ORIGINAL ARTICLE

Pediatric Patients With Common Variable Immunodeficiency: Long-term Follow-up

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Abstract

Background: Common variable immunodeficiency (CVID) is the most common form of symptomatic primary immunodeficiency disease. It is characterized by hypogammaglobulinemia, increased predisposition to infections, autoimmunity, and cancer.
Objectives: This study was performed to evaluate the clinical and immunological features of a group of pediatric patients with CVID.
Methods: The study population comprised 69 individuals with CVID diagnosed during childhood.
Results: The patients were followed up for a mean (SD) period of 5.2 (4.3) years. The mean diagnostic delay was 4.4 (3.6) years, which was significantly lower in patients who were diagnosed recently. Children were classified according to 5 clinical phenotypes: infections only (n=39), polyclonal lymphocytic infiltration (n=17), autoimmunity (n=12), malignancy (n=7), and enteropathy (n=3). Postdiagnosis survival (10-year) was 71%.
Conclusions: The high percentages of pediatric patients with CVID in Iran may be due to the considerable prevalence of parental consanguinity in the region and an underlying genetic background.

Key words: Common variable immunodeficiency. Hypogammaglobulinemia. Pediatrics. Follow-up.

Resumen

Antecedentes: La inmunodeficiencia común variable (IDCV) es la forma más frecuente de inmunodeficiencia primaria sintomática. Se caracteriza por hipogammaglobulinemia, aumento de la susceptibilidad a infecciones, autoinmunidad y neoplasias malignas.
Objetivos: Este estudio se realizó para evaluar las características clínicas e inmunológicas de un grupo de niños con IDCV.
Métodos: En la población del estudio se incluyó a 69 personas con IDCV diagnosticadas durante la infancia.
Resultados: Los pacientes fueron sometidos a un período de seguimiento medio (DE) de 5,2 (4,3) años. El retraso medio en el diagnóstico fue de 4,4 (3,6) años, que fue significativamente inferior en los pacientes que fueron diagnosticados recientemente. Los niños se clasificaron en 5 fenotipos clínicos: solo infecciones (n = 39), infiltración linfocítica policlonal (n = 17), autoinmunidad (n = 12), neoplasia maligna (n = 7) y enteropatía (n = 3). La supervivencia tras el diagnóstico (10 años) fue del 71%.
Conclusiones: Los elevados porcentajes de niños con IDCV en Irán pueden deberse a la prevalencia considerable de consanguinidad parental en la región y a antecedentes genéticos subyacentes.

Palabras clave: Inmunodeficiencia común variable. Hipogammaglobulinemia. Niños. Seguimiento.

Introduction

Common variable immunodeficiency (CVID) comprises a heterogeneous group of disorders characterized by hypogammaglobulinemia, defective specific antibody production, and increased susceptibility to recurrent and chronic infection [1-4]. Patients with CVID more frequently have autoimmune disorders and cancer [5-9]. CVID affects both sexes equally. It has an estimated prevalence ranging from 1 case per 10 000 inhabitants to 1 case per 50 000 inhabitants [10-12] and is the most prevalent human primary immunodeficiency requiring medical attention. Despite several studies on the pathophysiology of CVID, the exact etiology of the disease remains unclear [13-22].

CVID may present at any point in a patient's lifetime, although the 2 major peaks of onset are childhood (5 and 10 years of age) and the third decade. Several published articles report that diagnosis of CVID is more commonly made between the age of 20 and 40 years [1]. In the large cohort study by Cunningham-Rundles and Bodian (248 patients) [1], 20% of patients were under the age of 12 years. In a survey of 95 Finnish patients with CVID, only 16 patients (16%) were children aged 16 years or younger [23]. CVID in children has received less attention than CVID in adults.

