

Clinical and Immunological Features of 65 Iranian Patients with Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by hypogammaglobulinemia and recurrent bacterial infections. The records of 65 patients with CVID (37 males and 28 females) in the age range of 24 to 537 months were reviewed. By the year 2003, 11 patients had died and seven patients could not be located. The total follow-up period was 221 patient-years. The median diagnostic delay (time between onset and diagnosis) in our patient group was 60 months. At the time of diagnosis, the baseline serum immunoglobulin G (IgG), IgM, and IgA levels were below the level normal for the patients' age; the medians for this group were 120, 10, and 0 mg/dl, respectively. All of the patients presented with infectious diseases at the time of onset, the most common of which were otitis media, diarrhea, pneumonia, and sinusitis. Acute and recurrent infections were also found in almost all of the patients, particularly involving respiratory and gastrointestinal systems. The most common infections, before diagnosis and during follow-up, were pneumonia, acute diarrhea, acute sinusitis, and otitis media. CVID should be considered in any patient with a history of recurrent infections and decreased levels of all serum immunoglobulin isotypes.

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiency disorders characterized by hypogammaglobulinemia in the absence of any recognized genetic abnormality (17, 18, 26). CVID patients have decreased serum immunoglobulin G (IgG) concentrations and usually a decreased serum IgA and/or IgM concentration in the presence of normal or low numbers of circulating B cells (17, 18). Patients have recurrent bacterial infections, most notably of the upper and lower respiratory tracts and gastrointestinal tract (1, 4, 7, 11, 17, 18, 28). Symptoms of recurring infection can start at any time of life, but there are peaks of onset during 1 to 5 and 16 to 20 years of age (17, 18, 28). The major bacteria involved in nearly all of these infections are encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Mycoplasmas are another microbial agent to which these patients are particularly susceptible (28). In addition to infectious complications, autoimmune diseases, especially autoimmune hemolytic anemia and autoimmune thrombocytopenia, are relatively common in patients with CVID (19, 53). Moreover, the incidence of lymphoma in patients with CVID is highly different from that in the healthy population (19, 39). Despite extensive investigations no unique defect has been identified for immune system abnormalities in CVID and the pathogenesis of CVID is still unknown (26). Therefore, the diagnosis of CVID is based only on a clinical history of recurrent infections associated with hypogammaglobulinemia in the presence of a variable number of circulating B cells and genetic

exclusion of other molecularly well defined hypogammaglobulinemias such as X-linked agammaglobulinemia (XLA) (33) and hyper-IgM syndrome, which are due to mutations of CD40 ligand (23); activation-induced cytidine deaminase (44); and X-linked lymphoproliferative disease (5, 42). Early diagnosis, management, and treatment are important, and failure to provide adequate therapy results in tissue and organ damage and various complications (7, 17, 28). The standard treatment for this disorder is regular immunoglobulin replacement, by either intravenous or subcutaneous administration (2, 3, 15).

The purpose of the present study was to determine the spectrum of clinical and immunological features of Iranian patients with CVID referred to our center over a period of 20 years.

MATERIALS AND METHODS

Patients. In Iran, an Iranian Primary Immunodeficiency Registry has been active since 1997, and 440 cases with a variety of primary immunodeficiency diseases were registered at the end of 2001 (6). Among the registered patients, the antibody deficiencies were the most common type of diagnosed immunodeficiencies ($n = 202$). In this study the charts of 65 registered patients with CVID diagnosed and treated at Children's Medical Center were reviewed. The diagnosis of CVID in our patients was made according to the standard criteria, including reduction of at least two serum immunoglobulin levels (serum IgG, IgA, and IgM) by 2 standard deviations from normal mean values for age (16, 43, 56). We excluded patients less than 2 years of age, because of a possible diagnosis of transient hypogammaglobulinemia. For excluding patients with a diagnosis of X-linked agammaglobulinemia, we used patient's history, family history of X-linked pattern of inheritance, and very low numbers of B cells (<1%) as measured by flow cytometry. Although occasional patients with low B-cell numbers may present as CVID when they express a *Btk* gene mutation, this is not a common phenomenon (33, 55).

Patients are considered related when there is a first- or second-degree family relationship.

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Laboratory testing. Blood samples of the patients were tested for the immunoglobulin level on the first visit using nephelometry methods, and the results were compared with the normal range of quantitative immunoglobulin levels. Further assessment was done by obtaining complete blood counts and isohemagglutinin titer and performing the Schick test. Before 1993, B- and T-cell subsets of patients were measured by rosette formation technique, and so for patients who were diagnosed before 1993 B- and T-cell subset measurements were repeated by flow cytometry. Pulmonary function tests were obtained, and other procedures, such as high-resolution computed tomography and endoscopy and biopsy, were performed if medically indicated. For those who had died, the cause of death was determined by review of the death certificate.

