ORIGINAL ARTICLE

Autoimmune Phenotype in Patients With Common Variable Immunodeficiency

H Abolhassani,[1] D Amirkashani,[1] N Parvaneh,[1] P Mohammadinejad,[1] B Gharib,[1] S Shahinpour,[1] A Hirbod-Mobarakeh,[1] M Mirghorbani,[1] M Movahedi,[2] M Gharagozlou,[2] N Rezaei,[1] A Aghamohammadi[1]

[1]Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Allergy and Clinical Immunology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background and objective: Autoimmune disorders occur with a higher incidence in common variable immunodeficiency (CVID) patients than in the general population. To describe the clinical features of the autoimmune phenotype in patients with CVID.
Methods: The hospital records of all diagnosed CVID patients referred to the Children's Medical Center Hospital in Tehran, Iran between 2000 and 2010 were reviewed. Patients were also classified according to the presence or absence of autoimmune disease.
Results: Of 52 patients studied, 26.9% (n=14) had shown at least 1 autoimmune manifestation during the study period. Autoimmune cytopenias and juvenile rheumatoid arthritis were the most common form of autoimmunity in our series. Autoimmunity was significantly associated with polyclonal lymphocytic infiltrative disorders (P=.017), increased serum Immunoglobulin (Ig) M levels (P<.001), decreased IgE values (P=.04) and diminished switched memory B-cell count (P<.001).
Conclusions: Because autoimmunity is one of the first manifestations in CVID, humoral immune system tests should be considered in autoimmune patients with a history of recurrent infection. The presence of polyclonal lymphocytic infiltrative disorders and decreased switched memory B-cells may predispose CVID patients to autoimmunity.

Key words: Autoimmune disorders. Common variable immunodeficiency. Clinical phenotypes.

Resumen

Antecedentes y objetivo: Las enfermedades autoinmunes se presentan asociadas, con una alta incidencia, en los pacientes con inmunodeficiencia común variable (IDCV), respecto a la población normal. El objetivo de este estudio fue describir los hechos clínicos del fenotipo autoinmune en pacientes con IDCV.
Métodos: Se revisaron las historias clínicas de todos los pacientes diagnosticados de IDCV del Medical Center Hospital de Teherán en el periodo de 2000-2010. Los pacientes fueron clasificados en dos grupos: con y sin enfermedades autoinmunes asociadas.
Resultados: De los 52 pacientes estudiados, un 26.9% (14 pacientes) habían mostrado al menos una manifestación de enfermedad autoinmune durante el tiempo del estudio. Las citopenias autoinmunes y la artritis reumatoide juvenil fueron las manifestaciones más frecuentes en nuestra serie. Encontramos en nuestros pacientes asociaciones significativas entre enfermedades infiltrativas polilinfocíticas (p=0.017), incremento de niveles de IgM sérica (p<0.001) y disminución de cifras de IgE (p=0.04) con desarrollo de autoinmunidad, así como una disminución de las células B memoria (p<0.001).
Conclusión: La autoinmunidad puede considerarse una de las manifestaciones iniciales en los pacientes con IDCV, por lo que se aconseja explorar el sistema inmunológico humoral mediante test in vitro, en aquellos pacientes con historias de infecciones de repetición. Por otra parte la presencia de enfermedades infiltrativas polilinfocíticas y la disminución de las células B memoria en pacientes con IDCV, pueden predisponer al desarrollo de una enfermedad autoinmune.

Palabras clave: Enfermedades autoinmunes. Inmunodeficiencia común variable. Fenotipos clínicos.

Introduction

Common variable immunodeficiency (CVID), which is the most prevalent symptomatic primary immunodeficiency disease (PID), constitutes a heterogeneous group of disorders characterized by hypogammaglobulinemia and recurrent bacterial infections that mainly affect the respiratory and gastrointestinal tracts [1,2]. Autoimmune and lymphoproliferative disorders occur with a higher incidence in patients with CVID than in the general population [1-3]. CVID can present at any age, but its 2 peaks of occurrence are in childhood and early adulthood [1]. The main defect in CVID is a failure in B-cell differentiation, with impaired secretion of immunoglobulins, although T-cell and dendritic-cell abnormalities have also been reported [1].

