions (Table 7). Abnormalities in serum IgM associated with secondary conditions such as SLE and certain neoplasms may be correlated with prognostic significance in disease progression or regression.[1] Isolated reduced IgM levels secondary to other primary illnesses as noted in Table 7 should be excluded before making a diagnosis of primary SIgMID.

Primary SIgMID is less common than secondary SIgMID because of other disease states. In a hospitalized population, secondary SIgMID was 20 times more prevalent than primary SIgMID (2.0% vs 0.1%).[4] SIgMID has been characterized as a rare primary immunodeficiency differentiated by a low serum IgM level, less than 2 SDs below healthy pediatric or adult controls or absolute levels of less than 20 mg/dL in infants and children. The earliest recognized cases were described in children in 1966.[28,48] Additional pediatric cases and the first adult cases were described in the late 1960s and were classified as dysgammaglobulinemia V.[8,9,27,47] During the subsequent 40 years, small series and isolated case reports have appeared, which have better characterized this illness.

Heterogeneous lymphocyte abnormalities have been reported in patients with SIgMID. It is speculated that SIgMID may result from a functional defect of B cells in the differentiation steps before IgM secretion. No abnormality has yet been discovered in the number of surface IgM molecules on

Table 6. Immunologic and Demographic Data of 36 Adult Patients With Selective IgM Immunodeficiency*

Case No./ sex/age at diagnosis, y	IgM, mg/dL (reference range, 50–271 mg/dL)	IgG, mg/dL (reference range, 694–1,618 mg/ dL)	IgA, mg/dL (reference range, 81–463 mg/dL)	IgE, IU/mL (reference range, <200 mg/dL)	AST result	IgG subclasses	Follow-up interval, mo
1/M/55	18	1,034	244	29	+	WNL	24
2/F/61	31	1,010	207	24	+	WNL	72
3/F/54	23	1,081	443	94	+	WNL	48
4/F/77	39	869	201	168	−	WNL	24
5/F/43	42	1,100	195	248	+	WNL	24
6/F/80	20	778	143	69	−	↓ IgG_1/ ↓ IgG_3	48
7/M/62	35	718	128	162	−	WNL	36
8/F/48	<20	1,145	268	29	+	WNL	60
9/M/44	21	1,590	172	50	+	NA	108
10/M/57	31	1,226	274	222	−	WNL	60
11/M/73	25	890	190	7	−	↓ IgG_3	60
12/F/60	30	883	210	171	+	↓ IgG_3	24
13/F/59	36	1,194	146	23	+	WNL	60
14/M/41	32	920	105	9	−	WNL	24
15/F/50	28	841	207	15	+	↓ IgG_3	24
16/M/37	25	580	197	11	+	WNL	182
17/M/32	37	554	172	17	−	WNL	24
18/M/52	38	1,193	323	153	+	WNL	36
19/F/43	27	772	128	63	+	↓ IgG_1	24
20/F/45	16	653	83	16	+	↓ IgG_1/ ↓ IgG_3	12
21/F/65	15	521	141	5	+	WNL	24
22/F/44	25	1,149	92	30	NA	WNL	24
23/M/66	31	1,040	205	NA	−	NA	240
24/F/49	36	1,355	150	16	+	WNL	72
25/F/53	33	707	144	5	+	↓ IgG_3	24
26/F/50	39	927	147	150	+	WNL	36
27/F/43	32	1,469	277	340	+	WNL	12
28/F/87	34	518	71	21	−	↓ IgG_1/ ↓ IgG_2/ ↓ IgG_3	12
29/M/61	19	1,052	553	25	+	WNL	12
30/F/37	40	900	105	10	+	WNL	36
31/F/69	29	819	97	<2	−	NA	12
32/F/52	12	762	148	12	+	↓ IgG_1/ ↓ IgG_3	12
33/M/79	45	1,160	104	7	−	WNL	12
34/F/60	31	593	110	NA	+	NA	12
35/F/55	33	893	219	NA	+/−	WNL	12
36/M/40	46	789	118	108		NA	12

Abbreviations and symbols: AST, allergy skin test; downward arrow, decreased; minus sign, negative; NA, not available; plus sign, positive; WNL, within normal limits.