Patients and Methods

Patient Selection

The study population comprised patients diagnosed with CVID between the ages of 4 and 16 years at the Children's Medical Center, a pediatric hospital affiliated to the Tehran University of Medical Sciences. A detailed questionnaire was completed for each patient to record demographic data, clinical manifestations, immunologic findings, long-term follow-up, complications, and mortality. Information on follow-up was gathered by regular visits and monthly prescription of intravenous immunoglobulin (IVIg). Follow-up was until the end of study, time of death, or last visit before discontinuation.

A definitive diagnosis of CVID was made according to the criteria of the European Society for Immune Deficiency and the Pan American Group for Immunodeficiency [24]. Diagnosis was based on a reduction in serum immunoglobulin (Ig) G level, at least 1 serum IgA and IgM level >2 SD of the normal mean values for age, and exclusion of other well-known immunodeficiency disorders. The patients' parents were considered to be related if parental consanguinity was of the first or second degree. Patients were divided into 5 clinical phenotypes using the criteria described for the European study [25], as follows: autoimmunity, polyclonal lymphocytic infiltration, malignancy, enteropathy, and infections only.

Laboratory Testing

Blood samples were tested for Ig levels and CD markers and compared with their normal quantitative range. Other laboratory tests included a complete blood count, isohemagglutinin titer, and Schick test. Measurements of B-cell and T-cell subsets of patients diagnosed before 1993 were repeated using flow cytometry, as the method used before 1993 was based on rosette formation. Pulmonary function tests were performed, as were other procedures when clinically indicated (eg, high-resolution computed tomography, endoscopy, and biopsy). Cause of death was recorded from the death certificate.

Statistical Methods

Immunological data and CD markers were evaluated using the results of the initial test performed at diagnosis. Linear regression was applied to determine the association between the time of onset of disease and diagnostic delay. The survival rate after the diagnosis of CVID was evaluated using the Kaplan-Meier method. Factors with a possible association with increased mortality were analyzed using the Cox proportional hazards model; the time variable was the interval between time of diagnosis of disease and time of death or most recent visit. We also compared the immunological parameters of patients who had died with those of live patients of the same age. The χ^2 test was used to analyze the differences between clinical presentations in live and dead patients and the Wilcoxon rank-sum test to calculate differences in immunological parameters. Values with a P value <.05 were considered significant. Data were analyzed using SPSS version 11.5.

Results

Patient Characteristics

We identified 93 patients diagnosed with CVID in the primary immunodeficiency database of the Children's Medical Center between 1984 and 2010. This sample included 69 patients (74.1%) who were under 16 years of age at diagnosis (35 males [50.7%] and 34 females [49.3%]). Patients were followed up for a total of 333 patient-years (mean [SD], 5.16 [4.33] years; range, 1-21 years). The mean diagnostic delay was 4.40 (3.59) years, which was significantly lower in the patients who were diagnosed in recent years (r=–0.42, R^2=0.017; P=.001). Figure 1 shows the inverse association between diagnostic delay and year of diagnosis. Demographic information and immunological data are shown in Table 1.

Family history of immunodeficiency was recorded, and first-degree parental consanguinity was observed in 50

Table 1. Demographic Information of 69 Children with Common Variable Immunodeficiency (CVID)

Parameter	Results
Number of patients, M/F	35/34
Mean (SD) age at the time of the study, y	14.07 (6.55)
Mean (SD) age at the time of onset, y	2.29 (2.86)
Mean (SD) age at the time of diagnosis, y	6.76 (4.2)
Mean (SD) diagnostic delay, y	4.4 (3.59)
Mean (SD) duration of follow-up, y	5.16 (4.33)
Patients with consanguineous marriage of parents, No. (%)	50 (72%)
Patients with diagnosis of CVID in a sibling, No. (%)	10 (14%)

