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Original Article

Comprehensive clinical and immunological features of 62 adult patients with selective primary IgM deficiency

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Abstract: Selective IgM Deficiency (SIgMD) is a recently incorporated disorder in the classification of primary immunodeficiency diseases. The purpose of this study was to present detailed clinical and immunological features in a cohort of 62 adult patients with SIgMD. A retrospective chart review of 62 patients between 2009 and 2017 with a diagnosis of SIgMD was performed for clinical and immunological features, and response to immunoglobulin therapy in symptomatic patients who also exhibited specific antibody deficiency. The majority of patients presented with recurrent and chronic upper and lower respiratory tract infections (73%), most often with recurrent sinusitis (29%), bronchitis (33%), pneumonia (21%), and recurrent urinary tract infections (16%). Forty three percent of patients had associated autoimmune diseases including Hashimoto's thyroiditis, and systemic lupus erythematosus. Approximately 35% of patients had atopic diseases, including allergic rhinitis and asthma. CD3+ T, CD4+ T, CD8+ T, and CD19+ B cells were normal in the majority of patients. IgG subclass deficiency was observed in approximately 22% of cases. Forty seven percent of patients exhibited specific anti-pneumococcal antibody deficiency. The six most common pneumococcal serotypes that were impaired in majority (>70%) of subjects included 3, 4, 9V, 9N, 12F, 23F. Eighteen (66%) of 27 patients with specific antibody deficiency received immunoglobulin therapy and almost all subjects responded to immunoglobulin therapy by decreased frequency of infections. No correlation was observed in immunological features, clinical manifestations, or response to therapy with serum IgM levels.

Keywords: Selective IgM deficiency, IgG subclasses, anti-pneumococcal antibodies, immunoglobulin therapy, autoimmunity

Introduction

Monomeric membrane-bound surface IgM expressed on B cells and serves as a component of B cell receptor (BCR) that is involved in signaling for B cells activation. Serum or secreted pentameric immunoglobulin IgM plays an important role in microbial defense, removal of apoptotic bodies, and in immune homeostasis by regulating inflammation and autoimmunity [1-4]. IgM mediates its effects on B cells via IgMFcR (FcμR). Mice deficient in secreted IgM and normal membrane bound IgM are impaired in IgG antibody responses and in protection against bacterial, viral, and fungal pathogens, and develop autoimmunity [5-9]. Mice lacking FcμR are also impaired in specific IgG antibody responses and develop autoantibodies as mice age [10, 11]. John Hobbs and colleagues first described selective IgM deficiency (SIgMD) in two children with systemic meningococcus infection presenting with meningitis [12]. Similar to mice, humans with SIgMD also present with recurrent bacterial and fungal infections and develop autoimmunity and autoimmune diseases [13-27]. Patients with SIgMD may be asymptomatic or present with infections ranging from mild to severe including sepsis and meningitis [12, 18-23]. After five decade SIgMD was incorporated in the International Union of Immunological Societies (IUIS) classification of primary immunodeficiency diseases [28]. In addition to infections, patients with SIgMD may present with autoimmune and/or allergic manifestations [12-16, 29]. Immunological analyses have reported in a small number of patients with SIgMD. The objectives of this study were to [A] provide a descriptive comprehensive analysis of clinical presentations and immunological features in a large cohort of patients with SIgMD, [B] identify the frequency of specific antibody deficiency, and common

pneumococcal serotypes that are impaired in majority of SIgMD patients with specific antibody deficiency, and [C] document the clinical response to immunoglobulin therapy.

Our data show that the majority of patients with SIgMD present with recurrent upper and lower respiratory tract infections, and a significant proportion of patients also manifest with autoimmune and allergic diseases. T cells, T cell subsets, and B cell numbers were normal in majority of cases; however, a small number of patients exhibited abnormalities of lymphocyte subsets. IgG subclass deficiency was observed in one fourth of patients. Furthermore, certain pneumococcal serotypes were more frequently impaired in SIgMD patients with specific antibody deficiency. Finally, those patients who received immunoglobulin therapy responded by decreased frequency or complete prevention of infections.

Materials and methods

Patients

The medical records of 62 patients with a diagnosis of SIgMD followed at the University of California at Irvine immunology clinics between January 2009 and November 2017 were reviewed. The diagnosis of selective IgM deficiency was defined as serum IgM below two standards of mean of controls with normal IgA, IgG [30]. Charts were reviewed for age, gender, initial clinical presentation with regard to recurrent infections, autoimmunity and autoimmune diseases, allergic diseases, malignancies, and response to administration of intravenous or subcutaneous immunoglobulin therapy. Data were also collected for multiple immunological parameters including levels of IgM and IgG subclasses, lymphocyte phenotypes, complement, specific antibodies to tetanus toxoid and *Streptococcus pneumoniae*. Subjects were de-identified. The UCI Institutional Review Board (human) approved this study. Informed consent was not required for this retrospective chart review.

