Original Article

Clinical and Immunological Features of Common Variable Immunodeficiency in China

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Abstract

Background: Common variable immunodeficiency (CVID) is one of the most common symptomatic primary immunodeficiency syndromes. The purpose of this article was to broaden our knowledge about CVID for better diagnosis and treatment.

Methods: Clinical and immunological features of 40 Chinese patients with CVID were analyzed retrospectively.

Results: The median age at onset was 11-year-old (range 4–51 years). The median age at diagnosis was 14.5-year-old (range 5–66 years). The average time of delay in diagnosis was 5.3 years (range 1–41 years). The most common main complaint was fever due to infections (35 cases, 87.5%). Pneumonia (28 cases, 70%) was the most common type of infections. Bronchiectasis was present in 6 patients (15%). Autoimmune disease was detected in 6 cases of CVID, and malignancy in 2 cases. The median total serum levels of IgG, IgA, and IgM at diagnosis were 1.07 g/L, 0.07 g/L, and 0.28 g/L, respectively. The percentages of $CD3^{-}/CD19^{+}$ B-cells were 1%–3.14%.

Conclusions: Infection is the most frequent presentation of CVID. Patients with unexplainable infections should receive further examination including serum immunoglobulin (Ig) and lymphocyte subset analysis. Regular and sufficient substitution with Ig is recommended.

Key words: Common Variable Immunodeficiency; Immunoglobulin; Infection; Intravenous Immunoglobulin Therapy; Lymphocyte Subset

Introduction

Common variable immunodeficiency (CVID) is one of the most common symptomatic primary immunodeficiency syndrome characterized by hypogammaglobulinemia and recurrent infections. The estimated incidence of CVID is between 1:10,000 and 1:50,000.[1] The incidence of CVID varies with regional differences and is a rare diagnosis among Asians.[2,3] Patients with CVID may present with recurrent bacterial infections of the respiratory and gastrointestinal tract. Some CVID cases manifest initially with autoimmune, granulomatous or lymphoproliferative complications. Due to the complexity of CVID, there is a wide spectrum of clinical presentations which may lead to misdiagnosis and delay in diagnosis. Early diagnosis and suitable treatment including intravenous immunoglobulin (IVIG) are vital for the prognosis of patients with CVID.

In this study, we reviewed 40 cases of CVID, 5 of which were diagnosed in Peking University First Hospital and 35 cases reported in Chinese literatures from 1984 to 2013 which had relatively complete information and confirmed diagnosis. We reviewed these cases in order to broaden our knowledge about this rare disease in China for better diagnosis and treatment.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.150092

Methods

Clinical cases collection and database search

The records of 5 CVID patients diagnosed within the last 13 years in Peking University First Hospital were retrospectively analyzed. CVID was diagnosed according to the diagnostic criteria of the European Society for Immunodeficiency Diseases (ESID).[1] China National Knowledge Infrastructure and Wan Fang Database were searched for collecting associated cases. Key words used for searching were CVID and primary immunodeficiency disease. Forty five articles associated directly with CVID were included initially, of which 28 articles had relatively complete information and were analyzed further. There were 35 cases reported in Chinese literatures from 1984 to 2013 which had a definite diagnosis which were further confirmed by ESID diagnostic criteria with complete information for analysis. The patients with the following status were excluded: the onset of age was lower than 4 years, the existence of lymphoid malignancy during the first 2 years of diagnosis, other known etiologies for hypogammaglobulinemia such as malignancies and associated chemotherapy, protein loss, drug and so on.

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Information of each CVID patient was collected including age at the onset of symptoms, age at diagnosis, clinical manifestations, and auxiliary examination especially the immunoglobulin (Ig) levels and lymphocyte subsets. The project was approved by the Institutional Review Board of Peking University First Hospital.

Results

Clinical characteristics of the patients

Demographic of the patients

Diagnosis of CVID was confirmed in 40 patients, 30 were males, and 10 were females. The median age at onset was 11-year-old (range 4–51 years). The median age at diagnosis was 14.5-year-old (range 5–66 years). The average time of delay in diagnosis was 5.3 years (range 1–41 years).

Infections

Recurrent infection was the most common clinical manifestation and the chief complain. But none of them was confirmed the diagnosis of CVID on their initial several times of visiting hospital. The average delay time in confirmed diagnosis was 5.3 years. The patients experienced repeated infections of different sites. In our study, the most common main complaint was fever due to infections (35 cases, 87.5%). The second most common complaint was cough or sputum (24 case, 60%), followed by diarrhea (9 cases, 22.5%). The relatively uncommon presentations were arthralgia (5 cases, 12.5%), hearing loss or ear discharging (4 cases, 10%), abdominal pain (2 cases, 5%), and edema (2 cases, 5%). The rare clinical symptoms were syncope (1 case, 2.5%) and dyspnea (1 case, 2.5%) [Table 1].

