Mortality and Morbidity in Common Variable Immunodeficiency

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Summary

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia, defective specific-antibody production resulting in recurrent bacterial infections. Delay in diagnosis and inadequate treatment result in increased irreversible complications and mortality. To determine persistent morbidities, mortality rate and survival in Iranian patients with CVID, hospital records of 72 (39 males and 33 females) diagnosed CVID patients were reviewed. Probabilities of survival after diagnosis of CVID were estimated from Kaplan–Meier life tables. Studied patients were enrolled over a 20-year period (1984–2005). The most commonly observed complication was bronchiectasis (24 cases), followed by splenomegaly, intestinal villous atrophy (11 cases), and failure to thrive (10 cases). Post-diagnosis survival was estimated as 65% for the first 6.5 years, which remains the same until 14 years after diagnosis when the survival curve drops to nearly 45%. The mortality rate among patients who had no regular visits and did not receive periodical IVIG was more remarkable when compared with those who had been followed up timely (p-value = 0.001). The most common cause of death was respiratory failure. Based on our observation, it can be highlighted that all patients with CVID, even under regular immunoglobulin replacement, need close monitoring for early detection of complications and introduction of appropriate management.

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia, defective specific-antibody production and increased susceptibility to recurrent bacterial infections [1–3]. CVID is a complex disease in which defects in terminal B cell differentiation, B cell activation after antigen stimulation, T cell signaling and cytokine expression have been observed [4]. The heterogenicity in clinical manifestations and immunological defects in CVID might be a reflection of heterogenicity of mechanisms leading to this disease.

Also the incidence of autoimmune and neoplastic disorders is high in this group of patients compared with normal population [1, 5]. CVID may present at any age but the peaks of presentation are in childhood and early adult life [3, 6]. Delay in diagnosis and inadequate treatment result in increased irreversible complications and mortality [7]. Several documented studies demonstrated that the mortality among CVID patients varies between 15–29% [1, 3, 4, 8, 9]. The large study of 248 patients with CVID [1] estimated that the post-diagnosis 20-years survival rate were 64 and 67% for males and females, respectively, compared with similar ages in the general population (92% for males and 94% for females). All of these documents showed that the patients with CVID are prone to infectious and non-infectious complications resulting in increased mortality and morbidity. Although, regular immunoglobulin replacement therapy is the standard treatment for CVID [3, 4, 10], and has improved patients’ quality of life, but the rate of mortality and life threatening morbidities are still high [7, 11]. Understanding of the risk factors responsible for morbidity and mortality in this group of patients can help the physicians to a better monitoring and management of the disease. The purpose of this study is to determine persistent morbidities, mortality rate and survival in Iranian patients with CVID.
whom has been referred to Children’s Medical Center Hospital during past 20 years (1984–2005).

**Materials and Methods**

**Patients**
In this study, we reviewed the hospital records of 72 diagnosed patients with CVID whom were treated at Children’s Medical Center. 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) [12, 13], 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. Patients with the diagnosis of presumed X-linked agammaglobulinemia, based on family history of X-linked pattern of inheritance and very low numbers of circulating B cells (<1%) were excluded.

**Methods**
A four-page questionnaire was developed, containing all the patient’s demographic information, including date of birth, first clinical presentation, age at onset of symptoms, age at diagnosis, history of recurrent and chronic infections, autoimmunity and malignancy and other complications. Follow-up information was obtained either by reviewing the patients’ hospital records or interviewing of patients. Diagnostic delay was considered as the time between onset of symptoms and the diagnosis. Follow-up duration was counted as the time between diagnosis and the date of either death or last visit. For those who had died, the cause of death was determined by reviewing death certificate, autopsy report, and/or by contacting the attending physician.

**Statistical methods**
Data analysis was performed using the SPSS statistical software package (version 11.0). Probabilities of survival after diagnosis of CVID were estimated from Kaplan–Meier life tables. The Cox proportional hazards model was used for the analysis of factors that might be associated with increased risk of death. Since there was a wide range of age, in order to compare age related survival, patients were clustered into two major groups (3–14 years and 14–56 years). The time between the age at diagnosis and the age at either death or last visit, was used as the ‘time’ variable. Differences in the median values of number of hospital admission per patient per year, diagnostic delay, and immunological parameters of those who had died were compared with that of live patients using Wilcoxon rank-sum tests. The difference between quality of management of live and dead patients, was tested by chi-square test.