Methods

Serum levels of immunoglobulin M, A, G, IgG subclasses using rate nephelometry, and autoantibodies were measured in our Department of Pathology and Laboratory Medicine. Pneumococcal antibody titers were obtained prior to and at 4 weeks post immunization with Pneumovax-23 vaccine by multi-analyte fluorescence detection (Arup Laboratories, Salt Lake City, UT, USA). Impaired specific antibody response to Pneumovax-23 was considered if post vaccination titers were either unprotective (<1.3 μg/dl) or <2 fold increase over pre-vaccination titers for more than 70% serotypes. CD3+ T, CD4+ T, CD8+ T, CD19+ B, CD3-CD16+CD56+ natural killer cells were analyzed by flow cytometry using specific monoclonal antibodies and isotype controls in Department of Pathology and Laboratory Medicine, University of California, Irvine.

Results

Clinical characteristics

Demographic data and clinical manifestations are shown in **Table 1**. Sixty-two patients were included in this study with a mean age of 56 years (range 12 years-90 years) with female predominance (female: male, 2:1). Serum IgM ranged between 4 mg/dl to 62 mg/dl (normal ranges 65 mg/dl to 265 mg/dl). The majority of patients initially presented with recurrent infections, which were predominantly recurrent upper respiratory tract infections (22%), chronic sinusitis (29%), and recurrent pneumonia (21%). Approximately 16% of patients presented with recurrent urinary tract infections. Few patients presented with sepsis and viral meningitis. In five patients with chronic respiratory infection, mycobacterial organisms (three with *M. avium complex* and two with *M. tuberculosis*) were identified. Three patients had documented bronchiectasis.

Approximately 43% of patients with SIgMD had associated autoimmune diseases; in few as presenting manifestations (**Table 1** and **Figure 1**). Hashimoto's thyroiditis was the most common autoimmune disease, followed by connective tissue autoimmune diseases including SLE, rheumatoid arthritis, Sjogren's syndrome, and mixed connective tissue disease. Neuromuscular autoimmune diseases included myasthenia gravis, and Gullian-Barre syndrome. Others included autoimmune thrombocytopenia and autoimmune neutropenia. Furthermore high titers of ANA (titers-1:80->1:320) were

Table 1. Clinical Manifestations in patients with selective IgM deficiency

Patient	Age	Sex	IgM	Clinical Manifestations	
				Recurrent or Chronic Infections	Allergic & Autoimmune Disease
1	35	F	33	Intertrigo and vaginal candidiasis	--
2	45	M	35	Cellulitis, recurrent URI	--
3	65	F	40	Lymphadenitis, sinusitis, Mycobacterium tuberculosis, bronchiectasis obliterans	Hypothyroidism, Sjogren's Syndrome
4	75	F	42	--	Guillian Barre Syndrome
5	42	F	56	HSV	--
6	49	F	13	Recurrent URI, pneumonia, and UTI	Asthma, Sjogren's Syndrome
7	60	M	38	--	Rheumatoid Arthritis
8	32	F	37	Recurrent UTI	Allergic Rhinitis, autoimmune neutropenia, thrombocytopenia
9	Deceased	M	61	--	ANA 1:160
10	60	F	23	Otitis media, pharyngitis, chronic sinusitis, pneumonias	Hashimoto's thyroiditis
11	57	M	39	Viral meningitis, recurrent URI and pneumonia	--
12	71	M	32	Herpes Zoster with post herpetic neuralgia	Hashimoto's thyroiditis, ocular myasthenia gravis
13	55	F	47	Chronic sinusitis, tooth abscess	Hashimoto's Thyroiditis, autoimmune pancreatitis, Celiac Disease
14	74	F	49	Recurrent URI	--
15	56	F	20	Chronic Sinusitis	Asthma, hypothyroidism
16	47	M	34	Recurrent URI, chronic sinusitis	--
17	12	F	34	Asceptic meningitis, Staph and fungal skin infections	Asthma, Allergic Rhinitis
18	59	F	62	Necrotizing fasciitis, MRSA abscesses, recurrent URIs, pharyngitis, sinusitis, pneumonia x 2, recurrent UTI	Asthma, hypothyroidism
19	90	F	25	--	Asthma, Allergic Rhinitis, Rheumatoid arthritis
20	85	M	52	Bronchitis, pneumonia	--
21	77	F	47	Recurrent pneumonia	--
22	51	F	12	Bronchitis, sinusitis, otitis media	Asthma, Hypothyroidism
23	56	F	52	Sinusitis	Allergic Rhinitis
24	44	M	40	Bronchitis, pneumonia, MAC infection	Asthma, Allergic Rhinitis
25	24	M	56	Sinusitis, pneumonia	ANA 1:180
26	39	M	41	Skin abscesses, cellulitis	--
27	51	F	32	Rec. URI, sinusitis, otitis media, Rec. UTI, vaginal bacterial infections	--
28	74	M	45	Recurrent URI	--
29	42	F	44	--	Hypothyroidism
30	17	M	50	--	Allergic Rhinitis, alopecia
31	40	M	43	Recurrent URI	--
32	65	F	35	Chronic Sinusitis	Asthma, Allergic Rhinitis, Guillan-Barre Syndrome
33	60	F	10	HSV, Chronic Fungal sinusitis	Celiac disease
34	57	F	43	Recurrent URI	Asthma, Allergic Rhinitis, Hyperthyroidism
35	35	F	35	Recurrent URI, chronic sinusitis	Hypothyroidism, Adrenal Insufficiency, Myasthenia Gravis
36	72	M	39	Bronchitis, sinusitis, pneumonias	--
37	63	F	39	Chronic bronchitis, chronic fungal sinusitis	Asthma, Allergic Rhinitis
38	67	F	53	Recurrent UTI	Allergic Rhinitis
39	87	M	27	Pneumonias, MAC infection	--
40	62	F	14	Pneumonias	SLE, cutaneous lupus
41	82	F	53	Recurrent UTI	SLE, APS
42	56	F	24	Recurrent URI	Allergic Rhinitis
43	44	M	15	Periodontal abscesses	Allergic Rhinitis
44	73	F	21	--	Allergic Rhinitis, hypothyroidism, ITP
45	60	M	52	Recurrent URI	--
46	72	F	4	Diverticulitis, Recurrent UTI	--
47	57	M	34	Skin Abscesses, Recurrent URI, sinusitis	ANA >1:320
48	79	F	64	Recurrent URI	--
49	50	M	46	Chronic sinusitis	--

