ORIGINAL ARTICLE

Correlation Between Common Variable Immunodeficiency Clinical Phenotypes and Parental Consanguinity in Children and Adults

A Aghamohammadi,[1] H Abolhassani,[1] K Moazzami,[1] N Parvaneh,[1] N Rezaei[1,2]

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

Abstract

Background: Common variable immunodeficiency (CVID) is a heterogeneous group of disorders with a wide range of clinical manifestations and immunological findings, which could possibly form the basis for classification into different phenotypes.
Objectives: This study was performed to distinguish between different clinical phenotypes in Iranian patients with CVID and compare complications and prognosis between these subgroups.
Methods: Ninety-three CVID patients were classified according to 5 clinical phenotypes: infections only (n=42), polyclonal lymphocytic infiltration (n=35), autoimmunity (n=10), malignancy (n=10), and enteropathy (n=9). The patients were further categorized into 4 groups based on age of diagnosis (cutoff, 13 years) and parental consanguinity.
Results: Grouping of patients showed that CVID children with parental consanguinity was the most frequent group (51%), followed by CVID children without parental consanguinity (21%), CVID adults without parental consanguinity (21%), and CVID adults with parental consanguinity (7%). There were significant associations between the group of CVID children with parental consanguinity and the polyclonal lymphocytic infiltration (*P*=.011) and enteropathy (*P*=.048) phenotypes. This group also had a higher mortality rate than other groups (*P*=.014). High serum levels of immunoglobulin M (IgM) at the time of diagnosis were associated with the eventual development of autoimmunity (*P*=.023). The adjusted odds ratio (OR) for mortality in all phenotypes showed that mortality was significantly increased in patients with the polyclonal lymphocytic infiltration phenotype (Mantel-Haenszel OR=5.3, CI=3.42-6.2).
Conclusions: Parameters such as parental consanguinity and early onset of disease could describe a subgroup of CVID patients characterized by more complications, poorer prognosis, and a need for greater medical care and attention.

Key words: Common variable Immunodeficiency. Phenotyping. Consanguinity.

Resumen

Antecedentes: La inmunodeficiencia común variable (IDCV) es un grupo heterogéneo de trastornos con una gran diversidad de manifestaciones clínicas y cambios inmunológicos, que puede posiblemente constituir la base para la clasificación en diferentes fenotipos.
Objetivos: El objetivo de este estudio fue distinguir entre diferentes fenotipos clínicos en pacientes iraníes con IDCV y comparar las complicaciones y el pronóstico entre estos subgrupos.
Métodos: Se clasificaron 93 pacientes con IDCV según 5 fenotipos clínicos: solo infecciones (n = 42), infiltración linfocítica policlonal (n = 35), autoinmunidad (n = 10), neoplasia maligna (n = 10) y enteropatía (n = 9). Los pacientes fueron clasificados, además, en 4 grupos en función de la edad en el momento del diagnóstico (valor de corte: 13 años) y la consanguinidad parental.
Resultados: La agrupación de los pacientes mostró que el grupo de niños con IDCV con consanguinidad parental era el más frecuente (51%), seguido del grupo de niños con IDCV sin consanguinidad parental (21%), el de adultos con IDCV sin consanguinidad parental (21%), y el de adultos con IDCV con consanguinidad parental (7%). Se observaron asociaciones significativas entre el grupo de niños con IDCV con consanguinidad parental y los fenotipos de infiltración linfocítica policlonal (*p*=0,011) y enteropatía (*p*=0,048). En este grupo también se observó una tasa de mortalidad superior a la del resto de grupos (*p*=0,014). Niveles séricos elevados de inmunoglobulina M

en el momento del diagnóstico se asociaron al desarrollo posterior de autoinmunidad (p=0,023). La oportunidad relativa (odds ratio) ajustada para mortalidad en todos los fenotipos mostró que la mortalidad fue significativamente mayor en los pacientes con el fenotipo de infiltración linfocítica policlonal (ORMantel-Haenszel = 5,3; IC = 3,42 6,2).
Conclusiones: Parámetros como la consanguinidad parental y la aparición temprana de la enfermedad pueden describir un subgrupo de pacientes con IDCV caracterizado por más complicaciones, un peor diagnóstico y la necesidad de más atención y cuidados médicos.

