Original Research Article

Clinical features of Immunological dysregulation in Common Variable Immunodeficiency in Iran

Abstract

Background: Common Variable Immune Deficiency (CVID) is a primary immunodeficiency with significant clinical manifestations. The aim of this study was to evaluate the clinical and immunological characteristics of CVID patients in Isfahan city, Iran.

Methods: Base on retrospective studies, data of 25 CVID Patients were collected from referrals to the Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences between 2007 and 2013. The patients were diagnosed according to the Immunodeficiency Disease criteria and all patients received Intravenous immunoglobulin (IVIG) as a fundamental part of the treatment at a mean dose of 500 mg/kg.

Results: The age at onset of disease was between 4 to 37 years and diagnosis was between 2 to 39 years. The median levels of IgG, IgM, and IgA were 36.75, 4.77 and1.05 mg/dL respectively. The percentage of CD19+ B cells, CD20+, CD3+, CD4+, CD8+, CD16+CD56+ cells was 8.35%, 8%, 80.88%, 28.72%, 38.88%, and 11.08% respectively. Sinusitis (79%), pneumonia (85%) and acute otitis media (40%) were the most common manifestations. In addition, Bronchiectasis was seen in about 25% and Autoimmunity (Thrombocytopenia, RA) was found in 33% of cases. Allergic symptoms were present in 8% of patients.

Conclusion: CVID patients can present with a wide range of manifestations such as infections, immunological dysfunctions (autoimmunity), allergy and malignancy. A variety of defects in both humoral and cell-mediated immune responses can occur in CVID patients.

Keywords: CVID, Immunodeficiency, Autoimmunity, Thrombocytopenia

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiency disorders and commonest primary immunodeficiency syndrome that characterized by hypogammaglobulinemia and recurrent bacterial infections (1). Genetic basis of these defects is still not well known in patients. It appears that most patients with CVID have a multi-gene defects (2). Rarely, patients have been diagnosed with a genetic defect. Genetic defect has been reported in the TACI, ICOS, BAFFR, CD19, CD20, CD21 and CD81 genes that lead to a severe cellular or humoral immune defect (3-6). Current estimates suggest a prevalence of approximately one in 25 000 in the general population (2).

The most common clinical manifestations of CVID are recurrent and chronic bacterial infections, especially respiratory infections. Also there is a high prevalence of autoimmune phenomena lymphoproliferative and/or granulomatous diseases (7). Laboratory finding in CVID patients are low level of serum immunoglobulin G (IgG) s with a decreased serum concentration of IgA and/or IgM (1).

The clinical perspective of CVID is quite broad, and it may occur at any age and stage of life (7). In these patients, susceptibility to lung disease, recurrent ear infections, colds, malignancies and autoimmune diseases have reported. Bronchiectasis is a common problem in CVID patients. Streptococcus pneumoniae and Haemophilus influenzae are the most common bacterial infection in these patients with common cold (7). Standard treatment for CVID requires periodic administration of intravenous immunoglobulin (IVIG). The aim of this study was to evaluate the clinical and immunological characteristics of CVID patients in Isfahan city, Iran.

Methods

Patients

Base on retrospective studies, data of 25 CVID Patients including 17 males and 8 females were collected from referrals to the Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences between 2007 and 2013. Patients were examined on the basis of laboratory information (IgG and IgM, or IgA levels reduced more than 2 SD) and clinical manifestation (recurrent infections and common cold), and the patients were diagnosed according to the Immunodeficiency Disease criteria (ESID). Demographic data were collected at inclusion using a self-administered patient questionnaire and medical data were recorded for each patient. The questions included biographic data on personal history with CVID, recurrent infections, selective IgA deficiency syndrome, autoimmune diseases and allergic problem. Also, patients were asked for date

of first recognized symptoms, recurrent infection in early childhood, and the history of persisting viral infections and severe or opportunistic systemic infections. All patients received intravenous immunoglobulin (IVIG) at diagnosis, and the mean dose was 500 mg/kg.

Statistical analysis

Results are shown as mean±SD (if the variable is normally distributed) and median (interquartile range) for continuous variables. Dichotomous and nominal variables were expressed as frequencies and percentages. All two-sided *P*-values (<0.05) were considered to be statistically significant. Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows (version 12.00, SPSS Inc., Chicago, IL, USA).