50	21	F	55	Recurrent shingles	Hashimoto's thyroiditis
51	59	F	50	Recurrent URI	Asthma, Hashimoto's thyroiditis
52	62	M	62	Bronchiectasis	Allergic Rhinitis, ANA 1:160
53	42	M	57	Chronic bronchitis	--
54	64	F	57	Chronic sinusitis	Asthma, Allergic Rhinitis
55	31	F	45	Pneumonia, Recurrent UTI	Asthma, Allergic Rhinitis
56	43	F	49	Onychomycosis, Recurrent otitis media, pharyngitis, sinusitis, thrush, and pneumonia , MAI, Bronchiectasis	Asthma, Allergic Rhinitis
57	44	F	51	URI, chronic sinusitis, chronic diarrhea, UTI	undifferentiated connective tissue disease
58	73	M	18	Pneumonia with sepsis, UTI	--
59	65	M	41	Recurrent Pneumonia	--
60	43	F	44	Recurrent and chronic HSV2 infection	Hypothyroidism
61	71	F	30	Chronic Fatigue	ANA 1:160
62	57	M	58	Varicella, Mycobacterium tuberculosis	Pemphigus Vulgaris

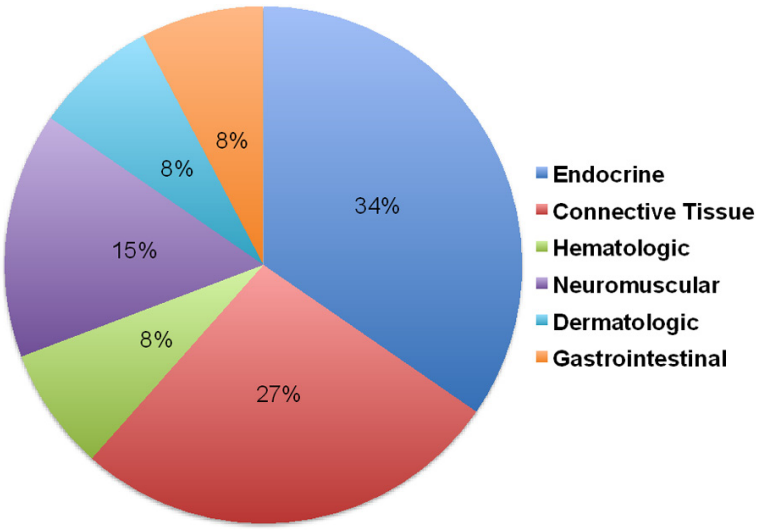

Figure 1. Distribution of various autoimmune diseases in SIgMD patients.

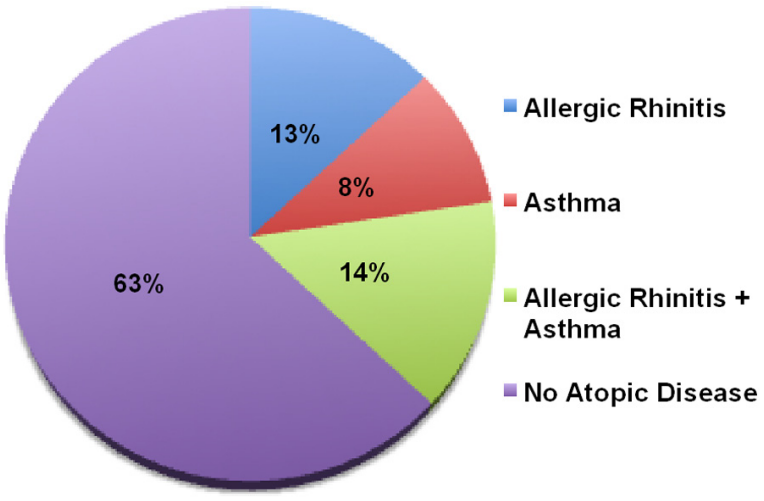

Figure 2. Distribution of allergic diseases in SIgMD patients.

present in 6 additional patients without a diagnosis of lupus.