Palabras clave: Inmunodeficiencia común variable. Fenotipado. Consanguinidad.

Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency disease [1-5]. It is a clinically heterogeneous disorder with recurrent bacterial infections, autoimmune manifestations, and lymphoproliferation [2, 6-10]. Attempts to identify the genes responsible for CVID have resulted in the detection of new monogenic defects in recent years [11]. Although various abnormalities in the innate and adaptive immune systems have been detected in CVID [12-20], the molecular bases of most phenotypes of the disease remain unknown.

It has been shown that certain groups of patients are particularly susceptible to early onset and more severe disease [21,22], while others display only mild to moderate clinical manifestations. As a result, several studies have attempted to classify subsets of patients on the basis of laboratory findings correlated with clinical features [21,23-25]. In a recent study performed in Europe, Chapel et al [1] classified CVID patients according to clinical phenotypes based on infectious and noninfectious manifestations [1]. Variability in clinical manifestations may reflect different pathogenic mechanisms. The effect of parental consanguinity and age of diagnosis of CVID has not been analyzed to date in such classifications.

The purpose of the present study was to classify patients into the same clinical phenotypes as those defined by Chapel et al [1] for European patients and to determine the relationship between these phenotypes and age of diagnosis and parental consanguinity.

Patients and Methods

Patients

The Immunodeficiency Clinic at the Children's Medical Center affiliated to the Tehran University of Medical Sciences in Iran is a referral center for both pediatric and adult patients with primary immunodeficiency diseases. From 1984 to 2009, 93 patients with CVID, who were diagnosed at older than 3 years and treated at this center, were selected to participate in the study. CVID was diagnosed on the basis of a reduction in at least 2 serum immunoglobulin (Ig) isotypes (serum IgG, IgA and/or IgM) by 2 SDs from normal mean values for the age of the patients.

Methods

A 2-page questionnaire was designed to collect information such as date of birth, age of onset of symptoms, age of diagnosis, and history of infectious and noninfectious complications.

Clinical Phenotyping

The patients were divided into 5 clinical phenotype groups using the criteria described for the European study [1]. The phenotypes were autoimmunity, polyclonal lymphocytic infiltration, malignancy, enteropathy, and infections only. Information on overlapping phenotypes was also recorded in all cases.

Grouping of Patients

The patients were categorized into 4 groups depending on the age of diagnosis (childhood [<13 years] or adulthood [>13 years]) and on the presence or absence of parental consanguinity.

Statistical Analysis

To explore the effect of parental consanguinity and age of diagnosis, we used the exact Fisher test for numbers or percentages in each phenotype category. Adjusted odds ratios (ORs) for mortality were calculated by logistic regression analysis in each clinical phenotype. Probabilities of survival after diagnosis of CVID were estimated using Kaplan–Meier life tables.

Results

Characteristics of Patients

Ninety-three CVID patients (54 male, 39 female) aged 4 to 58 years were included in the study. The demographic and immunological data corresponding to the group as a whole are presented in Table 1. The median age at the time of disease onset was 2 years (range, 0.5-46 years); 65 patients (70%) had their first manifestations before 5 years of age. The median age of diagnosis was 8 years (range, 3-54 years), with a median diagnostic delay of 6 years (range, 1-29 years). Sixty-five patients (70%) were diagnosed during childhood. The time from onset of symptoms to inclusion in the study was more than 10 years for 49 patients (52%) and more than 18 years in 15 (16%) of these patients. Fifty-four patients (58%) were the result of consanguineous marriages. The rate of parental consanguinity was significantly higher in the children than in the adults (47% vs 7%, P=.002).