HLA typing. HLA typing was performed using a standard microlymphocytotoxicity technique. Briefly, Terasaki microtiter plates (Nunc, Denmark) containing various anti-HLA class I and class II antisera (Blood Transfusion Center) were seeded with 3×10^3 to 4×10^3 immortalized B cells. After incubation at room temperature and addition of rabbit complement, cell variability was determined using 5% eosin dye (Merck, Germany) under an inverted microscope. Normal AB blood group serum was used as a negative control, and antilymphocyte globulin and anti-HLA DR (polyspecific) antibodies were used as positive controls for HLA class I and class II microplates, respectively. Results were compared with the control group, which consisted of 85 Epstein-Barr virus-transformed B-cell lines established from healthy individuals.

Statistical methods. Data analysis was done using the SPSS statistical software package (version 11.0). Initial testing results were used for the evaluation of immunologic values and CD markers. A linear regression to determine the association between year of disease onset and delay in diagnosis was used.

RESULTS

Characteristics of patients. From 1984 to 2003, there were 65 patients at Children's Medical Center diagnosed as having CVID. There were 37 males and 28 females. The median age of patients at the time of the study was 136 months (range, 36 to 537 months) for males and 145 months (range, 24 to 504 months) for females. The median age at the time of disease onset was 24 months (range, 4 to 480 months) for males and 14 months (range, 5 to 96 months) for females, and median age at the time of diagnosis was 85 months (range, 25 to 513 months) for males and 103 months (range, 24 to 490 months) for females. On average, the median diagnostic delay in our patient group was 60 months (range, 0 to 476 months) (Table 1). Statistical analysis of these data was complicated by the fact that the diagnosis had increasingly been made at an earlier age and delay in diagnosis has significantly decreased in recent years ($r = -0.863$, $F = 183.8$, $P < 0.001$). A reverse association was observed between year of disease onset and delay in diagnosis (Fig. 1 and 2).

Total follow-up period was 221 patient-years (mean follow-up, 40.7 months; range, 0 to 199 months). By the year 2003, 11 patients had died and seven patients could not be located. The prevalence of consanguineous marriages was 66.2% (in 43 families) among our patients. Also, in 18 of these families, a history of recurrent infections in the siblings of the affected patient, with or without a documented diagnosis of immunodeficiency among them, was found, and 12 out of them had a family history of malignancy.

One of our patients at the time of diagnosis was found to have IgA deficiency but in follow-up changed to CVID (P53).

Serum immunoglobulin levels and lymphocyte studies. At the time of diagnosis, the baseline serum IgG level was 2 standard deviations (or more) below the normal level for age, and before treatment the median serum IgG level was 120 mg/dl (0 to 640 mg/dl; only one patient [P22] had an IgG level of more than 500 mg/dl), and that of other serum immuno-

globulins was 0 mg/dl for IgA (range, 0 to 235 mg/dl) and 10 mg/dl for IgM (range, 0 to 400 mg/dl). The level of IgA was under 10 mg/dl in 75.4% of patients. The serum IgM level was less than 25 mg/dl for 67.7% of patients (Table 2).

In 16 subjects (25.8%) a relative lack of CD4⁺ T cells (less than 400 cells/mm³) was found. In 37 out of 65 patients (56.9%), T-cell subset analysis, by immuno-flow cytometry, showed a reversed CD4/CD8 ratio.

All of our patients had B-cell numbers of more than 2%, and median CD19 was 10% (range, 2 to 47).

HLA classification. HLA typing with the PCR-sequence-specific primer method was done for 21 patients (14 female and seven male) and compared with that for 85 persons in the healthy control group. Expression of HLA DRB1 1303 was significantly increased in patients compared to control group (17.4% versus 0.5%, respectively; $P = 0.017$). HLA DQA1 0104 also was increased in patients, but the difference was not significant (4.76% versus 0.5%; $P = 0.07$). Frequency of HLA DQB1 0501-3 was decreased in patients but was not significant (9.52% versus 0.22%; $P = 0.06$).

Clinical manifestation. The main categories of associated diseases reported up to the time of the study included infection, gastrointestinal or pulmonary disease, autoimmune disease, hepatitis, granulomatous infiltrations, lymphoma, and cancer.

As seven subjects were currently unavailable but were not excluded from the total group, the frequency of these conditions is likely to be an underestimate. It must also be noted that the true incidence of some conditions would be particularly difficult to determine since many patients had never had biopsies.

(i) Spectrum of infections as the presenting illnesses. Among the 65 patients with CVID, 37 patients (56.9%) presented with a form of respiratory tract infection as the first manifestation of disease, including otitis media in 16 patients (24.6%), pneumonia in 15 patients (23.1%), and sinusitis in nine patients (13.8%) (Table 3). The other presenting infections included diarrhea in 18 patients (27.7%); skin involvement including cellulitis, omphalitis, eczema, and oral thrush in six patients (9.2%); pyelonephritis in three patients (4.6%); sepsis in one patient (1.5%) (P47); meningitis in one patient (1.5%) (P32); and osteomyelitis in one patient (1.5%) (P65). Also CVID was diagnosed in one of the patients following work-up for hepatosplenomegaly (P62) and in another case following work-up for failure to thrive (P11).

