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Clinical and immunological features of common variable immunodeficiency: a single center experience

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Clinical and immunological features of common variable immunodeficiency: a single center experience

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Objectives
The aim of the study was to perform a retrospective investigation describing the clinical and immunological spectrums of common variable immunodeficiency (CVID) at a single center during the period from January 2006 through to June 2013.

Backgrounds
CVID is the most common primary immunodeficiency. The inheritance of CVID is variable; the majority of cases are sporadic, but familial patterns of inheritance are seen in ~10–20% of cases. The hallmark of CVID is reduced serum levels of serum immunoglobulins, IgG, IgA, and or IgM, which leads to recurrent infections. CVID also has noninfectious manifestations such as autoimmunity, granulomatous disease, and malignancy.

Patients and methods
We reviewed the medical records of patients who had been diagnosed with CVID at the Immunology Clinic at Queen Rania Children's Hospital from January 2006 through to June 2013. Collected data included clinical presentation, demographics, associated autoimmune features, allergies, complications, mortality, and immunological workup at the time of diagnosis.

Results
The total number of patients was 17 [12 (71%) male and five (29%) female patients]; the median age at presentation was 5.1 years. Infections were the most common presentation; pneumonia was the most frequent at 71%, followed by sinusitis in 59% of patients. Cytopenias were the most frequent autoimmune association; they were reported in one-third of the patients. Lymphoproliferation was noted in 29%; two of them were due to Epstein–Barr virus infection. Bronchiectasis was diagnosed in four (24%) patients. Fourteen of 17 patients had immunoglobulin IgG, IgM, and IgA levels 2 SD below the mean for age, whereas three patients had low IgG and IgA and normal IgM levels.

Conclusion
Although our study was limited by its retrospective nature and it did not represent the entire population of CVID patients in our country, it emphasizes the importance for awareness of these disorders to improve CVID outcomes.

Keywords:
autoimmune cytopenia, common variable immunodeficiency, infections

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Introduction

Common variable immunodeficiency (CVID) is the most common primary immunodeficiency (PID) and the second most frequent PID after selective IgA deficiency [1]. CVID incidence ranges between 1: 25 000 and 1: 66 000 in North America and Europe [2]. It can present in both adults and children; at least 20% are diagnosed during childhood [3], unlike other PIDs, which are frequently diagnosed during childhood.

The inheritance of CVID is variable; the majority of cases are sporadic, but familial patterns of inheritance are seen in ~10–20% of cases [4].

In the last 10 years, monogenic defects associated with antibody deficiency have been described in a small subset of CVID patients that cause mutations or polymorphisms in the TNFRSF13B (TACI), CD19, ICOS, TNFRSF13C (BAFF-R), CD81, CD20, MSH5, and CD21 genes [3].

The hallmark of CVIDs is reduced serum levels of serum immunoglobulins IgG, IgA, or IgM [5], which leads to recurrent infections of the respiratory tract. Infections may also affect the central nervous system, skin, soft tissue, and gastrointestinal tract. Besides recurrent infections, CVID also has noninfectious manifestations or complications such as autoimmunity, granulomatous disease, gastrointestinal disease, and malignancy [6].

CVID diagnostic criteria have been defined by the European Society for Primary Immunodeficiencies (ESID) as reduction (≥2 SD below the mean for age)

in at least two immunoglobulin isotypes (IgG, IgM, IgA) with absence of isohemagglutinin, and/or a poor response to vaccines in patients over the age of 2 years. Other defined causes of hypogammaglobulinemia have been excluded (*http://www.esid.org*).

The Immunology Division at Queen Rania Children's Hospital in Jordan is a major referral center for PIDs in the country. We retrospectively reviewed the medical records of CVID children aged less than 14 years who had been diagnosed and were being followed up at our hospital since 2006. In this study we were able to describe the clinical presentation, autoimmune association, and long-term complications of pediatric CVID patients.