Phenotyping of Patients

Figure 1 shows the frequencies of the 5 clinical phenotypes analyzed in our patients. The most common phenotype was infections only (42 patients), followed by polyclonal lymphocytic infiltration (35 patients). Eighty-three patients (90%) had a single phenotype; of the remaining 10 patients, 7 had 2 phenotypes and 3 had 3 phenotypes. The median follow-up period in these 10 patients was 10.5 years (range, 8-22 years), which was significantly higher than that observed in patients with a single phenotype (median, 4 years; range, 2-14 years) (P=.024). A significant association was found between patients with the infections-only phenotype and a shorter diagnostic delay (P=.03, r=-0.87, R^2=0.6). The demographic and immunological data for the patients classified by phenotype are shown in Table 2.

Grouping of Patients By Age and Parental Consanguinity

Four groups were created based on age at diagnosis (cutoff, 13 years) and parental consanguinity. Group 1 comprised children with parental consanguinity (n=47); group 2, children without parental consanguinity (n=18); group 3, adults with parental consanguinity (n=7); and group 4, adults without parental consanguinity (n=21).

Correlation between Phenotypes and Groups

Comparison of the clinical phenotype results between groups showed significantly higher associations between group 1 and polyclonal lymphocytic infiltration (P=.11) and enteropathy (P=.48) (Table 3 and Figure 2). Likewise, lower frequencies of the infections-only phenotype was associated with group 4 (P=.001). There were no significant differences between the 4 groups in terms of the frequency of lymphoid malignancy (P=.091) or autoimmunity (P=.77) (Table 3).

Table 1. Demographic and Immunological Data for 93 Patients With Common Variable Immunodeficiency

Parameter	
Male/female, No. of patients	54/39
Age, median (range), y	14 (3-58)
Age at onset, median (range), y	2 (0.5-46)
Age at diagnosis, median (range), y	8 (3-54)
Diagnostic delay, median (range), y	6 (1-29)
Follow-up, median (range), y	5 (1-22)
IgG, mean (SD), g/L	1.23 (0.43)
IgM, mean (SD), g/L	0.24 (0.17)
IgA, mean (SD), g/L	0.16 (0.11)
CD3, mean (SD), %	71 (21)
CD4, mean (SD), %	32 (17)
CD8, mean (SD), %	37 (10)
CD19, mean (SD), %	14 (7)

Abbreviation: Ig, immunoglobulin.

Laboratory Findings

The mean (SD) immunoglobulin levels at the time of diagnosis were 1.23 (0.12) g/L for IgG, 0.24 (0.11) g/L for IgM, and 0.16 (0.13) g/L for IgA (Table 1). High serum levels of IgM at the time of diagnosis were associated with the subsequent development of the autoimmunity phenotype (P=.006). However, there was no correlation between increased IgM and the development of polyclonal lymphocytic infiltration or lymphoid malignancy. Levels of IgA and IgG did not predict any specific phenotype.

Analysis of data did not reveal any associations between the percentage of lymphocyte subsets and clinical phenotypes. Increased CD4/CD8 ratios were significantly associated with the enteropathy phenotype (P=.029).

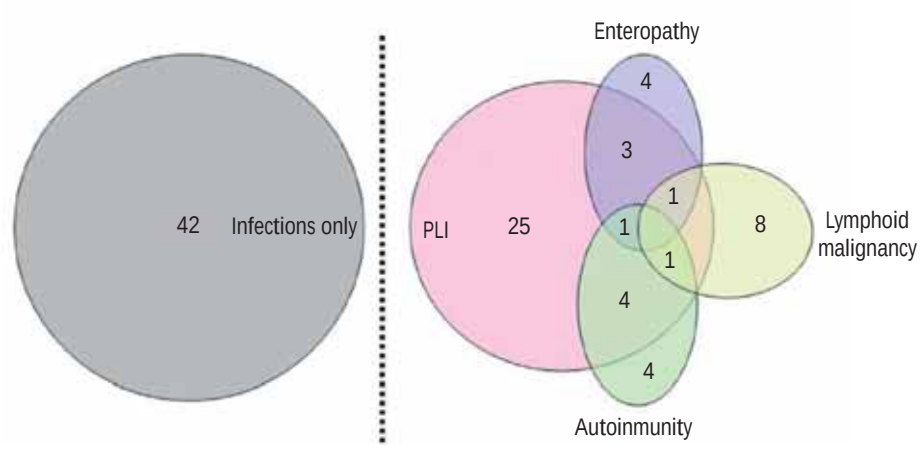

Figure 1. Frequency of clinical phenotypes in 93 patients with common variable immunodeficiency. PLI indicates polyclonal lymphocytic infiltration.