Some of our patients had two of these complications at the presenting time: four had otitis with sinusitis, two had pneumonia and diarrhea, one had otitis and diarrhea, one had otitis and pneumonia, and one had diarrhea with oral thrush.

(ii) Infections in the course of disease. Acute and recurrent infections were found in almost all of our patients, particularly involving respiratory and gastrointestinal systems (Table 4). Forty-eight out of 65 patients (73.8%) had pneumonia prior to diagnosis, and of these patients, 16 developed bronchiectasis. In seven patients the diagnosis of bronchiectasis was made according to the patient's history of chronic purulent cough, clubbing of the fingers, and X-ray findings and by excluding chronic bronchitis in them, and in 14 suspected patients high-resolution computed tomography was performed which showed bronchiectasis in nine of them.

TABLE 1. Descriptive data for patients^a

Patient no.	Sex	Age			Ig level (mg/dl)			CD (%)			CD4/CD8 ratio	Consanguinity	FH of immunodeficiency
		Current	At onset	At the time of Dx	IgG	IgM	IgA	CD3	CD4	CD8			
P1	M	5 y 2 m	9 m	4 y 11 m	50	10	5	65.14	43.86	32.01	1.37	Yes	No
P2	M	8 y 6 m	2 y	8 y 6 m	105	10	0	63.2	16	41.04	0.39	Yes	No
P3	M	25 y	4 y	25 y	40	5	0	86.4	41.56	45.7	0.91	No	No
P4	M	10 y 9 m	10 y 7 m	10 y 9 m	380	79	107	60	35	24	1.46	Yes	No
P5	F	8 y 1 m	5 m	8 y 1 m	20	30	24	66.38	35.23	31.29	1.13	Yes	No
P6	F	2 y	9 m	2 y	224	10	5	45.8	17.6	27.6	0.64	Yes	No
P7	M	33 y 7 m	28 y 6 m	33 y 6 m	190	22	33	73.5	20.1	50.2	0.40	Yes	No
P8	F	4 y 3 m	9 m	4 y 2 m	392	46	5	74.35	46.07	25.52	1.81	Yes	No
P9	F	2 y 7 m	1 y	2 y 6 m	50	10	5	38.42	13.99	28.17	0.50	Yes	No
P10	M	1 y 7 m	10 y	19 y 5 m	0	0	0	74.9	28	49	0.57	No	No
P11	M	43 y	40 y	42 y 9 m	20	26	0	54	31	22.5	1.37	No	No
P12	M	12 y 2 m	1 y	11 y 11 m	50	200	5	65.29	18.44	41.89	0.44	No	No
P13	M	11 y 11 m	4 y	11 y 8 m	50	10	5	67.59	20.85	43.85	0.48	No	No
P14	F	8 y 1 m	5 m	7 y 10 m	0	30	0	84	20.4	60.4	0.34	Yes	Yes
P15	F	2 y 8 m	1 y 2 m	2 y 5 m	120	10	0	75	24	42	0.57	Yes	No
P16	F	4 y 9 m	1 y 6 m	4 y 6 m	0	0	0	73.7	22.4	34	0.66	Yes	No
P17	M	6 y 11 m	1 y 2 m	6 y 7 m	150	30	20	74				Yes	No
P18	F	12 y 10 m	8 m	12 y 6 m	100	0	0	85.25	23.42	49.95	0.47	No	No
P19	M	3 y	7 m	2 y 8 m	120	10	5	32	15	4	3.75	Yes	No
P20	F	8 y 2 m	5 y 7 m	7 y 9 m	340	176	10	81.5	41.2	37.4	1.10	Yes	No
P21	M	26 y 2 m	20 y 10 m	25 y 7 m	120	33	20	75.9	19.4	57.2	0.34	No	No
P22	F	9 y 7 m	6 m	9 y	640	30	58	92.35	28.33	59.69	0.47	Yes	No
P23	M	4 y 3 m	9 m	3 y 7 m	320	10	5	74.07	41.24	33.06	1.25	Yes	No
P24	M	4 y 5 m	9 m	3 y 9 m	260	190	235	54	16.4	31.2	0.53	Yes	No
P25	F	5 y 6 m	11 m	4 y 10 m	0	7.5	0	36.5	1.41	15.69	0.09	Yes	No