Patients and methods

We reviewed the medical records of the patients who had been diagnosed with CVID at the Immunology Clinic at Queen Rania Children's Hospital from January 2006 through to June 2013. The diagnosis of probable CVID was made on the basis of Pan-American Group for Immunodeficiency (PAGID) and ESID [7]. Patient ages ranged from 1 to 14 years at the time of data collection. Collected data included clinical presentation, family history of PID, sex, age at presentation, age at diagnosis, associated autoimmune features, allergies, complications, and mortality. Laboratory data at the time of diagnosis included immunoglobulin levels, isohemagglutinin and antibody titer response to tetanus immunization, complete blood counts and differential, and lymphocyte subsets. IgG trough levels were evaluated during intravenous immunoglobulin (IVIG) replacement therapy, and complete blood count and differential during regular follow-up. Data were collected in a Microsoft Excel 2010 Worksheet, and descriptive statistical analysis was performed. Our study was approved by the Ethical Committee of Royal Medical Services of Jordan.

Results

The total number of patients was 17 [12 (71%) male and five (29%) female patients]. The median age at presentation was 5.1 years (range 0.5–11 years). Two patients were diagnosed below the age of 2 years based on a family history of CVID in a sibling and a cousin and the presence of recurrent infections. The median duration of diagnostic delay, which is defined as the time elapsed from first clinical manifestation of the disease to the time of diagnosis, was 3.1 years (range 0.4–10 years). The first symptoms occurred at the median age of 2.1 years. The most common recurrent infections before diagnosis are listed in Table 1; pneumonia was the most frequent at 71% (n = 12), sinusitis was diagnosed in 59% (n = 10), and suppurative otitis media in 53% (n = 9); three patients with mastoiditis needed surgical drainage. Four patients had septicemia; one was due to *Pseudomonas* spp. after a ruptured appendicitis and peritonitis, and the rest were due to gram-positive bacteria. Enteritis was reported in five (29%) patients, three of them due to *Giardia* spp. and two caused by *Salmonella* spp. The vast majority of infections occurred before the initiation of immunoglobulin replacement therapy; all cases received IVIG at 400–500 mg/kg every 3–4 weeks to keep IgG troughs at 500–700 mg/dl. Only three patients suffered from infections while on IVIG; one patient had severe pneumonia and had to be admitted into the ICU, two patients had chronic rhinosinusitis, which needed surgical drainage and many courses of oral antibiotics.

Autoimmune association and complications are shown in Table 2. Cytopenias were the most frequent autoimmune association and were reported in one-third of the patients. The most common was autoimmune thrombocytopenia in 29% (n = 5), followed by autoimmune hemolytic anemia in 12% (n = 2) and isolated neutropenia in three patients. Two patients had inflammatory arthritis. One patient had discoid lupus but not full-blown systemic lupus erythematosus, and one patient had cutaneous leukocytoclastic vasculitis.

Table 1 Infections before diagnosis

	N (%)
Pneumonia	12 (71)
Sinusitis	10 (59)
Suppurative otitis media	9 (53)
Mastoiditis	3 (18)
Enteritis	5 (29)
Septicemia	4 (24)
Necrotizing fasciitis	2 (12)
Skin infection	4 (24)
Fungal infection	2 (12)
Meningitis	2 (12)

Table 2 Autoimmune association and complications

AI association	*N* (%)	Complication	*N* (%)
AIT	5 (29)	Bronchiectasis	4 (24)
AIHA	2 (12)	Stunted growth	4 (24)
Neutropenia	3 (18)	Lymphoproliferation	5 (29)
Lupus	1 (6)	Developmental delay	2 (12)
IBD	3 (18)	Hearing loss	2 (12)
Arthritis	2 (12)	HLH	1 (6)
Vasculitis	1 (6)	Splenomegaly	5 (29)
Celiac disease	1 (6)	Mortality	2 (12)

AI, autoimmune; AIHA, autoimmune hemolytic anemia; AIT, autoimmune thrombocytopenia; HLH, hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease.

Eighteen percent (n = 3) of the patients had chronic diarrhea affecting their growth parameters; their intestinal biopsies showed inflammatory bowel disease, and one patient was diagnosed with celiac disease after exclusion of other causes of celiac sprue.