Approximately 20% to 30% of patients with CVID develop autoimmune disorders, which sometimes present as the first manifestation of the disease [1]. Although many forms of autoimmunity have been described in CVID, including juvenile rheumatoid arthritis (JRA), pernicious anemia, autoimmune thyroiditis, alopecia areata, primary biliary cirrhosis, vitiligo, and systemic lupus erythematosus, the most common types reported are idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) [4].

Early diagnosis of antibody deficiency is important because delayed or inadequate treatment leads to more irreversible complications and increased mortality [5,6]. Autoimmune complications may be the first manifestation of CVID in patients with no remarkable history of recurrent or severe infections. As a result, it is important for physicians to be aware of these manifestations in order to reduce the diagnostic delay and establish timely immunoglobulin replacement therapy. Moreover, autoimmune conditions in CVID patients are poorly understood and, in many cases, difficult to manage in the clinical setting [7]. The aim of this article is to describe the clinical and laboratory features of autoimmune manifestations in patients with CVID and to compare these with the features of other forms of CVID in order to add to the knowledge in this area.

Patients and Methods

Patients

The Children's Medical Center Hospital (CMC), which is affiliated with Tehran University of Medical Sciences, is a referral center for patients with known or suspected PID in Iran. In this study, we reviewed the medical records of patients with a confirmed diagnosis of CVID who were referred to the CMC between 2000 and 2010. Diagnosis was made according to standard criteria [8], which included a reduction of at least 2 serum immunoglobulin (Ig) isotypes (serum IgG, IgA, and IgM) by 2 SDs from normal mean values for age and exclusion of other well-known immune system disorders. We excluded patients under 4 years of age to rule out a probable diagnosis of transient hypogammaglobulinemia of infancy. Patients for whom information could not be retrieved were also excluded. Information for patients who did not undergo regular follow-up at the CMC during the study period was obtained by contacting the patients, their treating physician, or by scheduling a new visit with an immunologist. The study was approved by the medical ethics committee of Tehran University of Medical Sciences.

Methods

A 6-page questionnaire was designed to collect all the necessary information, including date of birth, first clinical presentation, age at onset of symptoms, age at time of diagnosis, consanguinity of parents, past medical history, history of other complications including recurrent infections, malignancy, polyclonal lymphocytic infiltration, and enteropathy manifestations [9]. This questionnaire was completed for all patients included in the study using data from the Iranian PID Registry [2]. Laboratory findings were retrieved from the same database to confirm autoimmunity and determine immunoglobulin levels and lymphocyte subsets [10]. We scheduled autoantibody detection tests in cases where additional information was needed to define specific autoimmune diseases [11]. Other procedures, such as endoscopies and biopsies, were performed if medically indicated to confirm the diagnosis of the autoimmune disorder.

Statistical Analysis

All statistical analyses were performed using SPSS software version 16.0. We classified patients based on the presence or absence of autoimmunity. Comparisons between groups were performed using the *t* test (2-group comparisons) for continuous data and the χ^2 test to compare rates and ratios between groups. Differences were considered significant when the *P* value was lower than .05.

Results

At the final stage of the study, of the total number of patients identified with CVID (n=120), 52 patients (39 male and 13 female) were evaluated for autoimmune disease. The mean (SD) age of this selected group (n=52) was 13.6 (1.0) years at the time of study and 5.7 (4.7) years at the time of CVID diagnosis. Thirty-three patients (63.4%) were children of consanguineous parents and 16 patients (30.7%) had a family history of PID. The patients' immunologic laboratory data are summarized in Table 1.

Fourteen patients (26.9%) had at least 1 confirmed autoimmune disorder at the time of the study (Table 2). Two of these (14.2%) were diagnosed with an autoimmune disease before they developed recurrent infections or other signs of CVID. AIHA, JRA, and ITP were the most common autoimmune disorders in our series. The prevalence of autoimmune disease was 46.1% in female patients (6/13) and 20.5% in male patients (8/39). Although autoimmunity was more common in females, the difference with males was not significant (*P*=.086). Moreover a family history of PID was not significantly associated with autoimmunity (*P*=.29).

There was no significant difference between the ages of CVID patients with autoimmune disease and those without (Table 1).