Results

The data from the 25 CVID patients were reviewed in order to determine that each individual entailed the diagnostic criteria for CVID.

Demographics

Diagnosis was confirmed for 25 patients; they were 17(68%) male and 8 (32%) female. The median age of patients at the time of onset to symptoms was 8.4 years, and the median age at the time of diagnosis was 10.32 years (Table 1).

Immunoglobulin levels and CD markers

The median levels of IgG, IgM, and IgA were 36.75, 4.77 and 1.05 mg/d respectively (Table 2). The percentage of CD19+ B cells, CD20+, CD3+, CD4+, CD8+, CD16+CD56+ cells was 8.35%, 8%, 80.88%, 28.72%, 38.88%, and 11.08% respectively (Table 3).

Infections

The most frequent clinical manifestation was recurrent infections. All the patients had recurrent infections as the initial manifestation, except six patients had autoimmunity. Among infections, Sinusitis (79%), pneumonia (85%), and acute otitis media (40%) were the most common manifestations. Bronchiectasis was present in 25% of patients. Also allergic symptoms were present in 84% of patients (Table 5).

Organisms most commonly isolated from the respiratory tract were Streptococcus pneumonia, Pseudomonas aeruginosa, and Staphylococcus aureus. Also, Giardia lamblia and Salmonella enterica were the most frequent causes of gastrointestinal infections. But only two cases with disseminated Tuberculosis and herpes encephalitis were found in these patients.

Pulmonary disease

Bronchiectasis, detected through high-resolution computed tomography, was found in 8 (32%) patients at the time of evaluation for this study. Of the patients who suffered from pneumonia, 53.3% developed bronchiectasis (Table 4).

Autoimmunity

Six patients (24%) showed autoimmunity, including one female and five males as first manifestation (Table 5 and 6).

Allergy

Allergy was present in 21 (84%) patients. Manifestations were allergic rhinitis and asthma (15), rhinitis (3), atopic dermatitis (1), asthma and atopic dermatitis (1), and drug and food allergy (1) (Table 1).

Discussion

In this study, 25 patients with CVID, at a period of 6 years, were evaluated for clinical and immunological features during their follow-up in our center. The median age of our patients at the time of onset of symptoms was 8.4 years, and the median age at the time of diagnosis was 10.32 years. The delay in diagnosis of patients in Isfahan was similar to that reported in other studies in Spain and Turkey (1, 8-10). Hypogammaglobulinemia is the most common symptom in CVID, and the standard treatment for it is IVIg. Serum immunoglobulin levels reported in this study are similar to those reported previously (9). In our patients, we found a reduction in CD4+/CD8+ T cells ratio in comparison with normal samples (data not shown), which is explained by the decreased number of CD4 T cells. This finding has been previously described in Italian patients with CVID, and the decrease in

CD4+ T cells was associated with heterogeneous clinical features (11). In the present study, infection was the most common clinical manifestations that involved the upper and lower respiratory system, as reported previously (8, 12, 13). We also found that infection can affect several organs of the human body and almost all patients had been hospitalized due to infections. Moreover, the prevalence of bronchiectasis reported in this study was up to 32% that is higher than previously reported data (12-14). This difference may be due to late diagnosis of the disease.

The presence of autoimmunity in CVID patients was similar to that reported previously (15, 16). Autoimmune hepatitis might be one of the common autoimmune diseases which it needs to do more work on it in future. However, we also identified other autoimmune diseases, including thrombocytopenic purpura (ATP) Ulcerative Colitis, Rheumatoid Arthritis and Amyloidosis.

We also found a family history of autoimmunity in some patients (17). Our CVID cohort presents with comparable symptoms and disorders as previously reported. We consider that this study could be further complemented with patients from other countries.

Conclusion: The cause of heterogeneous manifestations in CVID could be defects in various components of humoral and cellular immunity. Today is believed that the genetic defects which the cause of CVID are probably polymorphisms rather than genetic disturbance.