P26	F	6 y 1 m	3 y	5 y 4 m	248	10	5	38.4	15.4	36.7	0.42	Yes	No
P27	F	13 y 7 m	3 y 6 m	12 y 10 m	50	12	0	69.11	22.11	40.04	0.55	Yes	No
P28	M	14 y 5 m	4 m	13 y 8 m	50	10	5	76.54	38.22	31.21	1.22	No	No
P29	F	7 y	3 y	6 y	350	33	0	89.5	53	36	1.54	No	No
P30	M	3 y 6 m	10 m	2 y 5 m	434	0	0	57.6	32.3	21.5	1.50	No	No
P31	F	12 y 11 m	1 y 11 m	11 y 10 m	330	16	10	62.7	22.3	38.8	0.57	Yes	No
P32	F	42 y	37 y 6 m	40 y 10 m	470	270	120	78	23	57	0.40	No	No
P33	M	7 y 7 m	3 y 6 m	7 y 1 m	430	0	0	62.2	24.5	37.6	0.65	No	No
P34	M	12 y 3 m	3 y 2 m	10 y 9 m	380	10	0	83.37	36.14	44	0.82	No	Yes
P35	F	4 y 1 m	5 m	2 y 6 m	50	10	5	38.42	13.99	26.17	0.53	Yes	No
P36	F	13 y 6 m	7 m	12 y	50	0	0	82.18	36.6	40.33	0.91	Yes	No
P37	M	4 y 4 m	5 m	2 y 8 m	75	0	0	53	25	20	1.25	Yes	No
P38	M	8 y 3 m	4 y	6 y 7 m	284	120	54	64.71	46.37	20.01	2.32	Yes	No
P39	F	4 y 4 m	2 y 1 m	2 y 2 m	0	400	0	61.47	40.41	12.06	3.35	Yes	No
P40	F	14 y 10 m	5 y 3 m	12 y 10 m	200	0	0	83.03	33.43	48.58	0.07	No	Yes
P41	M	15 y	6 y 4 m	12 y 9 m	130	0	0	88.9	50.96	35.46	1.44	Yes	No
P42	F	11 y 7 m	2 y 2 m	9 y 2 m	460	0	10	87.11	38.33	35.08	1.90	Yes	No
P43	M	8 y 8 m	8 m	6 y 2 m	0	200	0	33	50	35	1.43	No	No
P44	M	4 y 9 m	4 m	2 y 1 m	0	0	0	48.92	26.65	26.43	1.01	Yes	No
P45	M	5 y 4 m	2 y 3 m	2 y 6 m	140	10	5	77	31	25	1.24	Yes	Yes
P46	M	20 y 6 m	7 y 6 m	17 y 6 m	0	0	0	72	5	66	0.08	No	No
P47	M	9 y 5 m	2 y	6 y 2 m	50	10	5	88.27	31.85	55.48	0.57	Yes	No
P48	M	10 y 9 m	6 m	7 y 3 m	135	10	25	44.58	10.59	4.5	2.35	No	No
P49	M	44 y 4 m	11 m	40 y 8 m	50	10	0	70.4	23.95	40.14	0.60	No	No
P50	M	18 y 11 m	6 m	15 y 2 m	160	60	0	58.44	16.65	30.85	0.54	No	No
P51	F	17 y	1 y 6 m	11 y 6 m	330	16	10	62.7	22.3	38.8	57.47	Yes	No
P52	F	17 y 5 m	6 y 3 m	13 y 4 m	500	10	46	90.11	12.88	78.56	0.15	Yes	No
P53	F	18 y 11 m	2 y	14 y 7 m	342	10	0	42.83	31.61	19.89	1.60	Yes	No
P54	F	12 y 7 m	2 y 11 m	8 y 2 m	50	15	0	62.35	24.49	36.1	0.68	No	No
P55	F	24 y 3 m	8 y	18 y 11 m	0	0	0	88	20.3	48.9	0.42	Yes	No
P56	F	8 y 3 m	6 m	2 y 6 m	380	35	0	82.43	34.19	32.58	1.05	Yes	Yes
P57	M	15 y 7 m	1 y 4 m	9 y 8 m	0	10	0	65.2	28	30	0.93	Yes	No
P58	M	15 y 8 m	5 m	7 y 10 m	0	176	0	50.6	18	30	0.60	No	No
P59	M	12 y 4 m	5 m	3 y 11 m	103	9	10	65	31.7	34.2	0.93	Yes	No
P60	M	11 y 7 m	3 y 6 m	3 y 6 m	360	42	5	62.67	6.82	50.35	0.14	Yes	No
P61	F	23 y 4 m	2 y 1 m	15 y 1 m	50	10	0	79.25	40.42	35.23	1.15	Yes	No
P62	M	11 y 4 m	2 y 11 m	3 y 6 m	320	7.5	5	78.2	55.2	20	2.76	Yes	No
P63	M	44 y 9 m	34 y 1 m	35 y 1 m	125	0	0	79.6	25.05	54.61	0.46	No	No
P64	M	17 y 5 m	6 m	2 y 6 m	0	73	0	55	20	33	0.61	Yes	Yes
P65	F	17 y 6 m	1 y	2 y	0	0	0	88.6	66.2	19	3.48	Yes	No

^a Abbreviations: M, male; F, female; y, year(s); m, month(s); Dx, diagnosis; FH, family history.

