Original Article

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Infectious and Non-Infectious Complications among Undiagnosed Patients with Common Variable Immunodeficiency

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Abstract

Objective: Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia, defective specific antibody responses to pathogens and increased susceptibility to recurrent bacterial infections. Delay in diagnosis and inadequate treatment can lead to irreversible complications and mortality. In order to determine infectious complications among undiagnosed CVID patients, 47 patients diagnosed in the Children's Medical Center Hospital during a period of 25 years (1984–2009) were enrolled in this study.

Methods: Patients were divided into two groups including Group 1 (G1) with long diagnostic delay of more than 6 years (24 patients) and Group 2 (G2) with early diagnosis (23 patients). The clinical manifestations were recorded in a period prior to diagnosis in G1 and duration follow up in G2. The number of infections, non infectious complications, hospitalizations, and mortality rate was compared between the two groups.

Findings: The patients in G1 group had 500 episodes of infections before diagnosis in 256 patient-years (0.08 per patient per year) and 203 times of hospitalization (0.03 per patient per year), which were significantly higher than in G2 patients, who had 75 episodes of infections (0.015 per patient per year) and 88 hospital admissions (0.018 per patient per year) during 207 patient follow-up years. Frequency of enteropathies and liver diseases in G1 were also significantly higher than in G2. Lack of awareness about nature of disease, especially among rural and suburban physicians, single organ involvement as a site of clinical presenting, and predomination of non infectious presentation in G1 were the major factors of delayed diagnosis.

Conclusion: Diagnostic delay is a major concern in CVID patients, which could result in irreversible complications and mortality, while early diagnosis and proper initial treatment leads to better outcomes and quality of life.

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Key Words: Common variable immunodeficiency; Infections; Delay diagnosis; Immunodeficiency

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Introduction

Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary antibody deficiency, characterized by hypogammaglobulinemia, defective specific antibody responses to protein and polysaccharide antigens and increased susceptibility to recurrent bacterial infections [1-4]. In spite of several years of investigation into the nature of disease, the basic molecular defect of disease is still unknown [5].

The most common infectious complications in patients with CVID are respiratory infections, especially caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* [1,2,6,7]. Also, patients experience gastrointestinal symptoms, including chronic diarrhea and malabsorption[8,9]. Delay in diagnosis and inadequate treatment result in increased irreversible complications and mortality, whereas early diagnosis and appropriate treatment can improve quality life of patients [10]. The effectiveness of immunoglobulin replacement therapy for reducing serious bacterial infections in patients with hypogammaglobulinemia is well documented [11-18]. In our two previous reports, it has been shown that the annual incidence of pneumonia requiring treatment or hospitalization is significantly decreased [11,15].

Despite several studies on effectiveness of intravenous immunoglobulin in reduction of pneumonia incidence in CVID patients, the incidence of infectious complications among undiagnosed CVID patients in comparison with well-treated patients has not been studied yet. While keeping the patients untreated is unethical to evaluate morbidity and mortality in a cohort study, study of complications in long delayed diagnosed CVID patients at the time of diagnosis could be presumed as complications of undiagnosed patients. The purpose of this study is to determine frequency of complications among undiagnosed CVID patients compared with timely diagnosed and well-treated patients.

Subjects and Methods

Forty seven selected CVID patients, who had been referred and diagnosed during 25 years (1984–2009) in the Children's Medical Center, were chosen as subjects of this nested case-control study. These patients were divided into two groups of patients who were early diagnosed and patients with delayed diagnosis.

The diagnosis of CVID was made according to the diagnostic criteria of PAGID (the Pan-American Group for Immunodeficiency) and ESID (the European Society for Immunodeficiencies)[19,20], including reduction of at least two serum immunoglobulin isotypes (serum IgG, IgA and IgM) by two standard deviations from normal mean values for age. We excluded patients <2 years of age, because of a possible diagnosis of transient hypogammaglobulinemia.
Following definitions were used for time of onset and cut off point for diagnostic delay:
"Onset time of disease" is considered when a patient's infection score reached 25 points or more in three years, based on the modified infection scoring system [10,21].