Table 2. Demographic Data and Immunological Data for 93 Patients With Common Variable Immunodeficiency

Parameter	Polyclonal Lymphocytic Infiltration	Infections Only	Autoimmunity	Enteropathy	Lymphoid Malignancy	*P*
Patients, No.	34	42	10	9	10	.082
Male/female patients, No.	19/16	26/16	6/4	7/2	5/5	.091
Age, median (range), y	11 (3-34)	13 (4-19)	19 (14-44)[a]	17 (10-37)	16 (12-59)	.021
Age at onset, median (range), y	2 (1-13)	1 (0.5-3)	6 (1-23)	1 (0.5-7)	7 (2-46)[a]	.042
Age at diagnosis, median (range), y	7 (5-14)	5 (3-9)	15 (7-54)[a]	8 (4-28)	13 (6-33)	.048
Diagnostic delay, median (range), y	6 (4-10)	2 (1-11)[a]	9 (5-17)	5 (2-9)	11 (4-29)	.032
Follow-up, median (range), y	4 (1-8)	5 (2-11)	6 (1-14)	10 (3-19)	5 (1-22)	.19
IgG, mean (SD), g/L	1.02 (0.65)	1.14 (0.30)	1.32 (0.37)	1.20 (0.51	1.25 (0.43)	.40
IgM, mean (SD), g/L	0.21 (0.15)	0.14 (0.9)	0.53 (0.08)[a]	0.29 (0.10)	0.17 (0.11	.006
IgA, mean (SD), g/L	0.14 (0.04)	0.12 (0.05)	18 (9)	0.19 (0.04)	0.20 (0.06)	.23
CD3, mean (SD), %	69 (30)	68 (15)	72 (26)	75 (11)	67 (34)	.12
CD4, mean (SD), %	34 (14)	33 (10	32 (16)	39 (7)	34 (14)	.85
CD8, mean (SD), %	39 (21)	35 (12)	36 (17)	28 (11)	37 (18)	.18
CD4/CD8, mean (SD), %	0.87 (0.14)	0.94 (0.18)	0.89 (0.24)	1.39 a (0.25)	0.92 (0.11)	.029
CD19, mean (SD), %	9 (2)	9 (6)	8 (5)	13 (2)	14 (7)	.21

Abbreviation: Ig, immunoglobulin.
[a]Statistically significant at .05 by 1-way analysis of variance test.

Table 3. Comparison of Clinical Phenotypes According to Both Consanguinity and Time of Onset of Common Variable Immunodeficiency (CVID)

Phenotype	Total (n=93)	Early Onset (Pediatric CVID) (n=65)		Late Onset (Adult CVID) (n=28)		*P*
		Group 1: with consanguinity (n=47)	Group 2: without consanguinity (n=18)	Group 3: with consanguinity (n=7)	Group 4: without consanguinity (n=21)	
Polyclonal lymphocytic infiltration	35	22 (62.8)[a]	6 (17.2)	2 (5.7)	5 (14.2)	.011
Infections only	42	19 (45.2)[a]	7 (16.6)	3 (7.1)	13 (31)	.001
Autoimmunity	10	4 (40)	3 (30)	2 (20)	1 (10)	.77
Enteropathy	9	5 (56)[a]	2 (22)	0	2 (22)	.049
Lymphoid malignancy	10	3 (30)	3 (30)	0	4 (40)	.091

[a]Statistically significant at .05 by nonparametric *t* test.