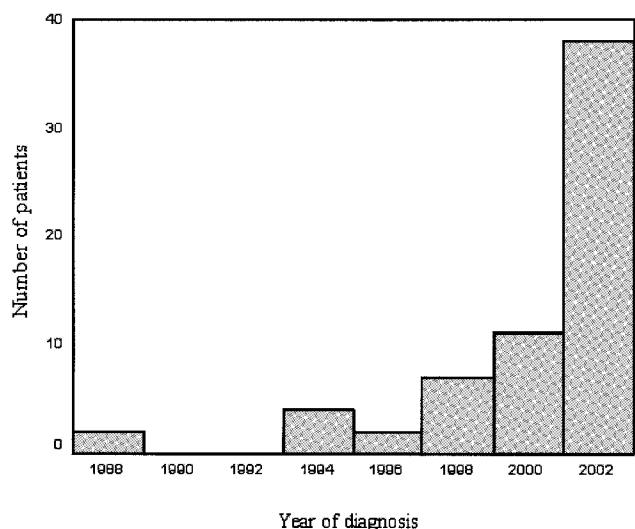


FIG. 1. Distribution of diagnosis year in patients with common variable immunodeficiency (n = 65).

Forty-one of our CVID patients (63.1%) had a history of recurrent otitis media, and 43 patients (66.2%) had sinusitis. Recurrent diarrhea was seen in 50 patients (76.9%). In 10 out of 65 patients (15.4%) unusual or opportunistic infections were seen, including oral candidiasis and *Pneumocystis carinii* pneumonia. Oral candidiasis developed in nine of these patients, and in another case *Pneumocystis carinii* pneumonia was found in a 17-year-old boy with severe lack of CD4⁺ T cells (less than 400 cells/mm³) (P64).

Prior to initiation of immunoglobulin administration, bacterial meningitis occurred in five patients. Other forms of infections and their frequencies before diagnosis were as follows: septic arthritis in nine patients, chronic or recurrent conjunctivitis in eight patients, superficial or deep abscesses in seven patients, and pyelonephritis in six patients. The most frequent

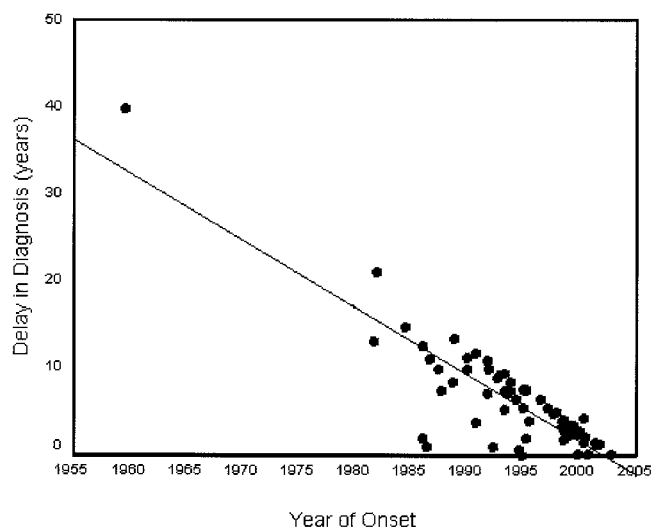


FIG. 2. Association between year of disease onset and delayed diagnosis of common variable immunodeficiency.

TABLE 2. Immunoglobulin levels and CD markers

Immunoglobulin or lymphocyte marker	Median (range) for:	
	Females (n = 28)	Males (n = 37)
Immunoglobulin (mg/dl)		
IgG	110 (0-640)	120 (0-434)
IgA	0 (0-120)	5 (0-235)
IgM	10 (0-400)	10 (0-200)
Lymphocyte marker (count)		
CD3	1,503 (355-7,455)	1,575 (516-8,012)
CD4	667 (47-2,386)	707 (114-4,364)
CD8	823 (165-4,403)	913 (64-4,328)
CD19	245 (36-1,470)	262 (34-4,376)

nonspecific symptoms were hepatomegaly in 13 patients, splenomegaly in 17 patients, and lymphadenopathy in 16 patients.

The most common organisms responsible for infections were *Pneumococcus* species (30%) and *Escherichia coli* (20%), but as necessary cultures were not done for many patients we cannot estimate the true incidence of each microorganism.

(iii) Gastrointestinal disease. Fifty-six patients had gastrointestinal problems. Inflammatory bowel disease (ulcerative colitis) was seen in one patient (P41). Six other patients had significant malabsorption without any known gastrointestinal disorder. One subject had Hirschsprung disease (P60).

Twenty-five patients had liver problems, of whom three had chronic active hepatitis (P41, P52, and P64), two had acute hepatitis (both resolved without any complication) (P48 and P53), one had hepatic cyst (P32), and three had biliary duct obstruction (P20, P22, and P32). Unfortunately there was no viral testing for any of these patients. Three patients had acute appendicitis and underwent surgical removal of the appendix (P4, P57, and P61). One subject had accessory spleen (P36). One patient had mesenteric lymphadenitis (P27).