Table 1. Immunologic Characteristics of Patients With Common Variable Immunodeficiency[a]

Variables	Patients			
	Patients (n=52)	Patients With Autoimmunity (n=14)	Patients Without Autoimmunity (n=38)	*P* Value
Absolute lymphocyte counts				
$CD3^+$ lymphocytes, cell/mL	1649.3 (917.5)	1877.1 (749.1)	1535.5 (1003.5)	.41
$CD4^+$ T cells, cell/mL	786.5 (538.3)	847.7(312.0)	755.9 (632.8)	.05[b]
$CD8^+$ T cells, cell/mL	886.9 (464.0)	749.5 (261.1)	955.6 (535.1)	.10
$CD19^+$ lymphocytes, cell/mL	579.9 (302.8)	786.2 (369.3)	340.2 (323.1)	.036[b]
Immunoglobulins				
IgG, mg/dL	230.8 (217.0)	209.6(162.8)	273.2 (30.1)	.07
IgM, mg/dL	51.7(9.5)	57.4 (35.0)	28.6 (21.9)	<.001[b]
IgA, mg/dL	27.0(6.9)	31.0 (8.4)	19.8 (12.7)	.25
IgE, IU/mL	3.30 (3.07)	2.51(2.05)	3.78 (1.4)	.04[b]

Abbreviation: Ig, immunoglobulin.
[a]Data are presented as mean (SD) unless otherwise specified.
[b]Statistically significant.

Table 2. Characteristics of 14 CVID Patients With Autoimmune Disorders in the Study Population

Patients	Sex	Age, y	Type of Autoimmunity	Consanguinity	Family History of PID
1	M	21	AIHA	Yes	No
2	M	21	JRA	Yes	No
3	M	18	Crohn disease	Yes	Yes
4	M	13	ITP	Yes	No
5	F	8	JRA	Yes	No
6	M	13	Autoimmune hepatitis	Yes	No
7	M	10	JRA	No	No
8	F	15	ITP	Yes	Yes
9	M	16	ITP	No	No
10	M	4	AIHA	No	Yes
11	F	2	AIHA	Yes	No
12	F	16	JRA	Yes	No
13	F	16	Autoimmune hepatitis	No	No
14	F	5	AIHA	Yes	No

Abbreviations: AIHA: autoimmune hemolytic anemia; CVID, common variable immunodeficiency; F, female; ITP: idiopathic thrombocytopenic purpura; JRA: juvenile rheumatoid arthritis; M, male; PID: primary immunodeficiency.

However the mean (SD) duration of disease in patients with autoimmunity (10.8 [5.9] years) was significantly higher than in those without (7.0 [2.3] years) (*P*=.004).

Although patients with consanguineous parents had a higher probability of developing an autoimmune disorder, the increase in risk was not significant. Ten (30.3%) of the 33 patients with consanguineous parents had autoimmunity compared with 4 (21.5%) of the 19 patients without (*P*=.46).

The polyclonal lymphocytic infiltration phenotype, which includes splenomegaly, lymphadenopathy, and granulomatous lesions, was significantly more common in autoimmune patients (42.8% vs 21.0%, *P*=.017).

With regard to the relationship between the use of medications and autoimmunity, the only significant association was found for trimethoprim–sulfamethoxazole (co-trimoxazole) (odds ratio, 0.35; *P*<.001). We consider this effect to be a confounder factor and performed all statistical analyses after eliminating this potential bias.

The mean (SD) serum level of IgM was significantly higher in patients with autoimmunity (57.4 [35.0] mg/dL) than in those without (28.6 [21.9] mg/dL, *P*<.001; Figure 1). A similar finding was observed for absolute B-cell count, which was also significantly higher in autoimmune patients (*P*=.036, Table 1). By contrast, patients with autoimmune disease had significantly

lower IgE levels (2.51 [2.05] vs 3.78 [1.4] IU/mL, *P*=.04) and a lower percentage of $CD27^+IgM^-IgD^-$ switched memory B cells (0.51% [0.04] vs 1.02% [0.72] of peripheral blood lymphocytes, *P*<.001).