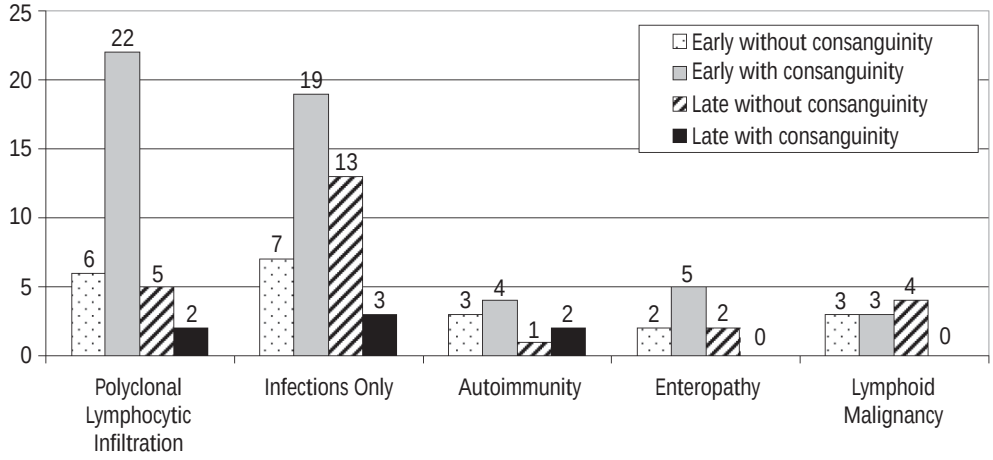

Figure 2. Comparison of clinical phenotypes according to both consanguinity and time of onset of common variable immunodeficiency.

Table 4. Crude Odds Ratios for Mortality Rate by Clinical Phenotype

Clinical Phenotype	Died/Total Patients (%)	Crude Odds (Dead/Alive Ratio)	Adjusted Odds Ratio for Mortality[a]	Confidence Interval
Polyclonal lymphocytic infiltration	16/35 (45.7)	16/19	4.5	3.42-6.2
Infections only	5/42 (11.9)	5/37	1.0[b]	–
Autoimmunity	4/10 (40)	4/6	1.28	0.81-1.32
Enteropathy	1/9 (11.1)	1/8	0.85	0.77-1.82
Lymphoid malignancy	4/10 (40)	4/6	1.87	0.86-2.54

[a]Odds ratio adjusted for sex, age and delay in diagnostic time.
[b]Calculated using infections only group as reference.

Table 5. Comparison of Iranian Common Variable Immunodeficiency Clinical Phenotypes With Previous Reports

Phenotype	United Kingdom, No. of Patients (%)	Sweden, No. of Patients (%)	Germany No. of Patients (%)	Czech Republic No. of Patients (%)	Iran, No. of Patients (%)
Polyclonal lymphocytic infiltration	37 (39)	15 (12)	21 (31)	22 (54)	35 (37)
Infections only	36 (37)	79 (61)	27 (40)	14 (34)	42 (45)
Autoimmunity	46 (48)	35 (27)	26 (38)	12 (29)	10 (10)
Enteropathy	12 (13)	4 (3)	7 (10)	6 (15)	9 (10)
Lymphoid malignance	5 (5)	1 (0.8)	4 (6)	0	10 (10)
Total	96	129	68	41	93

Survival and Mortality

The patients were followed up for a median of 5 years (range, 2-22 years) after diagnosis. Despite treatment with immunoglobulin replacement therapy (400-500 mg/kg every 3-4 weeks), 26 patients (28%) died during follow-up. Simple analysis based on mortality and delayed diagnosis only revealed that delayed diagnosis was significantly higher in the patients who had died (median, 7 years; range, 2-11 years) than in those who had survived (median, 4 years; range, 1-28 years). On calculating the crude OR for mortality, we found that patients with a longer diagnostic delay (>6 years) had a higher mortality rate (OR, 2.7; confidence interval [CI], 6-3.4) than the other patients. However, after adjusting for clinical phenotype, sex, and age, there were no significant associations between delayed diagnosis and mortality (Mantel-Haenszel OR [ORMH]=1.2; CI, 0.7-2.3).