* Mean ± SD values are as follows: age of patients, 55 ± 13.5 years; IgM, 30 ± 8.7 mg/dL; IgG, 937 ± 365 mg/dL; IgA, 185 ± 100 mg/dL; IgE, 70 ± 85 IU/mL; and follow-up interval, 44.5 ± 52.51 months.

peripheral B cells.[6,24–26,33,39,42,49,50] Secreted IgM messenger RNA has been noted to be normally expressed,[39] and the sequence of the IgM heavy chain gene has not been found to have any mutations or deletions.[51] A regulatory isotype-specific T-cell helper defect has been suggested in some studies,[6,26] whereas other studies have noted an increase in suppressor activity for IgM-committed B-cell differentiation.[6,42] T-cell–independent B-cell dysfunction has been reported in some cases.[49] The ability to make some functional IgM antibody in patients with SIgMID has been reported. IgM response to bacteriophage immunization has been demonstrated; however, the response is less than normal.[25] Naturally occurring IgM isohemagglutinins to red blood cell antigens have also been demonstrated.[25] Stoelinga and others,[27,28,52] however, reported absence of functional IgM responses to *Salmonella* O and H antigen vaccination. Others have reported poor or no response to polysaccharide capsular antibody.[29,50] Cell-mediated immunity appears to be normal in IgM-deficient patients.[6]

SIgAID is considered the most common primary immunodeficiency and SIgMID the second most common.[4] Nevertheless, SIgMID is regarded as an uncommon disorder and often neglected in the discussion of primary immunodeficiencies.[53,54] A discussion of SIgMID is notably absent

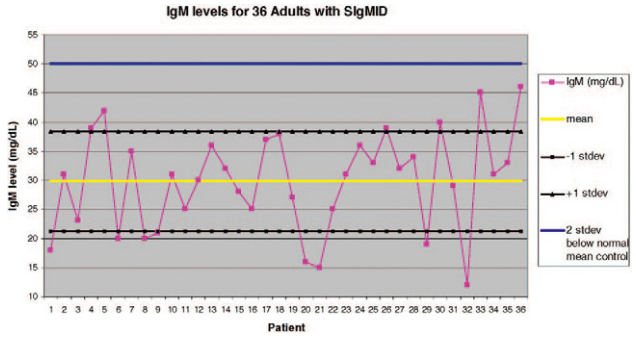

Figure 1. IgM levels for 36 adults with selective IgM immunodeficiency.

in recently published practice parameters on primary immunodeficiencies from an expert panel.[54] The prevalence of SIgMID has been reported to be less than that of SIgAID in an unselected white population of 3,213 individuals ages 4 to 87 years (Table 1).[3] In the atopic population, the prevalence of both SIgAID (4.5%) and SIgMID (ranging from 1.56% to 22%) may be higher than in the general population (Table 1).[4,34] According to our data, the prevalence (1:385) (0.26%) in an adult symptomatic population of patients going to an allergy and immunology practice may be much higher than previously reported by Palma-Carlos et al[14] as 1:15,000 (0.067%) (Table 1). The higher prevalence of SIgMID in our population may reflect a sicker adult population studied compared with the age unrestricted population prevalence reported by Palma-Carlos et al.[14] However, the prevalence of SIgAID (0.04%) or CVID (0.02%) in our population was notably lower than that reported by Palma-Carlos et al[14] (SIgAID, 0.43%; CVID, 0.37%). Asymptomatic patients with SIgMID were not identified in our retrospective analysis. Asymptomatic SIgMID patients have been described in up to 19% in some series.[4] Our reported prevalence rate may therefore be an underestimation. Extrapolation of a prevalence of SIgMID in the general population cannot be made from our analysis. It has been suggested that with a longer follow-up period many asymptomatic cases will transform into symptomatic cases.[4] These asymptomatic cases are typically found during the investigation of other diseases (autoimmune disease or cancer), in family members of patients with immunodeficiency, or by chance. All of our patients with SIgMID were identified as part of an evaluation due to a present illness, usually recurrent respiratory tract infections. The lack of susceptibility to infections during childhood and the negative family history of immunodeficiencies or infantile deaths in the families of our patients suggest SIgMID in our patients may have been acquired.

