ORIGINAL ARTICLE

Alteration in Humoral Immunity Is Common Among Family Members of Patients With Common Variable Immunodeficiency

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Abstract

Background: The prevalence of primary immunodeficiency (PID) in the relatives of patients with common variable immunodeficiency (CVID) and IgA deficiency is high. Allergic disorders have been recorded in patients with humoral immunodeficiency. We aimed to determine the frequency of humoral immunodeficiency and atopy in the relatives of patients with CVID.
Methods: The study population comprised 20 CVID patients and their relatives. All relatives were screened using a questionnaire covering demographic characteristics, warning signs of PID (adults and children), and core questions on asthma, rhinitis, and eczema from the International Study of Asthma and Allergies in Childhood (ISAAC). We also recorded absolute neutrophil and lymphocyte counts, serum immunoglobulin levels, pulmonary function values, and skin prick test results.
Results: The study sample comprised 20 patients with CVID (15 males, 5 females; mean [SD] age, 16.4 [9] years) and 63 first-degree relatives (18 mothers, 16 fathers, 16 sisters, 10 brothers, and 3 offspring). The rate of parental consanguinity was 75%. Of 17 family members with positive PID warning signs, 6 had concomitant hypogammaglobulinemia (3 low IgM levels, 2 selective IgA deficiency, and 1 partial IgA deficiency). The ISAAC questionnaire revealed allergic rhinitis in 3 mothers, asthma in 2 fathers, and 1 sibling. Skin prick testing revealed sensitization to aeroallergens in 31.6% of cases in addition to 1 parent and 1 sibling.
Conclusions: Almost half of the 20 families with a CVID patient had at least 1 additional member with hypogammaglobulinemia, leading us to recommend routine screening for relatives of CVID patients.

Key words: Allergy. Common variable immunodeficiency (CVID). Consanguinity. Family screening. Immunoglobulin A (IgA) deficiency. Hypogammaglobulinemia.

Resumen

Antecedentes: Es conocida la alta prevalencia de inmunodeficiencias entre los familiares de pacientes con inmunodeficiencia común variable (IDCV) y con déficit de IgA. Por otro lado, también se han descrito enfermedades alérgicas en pacientes con inmunodeficiencias humorales. El objetivo de este estudio ha sido el determinar la frecuencia de inmunodeficiencias humorales y de atopia entre los familiares de pacientes con IDCV.
Métodos: Se estudiaron familiares de pacientes con IDCV. Todos los miembros de la familias fueron seleccionadas por un cuestionario que incluyó la determinación de las características demográficas, las señales de alarma, en adultos y niños, de padecer inmunodeficiencias primarias (IDP) y preguntas del Estudio Internacional de Asma y Alergia en la Infancia (ISAAC) para el asma, la rinitis y el eczema. Además, se realizaron estudios analíticos sobre el contaje de neutrófilos y linfocitos, los niveles de inmunoglobulinas séricas, la función pulmonar y pruebas cutáneas prick.
Resultados: Se determinaron veinte casos de IDCV (15M, 5F, edad media: 16,4 ± 9 años) y se estudiaron un total de 63 parientes de primer grado (18 madres, 16 padres, 16 hermanas, 10 hermanos y 3 descendientes). La tasa de consanguinidad de los padres fue de 75%. En general, entre los 17 miembros de la familia con señales de alarma de padecer IDP, 6 tenían hipogammaglobulinemia concomitante; 3 bajos niveles de IgM, 2 selectivos y 1 con parcial déficit de IgA. El cuestionario ISAAC reveló rinitis alérgica en 3/18 de las madres; mientras que, el asma, en 2/18, de padres y de 1/26 de los hermanos. Finalmente, en las pruebas de punción cutánea se obtuvo una sensibilización a aeroalérgenos en el 31,6% de los casos, pero en ninguno de sus padres, hermanos o descendientes.
Conclusiones: En 20 familias de pacientes con IDCV, casi la mitad de sus miembros tenían al menos un individuo con hipogammaglobulinemia, por lo que recomendamos una exploración rutinaria entre todos los familiares de pacientes con IDCV.

Palabras clave: Alergia. Inmunodeficiencia común variable (IDCV). Consanguinidad. Estudio familiar. Déficit de inmunoglobulina A (IgA). Hipogammaglobulinemia.