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Table 1 Clinical and laboratory data of CVID patients

NO	Gender	Bronchiectasis	Autoimmune disease	lymphoid hyperplasia	others	IgG (mg/dl)	IgM (mg/dl)	IgA(mg/dl)
1	M	+	Autoimmune Hepatitis		Asthma/Allergic Rhinitis	3/25	<0.2	<0.3
2	M	+	Rheumatoid Arthritis		Asthma/ Allergic Rhinitis	276	0/09	0/02
3	M	+			Asthma/ Allergic Rhinitis	1/386	0/314	0/034
4	F					9/536	1/268	1/73
5	F			History of lymphoma	Asthma/ Allergic Rhinitis	2.8	0.28	0.34
6	F				Allergic Rhinitis	0/07	0/35	0.21
7	M				Allergic Rhinitis	absent	0.1	0.1
8	M	+	Autoimmune Hepatitis		Asthma /Allergic Rhinitis	2/87	0.33	0.2
9	M					4.6	0.186	0.3
10	M				Allergic Rhinitis	3/134	0/370	0/430
11	M	+			Allergic Rhinitis	0/350	0.2	0
12	M			Nodular Lymphoid Hyperplasia	Allergic Rhinitis	218	25	0
13	F				Asthma /Allergic Rhinitis	22	7	0.2
14	M		Ulcerative Colitis			185	0.07	0.4
15	F		Autoimmune Thrombocytopenia		Atopic Dermatitis	0.3	0.25	0
16	F					3.5	0.320	0.670
17	M				Allergic Rhinitis	18.5	0.233	0.07
18	M	+	Amyloidosis			3/306	0.2	0.1
19	M	+			Asthma and Atopic Dermatitis	100	80	20
20	F					7.6	0.3	0.38
21	M			Mesenteric Lymphadenopathy	Food Allergy	3/85	0/250	0.368
22	F				Allergic Rhinitis	1.453	0.160	0.210
23	M			Lymphadenopathy	Allergic Rhinitis	8.24	0.23	0.17
24	M	+			Allergic Rhinitis	<0/158	0/334	0/044
25	M					0.52	0.7	0.09

Table 2 Immunoglobulin levels

Immunoglobulin(mg/dl)	Median (range) for:		
	Male (n=17)	Female (n= 8)	Normal reference range
IgG	48.8 (0–276)	5.9(0.07-22)	768 to 1728 mg/dL
IgM	6.4(0.1–80)	1.24 (0.16–7)	38 to 266 mg/dL
IgA	1.32 (0–20)	0.46(0–1.73	99 to 396 mg/dL

Table 3 CD markers

Lymphocyte markers	Median (range) for:	
	Male (n=17)	**Female (n = 8)**
CD3	76% (53%-97%)	78% (58%-92%)
CD4	28% (4%-54%)	34% (19%-59%)
CD8	45% (18%-87%)	37.8 (23%-58%)
CD19	6.8% (0%-18%)	3.8% (0%-10%)
CD20	12% (0%-20%)	4.87% (0%-13%)
CD16/56	12.3% (4%-21%)	9.25% (3%-18%)

Table 4 Clinical manifestations

Clinical manifestations	**Male (n=18)**	**Female (n=7)**
Allergic diseases (n)	**14**	**7**
Bronchiectasis (n)	**8**	**0**
Autoimmune diseases (n)	**5**	**1**
Lymphoid hyperplasia (n)	**3**	**1**

Table 5 Phenotypes and conditions

Associated condition (n=25)	n	Percentage
Allergic disease	21	84%
Pneumonia	15	60%
Otitis media	9	36%
Sinusitis	8	32%
Bronchiectasis	8	32%
Diarrhea	5	20%
Autoimmunity	6	24%
Meningitis	2	8%
Chronic Septic arthritis	2	8%
Lymphoid hyperplasia	2	8%

Table 6 Sex Ratio in Autoimmunity

Autoimmunity	**Male (n=18)**	**Female (n=7)**
Thrombocytopenic purpura (ATP)	**0**	**1**
Autoimmune hepatitis	**2**	**0**
Ulcerative colitis	**1**	**0**
Rheumatoid Arthritis	**1**	**0**
Amyloidosis	**1**	**0**