Based on the normal range of total diagnostic delay derived from 193 CVID patients from Iranian registry[22], the "cut off point" of 6 years was calculated considering one standard deviation (1SD, $\alpha<0.05$) difference from the mean.

"Appropriate treatment" includes regular intravenous immunoglobulin therapy (400-600 mg/kg 3-4 weeks), prophylactic antibiotics, administration of antibiotic therapy at the first signs of infections, and regular out-patient visits.
We presumed the CVID patients with long diagnostic delays (G1) as the equivalent of undiagnosed patients. G1 included 24 patients who had a diagnostic delay more than 6 years. G2 included 23 individuals who had early diagnosis (<6 years) and received appropriate treatment, including immunoglobulin replacement therapy and prophylactic antibiotics as needed, during a long period of follow up (at least 5 years). The clinical features and complications of the G1 were compared with the group of CVID patients (G2), who were diagnosed early and received appropriate treatment.

While advancing age or difference between genders could be associated with more infections and more complications, we excluded the effect of age and gender differences as the confounding factors; the age at the time of diagnosis of G1 was matched with the current

age of the selected G2; male/female ratio was also equal in both groups. A four-page questionnaire was developed, containing patient's demographic information, first clinical presentation, age at onset of symptoms, age at diagnosis, history of recurrent and chronic infections, number of hospital admissions and absences from work or school.

In G1, the information about the number of episodes of infections was obtained during the period from onset of diseases to the time of diagnosis, by reviewing the patients' hospital records and interviewing. In G2, the number of episodes of infections was obtained after diagnosis (follow-up period) with immune-globulin replacement.

Follow-up duration was counted as the time between diagnosis and last visit/date of death. For those who died, the cause of death was determined by reviewing death certificate, autopsy report, and/ or by contacting the attending physician.

Infectious complications include sinusitis, otitis media, pneumonia, septic meningitis, encephalitis, lung abscess, septic arthritis, reactive arthritis, visceral abscess, skin abscess, chronic diarrhea, mastoiditis, liver diseases, and enteropathies. Non-infectious complications were obstructive lung disease, restrictive lung disease, bronchiectasis, renal failure, cirrhosis, hepatitis hepato/splenomegaly, inflammatory bowel disease, lymphoid hyperplasia, deafness, failure to thrive, immune thrombocytopenic purpura, autoimmune hemolytic anemia, neutropenia, and diabetes mellitus.

Differences in the median values of hospital admission number per patient per year, diagnostic delay, and immunological parameters of those who died were compared with that of live patients. Probabilities of survival after diagnosis of CVID were estimated from Kaplan–Meier life tables.

Table 1: Demographic and corresponding immunologic laboratory data for CVID patients with long diagnostic delays (Group 1) and CVID patients (Group 2)

Variables	Group 1: Untreated	Group 2: Early diagnosed
Number	24	23
Duration of study: median (range)	Delayed diagnosis: total years before diagnosis: 8.4 (6-32) years	Follow up years after diagnosis: 7 (4-21) years
Age : median (range)	Age at diagnosis 14.6 (8-42) years	Current age at time of study: 15.56(7-50) years
Sex : Male/Female	12/12	10/13
Delayed diagnosis: median (range)	8.4 (6-32) years	2.6 (0.5-5) years
Follow up years: median (range)	5 (1-15) years	7 (4-21) years
Total number of infections during study period	500	75
Total number of hospital admissions	203	88
Total number of non-infectious complications during study period	85	39
Total number of infections led to hospital admission	105	62
Hospital admission due to other causes	98	26
Bronchiectasis	14	8
Missed days from work or school	1563	626
Death	9	2

Findings

Patients' characteristics: In this study, 47 CVID patients (22 males and 25 females), who were diagnosed and followed-up over a 25-year period, were enrolled. Patients were divided into two groups (G1 and G2) based on diagnostic delay and follow-up periods.