The frequent types of infection were pneumonia (28 cases, 70%), gastrointestinal infection (12 cases, 30%), otitis media (7 cases, 17.5%), and sinusitis (5 cases, 12.5%). Bronchiectasis, detected through high-resolution computed tomography, was found in 6 patients (15%) due to repeated pneumonia [Figures 1 and 2]. And one of them received lobectomy of left lower lobe because of hemoptysis due to bronchiectasis. However, new bronchiectasis of middle and lower lobe of the right lung occurred for the uncontrolled and recurrent pneumonia. The less frequent sites of infections were abscess of abdominal organ, purulent pericarditis and skin infection. The more rare infections were arthritis, cholecystitis, viral meningitis, keratitis, and so on. Besides the bacterial infection, chronic infection of hepatitis B was detected in three patients. All of the patients were hospitalized several times due to infection per year [Figures 1 and 2, Table 1].

Autoimmune disease and neoplastic disease

Six cases (15%) were diagnosed with autoimmune diseases including juvenile idiopathic arthritis, immune hemolytic anemia, juvenile rheumatoid arthritis, anaphylactoid purpura, and muscle hypertrophy and myotonia myositis. Lymphoma was detected in two patients.

Auxillary examination

Serum immunoglobulins

The median total serum levels of IgG, IgA and IgM at diagnosis were 1.07 g/L (range 0.07–3.99 g/L, normal range: 7.23–16.85 g/L), 0.07 g/L (range 0–0.65 g/L, normal range: 0.69–3.82 g/L), and 0.28 g/L (<0.04–1.77 g/L, normal range: 0.63–2.77 g/L), respectively [Table 1].

Lymphocyte subset analysis by flow cytometry

Analysis of lymphocyte subsets expressed as a percentage of total lymphocytes. Six patients had complete data about the number of total B-cells, and there was a significant reduction in total B-cells. The percentage range of $CD3^-$/$CD19^+$ B-cells was 1%–3.14% (normal range: 5%–18%). The data of $CD3^+$ T-cells were collected in 11 patients and $CD3^+$ T-cells was 35.6%–96% (normal range: 50%–84%). Six of the 11 had increased level of $CD3^+$ T-cells and 2 decreased [Table 2].

Abdominal ultrasound

Appendicular perforation and abscess of iliac fossa were detected by abdominal ultrasound. Hepatosplenomegaly was observed in 8 cases (20%) and splenomegaly alone affected one case.

Treatment

All the patients started with IVIG (mean dose: 408 mg/kg) at diagnosis, and received antibiotic therapy and symptomatic treatment.

Discussion

CVID is a heterogeneous subset of hypogammaglobulinemias with unknown etiology. The diagnosis of CVID can be made if the following criteria are fulfilled: decreased serum level of IgG, IgA and/or IgM (at least two standard deviations below the mean), hyporesponsiveness to specific antigens, minimum age of four years, the absence of lymphoid malignancy during the first two years of diagnosis, and genetic exclusion of other known etiologies for hypogammaglobulinemia. Most important criteria are the exclusion of other primary immunodeficiencies and secondary causes of hypogammaglobulinemia due to malignancies, protein loss, drug, or infection and so on.[1]

CVID may occur at any age, and the age of onset is usually in the second to third decade of life although a smaller group of patients already manifest CVID in childhood.[2,3] In our study, the median age at onset of disease was 11-year-old. The heterogeneous onset age of the disease and heterogeneous clinical manifestations could be some of the reasons for the delay in CVID diagnosis.[4,5] In our study, the average time of delay in diagnosis was 5.3 years, in accordance with the literatures which showed that the rarity and high clinical variability of CVID led to a significant delay in diagnosis between four and nine years after onset of symptoms. The delay in diagnosis may lead to severe infection or structural damage of organs followed by multiple organ dysfunction and