We also compared the clinical and immunologic data between individuals with autoimmune cytopenias and other types of autoimmune disease. Those with cytopenia were older at the time of onset (*P*=.01, Table 3) and had significantly lower serum levels of IgA (16.2 [12.1] vs 27.7 [4.8] mg/dL, *P*=.048), and IgE (1.43 [0.9] vs 7.5 [3.2] IU/mL, *P*<.001).

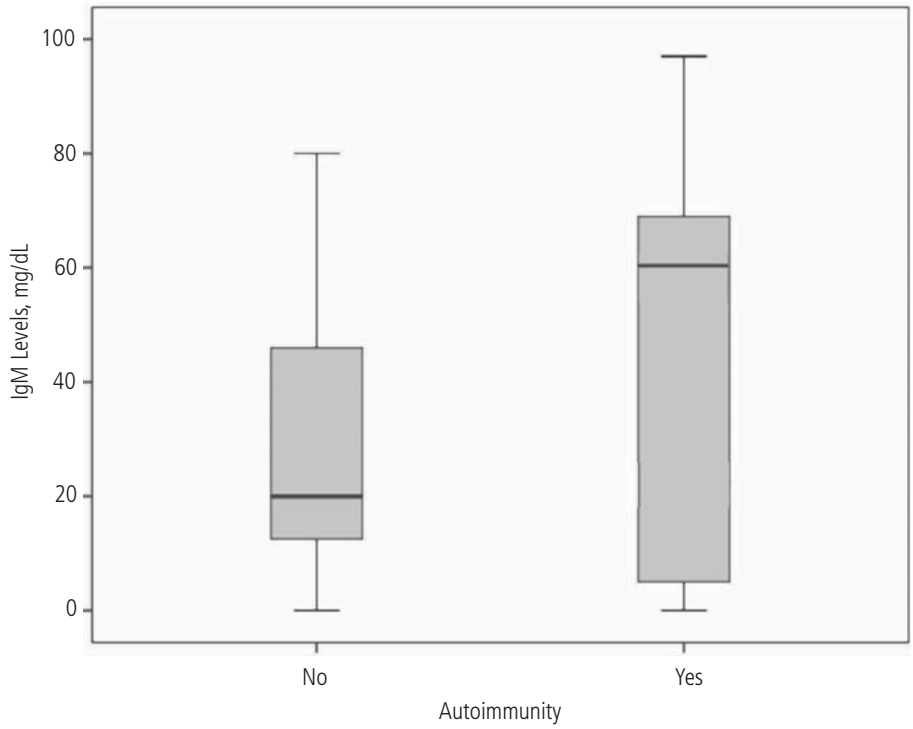

Figure. Comparison of immunoglobulin (Ig) M levels between patients with common variable immunodeficiency according to the presence and absence of autoimmune manifestations.

Table 3. Classification of Autoimmune CVID Patients Based on the Type of Autoimmunity[a]

Parameters	Autoimmune Cytopenia (n=7)	Other Types of Autoimmunity (n=7)	*P* Value
Clinical data			
Age at onset of disease, y	1.14 (0.8)	4.0 (3.2)	.01[b]
Age at time of diagnosis, y	5.14 (4.2)	7.6 (1.8)	.15
Male to female ratio	3:4	3:4	1.0
Parental consanguinity, No. (%)	2 (28.5)	2(28.5)	.72
PLI manifestation, No. (%)	4 (57.1)	2(28.5)	.29
Absolute Lymphocyte Counts			
$CD3^+$ lymphocytes, cell/mL	2232.8 (944.1)	1913.0 (700.6)	.51
$CD4^+$ T cells, cell/mL	950.4 (458.0)	937.9(326.2)	.14
$CD8^+$ T cells, cell/mL	691.2 (213.8)	818.2 (364.9)	.56
$CD19^+$ lymphocytes, cell/mL	685.4 (460.2)	787.9 (310.2)	.19
Immunoglobulins			
IgG, mg/dL	386.1 (254.0)	67.17 (11.5)	.07
IgM, mg/dL	53.5 (34.2)	29.0 (4.5)	<.001[b]
IgA, mg/dL	16.2 (12.1)	37.7 (4.8)	.048[b]
IgE, IU/mL	1.43 (0.9)	7.5 (3.2)	<.001[b]

Abbreviations: Ig, immunoglobulin; PLI, polyclonal lymphocytic infiltration.
[a]Data are presented as mean (SD) unless otherwise specified.
[b]Statistically significant.