In most primary immunodeficiencies, including CVID and SIgAID, the gammaglobulin deficiency is not absolute and low levels of immunoglobulins are present. In our study, we had no patients with complete IgM deficiency, which may reflect the rarity of such an occurrence. In the patient population of 3,213 individuals studied by Cassidy and Nordby,[3] only 1 patient had undetectable serum IgM

Table 7. Secondary Causes Associated With Reduced or Elevated Serum IgM Levels

Causes
Elevated serum IgM levels
Hyper-IgM immunodeficiency[70]
IgM myeloma[71]
Waldenstrom macroglobulinemia[71,72]
Sarcoma[1]
Melanoma[1]
Metastatic cancer[73]
Brain tumors[1]
Splenomegaly[4]
Biliary cirrhosis[72]
Sarcoidosis[71]
Seropositive rheumatoid arthritis[71]
SLE[71]
Malaria[9]
Bartonellosis[9]
Rickettsial endocarditis[9]
Cold agglutinin syndromes (transient)[71]
Acute Epstein-Barr virus infection[28]
Trypanosomiasis[72]
Pneumocystis carinii infection[28]
Neonatal infections
Rubella[71]
Toxoplasmosis[71]
CMV[71]
Herpes simplex virus[71]
Reduced serum IgM levels
Recurrent infections[54]
Thymic hypoplasia[4]
Celiac disease[4]
Autoimmune disease[40]
Nephrotic syndrome[71]
Protein-losing enteropathies[71]
Immunosuppressive drugs[54]
Certain malignancies
Lymphoma[4]
Hepatoma[72]
Ovarian cancer[1,74]
IgG or IgA myelomas
Leukemia[46,71]
Metastatic cancers[73]
Acquired immunodeficiency syndrome[71]
Several primary immunodeficiencies[54]
Wiskott-Aldrich syndrome
Ataxia-telangiectasia
CVID
Bruton agammaglobulinemia
SIgMID
Combined IgG and IgM immunodeficiency
Transient hypogammaglobulinemia of infancy
Primary amyloidosis[75]
Lymphangiectasia[71]
Chronic intestinal pseudo-obstruction[71]
Transplantation[71]
Primary chylous disorders[71]
Mycosis fungoides[4]
Benign paraproteinemia[4]

Abbreviations: CMV, cytomegalovirus; CVID, common variable hypogammaglobulinemia; SIgMID, selective IgM immunodeficiency; SLE, systemic lupus erythematosus.

levels (incidence, 0.03%). The male-female ratio in our study was 0.56:1 in contrast to that previously reported, where the male-female predominance ranged from 1.25:1 to 4:1.[3,4]

As with CVID and SIgAID, recurrent sinopulmonary infections have been reported as the most common presentations of SIgMID. In previously reported adult cases, 25% of individuals had recurrent respiratory tract infections. In our cohort, 64% had recurrent sinopulmonary infections. In contrast to CVID and SIgAID, where therapy with antibiotics is continued for extended periods and prophylactic antibiotics are used extensively, our patients responded to conventional courses of antibiotics and were not routinely treated with prophylactic antibiotics. We found no case of atypical or low-grade organisms causing infection or the occurrence of life-threatening infections. Even those in our cohort with IgG subclass deficiency and SIgMID did not experience severe infections as has been reported with SIgAID with IgG subclass deficiencies.[55] In contrast to SIgAID and CVID, only 2 reports of gammaglobulin treatment for SIgMID have been reported.[27,56] One patient in our SIgMID cohort received IVIG for asthma with improvement noted in asthma control and a reduction in respiratory tract infections. Intravenous immunoglobulin replacement may not be appropriate for most patients with SIgMID, particularly considering that gammaglobulin replacement has only trace amounts of IgM content.[57] However, for those SIgMID patients with life-threatening infections (particularly sepsis), IVIG may have a role. Failure of compensatory IgG responses in these patients may be helped by replacement gammaglobulin therapy.