On analyzing mortality by clinical phenotype, we found the highest rate for patients with polyclonal lymphocytic infiltration (45.7%), followed by those with autoimmunity and lymphoid malignancy (both 40%), infections only (11.9%), and enteropathy (11.1%), results which were concordant with the crude ORs calculated for mortality (Table 4). To determine the true relationship between mortality and the clinical phenotypes analyzed, we deconfounded other independent variables such as sex, age, and delay in diagnosis. The adjusted ORs in all the phenotypes showed that mortality was significantly higher in patients with polyclonal lymphocytic infiltration (ORMH=4.5; CI, 3.42-6.2) than the other groups (Table 4). Also, the survival rate in the infections-only group during the 15-year follow-up (approximately 86%) was significantly higher than that observed in the other clinical phenotypes collectively for the same period (59%) (P<.001).

Discussion

CVID is a heterogeneous group of disorders with a wide variety of presenting symptoms [2,3]. Although a substantial proportion of CVID patients develop infections, other phenotypes typically observed are autoimmunity, lymphoid malignancy, polyclonal lymphoid infiltration, and enteropathy. It has been shown that both outcome and prognosis vary within these subgroups of phenotypes [1].

Our study, which involved the clinical phenotyping of 93 Iranian CVID patients showed that the infections-only phenotype was the most frequent phenotype, affecting approximately half of the patients, followed by polyclonal lymphocytic infiltration. There were some differences between the frequencies of CVID phenotypes between our study and the results from European countries [1] (Table 5), possibly due to differences in genetic backgrounds.

Overlapping phenotypes were observed in 11% of our patients, which is lower than the figure of 17% reported for Europe by Chapel et al [1]. It should be noted that 61% of the European patients were followed for more than 18 years, while only 16% of our patients were followed for this period. The longer follow-up may explain the increased rates of overlapping phenotypes observed by Chapel et al. It is obvious that improvements in the management of patients with CVID in recent years have led to longer survival and consequently more complications [3, 26-28].

The grouping of patients showed that 50% of the group were under 13 years old and had consanguineous parents. Overall, the rate of parental consanguinity in Iran, particularly in CVID children, is much higher than in Western countries [29], which could suggest a possible role of autosomal recessive inheritance in our country [3,30].

In the current study, the polyclonal lymphocytic infiltration phenotype was significantly associated with the group of CVID children with consanguineous parents. This group also had higher mortality than the other groups. In a previous study performed at our center, we detected a positive relationship between parental consanguinity, childhood onset, and radiosensitivity [31]. Taken together, parameters such as radiosensitivity, consanguinity, and early childhood onset could describe a CVID subgroup with a specific single gene defect.

High serum levels of IgM at the time of diagnosis were associated with the development of the autoimmunity phenotype in our group, contrasting with the findings of the European study, which showed associations between high levels of IgM and the development of polyclonal lymphocytic infiltration and lymphoid malignancy [1]. However, high levels of IgM have been associated with the presentation and development of autoimmunity in other forms of primary immunodeficiency such as Wiskott-Aldrich syndrome in association with autoimmunity [32]. Also of interest, increased CD4/CD8 ratios were associated with the enteropathy phenotype in our study but with the autoimmunity phenotype in the European study [33].

We have previously shown that diagnostic delay has a direct impact on mortality in CVID [34]. In the present study, however, after adjusting for sex, age, and clinical phenotype, we found that high mortality was associated with the nature and severity of disease, which can be clarified by clinical phenotyping. In our group, the highest adjusted mortality rate was observed in patients with the polyclonal lymphocytic infiltration phenotype. In the European study, both the polyclonal lymphocytic infiltration and the lymphoid malignancy phenotypes were associated with high mortality [1].

Stratification of patients with CVID into distinct phenotypes may aid physicians to predict the outcome and prognosis of different patients with the same disease and also to provide proper management for patients who may require specific attention. The grouping of patients by age at diagnosis and parental consanguinity, correlated with clinical phenotyping, may also help to define more homogeneous subgroups (eg, CVID children with parental consanguinity), which could be useful for identifying the molecular bases of CVID in the future.

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Asghar Aghamohammadi

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

