ORIGINAL ARTICLE

Clinical and Immunologic Features of Pediatric Patients With Common Variable Immunodeficiency and Respiratory Complications

M Aydogan, AO Eifan, I Gocmen, C Ozdemir, NN Bahceciler, IB Barlan

Marmara University Medical Faculty, Division of Pediatric Allergy and Immunology, Istanbul, Turkey

Abstract

Background: Common variable immunodeficiency (CVID) is the term used to describe a heterogeneous group of B-cell deficiency syndromes characterized by hypogammaglobulinemia, impaired antibody production, and recurrent bacterial infections.
Objectives: To determine the clinical manifestations and perform an immunological analysis of pediatric CVID patients suffering from respiratory complications.
Methods: The records of 10 patients with CVID who were followed up from 1992 to 2005 (6 males and 4 females) with a median (interquartile range) age of 13.9 (10.4-19.4) years were reviewed. All patients met the standard criteria set for CVID.
Results: Median total serum levels of immunoglobulin (Ig) G, IgM, and IgA in mg/dL were 383.5 (239.2-574.5), 32.5 (17.0-117.0), and 12.5 (5.0-30.7), respectively. Median age at the onset of symptoms, at CVID diagnosis, and on starting intravenous Ig therapy was 4.0 (0.8-6.2), 9.4 (6.7-11.3), and 9.1 (7.0-11.6) years, respectively. Associated disorders were recurrent infections (100%), bronchiectasis (90%), and growth failure (80%), whereas malabsorption, malignant neoplasm, inflammatory bowel disease, and autoimmune disorders were less common. All bronchiectatic patients had a low percentage of B cells, with an average of 4% (range, 1%-7%). The characteristic computed tomography finding in patients with CVID was a multilobar pattern. Malignant neoplasm developed an average of 11.5 (range, 6.5-20.2) years after the diagnosis of CVID was made.
Conclusion: Recurrent respiratory infection should be evaluated to rule out CVID. Early diagnosis and intravenous Ig replacement therapy may reduce the frequency of respiratory infection. Low levels of serum Ig and percentage of B lymphocytes at diagnosis are important parameters for identifying patients at risk of structural lung damage.

Key words: Bronchiectasis. CVID. Pediatric. Primary immune deficiency.

Resumen

Antecedentes: El término inmunodeficiencia variable común (IDVC) nos sirve para describir un grupo heterogéneo de síndromes de insuficiencia de linfocitos B, caracterizados por la presencia de hipogammaglobulinemia, una alteración en la producción de anticuerpos e infecciones bacterianas recurrentes.
Objetivos: El objetivo fue determinar las manifestaciones clínicas y realizar un análisis inmunológico de pacientes de pediatría con IDVC que padecen complicaciones respiratorias.
Métodos: Se revisaron los datos de 10 pacientes con IDVC a los que se les realizó un seguimiento desde 1992 hasta 2005 (6 niños y 4 niñas) con una mediana (rango intercuartílico) de edad de 13,9 (10,4-19,4) años. Todos los pacientes cumplían con los criterios habituales acordados para la IDVC.
Resultados: La mediana de las concentraciones totales séricas de inmunoglobulina (Ig) G, IgM, y IgA en mg / dL fue de 383,5 (239,2-574,5), de 32,5 (17,0-117,0) y de 12,5 (5,0-30,7), respectivamente. La mediana de edad al inicio de los síntomas, el diagnóstico de IDVC y el tratamiento de Ig intravenosa inicial fue de 4,0 (0,8-6,2), 9,4 (6,7-11,3), y 9,1 (7,0-11,6) años, respectivamente. Los trastornos relacionados fueron las infecciones recurrentes (100 %), la bronquioectasia (90 %) y el retraso del crecimiento (80 %), mientras que la malabsorción, las neoplasias malignas, la enfermedad inflamatoria intestinal y los trastornos autoinmunitarios fueron menos habituales. Todos los pacientes con bronquioectasia presentaban un porcentaje de linfocitos B bajo, con una media del 4% (rango, 1% - 7%). La