Autoimmune phenomena are seen in association with several immunoglobulin deficiency syndromes.[13,23] Several investigators have noted selective IgM deficiency in SLE[38–41,58] and have correlated lower IgM levels with greater disease duration[38–41,58] and/or greater disease severity.[40]

SIgMID has been less commonly associated with other autoimmune diseases such as rheumatoid arthritis[59] and Hashimoto thyroiditis.[23] Autoantibodies against IgM, when performed and reported in SIgMID, have not been seen.[39] In our adult cases, autoimmune disease was distinctly uncommon (3%) compared with previously reported adult cases (14%).

Dysgammaglobulinemia has been reported with several gastrointestinal conditions.[10,21,60] In particular, celiac disease has been reported in association with several primary immunodeficiencies, including isolated severe IgA deficiency,[37,61] reduced IgA levels (20 to <60 mg/100 mL),[21,22,62] panhypogammaglobulinemia,[61] and isolated combined IgA and IgM deficiency.[62] SIgMID has been more frequently reported in celiac disease, including 30 (37%) of 75 adult cases, 5 (100%) of 5 childhood cases,[21] 11 (37%) of 30 untreated adult patients,[22] 8 of 11 untreated adult patients,[62] 6 of 11 untreated adults, and 2 of 7 treated adult patients.[62] Jejunal biopsy specimens of affected patients were no different from those of celiac patients with normal immunoglobulin levels. Of note, IgM levels returned to normal in most patients after a gluten-restricted diet,[62] and IgM levels decreased to below normal when diet restrictions were removed. It has been suggested that this form of IgM immunodeficiency is related to reduced synthesis secondary to lymphoreticular dysfunction stimulated by gluten antigen exposure.[22,62] The 2 cases of celiac disease in our cohort did not experience significant changes in serum IgM level on gluten restriction.

The prevalence of upper respiratory tract allergies and/or asthma was high in our adult study population (58% and 64%, respectively). An increased incidence of atopic diseases has been recognized in patients with CVID and SIgAID.[5,54] In previously reported cases of SIgMID adults, the incidence of atopic diseases was less common.[30] It is essential that patients with SIgMID and allergies undergo aggressive treatment to reduce allergic inflammation. Such treatment will reduce the risk of recurrent bacterial infection, especially in the ears, sinuses, and chest.[63]

Idiopathic anaphylaxis and idiopathic angioedema were seen in association with SIgMID in 11% and 14% of cases, respectively. Given the low prevalence of both idiopathic anaphylaxis (1:779)[64] and idiopathic angioedema without urticaria (1:10,000)[65] in the general population, the probability of these diseases independently occurring simultaneously with SIgMID because of chance alone is extremely low (0.00215% and 0.000168%, respectively). In contrast, in our study population, the incidence of SIgMID and idiopathic anaphylaxis was 0.029% (4/13,700), approximately 14 times higher than would be predicted by the joint probability calculation. Similarly, in our study population, we found the incidence of SIgMID and idiopathic angioedema to be 0.0365% (5/13,700) or 217 times higher than predicted by the joint probability calculation. The χ^2 tests of independence bear this out as well. The χ^2 tests of SIgMID with idiopathic anaphylaxis and SIgMID with idiopathic angioedema strongly reject the null hypothesis that idiopathic anaphylaxis or idiopathic angioedema are unrelated to SIgMID ($P < .001$). The data suggest that there is a positive correlation between the simultaneous occurrence of SIgMID with idiopathic anaphylaxis and SIgMID with idiopathic angioedema. The observation linking idiopathic anaphylaxis and idiopathic angioedema independently with SIgMID is a new finding. It is unclear how these diseases may be pathologically connected.

The increased risk of malignancy in primary immunodeficiencies is well recognized but poorly understood.[54] Both CVID and SIgAID are associated with a higher risk of gastrointestinal and lymphoid malignancies.[5,54] Malignancies have only been reported in 4 cases of previously reported adult cases. There was only 1 patient in our cohort who developed a malignancy—an isolated plasmacytoma. Studies with larger sample sizes are required to determine whether adult patients with SIgMID are really at risk of a

malignancy. The current data suggest that this is not the case.