Introduction

Common variable immunodeficiency (CVID) is characterized by decreased concentrations of immunoglobulins and recurrent infections. The genetic cause of CVID is unknown, and the disease sporadically affects individual patients. Identification of multiple affected family members with CVID and/or IgA deficiency and progression of some IgA-deficient patients to CVID support a major role for genetics and suggest that CVID and IgA deficiency are each a phenotypic variant in a spectrum of similar molecular defects [1,2].

While CVID is not generally found in more than 1 member of a family, about 10% to 20% of first-degree relatives may have a humoral immunity disorder, such as decreased immunoglobulin levels, IgG subclass deficiencies, and selective IgA deficiency [3-5]. The degree of involvement is thought to vary between populations, in part, depending on the frequency of consanguineous marriages [4].

Many patients with CVID and IgA deficiency have clinical histories suggestive of allergic respiratory disease [6,7]. It was suggested that the mucosal immunodeficiency observed in these conditions could facilitate inflammation, bronchial hyperresponsiveness, asthma, and allergic reactions to aeroallergens [6,7]. Accordingly, the protective role of secretory IgA against asthma and allergy in the early years of life has been confirmed [8,9].

In this study, we aimed to evaluate humoral immunity disorders and the presence of clinical warning signs of primary immunodeficiency (PID) among the first-degree relatives of patients with CVID. In addition, our previous observation that allergen sensitization is common among patients with CVID and IgA-deficient patients [10] prompted us to investigate whether prevalence of allergy is increased among their relatives.

Materials and Methods

The study population comprised 20 patients with suspected CVID and their relatives (16 fathers, 18 mothers, 26 siblings [10 males and 16 females], and 3 male offspring. All family members were screened using a questionnaire including demographic characteristics, warning signs of PID (adults and children) (Jeffrey Modell Foundation web site), and core questions on asthma, rhinitis, and eczema from the International Study of Asthma and Allergies in Childhood (ISAAC) [11].

The diagnosis of CVID was based on the clinical history and the diagnostic criteria of the European Society of Immune Deficiencies/Pan-American Group for Immunodeficiency [12]. The study protocol was approved by the Ethics Committee of Marmara Medical School. Informed consent was obtained from the participants or their parents.

All participants were screened for warning signs of PID. A complete blood count with differential was performed, and serum immunoglobulin levels (IgA, IgG, IgM, IgE) were determined. Nephelometry was used to quantify serum immunoglobulins (MININEPH human Ig kit, Binding Site Ltd). Serum levels of immunoglobulins (IgM, IgG, and IgA) were considered low when they were below the reference values for the patient's age. Isohemagglutinin titers and pneumococcal vaccine response were checked in these cases. Family members aged over 4 years with IgA levels below the reference values for age were diagnosed as having probable IgA deficiency; those with <7 mg/dL were considered to have selective IgA deficiency.

The allergy workup included screening with the ISAAC questionnaire, blood eosinophil count, serum IgE determination, pulmonary function, and skin prick testing. Pulmonary function tests were performed using maximal forced expiratory volume curves (Zan Flow Handy II; Zan Messgeraete GmbH) to explore occult lung abnormalities. Normal lung function test reference values (Polgar and Promadhat [13]) were used to generate the predicted values. The skin prick tests were performed with 20 common aeroallergens, including mites, latex, molds, pollens, animal dander, and insects (ALK-Abelló), as described previously [14].

Values are presented as mean (SD) and minimum and maximum. The statistical analysis was performed using SPSS version 15.0 (SPSS Inc).

Results

We studied 20 patients with CVID (15 males and 5 females; mean age, 16.4 [9] years) and 63 first-degree relatives (18