observación característica de la tomografía computerizada en los pacientes con bronquioectasia fue el patrón multilobular. Las neoplasias malignas se desarrollaron en una media de 11,5 (rango, 6,5 – 20,2) años después del diagnostico de la IDVC.
Conclusión: La infección respiratoria recurrente debería ser estudiada para descartar la IDVC. El diagnóstico precoz y el tratamiento de sustitución de Ig intravenosa pueden reducir la frecuencia de las infecciones respiratorias. Las bajas concentraciones de Ig sérica y el porcentaje de linfocitos B en el momento del diagnóstico son parámetros importantes para identificar a los pacientes con riesgo de padecer daños pulmonares estructurales.

Palabras clave: Bronquiectasia. IDVC. Pediatría. Insuficiencia inmunitaria primaria.

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous disorder that is characterized by low levels of immunoglobulin (Ig) G, IgA, and/or IgM, as well as normal or nearly normal numbers of circulating immunoglobulin-bearing mature B cells, impaired antibody response, and recurrent bacterial infections of the respiratory and gastrointestinal tracts by encapsulated bacteria [1-4]. Recurrent infections in children are a leading cause of morbidity and hospitalization worldwide. The clinical and immunological spectrum of CVID is quite broad, although relatively little is known about its features.

CVID is the second most frequent primary immunodeficiency disease following selective IgA deficiency and affects both sexes equally [5]. In CVID patients, increased susceptibility to chronic lung disease and autoimmune, gastrointestinal, neoplastic, and inflammatory disorders has been reported. Bronchiectasis is a particularly common medical problem leading to frequent hospitalization and severe respiratory impairment [2]. Patients are prone to respiratory tract infections that often result in pulmonary injury. The use of high-dose intravenous gammaglobulin has significantly decreased the frequency and severity of infections in patients with CVID [6]. However, despite Ig replacement therapy, pulmonary complications do occur [7,8].

In this study, we collected data retrospectively to determine the clinical conditions and immunologic parameters of CVID patients with respiratory complications.

Material and Methods

The records of 10 patients with a diagnosis of CVID who were attending the Division of Pediatric Allergy and Immunology at Marmara University Medical Faculty from 1992 to 2005 were studied. CVID was diagnosed using standard criteria [1], including low level of serum IgG, IgA, and/or IgM greater than 2 SD from the normal mean, absent or poor response to vaccines, and exclusion of other defined causes of hypogammaglobulinemia. Patients with primary immunodeficiencies due to defined underlying causes (Bruton agammaglobulinemia, CD40 ligand deficiency, ataxia-telangiectasia, and immunodeficiencies secondary to other diseases (chromosomal abnormalities, lymphoma, thymoma, asplenia, protein-losing enteropathy, nephrotic syndrome) or drugs were excluded. Total serum IgG, IgA, and IgM levels were measured by nephelometry (BN ProSpec systems, Dade Behring Marburg GmbH, Marburg, Germany). Immunoglobulin replacement therapy was stopped for a 2-month period during the summer and patients were immunized using 23-valent pneumococcal vaccine. Pneumococcal IgG was measured on the day of vaccination and 4 weeks later. A less than 2-fold increase in specific IgG response determined 4 weeks after vaccination was considered a deficient antibody response to polysaccharide antigens [9,10].

Lymphocyte subsets from peripheral blood were enumerated by means of fluorescent activated cell sorting (FACS) with the following cluster of differentiation (CD) antigens: total T cells ($CD3^+$), helper T cells ($CD3^+/CD4^+$), cytotoxic T cells ($CD3^+/CD8^+$), and B cells ($CD19^+$, $CD20^+$). The diagnosis of bronchiectasis was based on the presence of a chronic productive cough and characteristic high-resolution computed tomography (HRCT) findings. The diagnostic workup also included a complete blood count and blood biochemistry, chest and sinus x-rays, thoracic HRCT, and cultures of blood, urine, and stool. Gastro-endoscopy, bronchoscopy, and biopsy were performed as medically required. All patients received intravenous immunoglobulin (IVIG) replacement therapy at a dose of 500 mg/kg every 3 to 4 weeks.