**Results**
In this study, 72 CVID patients with Persian origin, including 39 (54.2%) males and 33 (45.8%) females, who were diagnosed and followed-up over a 20-year period (1984–2005), were reviewed. At the time of study, the median age of patients was 12.4 years (range: 2.2–56), and 45 patients (62.5%) were under 14 years. The median age at onset and that at diagnosis were two (range: 0.5–46) and eight (range: 2.5–54) years, respectively. We found that the median of diagnostic delay was 4 years (range: 0.5–46) and eight (range: 2.5–54) years, respectively. We found that the median of diagnostic delay was 4 years (range: 0.25–39). In 5 out of 72 patients, the diagnostic delay was <7 months. Excluding three patients who failed to be followed after diagnosis, the median duration of follow up for the remaining 69 patients were 4 years (0.5–18 years). Serum immunoglobulin levels and immunophenotyping of peripheral blood lymphocytes are summarized in Table 1. Out of 72, 40 (55%) patients showed a decrease in the CD4/CD8 ratio (median: 0.81, ranging from 0.08 to 1).

**Associated conditions**
A variety of persistent non-infectious conditions including malignancies, autoimmune disorders and several other morbidities afflicted these series of patients (Fig. 1); the most commonly observed complication was bronchiectasis (24 cases), followed by splenomegaly (14 cases), intestinal villous atrophy (11 cases), and failure to thrive (10 cases). Six cases in our series developed malignancies including Hodgkin disease diffused large B cell lymphoma and breast cancer. One patient developed pulmonary lymphoma of mucosa associated lymphoid tissue (MALT), which has been reported previously [14].
Two of three cases of Hodgkin disease were sibling and had positive family history. In our study, 22 (30%) out of 72 developed autoimmunity, including ITP (four patients), Evans syndrome (four patients), chronic active hepatitis (four patients), inflammatory bowel disease (nine patients) (ranging from non-specific colitis to ulcerative colitis and Crohn), and Myasthenia gravis (one patient).

Mortality and survival

By 2006, 16 (22.2%) patients died between 6 and 168 months after their diagnosis, 42 (58.3%) were known to be alive, and 14 (19.4%) could not be located. In dead patients, the median of age at onset was 2 years (ranging from 0.5 to 37 years) and that at diagnosis was 8.9 years (ranging from 2 to 42 years). The median of 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. In live patients, the median diagnostic delay was 3.7 years (0.25–39 years) and the median duration for follow up was 4.7 years (0.5–18). The patients of the dead group were hospitalized more frequently in comparison with the alive patients, after diagnosis ($p$-value = 0.001) (Table 2). While hospital admission decreased after diagnosis in alive patients, the number of admissions per patients per year did not differ after diagnosis in dead patients (Table 2). Excluding 14 patients who could not be located, survival analysis was performed for the 58 remaining patients. Out of 16 dead patients, seven died within the first 2 years after diagnosis. Post-diagnosis survival was estimated as 65% for the first 6.5 years, which remains the same until 14 years after diagnosis when the survival curve drops to nearly 45% (Fig. 2). The survival rate was not shown to be influenced by delayed diagnosis, type of complications, serum levels of IgG and B lymphocyte count at the time of diagnosis. The mortality rate among patients who had not regular visits and did not receive periodical IVIG was more remarkable when compared with those who had been followed up.

![Figure 1](https://example.com/fig1.png)

**Fig. 1.** Associate conditions in Iranian patients with CVID. FTT, failure to thrive; IBD, inflammatory bowel disease; NLH, nodular lymphoid hyperplasia; CAH, chronic active hepatitis; deafness, sensorineural deafness; DLCL, diffused large cell lymphoma of B cell.
The most common cause of death was respiratory failure (Table 3).

Discussion

CVID is a heterogeneous primary immunodeficiency with variable immunological and clinical manifestations. In this study, 72 patients with CVID who had been referred to our center over a period of 20 years were evaluated for morbidity and mortality. The median age at diagnosis was 8 years (range: 3–54 years) which is markedly less than that in previous studies [1, 15]. The average age at diagnosis in 50 studied CVID patients by Hermans, et al. [15] and 248 cases reported by Cunningham-Rundles and Bodian [1], were 41.9 and 31 years, respectively. This discrepancy in age at diagnosis could be somehow due to the selection of patients from a pediatric hospital in our study; however, adult patients with antibody deficiencies are referred to this center as well. Despite the general idea that CVID is usually a late onset disorder, we showed that it could present early in childhood. The median of diagnostic delay in our patients was 4.04 years. A survey in the northwest region of England [11] showed that the average delay in diagnosis was 2.5 years in children and 5.5 years in adults. In another cohort in the United States [1], the diagnostic delay in 248 CVID patients was 4–6 years. All these data show the low awareness of general practitioners resulting in a considerable delay of diagnosis. Seymour, et al. [7] compared the median diagnostic delay between 1989 and 2005. They showed that a reduction in diagnostic delay could be achieved by enriching the knowledge and awareness of physicians about primary immunodeficiencies [16].

The hallmark of CVID is hypogammaglobulinemia, and the standard treatment is immunoglobulin replacement either with intravenous immunoglobulin (IVIG) or subcutaneous [17]. Although this therapeutic strategy has altered the spectrum of complications, a number of medical conditions continue to complicate the disorder [4, 18–21].