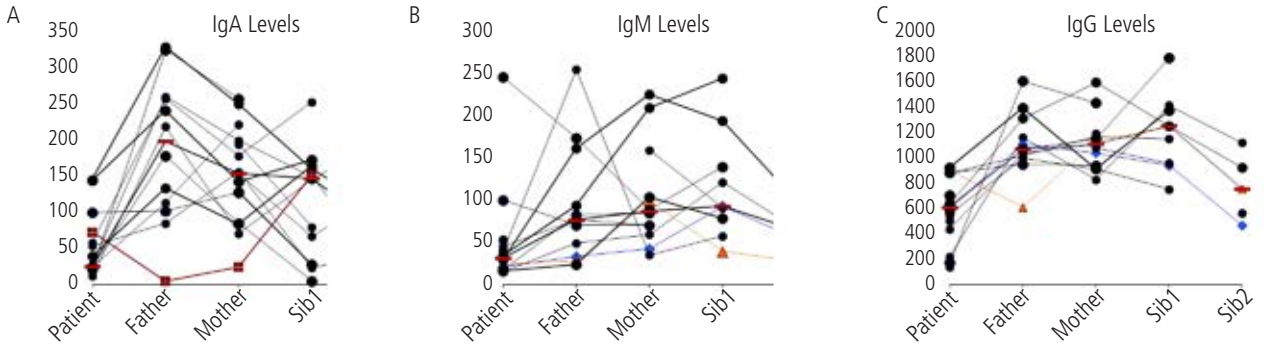

Figure. Immunoglobulin levels of index cases and their relatives. A, IgA. B, IgM. C, IgG. Multiply affected families are shown in colored plots: Blue markers show values of the family members of patient 3 and orange those of patient 7. The brown square marker shows values for patient 20 and his sons.

Table 1. Characteristics of the Parents of Patients With Common Variable Immunodeficiency

	Mean	Range	Standard Deviation
Mothers			
Age, y	40	(18-60)	11
ANC/mm^3	4387	(3000-7200)	1243
ALC/mm^3	3340	(1400-16000)	3557
Eosinophils/mm^3	147	(0-400)	136
IgA, mg/dL	158	(70-254)	57
IgM, mg/dL	94	(35-223)	54
IgG, mg/dL	1123	(822-1580)	197
IgE, mg/dL	58	(4-318)	86
IgG1, mg/dL	675	(478-1120)	183
IgG2, mg/dL	365	(206-566)	133
IgG3, mg/dL	64	(28-129)	30
FEV_1 (percent predicted)	103	(77-138)	17
Fathers			
Age, y	43	(29-60)	8
ANC/mm^3	4964	(2400-6100)	1122
ALC/mm^3	2318	(1500-3300)	564
Eosinophils/mm^3	145	(0-300)	82
IgA, mg/dL	201	(84-325)	86
IgM, mg/dL	95	(24-252)	76
IgG, mg/dL	1132	(605-1590)	259
IgE, mg/dL	187	(3-731)	250
IgG1, mg/dL	687	(374-1060)	209
IgG2, mg/dL	334	(155-431)	95
IgG3, mg/dL	58	(29-103)	32
FEV_1 (percent predicted)	97	(76-131)	14

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; FEV_1, forced expiratory volume in 1 second.

Table 2. Characteristics of the Siblings of Patients With Common Variable Immunodeficiency

	Mean	Range	Standard Deviation
Age	16	(3-29)	7
ANC/mm^3	3906	(1900-7200)	1404
ALC/mm^3	2872	(1500-6100)	1274
Eosinophils/mm^3	150	(0-700)	172
IgA, mg/dL	114	(5-250)	69
IgM, mg/dL	86	(28-192)	44
IgG, mg/dL	1053	(465-1770)	368
IgE, mg/dL	41	(1-251)	62
IgG1, mg/dL	744	(339-1000)	199
IgG2, mg/dL	356	(43-891)	264
IgG3, mg/dL	56	(16-150)	39
FEV^1 (percent predicted)	103	(83-126)	13

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; FEV_1, forced expiratory volume in 1 second.

mothers, 16 fathers, 16 sisters, 10 brothers, and 3 offspring). The frequency of parental consanguinity in the cohort was 75%. The demographic and laboratory data of parents and siblings are presented in Table 1 and Table 2, respectively. The immunoglobulin levels of patients, parents and siblings are presented in the Figure.

PID warning signs were present in 5 fathers (31%), 3 mothers (16.7%), 6 siblings (23.1%), and all 3 offspring. Low IgA was detected in 3 siblings (1 selective, 2 partial) and in 2 offspring (1 selective, 1 partial). Low IgM was detected in 4 fathers, 2 mothers, and 2 siblings. Low IgG was detected in 1 father, but not in the mothers, siblings, or offspring.

Of the 17 family members with positive PID warning signs, 6 had concomitant hypogammaglobulinemia (3 with low IgM, 2 with selective IgA deficiency, and 1 with partial IgA deficiency). Both parents of patient 3 had low IgM levels and recurrent sinusitis. The father of patient 2 had low IgM and recurrent oral mucosa and skin infections (impetigo). The sister of patient 14 had low IgA and recurrent sinusitis.

Six parents (2 mothers and 4 fathers) had low IgM, 1 father also had low IgG, while none had low IgA. Five siblings had low immunoglobulin levels (3 IgA and 2 IgM).