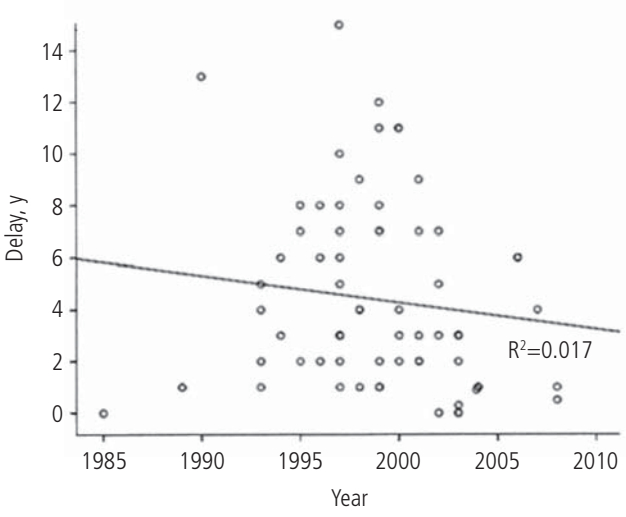

Figure 1. Correlation between diagnostic delay and time of diagnosis.

patients (72.4%); 10 patients (14.4%) who had a sibling with CVID were defined as multiple cases. These patients did not differ significantly from the rest of the study population in age at onset, age at diagnosis, mortality rate, or parental consanguinity. The clinical features of multiple cases are summarized in Table 2.

Serum Immunoglobulin Levels and Lymphocyte Studies

The mean serum levels were as follows: IgG, 286.86 (275.62) mg/dL (range, 0-240 mg/dL); IgA, 18.39 (31.74) mg/dL (range, 0-20 mg/dL); and IgM, 39.92 (36.92) mg/dL (range, 0-640 mg/dL). The mean values of IgG, IgM, and IgA were also compared for different age groups and are shown in Table 3.

The mean number of white blood cells was 11 754.7 (7540.4) cells/mm^3, and the mean percentage of lymphocytes was 39.9% (10.6%). Lymphocyte markers were measured in all patients, and the mean percentage for CD3, CD4, CD8, and CD19 was 70.45 (17.7), 30.98 (13.2), 36.68 (13.87), and 11.39 (1.45), respectively. Lower than normal values of CD markers were observed, as follows: CD3 in 5 patients (7.2%),

Table 2. Clinical Characteristics of Multiple Cases

Pair	Patient	Sex	Consanguinity	Cause of Death	Characteristics
1	1	Male	No	NA	Diarrhea, otitis media, and sinusitis
	2	Male	No	NA	
2	3	Male	Yes	NA	Otitis media, diarrhea, clubbing, and hepatomegaly
	4	Female	Yes	Pneumonia	
3	5	Male	No	Hodgkin lymphoma	Hodgkin lymphoma, pneumonia, meningitis, lymphadenopathy, and splenomegaly
	6	Female	No	Hodgkin lymphoma	
4	7	Male	Yes	NA	Pneumonia and diarrhea
	8	Female	Yes	NA	
5	9	Female	Yes	NA	Hypothyroidism

Abbreviation: NA, not applicable.

Table 3. Immunologic Findings of 69 Pediatric Patients With Common Variable Immunodeficiency[a]

	Total	Age 2-5 y	Age 6-10 y	Age 10-16 y
No.	69	31	23	15
IgG, mg/dL	286.86 (275.62)	239.83 (218.00)	298.54 (267.2)	366.13 (378.21)
IgA, mg/dL	18.39 (31.74)	17.16 (32.57)	20.57 (28.20)	17.60 (16.67)
IgM, mg/dL	39.92 (36.92)	34.05 (21.73)	42.8 (26.0)	38.9 (24.7)
CD3, %	70.45 (17.75)	66.03 (17.40)	71.12 (20.66)	77.81 (10.91)
CD4, %	30.98 (13.29)	29.6 (16.01)	33.26 (10.76)	30.16 (11.2)
CD8, %	36.68 (13.87)	30.61 (11.37)	40.78 (14.13)	42.54 (14.05)
CD19, %	11.39 (11.45)	10.32 (12.25)	14.03 (13.06)	9.51 (6.11)

Abbreviations: Ig, immunoglobulin.
[a]Values are expressed as mean (SD) unless indicated otherwise.