CONCLUSION

The literature recognizes SIgMID as a rare immunodeficiency, usually associated with life-threatening or debilitating illnesses.[6] This report provides a more comprehensive description of SIgMID in adults than was previously reported. Based on our adult cohort of SIgMID, this primary immunodeficiency may be more frequent than previously thought. The incidence in our symptomatic adult population was 1:385. This frequency may be an underestimation, since asymptomatic cases were not identified. No distinct sex differences were noted, and there were no familial cases of humoral immunodeficiency observed. In our population of adult patients, recurrent infections, predominantly respiratory, were common but not severe or life threatening. Opportunistic infections were not seen. Recurrent rhinosinusitis was the most common infection followed by bronchiectasis, pneumonia, and recurrent otitis media. Antimicrobial treatment was frequent but not prolonged, and prophylactic antibodies were not required. Only 1 patient received IVIG treatment, primarily for refractory asthma and not SIgMID. The noted coexistence of uncommon diseases such as nasal polyposis (19%), bronchiectasis (14%), idiopathic angioedema (14%), and idiopathic anaphylaxis (11%) should lead physicians to consider SIgMID in the differential diagnosis of these latter diseases in addition to patients with recurrent infections. No patients in our cohort developed a lymphoproliferative disorder or gastrointestinal cancer, and transformation to panhypogammaglobinemia was not observed. SIgMID in adults may be an underdiagnosed primary immunodeficiency with less severe infectious, autoimmune, and malignant complications than that observed previously. Larger collaborative studies and/or a national registry will be needed to better define the molecular genetics, clinical, demographic, and immunologic features of this disorder.

ACKNOWLEDGMENTS

We acknowledge Sandy Dallabrida for her expertise in the manuscript preparation and Michelle Daly for her assistance in data collection.

REFERENCES

1. Lee YT. Quantitative change of serum protein and immunoglobulin in patients with solid cancers. *J Surg Oncol*. 1977;9: 179–187.
2. Buckley CE, Dorsey FC. Serum immunoglobulin levels throughout the life-span of healthy man. *Ann Intern Med*. 1971; 75:673–682.
3. Cassidy JT, Nordby GL. Human serum immunoglobulin concentrations: prevalence of immunoglobulin deficiencies. *J Allergy Clin Immunol*. 1975;55:35–48.
4. Hobbs JR. IgM deficiency. *Birth Defects*. 1975;11:112–116.
5. Strober W, Sneller MC. IgA deficiency. *Ann Allergy*. 1991;66: 363–375.
6. Levitt D, Cooper MD. IgM production: normal development and selective deficiency. In: Seligmann M, Hitzig WH. *Primary Immunodeficiencies.* Vol 3. Amsterdam, the Netherlands: Elsevier/North-Holland Press; 1980.
7. Gilbert C, Hong R. Qualitative and quantitative immunoglobulin deficiency. *Am J Med*. 1964;37:602–609.
8. Haddad ZH, Allen RF, Towner JW, Wilson MG. IgA, IgM, and partial deletion of chromosome 18. *Lancet*. 1969;2:678.
9. Hobbs JR, Milner RDG, Watt PJ. Gamma-M deficiency predisposing to meningococcal septicaemia. *BMJ*. 1967;4:583–586.
10. Ross IN, Thompson RA. Severe selective IgM deficiency. *J Clin Pathol*. 1976;29:773–777.
11. Chandra RK, Kaveramma B, Soothill JF. Generalised non-progressive vaccinia associated with IgM deficiency. *Lancet*. 1969;2:687–689.
12. Kelly S, Storm E, Juckett D. Immunoglobulin M in meningococcemia. *N Y State J Med*. 1970;70:1298–1299.
13. Hobbs JR. Immune Imbalance In dysgammaglobulinaemia type IV. *Lancet*. 1968;1:110–115.
14. Palma-Carlos AG, Silva SL, Palma-Carlos ML. Incidence of primary immunodeficiencies in allergy and clinical immunology [abstract]. *Ann Allergy Asthma Immunol.* 2005;94:P123.
15. Østergaard PA. A girl with recurrent infections, low IgM and an abnormal chromosome number 1. *Acta Paediat Scand*. 1973; 62:211–215.
16. Al-Herz W, McGeady SJ, Gripp KW. 22q11.2 Deletion syndrome and selective IgM deficiency: an association of a common chromosomal abnormality with a rare immunodeficiency. *Am J Med Genet*. 2004;127A:99–100.
17. Conley ME, Wang WC, Parolini O, Shapiro DN, Campana D, Siminovitch KA. Atypical Wiskott-Aldrich syndrome in a girl. *Blood*. 1992;80:1264–1269.
18. Kondo N, Ozawa T, Kato Y, et al. Reduced secreted μ mRNA synthesis in selective IgM deficiency of Bloom's syndrome. *Clin Exp Immunol*. 1992;88:35–40.
19. Ozawa T, Kondo N, Motoyoshi F, Kasahara K, Orii T. DNA mutation induced in the sequence upstream of the secreted MYU C-terminal coding sequence by ultraviolet irradiation in the cell line of Bloom's syndrome. *Eur J Immunogenet*. 1995; 22:163–169.
20. Rawal M, Sher TH, Hostoffer RW. Russel-Silver syndrome and selective IgM deficiency [abstract]. *J Allergy Clin Immunol.* 2005;115;S153.
21. Hobbs JR, Hepner GW. Deficiency of γM-globulin in celiac disease. *Lancet*. 1968;1:217–220.
22. Blecher TE, Brzechwa-Ajdukiewicz A, McCarthy CF, Read AE. Serum immunoglobulins and lymphocyte transformation studies in celiac disease. *Gut*. 1969;10:57–62.
23. Kimura S, Tanigawa M, Nakahashi Y, et al. Selective IgM deficiency in a patient with Hashimoto's disease. *Intern Med*. 1993;32:302–307.
24. Mayumi M, Yamaoka K, Tsutsui T, et al. Selective immunoglobulin M deficiency associated with disseminated molluscum contagiosum. *Eur J Pediatr*. 1986;145:99–103.
25. Guill MF, Brown DA, Ochs HD, Pyun KH, Moffitt JE. IgM deficiency: clinical spectrum and immunologic assessment. *Ann Allergy*. 1989;62:547–552.
26. De La Concha EG, Garcia-Rodriguez MC, Zabay JM, et al. Functional assessment of T and B lymphocytes in patients with selective IgM deficiency. *Clin Exp Immunol*. 1982;49:670–676.
27. Stoelinga GBA, van Munster PJJ, Slooff JP. Antibody deficiency syndrome and autoimmune haemolytic anaemia in a boy