The clinical histories were examined to determine age at onset of symptoms, age at the time of diagnosis, age at initiation of IVIG therapy, history of recurrent infections, associated conditions, cause of infection, and HRCT findings.

Statistical Analysis

The quantitative variables were expressed as the median (interquartile range [IQR]). Considering that the number of cases is small, a nonparametric test (Mann-Whitney) was performed to compare these quantitative variables. Statistical significance was set at $P < .05$. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 11.0.

Results

Of the 10 CVID patients, 6 were male, aged 5.8 years to 23.2 years with a median of 13.9 years. Median (IQR) age at the onset of symptoms was 4.0 (0.8-6.2) years, with a median age at diagnosis of CVID and on starting initial IVIG therapy

Table 1. Demographic and Immunologic Findings for Patients with Common Variable Immunodeficiency

Patient Number	Sex	Age, y and m			Ig level (mg/dL)			CD (%)				CD4/CD8 Ratio	Isohemagglutinin	Vaccination Response	
		Current	At Onset	At Diagnosis	IgA	IgM	IgG	CD3	CD4	CD8	CD19			Before (µg/dL)	After (µg/dL)
P1	M	5 y 8 m	4 m	2 y 8m	5	43	402	76	39	37	18	1.05	-	0.6	1.1
P2	F	7 y 2 m	1 y	4 y 2 m	5	156	234	63	32	32	7	1	-	0.6	0.3
P3	M	11 y 5 m	8 m	8 y	5	17	561	65	48	40	3	1.2	-	3	1.6
P4	F	11 y 6 m	6 y	11 y 5 m	7	17	241	61	41	31	5	1.32	+	1.3	1
P5	M	11 y 9 m	6 y 8 m	9 y 8 m	13	104	615	57	42	44	6	0.95	-	1.8	1
P6	M	16 y	7 y 5 m	7 y 5 m	77	18	745	87	72	21	4	3.43	-	2.3	3.3
P7	M	18 y 3 m	8 m	11 y 2 m	51	274	400	76	17	63	2.8	0.27	-	0.6	1.2
P8	M	18 y 5 m	3 y	9 y	12	27	350	63	41	38	3	1.08	-	0.6	0.3
P9	F	22 y 2 m	5 y	18 y	24	17	141	89	52	35	6	1.4	-	0.6	0.3
P10	F	23 y 2 m	5 y	11 y	22	38	367	54	14	35	1	0.4	-	5.2	3.4
Median		13.9 y	4.0 y	9.4 y	12.5	32.5	383.5	64.0	41.0	36.0	4.5	1.1		0.9	1.0
(Interquartile range)		(10-19)	(0.8-6)	(6-11)	(5-30)	(17-117)	(239-574)	(60-78)	(28-49)	(31-41)	(2.9-6.2)	(1.1-1.3)		(0.6-2.5)	(1-2)

of 9.4 (6.7-11.3) years and 9.1 (7.0-11.6) years, respectively. The average delay in diagnosis was 5.7 (2.8-8.0) years.

Median total serum levels of IgG, IgM, and IgA in mg/dL were 383.5 (239.2-574.5), 32.5 (17.0-117.0), and 12.5 (5.0-30.7), respectively. Other demographic and immunologic findings are shown in Table 1. Females had low total IgG with a median of 237.5 (164.2-335.5) mg/dL compared with males, who had 481.5 (387.5-647.5) mg/dL (P = .019). Otherwise, there were no significant differences in terms of age, age at onset of symptoms, age at diagnosis, average diagnostic delay, and other immunologic parameters (data not shown). Out of 10 patients, 1 had a positive isohemagglutinin titer of 1/16 and the rest were nonresponsive. The median antibody response to polysaccharide antigens before and after pneumococcal vaccine was 0.9 (0.6-2.5) and 1.0 (0.3-2.0) µg/dL, respectively.