Allergic manifestations were observed in 35% of patients and included allergic rhinitis (13%), asthma (8%), and 14% with combined allergic rhinitis and asthma (**Table 1** and **Figure 2**). Several of these patients also have autoimmune diseases.

Malignancies included 2 patients with monoclonal gammopathy of undetermined significance (MGUS), and one each of multiple myeloma, non-Hodgkin lymphoma, thyroid cancer, gastric cancer, and oropharyngeal carcinoma (data not shown). One patient each with SIgMD developed MGUS and non-Hodgkin's lymphoma 1-3 years following the diagnosis of SIgMD.

Immunologic data

IgG subclasses: Approximately 22% SIgMD patients had reproducibly low (on at least 2 separate occasions) levels of IgG subclasses; total IgG levels were normal (**Table 2**). Four patients (6%) had low IgG1, 2 (3%) had low IgG2 subclass, 7 (11%) had low IgG3, and only 1 (1.5%) patient had low serum IgG4. One patient each had combined IgG2 plus IgG3, and IgG1 plus IgG3 subclass deficiency. To determine any relationship with serum IgM levels,

Table 2. IgG subclasses and Lymphocyte subsets in Patients with Selective IgM Deficiency

Patient	IgG1	IgG2	IgG3	IgG4	CD3	CD4	CD8	CD19	CD16
1	377	386	39	26	529*	302*	202	126	168
2	514	383	94	25	1129	856	306	19*	124
3	696	147*	27	2*	5468	449*	97	90*	112
4	738	358	40	37	ND	ND	ND	ND	ND
5	468	610	45	43	ND	ND	ND	ND	ND
6	469	115*	15*	17	1555	1060	471	636	213
7	458	466	146	14	1470	693	777	546	102
8	820	434	153	10	ND	ND	ND	ND	ND
9	357	179	37	67	561*	499	68*	115	156
10	301	283	11*	18	ND	ND	ND	ND	ND
11	587	300	97	13	1736	1459	277	87*	57
12	707	569	103	49	ND	ND	ND	ND	ND
13	688	442	43	17	ND	ND	ND	ND	ND
14	640	175	75	14	1045	464*	632	279	102
15	642	343	178	18	1478	1152	326	106	198
16	388	360	38	10	ND	ND	ND	ND	ND
17	820	196	29	13	1703	819	690	279	110
18	454	432	96	12	1238	586	714	106	178
19	622	167	24	16	1651	1093	579	279	87
20	313	355	25	23	1341	1041	265	194	103
21	399	414	72	44	1255	959	296	99*	57
22	549	232	56	14	1411	953	441	174	154
23	618	272	18	31	1592	1184	391	161	76
24	449	244	23	22	832	456*	369	168	199
25	877	269	47	23	766	467*	287	121	147
26	620	282	30	69	ND	ND	ND	ND	ND
27	505	340	22	34	ND	ND	ND	ND	ND
28	361	469	24	34	782	598	173	407	296
29	438	261	37	13	1018	776	228	108	79
30	624	282	26	33	674	393*	225	182	104
31	979	125	18*	32	ND	ND	ND	ND	ND
32	624	370	56	16	ND	ND	ND	ND	ND
33	515	284	31	29	ND	ND	ND	ND	ND
34	487	237	40	17	ND	ND	ND	ND	ND
35	536	314	39	31	ND	ND	ND	ND	ND
36	562	416	42	58	573*	469*	97	535	102
37	251*	565	49	25	991	778	195	141	122
38	534	576	55	43	ND	ND	ND	ND	ND
39	524	496	79	20	962	431*	526	87*	201
40	345	402	43	24	ND	ND	ND	ND	ND
41	530	343	79	9	ND	ND	ND	ND	ND
42	312*	477	38	31	ND	ND	ND	ND	ND
43	425	248	33	44	715	445*	245	422	74
44	526	224	51	8	ND	ND	ND	ND	ND
45	444	311	44	15	832	443*	378	166	256
46	727	205	101	0.6*	ND	ND	ND	ND	ND
47	446	330	18*	33	ND	ND	ND	ND	ND
48	560	365	31	48	858	741	117	245	187

49	425	344	20*	30	1472	1004	469	66*	68
50	818	236	48	9	1338	722	546	115	188
51	454	432	96	12	1238	568	714	66*	146
52	816	456	31	36	803	535	211	281	204
53	566	153	65	40	ND	ND	ND	ND	ND
54	636	243	26	151	2134	1469	655	165	177
55	316*	418	43	106	1330	700	490	56*	212
56	538	403	39	28	1991	1526	487	68*	232
57	267*	308	21*	22	1536	1018	499	134	88
58	615	198	37	53	865	646	307	312	104
59	525	449	18*	8	1157	909	231	186	189
60	404	374	24	12	1018	776	229	204	76
61	932	194	33	9	1908	128*	683	139	226
62	833	517	26	29	257*	49*	198	101	12*

ND-Not done, Normal ranges (mg/dl) for IgG1 (342-1,118), IgG2 (148-525), IgG3 (21-114), IgG4 (7-88; 69-162). Normal ranges for absolute count (mm^3/ml) CD3 (619-1847), CD4 (490-1194), CD8 (85-279), CD19 (110-660), CD16 (12-349). *-low. Low IgG1-4/62, IgG2-2/62, IgG3-7/62, IgG4-2/62; IgG2+4-1, IgG2+3-1; IgG1+3-1. Low CD3-4/41, CD4-12/41, CD8-1/41, CD19-8/41, CD16 1/41.