with isolated IgM deficiency dysimmunoglobulinaemia type 5. *Acta Paediatr Scand*. 1969;58:352–362.
28. Kouvalainen K, Backman A, Rehtijärvi K. Chronic moniliasis, pyodermia and impaired capacity to form gamma-M antibodies. *Ann Paediatr Fenn*. 1966;12:256–262.
29. Yocum MW, Strong DM, Chusid MJ, Lakin JD. Selective immunoglobulin M (IgM) deficiency in two immunodeficient adults with recurrent staphylococcal pyoderma. *Am J Med*. 1976;60:486–494.
30. Jones DM, Tobin BM, Butterworth A. Three cases of meningococcal infection in a family, associated with a deficient immune response. *Arch Dis Child*. 1973;48:742–743.
31. Faulk WP, Kiyasu WS, Cooper MD, Fudenberg HH. Deficiency of IgM. *Pediatrics*. 1971;47:399–404.
32. Brilliant LB, Nakano JH, Kitamura T, Hodakevic LN, Bharucha PB. Occupationally-acquired smallpox in an IgM-deficient health worker. *Bull World Health Organ.* 1981;59:99–106.
33. Inoue T, Okumura Y, Shirahama M, Ishibashi H, Kashiwagi S, Okubo H. Selective partial IgM deficiency: functional assessment of T and B lymphocytes *in vitro*. *J Clin Immunol*. 1986; 6:130–135.
34. Kaufman HS, Hobbs JR. Immunoglobulin deficiencies in an atopic population. *Lancet*. 1970;3:1061–1063.
35. Silver HKB, Shuster J, Gold P, Freedman SO. Leukopenia, leukoagglutinins, and low IgM in a family with severe febrile illnesses. *Clin Immunol Immunopath*. 1973;1:220–230.
36. Dworzack DL, Murray CM, Hodges GR, Barnes WG. Community-acquired bacteremic *Achromobacter xylosoxidans* type III pneumonia in a patient with idiopathic IgM deficiency. *Am J Clin Pathol*. 1978;70:712–717.
37. Crabbé PA, Heremans JF. Selective IgA deficiency with steatorrhea: a new syndrome. *Am J Med*. 1967;42:319–326.
38. Raziuddin S, Danial BH. $OKT4^{+}$ T cell deficiency and an association of immunoglobulin deficiency in systemic lupus erythematosus. *Clin Exp Immunol*. 1988;72:446–449.
39. Takeuchi T, Nakagawa T, Maeda Y, et al. Functional defect of B lymphocytes in a patient with selective IgM deficiency associated with systemic lupus erythematosus. *Autoimmunity*. 2001; 34:115–122.
40. Senaldi G, Ireland R, Bellingham AJ, Vergani D, Veerapan K, Wang F. IgM reduction in systemic lupus erythematosus. *Arthritis Rheum*. 1995;38:1713.
41. Saiki O, Saeki Y, Tanaka T, et al. Development of selective IgM deficiency in systemic lupus erythematosus patients with disease of long duration. *Arthritis Rheum*. 1987;30:1289–1292.
42. Ohno T, Inaba M, Kuribayashi K, Masuda T, Kanoh T, Uchino H. Selective IgM deficiency in adults: phenotypically and functionally altered profiles of peripheral blood lymphocytes. *Clin Exp Immunol*. 1987;68:630–637.
43. Hermans PE, Diaz-Buxo JA, Stobo JD. Idiopathic late-onset immunoglobulin deficiency: clinical observations in 50 patients. *Am J Med*. 1976;61:221–237.
44. Vogelzang NJ, Corwin H, Finlay JL, et al. Clear cell sarcoma and selective IgM deficiency: a case report. *Cancer*. 1982;49: 234–238.
45. Matsushita S, Inoue T, Okubo H. A case of selective IgM deficiency: isotype-specific suppressor T lymphocytes. *Jpn J Med*. 1984;23:149–151.
46. Takenaka T, Nakamine H, Nishihara T, Tsuda T, Tsujimoto M, Maeda J. Prolymphocytic leukemia with IgM hypogammaglobulinemia. *Am J Clin Pathol*. 1983;80:237–242.