Of note, 3 patients in the cohort had more than 1 affected relative (Table 3). The father of patient 7 had low IgM and IgG levels, with no history of recurrent infection. Meanwhile, 1 of his sisters had low IgA and IgM levels. Further evaluation of this sister revealed chronic respiratory abnormalities and nodules in thoracic computed tomography (subsequently treated with intravenous immunoglobulin); the other sister had low IgM levels with accompanying chronic liver disease due to hepatitis B infection. Both the mother and the father of patient 3, who were related, had low IgM levels and a positive history of recurrent infection (both had PID warning signs). The father had a history of recurrent sinusitis and chronic respiratory symptoms. Meanwhile, his sister had a low IgA level with no history of infections. All 3 offspring of patient 20 had recurrent otitis media, and 2 had low IgA levels.

The ISAAC questionnaire revealed allergic rhinitis in 3 mothers (16.7%), but not in the fathers or siblings. Asthma was detected in 2 of the fathers, 1 of the siblings, and none of the mothers. One of the 3 mothers with allergic rhinitis had low IgA levels, and another had low IgM levels. One of the 2 fathers with symptoms of asthma had a low IgM level. None of the offspring had allergic manifestations.

Skin prick testing revealed sensitization to aeroallergens in 6 patients with CVID (3 to house dust mite and 3 to grass pollens), and 9 patients were diagnosed with asthma by a physician. A sibling of patient 17 and the mother of patient 20 were sensitized to latex and house dust mite, respectively. Neither the parents nor the siblings had a forced expiratory volume in 1 second below 75%. Atopic dermatitis was diagnosed by a physician in 2 mothers and 1 father.

Discussion

We report our data on PID screening of the family members of 20 CVID patients, 15 of whom were children of consanguineous marriages. Eleven relatives of 9 index patients had deficiencies in at least 1 major Ig isotype. Additionally,

Table 3. Features of Index Cases and Humoral Alterations Detected in Family Members

Index Case	Age, y	Gender	Consanguinity	Mothers						Fathers						First Siblings								Second Siblings							
				Age, y	PID Warning Sign	IgE, IU/mL	IgA, mg/dL	IgM, mg/dL	IgG, mg/dL	Age, y	PID Warning Sign	IgE, IU/mL	IgA, mg/dL	IgM, mg/dL	IgG, mg/dL	Age, y	Gender	PID Warning Sign	IgE, IU/mL	IgA, mg/dL	IgM, mg/dL	IgG, mg/dL	Age, y	Gender	PID Warning Sign	IgE, IU/ml	IgA, mg/dL	IgM, mg/dL	IgG, mg/dL
P2	21	M	–	47	–	16.3	70	59	822	53	+	42.8	216	49[a]	1150	26	F	+	10	144	120	1400	29	M	0	34	200	66	1110
P3	11	M	+	23	+	3.7	197	42[a]	1030	38	+	53	257	33[a]	1100	13	F	–	10	147	92	930	3	F	0	11	<23[a]	55	465
P5	13	M	+	36	–	31	152		1180	39	–					16	M	–					4	M	+	3	24[a]	64	558
P7	10	M	+	39	+	9	154	98	1120	44	–	3	84	28[a]	605[a]	17	F	–	1	<23[a]	39[a]	1240	15	F	0	5	46	28[a]	750
P13	16	M	+	44	–	182[a]	176	35[a]	1160	49	–	70	254	252	1010	20	M	+	15	250	57	1140							
P14	18	F	–	39	–	15	84	88	1140	41	–	41	176	172	1060	15	F	+	35	5[a]	138	1770							
P16	24	M	–	44	–	70	141	103	904	48	–	318[a]	238	24[a]	1380	21	F	+	52	171	78	1360							
P19	17	M	+	36	–	7	127		1220	39	+					6	F	–	1	28[a]		560	19	M	0				

[a]Low levels of serum immunoglobulins.

PID warning signs were evident in 17% of mothers, 23% of siblings, and all 3 offspring. Most remarkably, IgM levels were low in 4 fathers. Despite the relatively high frequency of sensitization to aeroallergens in the index patients, none of their family members were found to be allergic.

The genetic cause of CVID is unknown, and most cases are sporadic in individual patients. However, identification of familial CVID cohorts and the progression of some IgA-deficient patients to CVID indicate a strong genetic component [2]. During the past 2 decades, considerable effort has been invested in understanding the genetic background of CVID [15]. Approaches have included genome-wide linkage analysis and family studies, evaluation of index families with several affected members, analysis of inheritance of recessive genes that are important for B-cell development, single-nucleotide polymorphism and copy number studies, and targeted gene approaches.