CD4 in 23 patients (33.3%), CD8 in 63 patients (91.3%), and CD19 in 34 patients (49.3%). The CD marker values for the different age groups are shown in Table 3.

Clinical Phenotypes

At the time of diagnosis, almost all of the patients had a history of acute, chronic, or recurrent infections. In 44 patients (63.7%), respiratory tract infection was the first presentation of CVID. The most common clinical presentations at diagnosis were pneumonia (22 patients, 31.8%), diarrhea (13 patients, 18.8%), and sinusitis (13 patients, 18.8%). The other presenting infections included otitis media (10 patients, 14.5%), skin involvement (including cellulitis, omphalitis, and eczema, [4 patients, 5.8%]), fever of unknown origin (2 patients, 2.9%), and oral thrush, osteomyelitis, and septic arthritis (1 patient each, 1.4%) (Table 4). The number of infected cases and episodes of infection and the mean number of infectious episodes in infected patients and the whole population are shown in Table 5.

Table 4. Presenting Illnesses

Type of disorder	No.	%
Pneumonia	22	31.9
Sinusitis	13	18.8
Diarrhea	13	18.8
Otitis media	10	14.5
Skin involvement	4	5.8
Fever of unknown origin	2	2.9
Oral thrush	2	2.9
Encephalitis	1	1.4
Osteomyelitis	1	1.4
Septic arthritis	1	1.4

Table 5. Numbers of Infected Cases, Episodes of Infection, Mean Number of Infection Episodes in Infected Patients and the Whole Group in 69 CVID Patients

Type of Infection	Number of Infected Patients	Number of Infectious Episode	Mean Number of Infectious Episodes per Case	Mean Number of Infectious Episodes in the Whole Group
Cellulitis	5	5	1	0.07
Conjunctivitis	17	38	2.23	0.55
Encephalitis	5	140	2	0.14
Esophagitis	4	4	1	0.06
Gastroenteritis	40	225	5.62	3.26
Hepatitis	3	3	1	0.04
Impetigo	2	2	1	0.03
Mastoiditis	2	2	1	0.03
Meningitis	6	8	1.33	0.12
Oral thrush	7	9	1.28	0.13
Osteomyelitis	1	1	1	0.01
Otitis media	40	202	5.05	2.39
Pharyngitis	5	11	2.2	0.16
Pneumonia	53	227	4.28	3.29
Pyelonephritis	3	13	4.33	0.19
Sepsis	2	2	1	0.03
Septic arthritis	10	18	1.8	0.26
Sinusitis	41	214	5.11	3.1
Urinary tract infection	8	15	1.87	0.22

Bronchiectasis was the most common respiratory complication (21 patients, 30.4%). However, 39 patients presented only manifestations of infection, and the remaining cases had a history of noninfectious clinical phenotypes, as follows: polyclonal lymphocytic infiltration (17), autoimmunity (12), malignancy (7), and enteropathy (3). The most prevalent reported blood/lymph system abnormality was splenomegaly in 27 patients (39.1%), although lymphadenopathy was documented in 17 patients (24.6%). Three patients (4.3%) had malabsorption of unknown origin, although their condition was compatible with enteropathy.

Twelve patients (17.3%) had autoimmune disease, including hemolytic anemia in 6 patients, neutropenia in 3, immune thrombocytopenia in 2, and alopecia areata and thyroiditis in 1. Both patients with immune thrombocytopenia responded favorably to corticosteroids and high-dose IVIg and did not require splenectomy.

Seven patients had lymphoma (3 with Hodgkin disease and 1 with non-Hodgkin lymphoma). Two siblings (brother and sister) were diagnosed with Hodgkin disease (as were their father and uncle), and both died 1 year after diagnosis.