Table 3. Pneumococcal Serotypes in patients with SIgMD with specific antibody deficiency

S. pneumococcal Serotypes	All Patients # (%) patients with unprotected titers* and/or impaired response	IgM < 30 mg/dL # (%) patients with unprotected titers* and/or impaired response	IgM > 30 mg/dL # (%) patients with unprotected titers* and/or impaired response
1	18 (67%)	4 (50%)	14 (74%)
2	5 (19%)	2 (25%)	3 (16%)
3	21 (78%)	7 (88%)	14 (74%)
4	26 (96%)	8 (100%)	18 (95%)
5	13 (48%)	4 (50%)	9 (47%)
26 (6B)	16 (59%)	5 (63%)	11 (58%)
51 (7F)	17 (63%)	6 (75%)	11 (58%)
8	15 (56%)	5 (63%)	10 (53%)
68 (9V)	19 (70%)	7 (88%)	12 (63%)
9 (9N)	21 (78%)	6 (75%)	15 (79%)
34 (10A)	8 (30%)	3 (38%)	5 (26%)
43 (11A)	6 (22%)	3 (38%)	3 (16%)
12 (12F)	23 (85%)	7 (88%)	16 (84%)
17 (17F)	8 (30%)	2 (25%)	6 (32%)
14	12 (44%)	5 (63%)	7 (37%)
19 (19F)	16 (59%)	4 (50%)	12 (63%)
20	3 (11%)	2 (25%)	1 (5%)
22 (22F)	10 (37%)	4 (50%)	6 (32%)
23 (23F)	22 (81%)	6 (75%)	15 (79%)
54 (15B)	6 (22%)	3 (38%)	3 (16%)
56 (18C)	12 (44%)	4 (50%)	8 (42%)
57 (19A)	4 (15%)	3 (38%)	1 (5%)
70 (33F)	8 (30%)	3 (38%)	5 (26%)

*Unprotected titers were serotypes with <1.3 μg/dl, Impaired response was <2 fold increase in post vaccination titers from baseline 34/62=55% patients with Specific Antibody Deficiency Reported in chart, but no supporting pre and post serotypes available 10 of 13 (77%) with IgM <30 mg/dl had low response to Pneumovax-23.

Table 4. Clinical Response to Immunoglobulin Therapy

Patient	Dose (mg/kg)	IgG Trough (mg/dL)	Immunoglobulin Therapy	Infections Prior to Therapy (Annual Rate)	Infections Post-Therapy (Annual Rate)
2	396	1010	IVIG 35 g q4 weeks	Recurrent URI	No Infections
13	463	1390	IVIG 25 g q3 weeks	Recurrent sinus infections, frequency not recorded	Persistent recurrent sinus infections, frequency not recorded
15	334	1100	IVIG 30 g q4 weeks	Recurrent sinusitis x3, 1 URI	No infections
23	421	980	IVIG 35 g q4 weeks	3-4 sinus infections per year, URI, 1 sinusitis	Reduced frequency of infections, exact numbers not recorded
24	419	892	SCIG 10 g q weekly	Recurrent pneumonias	No infections
26	554	1130	IVIG 45 g q4 weeks	Multiple resistant MRSA skin infections	One cellulitis and one abscess
32	360	1190	IVIG 25 g q4 weeks	Recurrent sinusitis, recurrent UTI	1 sinusitis, 1 UTI
35	410	1200	SCIG 6 g qweekly	Recurrent sinusitis and URI	0 to 1 sinusitis/URI
36	400	940	fSCIG 40 g q4 weeks*	3-6 pneumonias, 3 sinus infections, 1 bronchitis	1 bronchitis
37	522	1030	IVIG 30 g q4 weeks	Chronic sinusitis x4-5	No infections
39	420	921	IVIG 30 g q4 weeks	Recurrent infections, type and frequency not recorded	No infections
43	369	1012	SCIG 12 g q10 days	Chronic sinusitis, recurrent dental, periodontal abscesses	1 bacterial infection, 2 viral infections, no abscesses
46	612	1510	SCIG 10 g qweekly	Recurrent UTI, frequency not recorded	No infections
56	390	1030	IVIG 25 g q4 weeks	Otitis media x5, pharyngitis x12, pneumonia x3, sinusitis x3, chronic MAI infection	1 otitis media, 1 pneumonia, persistent MAI infection
57	358	999	SCIG 6 g qweekly	Recurrent UTI x3 and URI x5	1 UTI and 2 URI
59	516	1110	SCIG 12 g qweekly	Recurrent pneumonia	No pneumonias
61	397	1120	IVIG 25 g q4 weeks	On IVIG for Neurologic disease	Neuropathy improved
62	800	1540	IVIG 50 g q4 weeks	On IVIG for pemphigus vulgaris	Pemphigus improved

*fSCIG - enzyme-facilitated subcutaneous immunolgobulin.

patients with SIgMD were divided into those with serum IgM levels of ≤30 mg/dl and those with serum IgM >30 mg/dl. Twenty three percent (14 patients) of the patients had serum IgM level <30 mg/dl (**Table 1**); two patients has serum of <10 mg/dl. Four of 12 (33%) SIgMD patients with serum IgM ≤30 mg/dl had IgG subclass deficiency as compared to 3 (19%) in patients with serum IgM >30 mg/dl. No difference was observed in type of IgG subclass deficiency between patients with SIgMD with serum IgM of ≤30 mg/dl and those with serum IgM of >30 mg/dl.

