Adult Common Variable Immunodeficiency

Jing Dong, MD, Hongda Liang, MS, Dawei Wen, MS and Jibo Wang, MD

ABSTRACT

Background: Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia, defective antibody production and recurrent upper and lower respiratory tract infections. The diagnosis in adult patients is often thought to be rare, and thus misdiagnosis often occurs. A limited number of cases of adult-onset CVID have been reported in China, and the features of the syndrome remain unclear. The objective of this study was to describe the main characteristics of CVID, and evaluate the treatment of adult patients who present with CVID.

Materials and Methods: This was a retrospective analysis of 8 patients with CVID from different departments in 1 center in China. Patients were diagnosed according to the diagnostic criteria of the European Society for Immunodeficiency Diseases. Demographics, clinical and immunological data from each patient were collected and a statistical analysis was undertaken.

Results: The mean age at diagnosis was 43 ± 13.7 years, whereas the mean duration of diagnostic delay was 10.5 years. The median total serum levels of immunoglobulin (Ig) G, IgA and IgM at diagnosis were 2.5 ± 0.59, 0.23 ± 0.05 and 0.17 ± 0.05 g/L, respectively. A total of 7 patients also had a low $CD4^+/CD8^+$ ratio. All patients presented with recurrent respiratory infections. Regular infusions of intravenous immunoglobulin every 3 weeks substantially reduced pneumonic episodes.

Conclusions: Diagnosis is often delayed in adult CVID. Pulmonary infections and diseases were the most frequent presentations at onset of the disease. Regular intravenous immunoglobulin infusions were beneficial in controlling recurrent infections.

Key Indexing Terms: Common variable immunodeficiency; Adult; Infection. **[Am J Med Sci 2016;351(3):239–243.]**

INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiencies, which is characterized by low immunoglobulin (Ig) G and IgA levels and occasionally low IgM levels. The etiology of CVID is unknown, but it is most likely a syndrome that is caused by a variety of distinct disease entities.[1] Clinically, patients with CVID have recurrent bacterial infections of the respiratory tract, including sinusitis, otitis media, bronchitis and pneumonia. Moreover, recurrent pulmonary infections can lead to chronic diseases such as bronchiectasis.[2]

CVID is the most prevalent primary immunodeficiency with an incidence that is estimated at 1:50,000-1:200,000.[2,3] The disorder may occur at any age, but in most patients, onset occurs in the second decade of life, and for this reason, physicians often consider CVID a rare condition in elderly patients, which might result in a diagnostic delay. Few reports in China have focused on adult CVID. To describe the main characteristics of the disease, and evaluate treatment of adult patients with CVID in China, this study reports on a group of patients in whom the diagnosis of CVID was made at a mean age of 43 years.

PATIENTS AND METHODS

Patients

All patients were either "In-Patients" or "Out-Patients" of the Affiliated Hospital of Qingdao University, and were recruited to the study between January 2011 and January 2014. The hospital is the largest tertiary referral center in Qingdao City that has a population of 8 million people. All patients were followed every 2 months during the 3 years after CVID was established. Patient records were retrospectively studied. Information from each CVID subject was collected by means of a structured questionnaire that was applied by a single physician. Demographics, age at onset of symptoms, age at diagnosis, pedigree, clinical manifestations, laboratory results, current infections, autoimmunity, lymphoproliferative disease, allergy and malignancies, family history of primary immunodeficiency diseases (PIDs), lymphocyte subsets and Ig levels at the first clinical visit and route and dosage of Ig were collected and analyzed. Episodes of lower respiratory tract infection (per patient and year) were recorded, and lung computed tomography scan analysis was done each time the patient presented with symptoms of low respiratory tract infection. The protocol was reviewed and approved by the local Ethics and Research Committees of the Affiliated Hospital of Qingdao University in accord with the guidelines of the International Conference on Harmonization, Good Clinical Practice and the Declaration of Helsinki.

Inclusion Criteria

The diagnosis of CVID was based on the European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency criteria[4]: Male or female patients with

a marked decrease in IgG levels (>2 standard deviations less than the mean age) and a marked decrease in the levels of at least 1 of the isotypes IgM or IgA, in addition to fulfilling all of the following criteria:

(1) onset of immunodeficiency at greater than 2 years of age,
(2) absence of isohemagglutinins, poor response to vaccines or both and
(3) exclusion of defined causes of hypogammaglobulinemia.