Table 6. Complications of Various Organs During Follow-up

Type	Number of Affected Patients	Number of Episodes
Gastrointestinal System		
Oral thrush	2	2
Aphthous lesions	11	14
Celiac disease	4	4
Giardiasis	9	24
Colitis	8	9
Malabsorption	3	3
Hepatomegaly	24	24
Cirrhosis	2	2
Liver abscess	1	1
Renal System		
Renal failure	1	1
Skin		
Atopic dermatitis	8	8
Urticaria	3	3
Warts	4	10
Skin abscess	6	8
Respiratory System		
Bronchiectasis	21	21
Asthma	3	3
Blood/Lymph System		
Peritonsillar abscess	7	7
Hemolytic anemia	6	6
Lymphadenopathy	17	23
Idiopathic neutropenia	3	3
Immune thrombocytopenic purpura	2	2
Pernicious anemia	1	1
Leukopenia	4	4
Splenomegaly	27	27
Lymphoma	7	7
Other Complications		
Failure to thrive	15	15
Clubbing	30	30

The other patient with Hodgkin disease had no positive family history and was alive at the end of this study. Diagnosis of non-Hodgkin lymphoma was confirmed by node biopsy. The lymphoma type was B-cell in all of the patients.

Other Organ Complications

Other common problems included failure to thrive (15 patients, 21.7%), clubbing (30 patients, 43.4%), atopic dermatitis in (8 patients, 11.5%), and warts (4 patients, 5.7%). Gastrointestinal abnormalities were recorded in 32 patients; aphthous lesions (11 patients, 15.9%) and giardiasis (9 patients, 13.0%) were the most notable findings. Inflammatory bowel disease was diagnosed in 2 patients (1 with ulcerative colitis and 1 with Crohn disease) (Table 6).

Mortality

During the 26-year study period, 15 patients (21.7%) died and the same number could not be located. Among the patients who died, the mean delay in diagnosis in those who died of CVID was significantly higher than in the available surviving patients (5.33 [3.55] vs 3.96 [3.27], P=.0001). However, mortality could be underestimated, since 15 patients could not be located at the end of this study.

The causes of death were pneumonia (5 patients), Hodgkin disease, septicemia, and hepatic failure (2 patients each), and echovirus encephalitis, alveolar hemorrhage, cardiac arrest, and Kawasaki disease (1 patient each).

Mortality was measured using the Kaplan-Meier technique. Excluding those patients who could not be located, 5- and 10-year survival rates were 79% and 71%, respectively (Figure 2). The mean survival time was 15.29 (2.8) years (range, 12.72-17.86 years). Cox regression was applied to analyze the effect of various factors on the survival rate (age at the time of diagnosis, diagnostic delay, sex, consanguinity, presence of a sibling with diagnosis of CVID, and serum levels of immunoglobulins and CD markers), although none were significant.

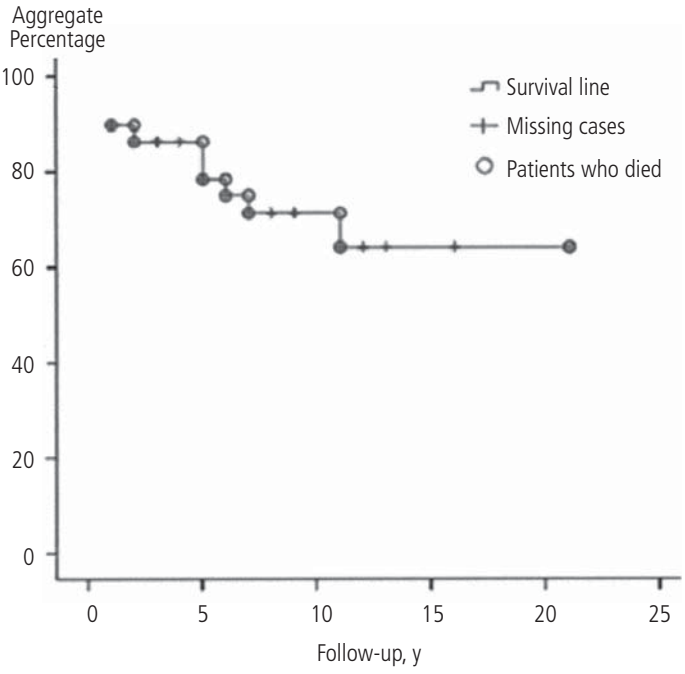

Figure 2. Survival curve of 69 children affected by common variable immunodeficiency.