Discussion

Finally, 27% of patients with CVID in this series had autoimmune manifestations. Despite the high number of consanguineous marriages in Iran [12], the prevalence of autoimmunity in our series was not dissimilar to figures reported by studies from other countries, in which clinical or serologic autoimmune manifestations were found in 22% of American patients [1], 25.89% of Italian patients [13], and 37% of French patients [14].

In agreement with previous studies on CVID [1,4], over 50% of CVID patients with autoimmune disease have hematologic cytopenias, such as AIHA and ITP [15,16]. Both ITP and AHIA are rare in the general population (annual incidence of 1.0-12.5 and 1-3 cases per 100 000 population, respectively) [17].

JRA was very common in our series (28.5% of autoimmune CVID cases), contrasting with previous reports. In a study of 248 CVID patients, 6% and 4.8% of the patients had ITP and AIHA, respectively, while JRA occurred only in 1.6% of cases [1]. Autoimmune hepatitis and Crohn disease were other autoimmune manifestations in our patients. Cunningham-Rundles et al [1] also reported that approximately 6% of the patients in their study had inflammatory bowel disease and 2.8% had hepatitis due to an unknown cause [1].

Environmental and genetic factors can influence the incidence of autoimmune diseases. One of the most well-defined and influential factors is sex [18]. Although most of the patients with autoimmunity in our series were male, prevalence was higher in females, coinciding with previous reports [19]. It has been shown that sex hormones can influence both helper T cell 1 and 2 responses and even fluctuations in these hormones can affect the severity of autoimmunity [18]. The X chromosome complement may also directly contribute to the development of autoimmunity in females. Theoretically, more antigen heterogeneity in women could be assumed due to random X chromosome inactivation in somatic cells [18].

Co-trimoxazole had quite a significant reverse relationship with autoimmunity in our patients. This drug, which has not been considered a confounder in previous reports, is used as a prophylactic antibiotic in PID patients. By inhibiting nuclear factor-κB signaling activation, it can contribute to both anti-inflammatory and immunosuppressive effects [20]. Secondary effects on T cells may be responsible for the effect of co-trimoxazole on the prevention of autoimmunity in CVID patients. There has also been a report of successful treatment of certain autoimmune diseases such as alopecia areata with co-trimoxazole [21].

We found a strong association between autoimmunity and increased IgM and decreased IgE levels at the time of diagnosis. In other forms of PID, such as Wiskott-Aldrich syndrome, an association between high levels of IgM and development of autoimmunity has been previously reported [22]. In a European study, Chapel et al [23] reported associations between high IgM levels and the development of polyclonal lymphocytic infiltration and lymphoid malignancy [23]. We observed decreased levels of switched memory B cells in CVID patients with autoimmune disease. In fact, it could be suggested that a hidden defect in the class switching recombination leads to IgM increases, IgE decreases, and autoimmunity. It also predisposes individuals with CVID to overexpression of enzymes needed for both class switching and somatic hypermutation (eg, activation-induced cytidine deaminase) to compensate for this defect [24].

The strong correlation between autoimmunity and the polyclonal lymphocytic infiltration phenotype observed in this study may support the hypothesis that the origin of these disorders lies in immune dysregulation in selected CVID patients [25]. Similar molecular evidence has been described in both phenotypes, including a defect in the *TACI* gene [26], ineffective B-cell receptor signaling or other abnormal ligand interactions [16], elevated serum levels of special cytokines such as BAFF or APRIL [27], uncontrolled somatic hypermutation [28], reduced $IgD^{-}CD27^{+}$ [29,30] and $CD21^{-}$ B cells [31], increased CD4/CD8 ratios, and decreased $CD4^{+}CD25$(high) $Foxp3^{+}$ regulatory T cells [32]. Surprisingly, defects of this type are also seen in autoimmune cytopenias.

By contrast, there have been reports of an association between repeated antigen exposure due to early recurrent infections, special human leukocyte antigen haplotypes, and defects in classical complement pathway (mannose-binding lectin polymorphisms), which result in immune complex formation or defective pathogen clearance, in CVID patients with other types of autoimmunity such as SLE and JRA [19].