Lymphocyte subsets: The lymphocyte subsets data were available for 40 patients. In majority of cases, number of CD3+ T cells, CD4+ T cells, CD8+ T cells, and CD19+ B cell were normal (**Table 2**). However, CD3+ T cells were reduced in 4 (10%) subjects, 12 (30%) patients had low CD4+ T cells, only one patient had low CD8+ T cells, and CD19+ B cells were decreased in 5 (12.5%) subjects. Three patients had combined low CD3+ and CD4+ T cells. None of the patients had lymphopenia of combined CD3+, CD4+, and CD8+ T cells. Only two patients (5%) with a serum IgM <30 mg/dl had low T cell subsets (CD4+ T cells).

Specific antibody responses: The pre and post pneumococcal vaccination specific antibody titers were available in 57 patients. Twenty-seven of 57 patients (47%) had unprotected levels of (<1.3 ug/ml) or impaired (<2 fold increase over baseline) anti-S*treptococcus pneumoniae* antibody responses against more than 70% serotypes following Pneumovax-23 vaccination (**Table 3**), thereby establishing a diagnosis of specific antibody deficiency. Upon review of individual pneumococcal serotypes, 6 serotypes including serotypes 3, 4, 9N, 9V, 12F, 23F were found to be unprotected and/or impaired to vaccination in >70% of patients, (**Table 3**). When data were analyzed for patients with serum IgM ≤30 mg/dl vs serum IgM >30 mg/dl, the most frequently unprotected/impaired pneumococcal serotypes, in patients with serum IgM ≤30 mg/dl included 3, 4, 7F, 9V, 9N, 12F, and 23F, and in patients with IgM >30 the most common unprotected/impaired pneumococcal serotypes were 1, 3, 4, 9N, 12F, and 23F.

Only 3 of 25 patients in whom antibodies to tetanus toxoid were tested demonstrated impaired response to tetanus toxoid (data not

shown). One of these patients was recently reported [18].

Complement components: Complement levels (CH50, C3, C4) were available in 26 patients and were essentially normal with the exception of decreased C3 levels seen in 4 patients and decreased C4 in 1 patient (data not shown).

Response to immunoglobulin therapy

A total of 18 symptomatic patients received immunoglobulin therapy, however, one patient each received immunoglobulin therapy primarily for associated pemphigus vulgaris and for associated polyneuropathy (**Table 4**). Therefore, a total of 16 SIgMD patients received immunoglobulin therapy for recurrent infections; 15 of which had specific antibody deficiency and one patient had associated IgG subclass deficiency without specific antibody deficiency. Eight of the 15 SIgMD patients (53%) with specific antibody deficiency experienced reduced frequency of infections and 7 patients (47%) had a complete response to immunoglobulin therapy with no subsequent infections. When data were analyzed for route of administration, 4 of 7 patients who had complete resolution of infection were on intravenous immunoglobulin (IVIG) and 3 of 7 were on subcutaneous immunoglobulin (SCIG).

Discussion

Selective IgM deficiency is a recently classified primary immunodeficiency disease [28]. The true prevalence of SIgMD is not known. The prevalence has ranged from 0.03% to 2.1% [31-33]. Such variations are due to different populations studied, and levels of serum IgM used for the definition of selective IgM deficiency. In a community based surveillance study of 3,000 individual, the prevalence of complete absence of serum IgM was reported to be 0.03% [31]. Ozen et al reported prevalence of 2.1% among 131 children with primary immunodeficiencies [33]. Entezari et al [32], in screening of 3000 healthy blood bank donors in Iran, reported prevalence of SIgMD as 0.37%; SIgMD was considered as serum IgM level less than 2 SD below the mean for healthy controls [30]. Current study has identified 62 patients with SIgMD in our academic tertiary referral Immunology clinic with a total of 630 patients with various primary immunodeficiencies. There is no definitive inheritance pattern for SIgMD. In our cohort of patients we have SIgMD in two families; one mother and daughter, and the other father and a son. Jones et al [34] described 8 of 9 children in a family with low IgM, and three of them had meningococcal meningitis. Yocum et al [22] described SIgMD in a family with affected male members in three generations. Patient had no serum IgM and presented with recurrent Staphylococcal pyoderma. Father and one son had low IgM and were asymptomatic. Faulk and colleagues [35] described a child with undetectable serum IgM and pseudomonas infection. His father also had low IgM. Buckley and Sidbury [36] observed low serum IgM in the mother of 3 sibs; one presented with agammaglobulinemia.