Discussion

CVID is the most prevalent symptomatic primary immunodeficiency disease. The objectives of this study were to compensate the lack of information about long-term follow-up of children with CVID and to provide clinical and immunological data. In western countries, onset of CVID is usually after puberty, during the second or third decade of life [24,26]. Quinti et al [27] analyzed 224 Italian CVID patients, of whom 33% were under 14 years; our previous study on 65 CVID patients [2] showed that 81.5% of patients were under 18 years. Moreover, the mean age at diagnosis in our study was lower than that recorded in almost all other reports on CVID patients [28-30].

The low mean age recorded in our database may be due to the high rate of parental consanguinity in Iran, which also leads to a higher rate of multiple cases. The overall rate of consanguinity in the Iranian population is 38.6% [31,32]. Although the etiology and pathogenesis of CVID remain unknown [33], early onset of the disease and parental consanguinity indicate an autosomal recessive etiology. It has been suggested that all members of a patient's family should undergo screening for primary immunodeficiency in order to provide an early diagnosis of CVID and decrease the rate of complications, visits to the physician, hospitalization, and disease-related costs [34].

The incidence of pediatric CVID is also affected by physician awareness and the availability of advanced tools that can provide an earlier diagnosis of patients in childhood [1,35]. The average diagnostic delay in our population was 4.4 years, which was significantly lower in patients diagnosed in recent years. A survey in England by Blore et al [36] showed an average delay of 2.5 years for diagnosis of CVID in children. In the United States, Cunningham-Rundles and Bodian [1] showed that the diagnostic delay was 4 to 6 years. In our previous study of 65 Iranian patients with CVID [2], the average diagnostic delay was 5.1 years. It seems likely that the frequency of adult CVID will decrease in the coming years as a result of increased awareness of primary immune deficiencies among physicians and the development of more advanced diagnostic methods.

In our previous study of 93 patients [37], we showed that the most common phenotype was infection only (45%), followed by polyclonal lymphocytic infiltration (37%), autoimmunity (10%), lymphoma (10%), and enteropathy (10%). The present study revealed different percentages of clinical phenotypes in children. Infection only (56.5%) and autoimmunity (17%) were more frequent, malignancy (10%) and polyclonal lymphocytic infiltration (24%) had a similar frequency, and enteropathy (4.5%) had a lower frequency in children with CVID. Moreover, 10% of all CVID patients in our previous study had overlapping clinical phenotypes, a finding that was similar to those of the present study (12%) [37].

In the study by Cunningham-Rundles and Bodian [1], the factors affecting survival were low levels of IgG at diagnosis, low B-cell count, and insufficient response of T cells to phytohemagglutinin mitogen. In the present study, the factors considered to affect survival were age at diagnosis, diagnostic delay, sex, parental consanguinity, presence of siblings with CVID, and levels of Ig and CD markers; however, none of these factors had a significant impact. Although 15 patients (21%) had died at the end of the study, mortality in our previous study of 93 CVID patients was 28%. Cunningham-Rundles and Bodian found a similar rate (23%); Quinti et al [27] recorded a much lower rate (6%).

In almost all of the main studies on CVID, the most common causes of death were respiratory failure due to infection and lymphoma. Based on the findings of this study, pulmonary infections are the most prevalent complications of CVID at diagnosis and during follow-up.

Development of CVID complications despite regular and sufficient treatment with IVIg emphasizes the importance of health care and regular visits to physicians for early diagnosis and treatment of CVID complications. The high number of children affected by CVID in Iran may be due to the high rates of parental consanguinity and an underlying genetic background.

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