Allergic disorders were a common association in CVID patients, noted in 35% of cases, including allergic rhinitis, asthma, eczema, and food allergies.

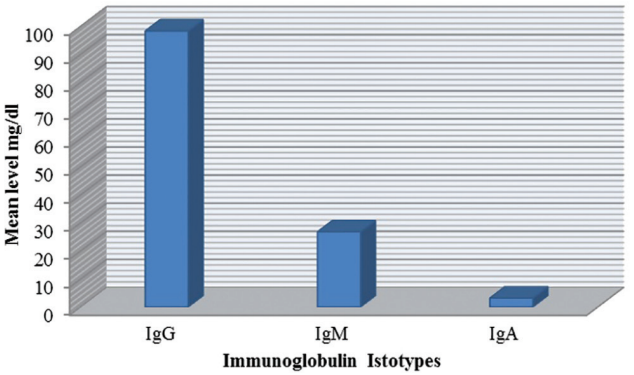
Lymphoproliferation was noted in 29% (n = 5) of patients, in two of them (one boy and one girl) due to Epstein–Barr virus infection; the girl died after she developed hemophagocytic lymphohistiocytosis (HLH). Bronchiectasis was diagnosed in four (24%) patients before IVIG replacement therapy; two of them had chronic lung disease and digital clubbing but showed significant reduction in infection frequency after IVIG treatment. Growth was stunted in 24% of patients; two had conductive hearing loss and two had developmental delay due to central nervous system infections.

Fourteen of 17 patients had immunoglobulin IgG, IgM, and IgA levels 2 SD below the mean for age, whereas three patients had low IgG and IgA and normal IgM levels and four patients had undetectable IgA levels. The mean IgG level was 98.3 mg/dl, IgM was 26.8 mg/dl, and IgA was 3.2 mg/dl (Fig. 1). All patients with blood group O, A, and B showed low to absent isohemagglutinin titers.

The flow cytometric analysis of lymphocyte subsets was carried out and included CD3, CD4, CD8, CD19, and CD16 + 56. The results are shown in Figs 2 and 3. The mean absolute lymphocyte count was 4533/μl; the percentage of CD3, CD4, CD8, CD19, and CD16 + 56 ranged from 33 to 81%, 11 to 68%, 22 to 30%, 3 to 16%, and 4 to 28%, respectively. The mean counts for CD3, CD4, CD8, CD19, and CD16 + 56 were 3016, 2044, 973, 445, and 893/μl, respectively. One patient had CD4 lymphopenia at 451/μl and had inflammatory bowel disease-like enteropathy. One patient had B-cell lymphopenia at 147/μl and had bronchiectasis.

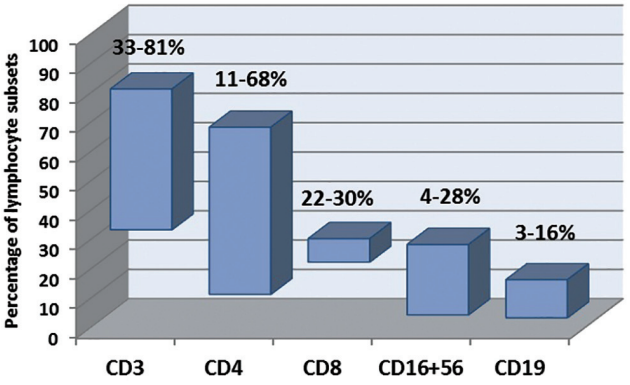
None of our patients had malignancy. The mortality rate was 12% (n = 2), one due to refractory HLH and the other due to severe septicemia.

Figure 1



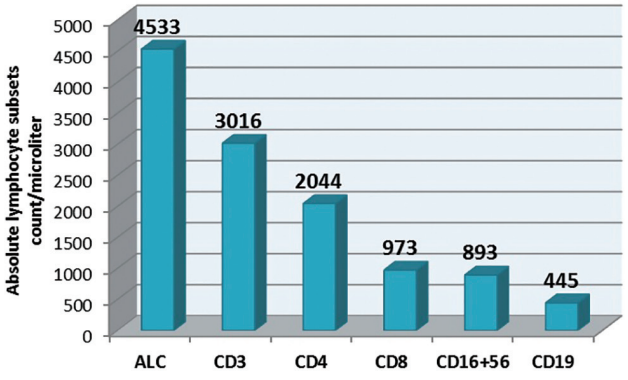
Mean immunoglobulin IgA, IgM, and IgG mean levels in mg/dl at the time of diagnosis.