While a number of patients with SIgMD may be asymptomatic, symptomatic patients present with recurrent bacterial, viral, and fungal infections reviewed in [14]. Similarly mice defective in secretory IgM are susceptible to bacterial, viral, and fungal infections [6, 9]. In our cohort, most common presentation was upper and lower respiratory tract infections, including recurrent pneumonia. The initial presenting manifestation of recurrent infections with a predilection for the upper and lower respiratory tract, has previously been reported in 64% to more than 80% of patients with SIgMD [15-17, 29]. Although generally not considered increased frequency of UTI in antibody deficiency diseases, in our cohort 16% of patients had recurrent UTI. One of the patients in our cohort with SIgMD and IgAλ MGUS (monoclonal gammopathy of undetermined significance) presented with recurrent urinary tract infection [37]. Chovancova et al [17] also reported 3 of 17 patients [17%] with recurrent UTI.

In addition to infections, an increased prevalence of allergic diseases has also been described in adult patients with SIgMD reviewed in [13, 14]. Prior studies have reported a variable range of 25% to 47% of patients with SIgMD who also had a diagnosis of allergic rhinitis and/or asthma [15, 16, 38]. Goldstein et al [16] reported asthma in 47% and allergic rhinitis in 36% of 37 adult patients with SIgMD. In our cohort, 35% of patients had allergic manifestation with 8% with asthma alone, 14% with allergic rhinitis and asthma, and 13% with allergic rhinitis alone. Chovancova et al [17] reported bronchial asthma in 18% and allergic rhinitis

in 47% of 17 adult patients with SIgMD. These differences in the frequency of allergic disease in SIgMD could be due to relatively smaller number of patients in other studies.

IgM plays an important role in immune tolerance [1, 2] and mice deficient in secreted IgM or deficient in FcuR have an increased tendency to spontaneously develop as well as accelerate the production of autoantibodies [7, 8, 10, 11]. The association of autoimmune disease and SIgMD has been described in studies of small number of patients with a prevalence ranging from 3% to 30% [15, 17, 24-27]. In our cohort, we observed a significantly higher rate (42%) of autoimmunity and autoimmune disease with predominance of Hashimoto's thyroiditis and SLE. In addition, 10% of patients had high titers of ANA without clinical evidence or diagnosis of lupus. This would be consistent with the observations that normal human IgM suppress anti-thyroglobulin and anti-DNA antibody activities [39]. Furthermore, Ehrenstein and colleagues (8) demonstrated that serum IgM deficient mice are more susceptible to spontaneously develop serum anti-DNA IgG antibodies, and glomerular deposition of IgG and complement. Chovancova et al [17] in their 17 adult patients with SIgMD, reported 4 patients with SLE, and 5 additional patients with positive ANA without a diagnosis of SLE (50%); however, their cohort had no patients with Hashimoto's thyroiditis or presence of anti-thyroid peroxidase or anti-thyroglobulin antibodies. In contrast, Goldstein et al [16] did not observe any subject with SLE; however 6 patients had hypothyroidism, and 2 of 19 patients with autoimmune thyroiditis (positive thyroid autoantibodies). Normal IgM has also been shown to suppress experimental myasthenia gravis in SCID mice model [40]. One of our patients had ocular myasthenia with high titers of anti-choline receptor antibodies. It is also interesting that autoimmune diseases are less frequent in pediatric SIgMD [27]. In Mice deficient in secretory IgM and in FcμR also develop autoimmunity and autoimmune diseases as mice age [7, 8, 12, 13].

A number of malignancies have described in SIgMD patients as case reports. These include clear cell sarcoma, non-Hodgkin's lymphoma, promyelocytic leukemia, and hepatocellular carcinoma reviewed in [14]. In our cohort, 3 patients had plasma cell dyscrasia; one with MGUS, and two with multiple myeloma, and one each with non-Hodgkin's lymphoma, gastric carcinoma, thyroid carcinoma, and oropharyngeal carcinoma. MGUS and non-Hodgkin's lymphoma were developed few years after the diagnosis of SIgMD. Whether there is an increased prevalence of lymphoid malignancies in SIgMD remains unclear and would require study of much larger population of patients.

Surface IgM+ B, CD20+ B, and CD19+ B cells are normal in majority of SIgMD patients [15, 22, 41]. However, low to complete absence of B cells have been reported in small number of patients with SIgMD [15, 22, 42]. In our cohort 8 patients had low number of CD19+ B cells. Mice deficient in secretory IgM or FcμR also have normal numbers of surface IgM+ B cells; however, they have deficiency of germinal centers [5, 10]. In 1971, Faulk et al [35] described hypoplastic follicles lacking a germinal center in a child with SIgMD. Our current cohort includes 20 patients in whom we previously reported decreased germinal center B cells, and regulatory B cells [43].

T cell and CD4+ and CD8+ T cell subset proportions and number are normal in majority of SIgMD patients [15, 43-45]. However, alterations in subsets of patients have been reported [46, 47]. In our cohort, a significant number of patients had low numbers of CD4+ T cells. Our cohort includes 20 patients with SIgMD in whom we previously reported normal proportions of naïve, central memory, effector memory, and terminally differentiated effector memory subsets of CD4+ and CD8+ T cells, and increased CD8 Treg cells [43].