47. Buckley RH, Sidbury JB Jr. Hereditary alterations in the immune response: coexistence of 'agammaglobulinemia', acquired hypogammaglobulinemia and selective immunoglobulin deficiency in a sibship. *Pediatr Res*. 1968;2:72–84.
48. Schaller J, Davis SD, Ching Y, Lagunoff D, Williams CPS, Wedgwood RJ. Hypergammaglobulinæmia, antibody deficiency, autoimmune haemolytic anæmia, and nephritis in an infant with a familial lymphopenic immune defect. *Lancet*. 1966;2:825–829.
49. Yamasaki T. Selective IgM deficiency: functional assessment of peripheral blood lymphocytes *in vitro. Intern Med*. 1992;31: 866–870.
50. Andrew SL, Huston DP. Isolated IgM anti-polysaccharide deficiency [abstract]. *J Allergy Clin Immunol*. 1988;81:290.
51. Boes M, Schmidt T, Linkemann K, Beaudette BC, Marshak-Rothstein A, Chen J. Accelerated development of IgG autoantibodies and autoimmune disease in the absence of secreted IgM. *Proc Natl Acad Sci U S A*. 2000;97:1184–1189.
52. Thong YH, Maxwell GM. Primary selective deficiency of immunoglobulin M. *Aust N Z J Med*. 1978;8:436–438.
53. Bonilla FA, Geha RS. Update on primary immunodeficiency diseases. *J Allergy Clin Immunol*. 2006;117:S435–S441.
54. Bonilla FA, Bernstein L, Khan DA, et al, eds. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94(5 Suppl 1): S20–S30.
55. Hammarström L, Vorechovsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). *Clin Exp Immunol*. 2000;120:225–231.
56. Fallon KE. Inability to train, recurrent infection, and selective IgM deficiency. *Clin J Sport Med*. 2004;14:357–359.
57. Siegel J. Immune globulins: therapeutic, pharmaceutical, & cost considerations. *Pharm Prac News Special Edition.* 2005:15–19.
58. Sivri A, Hascelik Z. IgM deficiency in systemic lupus erythematosus patients. *Arthritis Rheum*. 1995;38:1713.
59. Bandilla KK, Pitts NC, McDuffie FC. Immunoglobulin M deficiency in the immune response of patients with rheumatoid arthritis. *Arthritis Rheum*. 1970;13:214–221.
60. Record CO, Shilkin KB, Eddleston ALWF, Williams R. Intrahepatic sclerosing cholangitis associated with a familial immunodeficiency syndrome. *Lancet*. 1973;6:18–20.
61. Asquith P, Thompson RA, Cooke WT. Serum-immunoglobulins in adult celiac disease. *Lancet*. 1969;2:129–131.
62. Brown DL, Cooper AG, Hepner GW. IgM Metabolism in celiac disease. *Lancet*. 1969;2:858–861.
63. Mucha SM, Baroody FM. Relationships between atopy and bacterial infections. *Curr Allergy Asthma Rep*. 2003;3:232–237.
64. Patterson R, Hogan MB, Yarnold PR, Harris KE. Idiopathic anaphylaxis: an attempt to estimate the incidence in the United States. *Arch Intern Med*. 1995;155:869–871.
65. Fox RW. Chronic urticaria and/or angioedema. *Clin Rev Allergy Immunol*. 2002;23:143–145.
66. Endoh M, Kaneshige H, Tomino Y, Nomoto Y, Sakai H, Arimori S. Selective IgM deficiency: a case study. *Tokai J Exp Clin Med*. 1981;6:327–331.
67. Karsh J, Watts CS, Osterland CK. Selective immunoglobulin M deficiency in an adult: assessment of immunoglobulin production by peripheral blood lymphocytes *in vitro. Clin Immunol Immunopathol*. 1982;25:386–394.
68. Moffitt JE, Guill MF, Wray BB, Brown DA, Peacocke NW, Ades EW. Effect of interleukin-2 and mitogen on *in vitro*