Bronchiectasis is a common complication and its development is a serious medical problem [22, 23]. Cunningham-Rundles and Bodian [1] found out that 10 out of 248 patients developed bronchiectasis. Using computed tomographic scanning, Busse, et al. [24], showed 18 (42%) out of 42 patients with history of recurrent pneumonia, had bronchiectasis. A high-resolution CT scan of chest revealed bronchiectasis in 24 (33%) of our patients. Despite sufficient immunoglobulin replacement, some CVID patients are still susceptible to develop bronchiectasis. Several factors may contribute to this susceptibility. According to the study performed by Carsetti, et al. [25] and our unpublished data, the reduced number of switched memory B cells and impaired specific antibody production are risk factors for development of bronchiectasis.

As we observed in 30% of our patients autoimmune disorders are of common non-infectious complications among the patients CVID [26]. These include mainly idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) [27–31]. ITP and AIHA can be the presenting features of CVID. IVIG administration reduces the frequency of infections, but does not always prevent autoimmunity. Anti-CD20 immunomodulator has shown some efficacy in treatment of ITP in CVID [26].

Children with antibody deficiency grow normally unless they develop severe complications such as
bronchiectasis. Malabsorption due to gastrointestinal infections can cause FTT in some patients [32]. In our series, 10 cases developed FTT whose major cause was bronchiectasis in five and malabsorption in the remaining. Multi systemic granulomatous disease usually develops in liver, spleen or lungs, and is associated with significant morbidity and early mortality. The etiology of granulomatous disease in patients with CVID is unknown and optimal treatment of granulomatous disease remains to be established [19, 33–39]. One of our patients, with both hepatic granuloma and Evans’ syndrome, finally died of hepatic failure (Table 3).

Malignancies can seriously threaten CVID patients. Several surveys indicated the increased risk of cancer, especially lymphoma and gastric adenocarcinoma in CVID [5, 9, 40–43]. The risk increases as the patients survive to an older age [43]. In our study, six cases (8.3%) developed malignant disorders including three cases of Hodgkin disease (with a familial pattern in two related cases), one case of diffused large cell lymphoma, one case of pulmonary MALT lymphoma and one case of breast cancer. All the cases that developed lymphoma presented their first manifestation of malignancy in their second decade of life.

Kinlen, et al. [40] calculated an overall increase of five fold for all types of cancers which was 47-fold for stomach cancer and 30-fold for lymphoma. Another combined study [5] done on 176 CVID patients have estimated a 1.8-fold rise in the risk of all types of malignancy. There are also some other benign manifestations including nodular lymphoid hyperplasia, splenomegaly and generalized lymphadenopathy [9, 40]. Six (8.3%) and 14 (19.4%) subjects in our series developed nodular lymphoid hyperplasia and splenomegaly, respectively.

During the follow-up period, the rate of mortality was 27% (16 of 58) whereas 14 patients could not be located. If none of the unavailable patients were dead, the mortality rate in our cohort would be 22%. Thus, the true mortality lies between 22% and 27%. The rate of mortality in different studies was reported to be between 15% and 29% [1, 9].

In 1999, Cunningham-Rundles and Bodian showed that low count of B lymphocytes, low serum level of IgG and poor proliferative response of T cell to phytohemaglutinin (PHA) can act as independent predictive factors for survival.

We showed that the medical condition and the number of admissions of deceased patients did not change with standard therapy. In addition, the majority of dead patients were in poor medical condition due to several systemic diseases at the time of diagnosis. This justifies the first drop in the survival curve over the 6.5 years after diagnosis.

CVID is a heterogeneous group of antibody deficiencies, characterized by low levels of serum immunoglobulins and increased incidence of infections. The immunoglobulins replacement therapy is the treatment of choice but does not always prevent the autoimmune and neoplastic disorders. This necessitates close surveillance of patients to prevent the non-infectious complications.

<table>
<thead>
<tr>
<th>ID</th>
<th>Age (years, months)</th>
<th>Cause of death</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>6 y, 10 m</td>
<td>Pneumonia</td>
<td>Malabsorption and growth retardation</td>
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<td>P2</td>
<td>3 y, 6 m</td>
<td>Respiratory failure</td>
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<tr>
<td>P3</td>
<td>11 y, 6 m</td>
<td>Hodgkin</td>
<td></td>
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<td>P4</td>
<td>9 y, 7 m</td>
<td>Respiratory failure (pneumonia)</td>
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<td>2 y, 11 m</td>
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<tr>
<td>P6</td>
<td>14 y</td>
<td>Hodgkin</td>
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<tr>
<td>P7</td>
<td>43 y</td>
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<tr>
<td>P8</td>
<td>4 y, 4 m</td>
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<tr>
<td>P9</td>
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<tr>
<td>P16</td>
<td>17 y, 6 m</td>
<td>Hepatic failure</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3

Cause of death and comorbidities

References

2. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in