Demographic and corresponding immunologic laboratory data for both groups are shown in table 1. The median age at diagnosis for the patients in G1 was 14.6 years (8-42 years), while diagnostic delay ranged between 6 and 32 years (median 8.4 years, totally 256 patient-years). In G2, the median age at time of study was 15.5 years (7-50 years). Patients in this group were followed for 207 patient-years (median 7 years, range 4-21 years). The median diagnostic delays were 8.4 (range 6-32) years and 2.6 (range 0.5-5) years in G1 and G2, respectively. Immunological data of these two groups are presented in table 2.

Seventy seven percent of patients in G1 were referred from rural and suburban areas, whilst 67% of G2 patients lived in Tehran, the capital of Iran, and other major cities of the country.

Infection and non-infectious complication pattern: The G1 patients had 500 episodes of infection in 256 years of pre-diagnosis period (0.08 per patient per year) and 203 times of hospitalization (0.03 per patient per year), which were significantly higher than in G2 patients, who had 75 episodes of infection (0.015 per patient per year, *P*=0.048) and 88 hospital admissions (0.018 per patient per year, *P*=0.001) during 207 patient-years of follow up (Table 3).

Seventy percent of total hospitalization in G1 and 51% (*P*=0.001) in G2 were due to infectious diseases. G1 patients missed more days (3054 days) from work/school, when compared with 1320 days in G2 (*P*=0.002).

Infections in G1 were more frequent than in G2 (Table 3). For example the rate of pneumonia significantly differed (*P*=0.001) between G1 (0.3 patient per year) and G2 (0.1 patient per year). The most prevalent infections in G1 were sinusitis and otitis media (166 of 500, 33%), while chronic diarrhea was the most common manifestation in G2 (27 of 75, 36%). Some clinically important infections (lung abscess, encephalitis, septic arthritis, bacterial meningitis and abdominal abscess) were only documented in G1 patients.

About 72% of patients in G1 presented with infections limited to one organ, mainly respiratory or gastrointestinal tracts; while a few G2 patients (18%) presented with single-organ involvement and most patients had multi-organ involvement. Non-infectious presentations (allergy and autoimmunity) were major problems in 92% of the G1 patients, whereas infections were the dominant picture of the G2 patients.

Bronchiectasis was the main complication,

Table 2: Immunological data of CVID patients with long diagnostic delays (Group 1) and CVID patients (Group 2)

Variable	Group 1: Untreated	Group 2: Early diagnosed
Ig*G (mg/dl)	200±83	254±27
IgM (mg/dl)	19±3	43±27
IgA (mg/dl)	21±9	15±5
WBC‡ (/mm³)	6992±609	7411±591
Lymph (%)	54±18	51±25
PMN§ (%)	37±13	35±27
CD3 (%)	75±26	69±25
CD4 (%)	31±12	31±15
CD8 (%)	42±15	31±16
CD19 (%)	9±3	13±5

* Ig: Immunoglobulin; ‡ WBC: White Blood Cell; § PMN: Polymorphonuclear

Table 3: Infection and non infectious complications among CVID patients with long diagnostic delays (Group 1) and CVID patients (Group 2)

Non infections	G2	G1	*P*-value	Infections	G2	G1	*P*-value
Obstructive lung disease	0	0.041	0.01	**Sinusitis/ Otitis media**	0.082	0.687	0.003
Restrictive lung disease	0	0.166	0.032	**Pneumonia**	0.103	0.382	0.001
Bronchiectasis	0.391	0.54	>0.05	**Septic meningitis**	0	0.041	0.034
Renal failure	0.043	0.083	>0.05	**Encephalitis**	0	0.018	0.032
Cirrhosis	0.347	0.291	>0.05	**Lung abscess**	0	0.090	0.01
Hepatitis	0.043	0.208	>0.05	**Septic arthritis**	0.002	0.058	0.027
Hepato/splenomegaly	0.130	0.375	0.046	**Reactive arthritis**	0.017	0.061	0.031
Inflammatory bowel disease	0	0.083	>0.05	**Visceral abscess**	0	0.017	0.041
Lymphoid hyperplasia	0.043	0.208	>0.05	**Skin abscess**	0.012	0.023	>0.05
Deafness	0.260	0.333	>0.05	**Chronic diarrhea**	0.136	0.612	0.005
Failure to thrive	0.130	0.666	0.043	**Mastoiditis**	0.002	0.020	>0.05
Immune thrombo-cytopenic purpura	0.08	0.208	>0.05	**Liver diseases**	0.06	0.1	0.048
Autoimmune hemolytic anemia	0	0.083	>0.05	**Enteropathies**	0.13	0.699	0.012
Neutropenia	0.043	0	>0.05	**Hospitalization**	0.430	0.996	0.001
Diabetes mellitus	0	0.083	>0.05	**Missed days from work/school**	0.42	3.9	0.002