Several investigators have reported IgG subclass deficiency in a subset of SIgMD patients [15-17, 48]. Goldstein et al [16], in their retrospective study of 37 adult patients with SIgMD, observed IgG subclass deficiency in 25%. Chovancova et al [17] observed selective IgG subclass deficiency in 6 of 14 patients (42%); this high percentage may be due to small number of patients studied. In our cohort, 22% of patients had reproducibly low IgG subclasses; IgG3 subclass deficiency was most frequent. No difference was observed in the frequency or the type of IgG subclass deficiency when we compared patients with serum IgM levels ≤30

mg/dl versus patients with serum IgM of >30 mg/dl.

In a number of smaller studies, several investigators have reported impaired specific antibody responses to both T-cell independent polysaccharide and T-cell dependent protein-conjugated vaccines in symptomatic patients with SIgMD. Guill et al [21] reported decreased specific antibody response to both tetanus toxoid and *Streptococcus pneumoniae.* La Concha et al [47] observed no IgG specific antibodies response to repeated vaccination with tetanus toxoid in two patients with SIgMD with complete absence of serum IgM. Hong and Gupta [20] also reported lack of specific antibody responses against *Streptococcus pneumoniae* and tetanus toxoid in a patient with SIgMD manifested with pneumococcus sepsis. Yocum et al [22] reported impaired or lack of specific antibody response against KLH and typhoid antigens. Boes et al [5] reported impaired IgG antibody responses to NP-KLH in targeted mutant selective IgM deficient mice. Yel et al [15], observed impaired IgG-specific anti-pneumococcal antibody response in 45% of patients with SIgMD. Goldstein et al [16] also reported lack of protective or no specific antibody response to pneumococcal vaccine in 2 patients with SIgMD; one of them had complete lack of serum IgM. Chovancova et al [17] reported low titers of isohemagglutinins in their cohort of 17 patients. No data were presented in their cohort of patients for specific antibodies against polysaccharide or protein antigens. In our cohort of 62 patients with SIgMD, 47% had unprotected or impaired specific anti-pneumococcal IgG antibody response; however, impaired response to tetanus toxoid was observed only in a small of patients. Furthermore, we did not observe any correlation between serum IgM levels and specific antibody deficiency; impairment of specific antibody response was similar between proportions of patients with serum IgM ≤30 mg/ml vs >30 mg/dl. IgG specific antibody response to both T-dependent and T-independent antigens are also impaired in mice deficient in IgM secretion [5] and in FcμR [10] that is associated with decreased germinal center formation. We have also reported decreased germinal center B cells in a subset of patients with SIgMD [43].

We further investigated the specific pneumococcal serotypes that were most commonly impaired in our cohort of patients. Majority of patients (>70%) displayed unprotected or impaired specific antibody response against serotypes 3, 4, 9N, 9F, 12F, 23F; and they were similar in SIgMD patients with serum IgM ≤30 mg/dl and with serum IgM >30 mg/dl.

Immunoglobulin administration has been mainstay in the treatment of antibody deficiency diseases. Since a subset of symptomatic patients with SIgMD exhibit impaired IgG specific antibody responses, immunoglobulin treatment has been administered in a small number of patients with SIgMD with decreased frequency of infections and requirements of antibiotics [15, 20, 24, 49-51]. Yel et al [15] reported beneficial effect of immunoglobulin therapy in 5 patients with SIgMD who were treated with IVIG. Goldstein and colleagues [49], in a retrospective study, observed clinical improvement with high dose IVIG in four patients with SIgMD with comorbidity of bronchiectasis and asthma. Patel et al [50] reported beneficial effect of SCIG in a patient with SIgMD with specific antibody deficiency and recurrent multiple infections. Stoelinga et al [24] and Fallon [51] also reported beneficial effects of IVIG. Hong and Gupta [20] reported resolution of infection in a patient with SIgMD with impaired specific antibody response to both T-dependent and T-independent antigens that presented with *Streptococcus pneumoniae* sepsis. In our largest cohort of 16 SIgMD patients treated with immunoglobulin 7 of 16 had no further infections and in remainder frequency of infections markedly reduced. These patients have been followed for 2-5 years. No difference was observed between routes of immunoglobulin administration for complete prevention of infections. Furthermore, no difference was observed in response between patients with serum IgM <30 mg/dl and serum IgM >30 mg/dl. Both patients with SIgMD with polyneuropathy and SIgMD with psoriasis responded to high dose IVIG therapy.

In summary, majority of symptomatic SIgMD patients present with upper and lower respiratory infections, and often life-threatening meningitis and sepsis. Allergic and autoimmune diseases and autoimmunity are relatively common in SIgMD. CD3+, CD4+, CD8+ and CD19+ B cells are normal in majority of patients. IgG subclass deficiency and impaired specific antibody responses are observed in significant pro-

portion of patients. These patients respond clinically to immunoglobulin therapy regardless of route of administration.

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Disclosure of conflict of interest

Sudhir Gupta has participated in clinical trials from Octapharma, USA at University of California, Irvine.

Abbreviations

SIgMD, selective IgM deficiency; MGUS, monoclonal gammopathy of undetermined significance; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

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