The complications of CVID observed in our patients were recurrent infections (100%), bronchiectasis (90%), growth failure (80%), malabsorption (60%), malignant neoplasm (40%), inflammatory bowel disease (30%), and, to a lesser extent, autoimmune disorders (1 patient with juvenile rheumatoid arthritis) (Table 2).

Recurrent respiratory infection (sinusitis, acute otitis media, pneumonia) was the most common associated disease, and all patients had pneumonia before IVIG therapy. In all but 1 of the patients, the clinical symptoms of bronchiectasis were confirmed by thoracic HRCT, and 1 patient had chronic respiratory disease with fibrotic changes. A multilobar pattern was the most common finding in HRCT in bronchiectatic patients. Other HRCT findings included enlarged hilar lymph nodes, nodules, a mosaic pattern, and atelectasis (Table 3).

The median age at diagnosis of bronchiectasis was 9.9 (7.1-11.6) years. Of the 9 bronchiectatic patients, 7 were diagnosed with CVID and bronchiectasis at the same time, whereas in 2, bronchiectasis developed 18 months later, despite IVIG therapy after the diagnosis of CVID. All bronchiectatic patients had a low percentage of B cells, with an average of 4% (range, 1%-7%).

Four patients had malignant neoplasms: 2 had non-Hodgkin lymphoma, 1 had Hodgkin lymphoma, and 1 had Wilms tumor. Malignant neoplasms developed a median of 11.5 (6.5-20.2) years after CVID was diagnosed.

Despite the dose of IVIG (500 mg/kg), patients with bronchiectasis had recurrent respiratory infection. During follow-up, Haemophilus influenzae and Streptococcus pneumoniae were the microorganisms most commonly isolated from sputum (Table 4).

Table 2. Complications of Common Variable Immunodeficiency

Patient Number	Respiratory Tract Infection	Growth Failure	Splenomegaly	Malabsorption	Inflammatory Bowel Disease	Bronchiectasis	Enlarged Lymph Nodes	Malignancy	Juvenile Rheumatoid Arthritis
P1	Pneumonia, sinusitis, otitis media	+	+	+	Ulcerative colitis	-	-	Wilms tumour	-
P2	Pneumonia, sinusitis, otitis media	+	-	+	Ulcerative colitis	+	+	-	-
P3	Pneumonia, sinusitis, otitis media	-	-	-	-	+	-	-	-
P4	Pneumonia, sinusitis, otitis media	+	+	+	-	+	-	-	-
P5	Pneumonia	+	-	+	-	+		-	-
P6	Pneumonia, sinusitis, otitis media	+	-	-	-	+	+	-	+
P7	Pneumonia, sinusitis, otitis media	-	+	-	-	+	-	Non-Hodgkin lymphoma	-
P8	Pneumonia	+	+	+	Ulcerative colitis	+	+	Hodgkin lymphoma	-
P9	Pneumonia	+	+	-	-	+	-	-	-
P10	Pneumonia, sinusitis, otitis media	+	+	+	-	+	-	Non-Hodgkin lymphoma	-

Table 3. Computed Tomography Findings in Patients With Common Variable Immunodeficiency

Computed Tomography Findings	N = 10
Bronchiectasis	
Multilobar bronchiectasis	6
Lobar bronchiectasis	3
Enlarged hilar lymph nodes	4
Nodules	3
Emphysema	2
Atelectasis	2
Mosaic pattern	1
Fibrotic change	1

Table 4. Microorganisms Isolated From the Sputum of Patients With Bronchiectasis

Microorganism	N = 10
Haemophilus influenzae	3
Streptococcus pneumoniae	2
Pseudomonas aeruginosa	1
Proteus mirabilis	1
Serratia marcescens	1
Staphylococcus aureus	1
Candida species	1

Discussion

The most important finding of this study was that CVID patients with respiratory complications had hypogammaglobulinemia, low levels of circulating B cells, and a deficient antibody response to polysaccharide antigens. The most common associated systemic disorder was recurrent infection, and even bronchiectatic patients who received IVIG at 500 mg/kg had recurrent respiratory infection.