The very high frequency of parental consanguinity in our study group points to a predominantly autosomal recessive mode of inheritance for this population. Studies of families with a consanguineous background have shown that the CVID phenotype is associated with mutations in key genes in B-cell biology, including *CD18*, *CD19*, *CD20*, *CD21*, inducible costimulator, transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI), and B cell–activating factor receptor (*BAFF-R*), a member of the TNF receptor superfamily [16].

Despite the relatively high rates of self-reported PID warning signs among family members (17 out of 63 patients), only 6 had concomitant hypogammaglobulinemia; 3 parents with low IgM and 1 sibling with selective IgA deficiency and 2 offspring with IgA deficiency. Conversely, in 6 out of 12 patients with at least 1 low Ig isotype, there was no clinical history suggestive of PID. In 1 of the families (parental consanguinity), IgM deficiency was detected in multiple members (the father and 2 sisters of patient 7). Moreover, both parents of patient 3, who were related, had low IgM with recurrent infections. This finding is in accordance with a report from Iran stating that the most common alteration in humoral immunity in the family members of CVID patients was in IgM; 3 fathers and a brother had low IgM levels in their cohort [4]. We previously demonstrated that low IgM level was associated with persistent hypogammaglobulinemia and a more severe phenotype in a cohort of children with hypogammaglobulinemia who were followed for an average of 4 years [10].

It was suggested that only a subset of CVID is genetically related to IgA deficiency; this is likely the case in CVID patients who have relatives with IgA deficiency/CVID [3,7,18]. Earlier findings on family members with IgA deficiency and CVID identified susceptibility loci within the HLA region on chromosome 6p, where linkage analysis indicated a putative susceptibility locus termed *IGAD1* [19]. Subsequent findings also suggested that selected *HLA-DQ/DR* haplotypes conferred either protection from or susceptibility to IgA deficiency and CVID [20]. The strong influence of the major histocompatibility complex region was also noted in more recent cohorts [21,22]. Other studies on families with autosomal inheritance patterns pointed to a pathogenic gene for autosomal-dominant CVID/IgA deficiency on chromosome 4q [23].

Screening of family members of index cases showed that about one-third of multiply affected families had both CVID and IgA deficiency in first-degree relatives, implying that a large subset of cases diagnosed as CVID represent a more severe manifestation of a common defect [20,24]. In the current study, 3 siblings had IgA deficiency (2 partial and 1 selective). Only the patient with selective IgA deficiency had recurrent infections; the other 2 were asymptomatic. Additionally, 2 of the 3 offspring of patient 20 had IgA deficiency. Similarly, in an Iranian study in which relatives of 23 CVID patients were evaluated, 2 out of 64 relatives were found to be IgA-deficient [4].

The association between low Ig levels and allergic disorders is the subject of debate [6,25-29]. The inconsistency is partly due to differences in patient characteristics and to the outcome parameters investigated. In a population of adults who underwent screening, the researchers failed to demonstrate a higher atopy rate among those with IgA deficiency. On the other hand, increased prevalence of allergy has been reported among various pediatric patient groups with low IgA who mainly attended hospital with respiratory complaints [6,27,29]. Similarly, asthma is a frequent manifestation of hypogammaglobulinemia among young children [30]. In Turkish young adults, the prevalence of asthma, current wheeze, and seasonal rhinitis was reported to be 2.1%, 6.9%, and 12.7% in males and 2.5%, 7.2%, and 14.5% in females, respectively [31]. In the present study, 3 out of 16 mothers had rhinitis, and 2 of these had low immunoglobulin levels. Likewise, 1 of the 2 fathers with asthma had low IgM. However, despite the high frequency of hypogammaglobulinemia among the family members of CVID patients, allergic sensitization was not observed. High atopy rates among the index patients may be attributable to their low IgA levels, a condition previously recognized as a risk factor for atopy [9].

In conclusion, we found that many relatives of CVID patients display either a clinical history suggestive of PID or alterations of humoral immunity. It is noteworthy that 75% of our patients were the children of a consanguineous marriage. Six patients had PID warning signs and with hypogammaglobulinemia, 3 parents had low IgM levels, and 1 sibling had selective IgA deficiency, thus justifying clinical screening of the family members of CVID patients until more targeted genetic approaches become available.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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