immunoglobulin production by peripheral blood lymphocytes from patients with selective IgM deficiency. *Ann Allergy*. 1988; 61:424–427.
69. Kohli-Pamnani A, Kantor F. Clinical features of selective IgM deficiency [abstract]. *Ann Allergy Asthma Immunol*. 2006;96: 137.
70. Winkelstein JA, Marino MC, Ochs H, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine*. 2003;82:373–384.
71. Pagana KD, Pagana T. *Mosby's Diagnostic & Laboratory Test.* 6th ed. 2003:529–532.
72. McKelvey EM, Fahey JL. Immunoglobulin changes in disease: quantitation on the basis of heavy polypeptide chains, IgG (γG), IgA (γA), and IgM (γM), and of light polypeptide chains, type K (I) and Type L (II). *J Clin Invest*. 1965;44:1778–1787.
73. Dostálová O, Wagnerová V, Schön E, Wagner V, Jelínek J. Serum immunoglobulin levels in cancer patients, III: immunoglobulin levels and metastases of malignant tumors. *Neoplasma*. 1977;24:177–191.
74. Hughes NR. Serum concentrations of G, A, and M immunoglobulins in patients with carcinoma, melanoma, and sarcoma. *J Natl Cancer Inst*. 1971;46:1015–1028.
75. Weiler CR, Bankers-Fulbright JL. Common variable immunodeficiency: test indications and interpretations. *Mayo Clin Proc*. 2005;80:1187–1200.
76. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: clinical correlates and responses to pneumococcal vaccine. *Clin Immunol*. 2004;121:93–97.
77. Cunningham-Rundles C, Pudifin DJ, Armstrong D, Good RA. Selective IgA deficiency and neoplasia. *Vox Sang*. 1980;38: 61–67.
78. Bachmann R. Studies on the serum γA-globulin level III: the frequency of A-γA-globulinemia. *Scand J Clin Lab Invest*. 1965;17:316–320.
79. Lilac D, Sewell WAC. IgA deficiency: what we should – or should not – be doing. *J Clin Pathol*. 2001;54:337–338.

Requests for reprints should be addressed to:
Marc F. Goldstein, MD
Allergic Disease Associates, PC/The Asthma Center
205 N Broad St, Suite 300
Philadelphia, PA 19107
E-mail: gpike35@aol.com