CVID is one of the most frequent primary hypogammaglobulinemias and manifests as a wide variety of associated immunologic defects and clinical signs and symptoms.

Early diagnosis of primary hypogammaglobulinemia is considered to be important, because intensive treatment may prevent the development and progression of pulmonary changes [7,8,11]. Early IVIG has been shown to reduce the number of sinopulmonary infections [6,11], although Kainulainen et al [12] reported that silent progression of pulmonary changes can occur in patients despite maintenance of preinfusion IgG concentrations of 500 mg/kg or more. In our study, the diagnostic delay was 5.7 years, which may explain the recurrence of respiratory infections and progression of bronchiectasis.

Two of our patients had B-cell counts below 3%; this could be considered as congenital agammaglobulinemia, although their IgG values were higher than 200 mg/dL. It has been reported that B-cell counts in CVID patients can be normal or reduced and that approximately 13% of patients have a B-cell count of less than 3% in peripheral blood lymphocytes [2,11], as seen in 2 of our patients.

In previous studies, the immunologic parameters associated with poorer prognosis in CVID patients were low percentage of B cells, poorer T-cell response to phytohemagglutinin, and a lower level of serum IgG. The clinical manifestations with the highest morbidity and mortality were lymphoma and chronic lung disease [2]. Interestingly, some patients with CVID do not have recurrent infection or are completely asymptomatic. Alachkar et al [13] have recently shown that the low percentage of switched memory $CD19^{+}CD27^{+}IgD-$ B cells is the most important prognostic marker of bronchiectasis and splenomegaly in CVID patients. Our study showed that the delay in diagnosis and standard IVIG replacement therapy at 500 mg/kg (administered to most of our patients with low levels of B lymphocytes at diagnosis) indicates a higher incidence of bronchiectasis and that it is the strongest predictor of chronic lung diseases, as reported elsewhere [14,15].

Patients with CVID have recurrent sinopulmonary infections, such as sinusitis, otitis media, bronchitis, and pneumonia. Upper and lower respiratory tract infections caused by encapsulated bacteria, such as *S pneumoniae, H influenzae, Staphylococcus aureus,* and *Pseudomonas aeruginosa,* are the most important clinical manifestations leading to chronic lung disease, bronchiectasis, and, eventually, death [10,16]. Bronchiectatic patients in this study were mostly colonized by *H influenzae* and *S pneumoniae*.

Approximately 20% of CVID patients develop 1 or more autoimmune diseases [2,17], indicating that CVID is a disease of abnormal immune regulation, as well as an immunodeficiency. In our study group, 1 of the patients developed juvenile rheumatoid arthritis.

Thirty percent of the patients had histologic findings suggestive of inflammatory bowel disease (ulcerative colitis), as reported elsewhere [2,11]. CVID patients have an increased incidence of lymphoproliferative disease, and benign lymphoproliferative disorders are more common than lymphoma. However, the relative risk of lymphoma increases by as much as 30-fold in CVID patients compared with the normal population [18]. Thirty percent of our patients developed lymphoma, whereas splenomegaly and enlarged lymph nodes affected 6 and 3 patients, respectively.

In conclusion, the clinical spectrum of CVID is diverse: some patients experience few infections, whereas others have a poor prognosis. Susceptibility to recurrent respiratory infection should be evaluated to rule out CVID. Early diagnosis and IVIG replacement therapy should reduce the frequency of respiratory infection. Low levels of serum Ig and B cells at diagnosis might help identify patients with a high risk of developing bronchiectasis and can be an important indicator for early antibiotic prophylaxis and IVIG therapy.

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Aarif O Eifan

Marmara University Medical Faculty,
Pediatric Allergy&Clinical Immunology
Altunizade, Uskudar
Istanbul, Turkey
E-mail:elfano@yahoo.com