In a recent study, Boileau et al [33] studied differences in clinical and immunologic data of 116 CVID patients (55 with autoimmune cytopenias and 61 with other types of autoimmunity). They noted that diagnosis was made later in the first group of patients (43 vs 29 years), supporting our findings. They also found that ITP and AIHA were more closely associated with splenomegaly, but unlike us, they did not find such an association for granulomatous disease. More clinical studies are needed to investigate the value of classification of types of autoimmune disease in CVID.

Although treatment of PID is complicated by the restrictions and cautions associated with immune suppression [34,35], increased doses of intravenous immunoglobulin [4], lower doses and shorter cycles of corticosteroids [19], anti-CD20 monoclonal antibody (rituximab) [36], and tumor necrosis factor α antagonists (infliximab) can be used to treat CVID with autoimmunity [35].

Conclusions

Autoimmunity is one of the first manifestations of CVID, and humoral immune system tests should therefore be considered in autoimmune patients with a history of recurrent infection. The presence of polyclonal lymphocytic infiltrative disorders and decreased switched memory B cells in CVID may predispose patients to autoimmunity.

Funding

This work was supported by a grant (88-04-30-9644) from Tehran University of Medical Sciences.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34-48.
2. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, Movahedi M, Gharagozlou M, Ghazi BM, Mahmoudi M, Mansouri D, Arshi S, Trash NJ, Akbari H, Sherkat R, Hosayni RF, Hashemzadeh A, Mohammadzadeh I, Amin R, Kashef S, Alborzi A, Karimi A, Khazaei H. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol. 2002;22:375-80.
3. Abolhassani H, Aghamohammadi A, Imanzadeh A, Mohammadinejad LP, Sadeghi B, Rezaei N. Malignancy phenotype in common variable immunodeficiency. J Investig Allergol Clin Immunol. 2012;22:133-4.
4. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun. 2005;25:57-62.
5. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol. 2005;58:546-7.
6. Rezaei N, Mohammadinejad P, Aghamohammadi A. The demographics of primary immunodeficiency diseases across the unique ethnic groups in Iran, and approaches to diagnosis and treatment. Ann N Y Acad Sci. 2011;1238:24-32.
7. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmun Rev. 2006;5:156-9.
8. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol. 2007;120:776-94.
9. Aghamohammadi A, Abolhassani H, Moazzami K, Parvaneh N, Rezaei N. Correlation between common variable immunodeficiency clinical phenotypes and parental consanguinity in children and adults. J Investig Allergol Clin Immunol. 2010;20:372-9.
10. Vodjgani M, Aghamohammadi A, Samadi M, Moin M, Hadjati J, Mirahmadian M, Parvaneh N, Salavati A, Abdollahzade S, Rezaei N, Srrafnejad A. Analysis of class-switched memory B cells in patients with common variable immunodeficiency and its clinical implications. J Investig Allergol Clin Immunol. 2007;17:321-8.
11. Shoenfeld Y, Cervera R, Gershwin M. Diagnostic Criteria in Autoimmune Diseases. XIV ed: Humana Press. 2008.
12. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, Mirsaeid Ghazi B, Atarod L, Abolmaali K, Mahmoudi M, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Amin R, Kashef S, Hosseini RF, Mohammadzadeh I, Shabestari MS, Nabavi M, Moin M. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol. 2006;56:145-51.
13. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, Claudio P, Franco D, Maria Pesce A, Borghese F, Guerra A, Rondelli R, Plebani A. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol. 2007;27:308-16.
14. Boileau J, Mouillot G, Gerard L, Carmagnat M, Rabian C, Oksenhendler E, Pasquali JL, Korganow AS. Autoimmunity in common variable immunodeficiency: correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun. 2011;36:25-32.
15. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol. 2009;145:709-27.
16. Cunningham-Rundles C. Autoimmune manifestations in common variable immunodeficiency. J Clin Immunol. 2008;28 Suppl 1:S42-5.
17. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol. 2002;69:258-71.
18. Rubtsov AV, Rubtsova K, Kappler JW, Marrack P. Genetic and hormonal factors in female-biased autoimmunity. Autoimmun Rev. 2010;9:494-8.
19. Brandt D, Gershwin ME. Common variable immune deficiency and autoimmunity. Autoimmun Rev. 2006;5:465-70.
20. Weber CK, Liptay S, Wirth T, Adler G, Schmid RM. Suppression of NF-kappaB activity by sulfasalazine is mediated by direct inhibition of IkappaB kinases alpha and beta. Gastroenterology. 2000;119:1209-18.
21. Rozin AP, Schapira D, Bergman R. Alopecia areata and relapsing polychondritis or mosaic autoimmunity? The first experience of co-trimoxazole treatment. Ann Rheum Dis. 2003;62:778-80.
22. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, de Saint Basile G, Delaunay J, Schwarz K, Casanova JL, Blanche S, Fischer A. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics. 2003;111:e622-7.
23. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, Fieschi C, Thon V, Abedi MR, Hammarstrom L. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112:277-86.
24. Salek Farrokhi A, Aghamohammadi A, Pourhamdi S, Mohammadinejad P, Abolhassani H, Moazzeni SM. Evaluation of class switch recombination in B lymphocytes of patients with common variable immunodeficiency. J Immunol Methods 2013.
25. Podjasek JC, Abraham RS. Autoimmune Cytopenias In Common Variable Immunodeficiency. Front Immunol. 2012;3:189.
26. Salzer U, Bacchelli C, Buckridge S, Pan-Hammarstrom Q, Jennings S, Lougaris V, Bergbreiter A, Hagena T, Birmelin J, Plebani A, Webster AD, Peter HH, Suez D, Chapel H, McLean-Tooke A, Spickett GP, Anover-Sombke S, Ochs HD, Urschel S, Belohradsky BH, Ugrinovic S, Kumararatne DS, Lawrence TC, Holm AM, Franco JL, Schulze I, Schneider P, Gertz EM, Schaffer AA, Hammarstrom L, Thrasher AJ, Gaspar HB, Grimbacher B. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. Blood. 2009;113:1967-76.
27. Knight AK, Radigan L, Marron T, Langs A, Zhang L, Cunningham-Rundles C. High serum levels of BAFF, APRIL, and TACI in common variable immunodeficiency. Clin Immunol. 2007;124:182-9.
28. Cunningham-Rundles C. Autoimmunity in primary immune deficiency: taking lessons from our patients. Clin Exp Immunol. 2011;164 Suppl 2:6-11.

29. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M, Hernandez M, Detkova D, Bos PR, Poerksen G, von Bernuth H, Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-van der Cruyssen F, Le Garff M, Debre P, Jacobs R, Jones J, Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE, Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M, Oksenhendler E, Peter HH, Warnatz K. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111:77-85.
30. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99:1544-51.
31. Isnardi I, Ng YS, Menard L, Meyers G, Saadoun D, Srdanovic I, Samuels J, Berman J, Buckner JH, Cunningham-Rundles C, Meffre E. Complement receptor 2/CD21- human naive B cells contain mostly autoreactive unresponsive clones. Blood. 2010;115:5026-36.
32. Genre J, Errante PR, Kokron CM, Toledo-Barros M, Camara NO, Rizzo LV. Reduced frequency of CD4(+)CD25(HIGH)FOXP3(+) cells and diminished FOXP3 expression in patients with Common Variable Immunodeficiency: a link to autoimmunity? Clin Immunol. 2009;132:215-21.
33. Boileau J, Mouillot G, Gerard L, Carmagnat M, Rabian C, Oksenhendler E, Pasquali JL, Korganow AS. Autoimmunity in common variable immunodeficiency: correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun. 2011;36:25-32.
34. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Curr Allergy Asthma Rep. 2009;9:347-52.
35. Lopes-da-Silva S, Rizzo LV. Autoimmunity in common variable immunodeficiency. J Clin Immunol. 2008;28 Suppl 1:S46-55.
36. Giulino LB, Bussel JB, Neufeld EJ. Treatment with rituximab in benign and malignant hematologic disorders in children. J Pediatr. 2007;150:338-44, 44 e1.

Manuscript received November 14, 2012; accepted for publication January 11, 2013.

Asghar Aghamohammadi

Children's Medical Center Hospital
62 Qarib St., Keshavarz Blvd.
Tehran 14194, Iran
E-mail: aghamohammadi@sina.tums.ac.ir