Twelve patients underwent upper endoscopy, four underwent lower endoscopy, and two patients underwent both. The most common endoscopic findings were as follows: colitis

TABLE 3. Frequency and spectrum of presenting illnesses

Type of disorder	No.	%
Otitis	16	24.6
Diarrhea	16	24.6
Pneumonia	15	23.1
Sinusitis	9	13.8
Dysentery	2	3.1
Eczema	2	3.1
Oral thrush	2	3.1
Pyelonephritis	2	3.1
Sepsis	1	1.5
Omphalitis	1	1.5
Cellulitis	1	1.5
Meningitis	1	1.5
Osteomyelitis	1	1.5
UTI ^a	1	1.5
FTT ^b	1	1.5

^a UTI, urinary tract infection.

^b FTT, failure to thrive.

TABLE 4. Frequency and spectrum of infections occurring in the course of disease

Type of infection	Before diagnosis		After diagnosis		Total	
	No. of cases	Patient-year ^a	No. of cases	Patient-year	No. of cases	%
Pneumonia	48	0.68	22	0.29	55	84.6
Diarrhea	43	0.86	23	0.27	50	76.9
Sinusitis	36	0.48	18	0.21	43	66.2
Otitis	34	0.62	22	0.34	41	63.1
Eczema and dermatitis	12	0.04	6	0.04	17	26.2
Conjunctivitis	8	0.11	6	0.10	12	18.5
Oral thrush	7	0.02	2	0.01	9	13.8
Pyelonephritis	5	0.04	2	0.01	8	12.3
Cutaneous abscess	7	0.04	1	0.00	8	12.3
Meningitis	5	0.04	1	0.00	6	9.2

^a Patient-year indicates risk of being infected for any individual in 1 year.

(66%), esophagitis (30%), and gastritis (23%). Among 12 patients in whom upper gastrointestinal tract endoscopy was done villous atrophy was seen in eight patients (66.6%) and nodular lymphoid hyperplasia was seen in six (50%). Biopsies showed villous atrophy in five of six patients whose endoscopy results were normal.

(iv) Cancer. Two siblings developed Hodgkin's disease, and they had a positive family history of this disease in four of their relatives (P34 and P40). One subject developed non-Hodgkin's lymphoma (NHL) which was confirmed by a node biopsy report of pathology (P50). In all those studied these lymphomas were B cell in type.

(v) Autoimmune disease. Autoimmune disease occurred in 8 out of 65 (23%) patients. These diseases included immune thrombocytopenia (ITP) (P4, P36, and P47), hemolytic anemia (P39 and P47) or neutropenia (P5, P6, P9, P35, P41, and P64), red cell aplasia, thyroid disease (P53), and neuropathy. In patients with ITP, steroids and high-dose intravenous immunoglobulin (IVIg) were useful and splenectomy was not necessary. One patient had alopecia areata (P42), and one had psoriasis (P11).

Family members with immunodeficiency. Relatives of CVID patients may also be found to be immunodeficient. In our patient group six subjects had a positive family history of immunodeficiency (Table 1). There were two immunodeficient sibling pairs in our study with unaffected parents (P40 and P34, and P24 and P38).

Mortality. The median follow-up period in our patient group was 16.5 months (range, 0 to 186 months), during which 11 subjects died (from 3 to 179 months after their diagnosis, at age of onset of illness ranging from 2 to 97 months [median age, 57 months]). The causes of death were as follows: pneumonia in P14, P17, and P55; bowel perforation in P24; hepatic failure in P64; Hodgkin's disease in P34; apnea and cardiac arrest in P37; low platelet and fever in P44; severe infections in P58, P16, and P19.

Excluding the seven patients who could not be located, this shows a mortality of 19% (11 of 58). If none of the seven patients who were not found had died, the mortality rate for the group would be 16.9%. Thus, the true mortality lies between 16.9 and 19%. Patients who died included three females and eight males. The mean age of females at the time of death was 148 months, and that of males was 103 months. Mortality

rate was 40% after a 5-year follow-up period (5-year survival rate of 60%).

DISCUSSION

Common variable immunodeficiency is a heterogeneous primary immunodeficiency disorder with variable immunological defects and clinical manifestations. In this study, 65 patients with CVID, referred to our center over a period of 20 years, were evaluated for clinical and immunological features during their follow-up in our center. There are different reports about CVID patients (17, 18, 27). The average ages at the time of diagnosis in reports by Hermans et al. in 1976, which included 50 patients (27); Cunningham-Rundles in 1989, including 103 patients (18); and Cunningham-Rundles and Bodian in 1999, including 248 cases (17), were 41.9 years, 28 years, and 31 years, respectively. In our study the mean age of patients at the time of diagnosis was 7.1 years for males and 8.6 years for females, which is somewhat less than other published data. This difference between our patients and other reports may be due to selection of our patient population from a pediatric center. However, adult patients with CVID are referred to this center also.