which was confirmed with high resolution computed tomography in 14 out of 24 (58%) patients of G1, and 8 out of 23 (34%) cases in G2 (*P*=0.032).

Abnormal pulmonary function which was documented by spirometry is another complication in only 5 patients of G1 (20%), but none of G2. Failure to thrive (FTT) recorded in 16 cases in G1, which was significantly higher than 3 in G2 (*P*=0.043).

Mortality and survival: By the time of study, 9 patients in G1 (40%) and 2 in G2 (8%) (*P*=0.009) were dead. These cases in G1 died between 1 and 9 years after diagnosis. In the dead patients, the median age at onset of disease for G1 was 4 years (range 1-15 years) and that at diagnosis was 12 years (range 8-24 years). The median diagnostic delay and follow up in this group were 5.6 years (1.58–11.5 years) and 2.5 years (0.33–14 years), respectively.

Survival analysis was performed for two groups. Among 9 dead patients in G1, seven died within the first 5 years after diagnosis. Post-diagnosis survival of G2 was estimated as 96% for the first 5 years, which remained the same until 15 years after diagnosis, when the survival curve drops to nearly 91% (Fig 1).

The mortality rate among G1 patients was significantly higher than among G2 patients (*P*= 0.005). The most common cause of death was respiratory failure, followed by hepatic failure.

Discussion

CVID is the most common symptomatic primary immunodeficiency, with prevalence of 1:91000 in our region[22], and variable immunological and

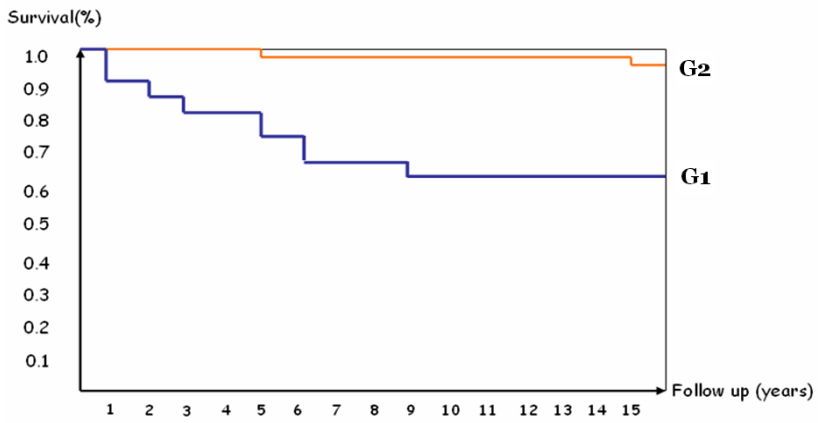

Fig 1: Kaplan Meier and Survival rate of CVID patients with long diagnostic delays (G1) and CVID patients (G2) during 15 years follow up

clinical manifestations[1,2,23-25]. Here we selected the CVID patients with long diagnostic delays (G1) as the equivalent of untreated patients and compared their clinical features and complications with a group of CVID patients (G2), who were diagnosed early and received appropriate treatment.

CVID patients usually experience recurrent infections in different organs, mainly in the respiratory system. In this study, we documented a 6.5 fold difference between frequency of infections in G1 and G2 during the same total of years. Indeed, the number of non-infectious complications such as liver disease and enteropathies was more common in G1 (2.5 times more than in G2). Bronchiectasis was the most frequent complication, which was detected in both groups. Although immunoglobulin replacement therapy has reduced the frequency of recurrent infections, our results showed that a fraction of CVID patients develops chronic lung disease and bronchiectasis despite receiving such therapy. In two large cohort studies, upper respiratory infections were the most frequent presentations, and bronchiectasis developed in 4-14% of affected patients[2,26]. The progression of lung disease in these patients could be due to influence of different factors such as low numbers of memory B cells, defective somatic hypermutation and unknown immune dysregulations other than the hypogammaglobulinemia[26-29].