Patients with secondary hypogammaglobulinemia (ie, long-term steroid therapy, lymphoma or protein-losing enteropathy), isolated primary IgA deficiency or X-linked agammaglobulinemia were excluded. Serum was assayed for isohemagglutinins by standard agglutination tests. Lymphocytes subsets and Bruton's tyrosine kinase gene (Btk) protein levels were determined by flow cytometry.

Statistical Analysis

Results are shown as mean ± standard deviation (ie, if the variable was normally distributed), and median (ie, interquartile range) for continuous variables. Dichotomous and nominal variables were expressed as frequencies and percentages. Basic comparisons between groups were performed using Student's *t* tests. All 2-sided $P < 0.05$ were considered statistically significant. Data were analyzed using the Statistical Package for Social Science (SPSS) statistical software program.

RESULTS

A total of 8 patients were included in this study. No patients had family history of PIDs, and no consanguinity of marriage was traced. The male-to-female ratio was 5:3. The mean age at the onset of symptoms was 32.5 ± 12.6 years (range: 15-49), with a mean age at diagnosis of CVID of 43 ± 13.7 years (range: 24-63) (Table 1). The mean interval between the manifestation of recurrent infection and the diagnosis of CVID was 10.5 years. At diagnosis, the mean Ig levels were as follows: IgG, 2.5 ± 0.59 g/L (normal range: 7-16); IgA 0.23 ± 0.05 g/L (normal range: 0.7-4.0) and IgM 0.17 ± 0.05 g/L (normal range: 0.4-2.3) (Table 1). No abnormalities were found in white blood cell counts. In all, 6 of the 8 patients had a decreased level of B cells and 7 patients presented a low $CD4^+/CD8^+$ ratio (Table 1). The absolute number of circulating T cells and complement components C3 and C4 were within normal limits. Antinuclear antibody was negative in all patients. None of the patients were positive for human immunodeficiency virus, hepatitis B or hepatitis C. Both liver and kidney function was normal in all 8 patients.

As shown in Table 1, all patients had respiratory symptoms, especially of the upper respiratory tract. The most common causative pathogen was *Streptococcus pneumonia* that was detected in 6 cases. *Pneumocystis carinii* was isolated in 2 patients who had low absolute $CD4^+$ T-cell counts. *Pseudomonas aeruginosa* and *Acinetobacter* were only isolated in patients with bronchiectasis. However *Candida albicans* and *Cladosporium* spp. were isolated in patients without bronchiectasis.

TABLE 1. Characteristics of 8 patients at the time of diagnosis of CVID.

Patient/ sex	Age at recurrent infection	Age at Dx of CVID	WBC ($\times 10^9$)	Hb (g/L)	PLT ($\times 10^9$)	IgG (g/L)	IgA (g/L)	IgM (g/L)	B cells (%)	$CD4^+/CD8^+$	Associated disorder
1/F	33	45	4.0	98	245	2	0.2	0.17	6.9	0.88	Respiratory tract infections; anemia
2/M	45	58	5.3	121	220	2.5	0.25	0.2	7.2	0.9	Pneumonia; otitis media
3/M	43	50	4.4	95	124	2	0.25	0.1	13.6	0.8	Respiratory tract infections; anemia
4/F	30	36	6.8	130	109	2.5	0.3	0.25	7.1	0.65	Pneumonia
5/M	17	28	4.9	122	160	1.8	0.2	0.1	6.4	1.2	Arthiritis; respiratory tract infections
6/M	15	24	5.1	134	210	3.2	0.15	0.23	6.8	0.76	Pneumonia
7/F	28	40	7.2	126	157	2.5	0.3	0.17	7.0	0.9	Pneumonia; appendicitis
8/M	49	63	6.2	128	180	2.2	0.2	0.15	10.5	0.95	Pneumonia; thyroiditis; herpes simplex
Mean	32.5	43	5.49	119.2	175.6	2.5	0.23	0.17	8.19	0.88	
SD	12.6	13.7	1.14	14.67	47.33	0.60	0.05	0.05	2.54	0.16	

Normal range: IgG 7-16 g/L; IgA 0.7-4.0 g/L; IgM 0.4-2.3 g/L; B cells: 7.3-18.2%; $CD4^+/CD8^+$: 0.98-1.94.
SD, standard deviation.