The median age of our patients at the time of onset of symptoms was 9 months, and the median age at the time of diagnosis was 6.1 years. An average diagnostic delay in our patient group was 5.1 years. A survey in the northwest region of England (13) showed that average delay in CVID diagnosis was 2.5 years in children and 5.5 years in adults. Also, in a study done by Cunningham-Rundles and Bodian (17) in the United States, the diagnostic delay in 248 CVID patients studied was 4 to 6 years. This delay markedly decreased over time, perhaps due to better diagnostic tools or methods; an increase in the knowledge of our physicians about primary immunodeficiency disorders, especially CVID; and the beginning of the registry program in Iran. In another study by Moin et al. of X-linked agammaglobulinemia patients in Iran, diagnostic delay also decreased over time (40).

In our patient group HLA DRB1 1303 was more frequent in CVID patients, and it may be considered a predisposing factor. In a study in 1998 (46) HLA DR3 was significantly higher in CVID patients than in the healthy population while in our study it did not show any statistically significant difference. In

our study none of the HLA DQB1 loci except DQB1 0501-3 was known as a predisposing or protecting factor in CVID, but in the study by Schroeder et al. (46) HLA DQB1 0201 was significantly higher in CVID patients. In a study in 1999 (22) the DQB1 0201, DQB1 0301, DQB1 0501, and DQB1 0602 alleles were not significantly different in frequency from the control group, which is compatible with our study. In a previous study in Iran (9) HLA A2 ($P < 0.02$) and A33 ($P < 0.001$) were significantly increased in CVID patients compared to controls. A significant negative association was also evident for DR2 ($P < 0.05$), DR7 ($P < 0.001$), DR52 ($P < 0.05$), and DQ52 ($P < 0.05$) alleles. Therefore, that study also confirmed involvement of the HLA complex in the presentation of CVID in the Iranian population.

Patients with CVID are more susceptible to recurrent infections, and these infections can occur at different sites. In our study 48 out of 65 patients (73.8%) had recurrent pneumonia and 16 of them developed bronchiectasis. The same frequency was noted in a study performed by Cunningham-Rundles and Bodian (17), and the result of their study showed that 190 out of 248 patients (76.6%) with CVID had at least one episode of pneumonia prior to treatment with immunoglobulin. Also they found that 10 out of 248 patients developed bronchiectasis. In another study, done by Busse et al. (14), among 50 patients with CVID, 42 patients (84%) had at least one episode of pneumonia before diagnosis, and by using computed tomographic scanning, 18 out of these 42 patients showed bronchiectasis. Infections are less severe in CVID patients than in XLA patients (40).

It can be concluded that respiratory infections are common medical problems in these groups of patients, and failure to provide adequate replacement therapy results in bronchiectasis, which may be the reason why our patients developed bronchiectasis more often than those in other studies. Development of bronchiectasis is a serious medical problem (32, 41), and all patients with persistent purulent sputum should be assessed and managed, jointly with a chest physician, to prevent progressive lung damage and to monitor functional impairment (12). Despite full replacement immunoglobulin therapy, patients with chronic chest infections always require physiotherapy, antibiotic therapy, bronchodilators, and local anti-inflammatory agents, if progression of lung damage is to be arrested.

In our study 41 out of 65 patients (63.1%) had a history of recurrent otitis media and 43 patients (66.2%) had recurrent sinusitis. It has been shown that immunologic defects have important roles in recurrent ear and sinus infections (47). A similar study done by Cunningham-Rundles and Bodian (17) showed that 243 out of 248 patients with CVID (98%) had recurrent sinusitis, otitis, or bronchitis, and according to another study in 1989 (18), 22% had developed chronic lung disease. Also, some studies show that resistant sinus infection can frequently be the first presenting symptom in immune deficiencies, especially antibody deficiencies (10, 38, 48), and the infections of the upper respiratory tract occur several years before the appearance of lower respiratory tract infections (34). Once the infections of the lower respiratory tract have started, the patients neglect the symptoms from the upper respiratory tract.

In our investigated group, 50 out of 65 (76.9%) patients had recurrent diarrhea. Recurrent or persistent diarrhea and/or

malabsorption may be due to infection, superinfection, food-sensitive enteropathy, autoimmune enteropathy, ulcerative colitis, and celiac disease. As gastrointestinal pathologies were more common in Iranian CVID patients, early endoscopic study is recommended in these patients.

Opportunistic infections including oral candidiasis and *Pneumocystis carinii* pneumonia were seen in 10 out of our 65 patients (15.4%). The isolation of an opportunistic agent in a child or occurrence of an unusually severe infection indicates T-lymphocyte deficiency (8). Although patients with antibody deficiencies have increased susceptibility to infection by common organisms such as *S. pneumoniae* and *H. influenzae* (12, 52) the T-lymphocyte deficiencies in some CVID patients (25) may lead some of them to develop opportunistic infections.