Figure 2



Percentage range of lymphocyte subsets in 17 patients at the time of diagnosis: the percentage range of CD3 (33–81%), CD4 (11–68%), CD8 (22–30%), CD19 (3–16%), and CD16 + 56 (4–28%).

Figure 3



Absolute lymphocyte count (ALC) and mean lymphocyte subset counts/μl.

Discussion

CVID is the most common clinically significant PID, occurring in about 1: 25 000 individuals [1]. It is characterized by increased susceptibility to respiratory infections and to a lesser extent to gastrointestinal tract infections; autoimmunity, granuloma formation, malignancy, and gastrointestinal manifestations are also seen [2,8].

To our knowledge, our study is considered the largest retrospective study for children with CVID in Jordan.

However, we could not estimate the exact incidence of this disease in Jordan as this cohort does not represent the actual number of patients in Jordan because a significant number of patients are being followed up elsewhere.

In our study the number of boys was twice that of girls, a finding consistent with data from previous studies [1,9]. However, other studies showed no sex-related difference [3]. Urschel *et al*. [2] reported a marked diagnostic delay of a median of 5.8 years, which may be due to overlapping with other pediatric disorders as well as insufficient awareness of these disorders. Although the diagnostic delay is shorter in our study, a median of 3 years, it is comparable to other studies [10]. Family history is critical in shortening the diagnostic delay as we could identify two patients below the age of 2 years based on family history and the presence of significant infections.

Respiratory tract infections were the most frequent infections; more than 2/3 of our patients had pneumonia, followed by sinusitis, a finding consistent with previous studies [2,9,10]. Around one-third of our patients had gastrointestinal infections. Oksenhendler *et al.* [6] reported gastrointestinal symptoms in 47% of their cohort. Whereas our results in this field are comparable to a previous report [2], other studies showed lesser frequencies of these symptoms [9,10].

Autoimmune disorders were seen in around one-third of our patients; more than one disorder may be found in the same patient. The most common was autoimmune cytopenia. Chapel *et al.* [11] reported autoimmune disorders in 42% of their European cohort, where autoimmune cytopenia was the most common disorder. Data from the USA reported autoimmune disease in 28.6% of CVID patients [12].

IVIG replacement therapy was given every 3–4 weeks to achieve the recommended trough level. Almost none of our patients needed hospitalization for serious infections while on therapy, emphasizing the importance for early administration of and close adherence to treatment.

There are many CVID classification schemes according to B-cell phenotype [13–15]. The aims of these classifications were to determine the clinical and immunologic phenotype of CVID patients and to correlate early-onset complications such as bronchiectasis, splenomegaly, and autoimmune disease with some CVID immunological phenotypes. EUROclass trial, a B-cell phenotypic classification of a large cohort of CVID patients initiated in eight European immunodeficiency centers, has improved and unified the different classification schemes [14]. In our study we could not run this classification as our lab does not have the facility to study naïve and memory B-cell phenotypes. Therefore, we could not explain why some patients had early respiratory complications, autoimmune diseases, and lymphoproliferation, whereas others did not or had a milder disease.

The mortality rate in our patients was reported to be 12%. A higher rate (around 20%) has been reported in other studies [10,16]. The causes of death were refractory HLH and severe septicemia. The lower rate in our patients may be due to the small size of our cohort, which is limited to the pediatric age group.

Conclusion

Our study is limited by its retrospective nature. It does not represent the entire CVID patient population in our country either. We also need a longer period of follow-up. However, our study emphasizes the importance for awareness of these disorders to improve the outcome. Early diagnosis and commencement of replacement therapy is critical to improving the patients' quality of life and overall prognosis.

Acknowledgements

Conflicts of interests

None declared.

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