Recurrent infections and complications have a great impact on the quality of life of the patients. Frequent hospitalizations, longer admission periods, and consequent missed days from work/school were determinants of delayed diagnosis, with frequency of three times more than in G2. Higher rate of hospitalization in the G1, because of isolated infections or non infectious complications, shows that this group was missed under medical health observation.

The survival rate in our study was shown to be significantly influenced by delayed diagnosis. Several patients (38%) in G1 succumbed to death after respiratory complications, which is significantly higher than the mortality rate of 8% in G2. The rate of mortality in CVID varied between 15% and 29% in different studies[1-4,7,10,30,31]. Our previous study on a large cohort of CVID patients revealed that the mortality rate among patients who had no regular visits and did not receive periodical intravenous immunoglobulin therapy was more remarkable, when compared with those who had been followed-up timely [32]. The rate of bacterial infections, days of antibiotic usage, days of fever and hospital admissions can be reduced following immunoglobulin therapy in CVID patients [11,12,14,33-36].

Diagnosis remains one of the major issues in CVID. Lack of awareness among general practitioners about primary immunodeficiencies, not only increases the diagnostic delay of

patients, but also decreases the quality of life and could cost them their lives.

A survey in the northwestern England showed that the average delay in diagnosis was 2.5 years in children and 5.5 years in adults[21]. In another cohort in the United States, the diagnostic delay in 248 CVID patients was 4–6 years[2]. The report from Iranian primary immunodeficiency registry showed that the median diagnostic delay in Iranian patients with CVID was 4 years [22]. All these data show the low awareness of medical health-care workers, resulting in a considerable delay in diagnosis. A reduction in diagnostic delay could be achieved by enriching the knowledge and awareness of physicians about primary immunodeficiencies[10,16]. The median diagnostic delay was 8.4 and 2.6 years in G1 and G2, respectively. This discrepancy in diagnostic delay between G1 and G2 could be due to several reasons: First, more patients in G1 presented with single organ infections (ie, sinusitis, otitis media, pneumonia); however, patients in G2 presented with multi-organ infections. The infections that are confined to a single organ may not raise the physicians' suspicion to the underlying immunodeficiency. Second, non-infectious presentations (autoimmunity and allergy) were more common in the G1 patients. There is a wrong assumption in some physicians that patients with immunodeficiency only present with infections rather than autoimmune or allergic disorders. Diagnosis as well as management of patients with primary immunodeficiencies mandates a multi-disciplinary approach. This will reduce the delay in diagnosis and the resulting morbidity in different organs. Third, patients in G1 were mostly referred from districts far away from the large University hospitals with well established clinical immunology departments.

While immunoglobulin replacement therapy is essential in treatment of patients with CVID, it was unethical to design a prospective study to keep a group of patients untreated. Thus we designed a retrospective study and a group of patients with long delayed diagnosis considered as undiagnosed and untreated patients until the time of diagnosis and their complications were assessed before that time. Another limitation of this finding was using 1SD more than means for cut point of delayed diagnosis, because of insufficient sample number when we used 2SD of 193 patients (= 7 patients).

Conclusion

Early diagnosis and appropriate treatment could improve quality of life of the patients, while diagnostic delay leads to accretion of morbidity and mortality in CVID patients. There is still widespread ignorance about the importance of primary immunodeficiencies and their association with recurrent bacterial infections, particularly in CVID. Putting altogether, the insufficient knowledge of general pediatricians as well as different specialists regarding the organ specific and non-infectious presentations of CVID and shortage of access to specialized clinical immunology centers seem to be the bases of experienced diagnostic delays.

Informing the health care personnel with warning signs of immunodeficiencies, promoting continued medical education for pediatricians regarding novel aspects of diagnosis and management and establishing more specialized centers for diagnosis of primary immunedeficiencies could decrease the diagnostic delay in this group of patients.

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