In addition to infection, a variety of autoimmune diseases occur in about 23% of patients with antibody deficiency (53). The most common autoimmune disorder is idiopathic thrombocytopenic purpura, followed by autoimmune hemolytic anemia (53). Although cytopenias are common in all the congenital immune diseases, they are particularly common in the antibody defects, common variable immunodeficiency, and selective immunoglobulin A deficiency. In a study by Cunningham-Rundles (19), it has been shown that 6% of patients with common variable immunodeficiency develop ITP, and autoimmune hemolytic anemia can occur in about 4.8% of this group of patients.

In some patients with antibody deficiencies, hematologic abnormalities were present as the first clinical manifestation; because of a major lack of awareness among clinicians, especially general practitioners and pediatric and adult general physicians, about antibody deficiency disorders and their complications, some patients who present first with hematologic abnormalities will be missed.

Although the association between cytopenias and congenital immune deficiency is unclear, defects in T-cell regulation, cytokine defects, abnormal apoptosis, and abnormal production of immunoglobulins with autoimmune features are potential mechanisms.

Hypogammaglobulinemia is the main feature in CVID, and therefore the standard treatment is IVIg. Although this treatment has changed the spectrum of illnesses, a large number of medical complications are still seen in these patients. Previously, bacterial meningitis, sepsis, and recurring pneumonia were commonly seen in hypoglobulinemic patients (18, 28, 29, 30, 50, 51, 54, 56). In our patients meningitis and sepsis occurred each in one patient as the presenting illness and five of our patients had meningitis prior to IVIg treatment, but no one developed sepsis when given standard amounts of IVIg and only one developed meningitis (Table 4). Overall, according to our data the occurrence of infection has decreased per case per year after IVIg therapy (Table 4).

Two siblings developed Hodgkin's disease, and they had a positive family history of this disease in four of their relatives. One subject developed non-Hodgkin's lymphoma which was confirmed by node biopsy report of pathology. In all those studied these lymphomas were B cell in type. The association between NHL and congenital immunodeficiency is well established, and most NHL cases appear in patients with T-cell defects (such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and severe combined immune deficiency, as well as

CVID) (49). In a study Cunningham-Rundles et al. estimated that females with CVID had a 438-fold-increased likelihood of developing NHL compared to the age-adjusted expected incidence (21).

There is an increased incidence of lymphoma and gastric carcinoma in patients with CVID (20, 24, 35, 45). However, as noted above there may have been difficulties in diagnosing lymphoma in the context of CVID, particularly before molecular techniques became available. Historical studies may therefore overestimate the occurrence of lymphoma by including nonclonal proliferative lesions. There is a suspicion that the occurrence of true lymphoma may be decreasing since the introduction of higher-dose IVIg regimens, compared with the period of IVIg treatment.

Nearly all patients in this group have had stable immunodeficiency, and serum immunoglobulin remained similarly reduced over time. Spontaneous resolution of immunodeficiency has been noted previously, suggesting that this immunodeficiency is not always an intrinsically permanent B-cell defect, or that this more transient form cannot currently be distinguished from CVID (17, 31).

The mortality rate in this group is high, between 16.9 and 19% over a median follow-up period of 20 months. In the first report by Cunningham-Rundles, mortality was 22% over a 13-year period (18), and in another report it was 23 to 27% over a follow-up period of 7 years (17).

Their prior report reflected more data for a period during which intramuscular immunoglobulin was the standard treatment, and the second report and our results show information which includes data collected 15 to 20 years after IVIg was introduced.

While the current data suggest that IVIg has not made an impact on mortality in CVID, a number of subjects referred to this medical center have been in poor medical condition and therefore had short life expectancies. These CVID subjects, with more systemic disease, have most likely increased the overall mortality rate for this patient group. An earlier report demonstrated 22% mortality over a 13-year period, 1960 to 1973 (37); a more recent report showed a 30% mortality for a group of 240 CVID subjects followed over a 30-year period (28). It appears that mortality rates exceed that for XLA, where the mortality in one study was 17% (36). The reasons for this are unknown, although gastrointestinal disease, lymphoma, and autoimmune disease are not commonly found in XLA patients (51). A potential explanation for these differences could be immune dysregulation in CVID due to additional T-cell defects that perhaps leads to additional medical complications.

Conclusion. The causes of CVID are unknown, and it is a heterogeneous group with antibody deficiency, accompanying immune dysregulation, T-cell deficiency, and poorly controlled inflammation leading to additional organ damage.

It is important to consider hypogammaglobulinemia in any patient with a history of recurrent infections at different organ systems, and patients should have a full assessment of immune system including measurement of serum immunoglobulin levels, IgG subclass levels, antibody function evaluation, and B- and T-cell subset enumeration. Serum immunoglobulin levels are interpreted in relation to the normal range for age. Diag-

nostic delay results in morbidity and complications in untreated patients.

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