Table 1: Features of the patients with CVID

Patient No.	Gender	Age at onset (years)	Age at diagnosis (years)	Chief complaint	Infection	IgG (g/L, NR: 7.23–16.85)	IgA (g/L, NR: 0.69–3.82)	IgM (g/L, NR: 0.63–2.77)
1	Male	4	18	Fever, sputum, hearing loss	Pneumonia, sinusitis, bronchiectasis, keratitis, otitis media, acute enteritis, viral meningitis	3.25	<0.07	0.11
2	Female	4	11	Fever, sputum, abdominal pain	Pneumonia, appendicular abscess, peritonitis, cholecystitis, EB virus infected	2.20	<0.07	0.25
3	Male	6	15	Fever, sputum	Pneumonia, bronchiectasis, sinusitis, viral hepatitis virus B	1.86	0.07	<0.04
4	Male	6	7	Fever	Pneumonia	0.34	<0.07	0.40
5	Male	5	7	Fever, sputum	Pneumonia, sinusitis	3.99	<0.07	<0.04
6	Male	29	30	Fever, hearing loss	Otitis media	1.00	0.12	0.32
7	Male	18	19	Fever, sputum	Pneumonia, bronchiectasis	0.07	0.25	0.18
8	Male	13	14	Fever, sputum	Pneumonia	0.11	0.22	0.16
9	Male	8	9	Fever, arthralgia, ear discharging	Pneumonia, otitis media, purulent pericarditis	0.16	0.18	0.67
10	Male	14	15	Fever, cough	Otitis media, pneumonia	0.20	0.05	<0.04
11	Male	23	24	Fever, sputum	Sinusitis, bronchiectasis	0.20	0.30	0.50
12	Male	12.5	14	Diarrhea	Gastroenteritis	0.21	0.25	0.16
13	Male	4	5	Fever, ear discharging, diarrhea	Bronchitis, purulent otitis media	0.33	0.06	0.04
14	Male	5	7	Fever	infectious mononucleosis, viral hepatitis type B	0.33	0.07	0.06
15	Male	26	28	Diarrhea	Gastroenteritis	0.33	0.07	0.10
16	Male	4	7	Fever, sputum	Pneumonia, otitis media, dermapostasis	0.33	0.07	0.04
17	Male	19	22	Diarrhea	Enteritis	0.37	0.14	0.04
18	Male	4	5	Fever, sputum	Pneumonia	0.47	0.06	0.06
19	Male	4	8	Fever, sputum	pneumonia, purulent otitis media, herpes zoster	0.61	0.07	0.30
20	Male	4	8	Fever, sputum	Gastroenteritis, skin infection, appendicitis, appendicular perforation, pneumonia, bronchiectasis	0.83	0.05	0.65
21	Male	7	11	Fever, abdominal pain	Abscess of iliac fossa, pneumonia, intestinal fistula, viral hepatitis type B	0.94	0.20	0.4
22	Male	4	10	Fever, sputum	Pneumonia	1.00	0.26	0.32
23	Male	8	14	Fever, sputum, diarrhea	Pneumonia, gastroenteritis	1.14	0.18	0.64
24	Male	33	40	Fever, arthralgia	Pneumonia, purulent sinusitis, gastroenteritis	1.16	0.07	0.53
25	Male	32	40	Fever, diarrhea, arthralgia	Gastroenteritis	1.55	0.15	0.43
26	Male	23	33	Fever, sputum	Pneumonia	1.60	0.22	1.77
27	Male	4	13	Fever, sputum	Pneumonia	1.70	0.65	0.65
28	Male	51	66	Fever, sputum, edema	Pneumonia, gastroenteritis	1.71	0.07	0.50
29	Male	5	28	Diarrhea	Gastroenteritis	1.80	0.60	0.46
30	Male	19	22	Fever, diarrhea	Pulmonary tuberculosis, gastroenteritis	1.84	0.18	0.21
31	Male	16	57	Fever, diarrhea, cough	Gastroenteritis, pneumonia	1.86	0.07	0.05
32	Female	26	29	Fever, sputum	Pneumonia, bronchiectasis	2.15	0.04	0.34
33	Female	35	36	Fever, sputum	Pneumonia	2.18	0.14	0.35
34	Female	12	13	Syncope	Bronchitis	2.20	0.07	0.17
35	Female	47	48	Fever, edema, dyspnea	Pneumonia, purulent pericarditis	2.30	0.12	0.36
36	Female	17	19	Fever, arthralgia	Arthritis	3.10	0.30	0.40
37	Female	39	41	Fever, cough, sputum, arthralgia	Pneumonia	3.46	0.25	0.32
38	Female	8	11	Fever, sputum	Pneumonia	3.80	0	0.84
39	Female	10	14	Fever, sputum	Pneumonia	3.92	0.07	0.04
40	Female	4	7	Fever, sputum	Pneumonia	3.25	0.07	0.11

NR: Normal range; EB: Epstein-Barr; CVID: Common variable immunodeficiency.

septic shock. To avoid delay in diagnosis or misdiagnosis, early recognition of the clinical manifestations of CVID followed by suitable and further auxiliary examinations is of great importance.

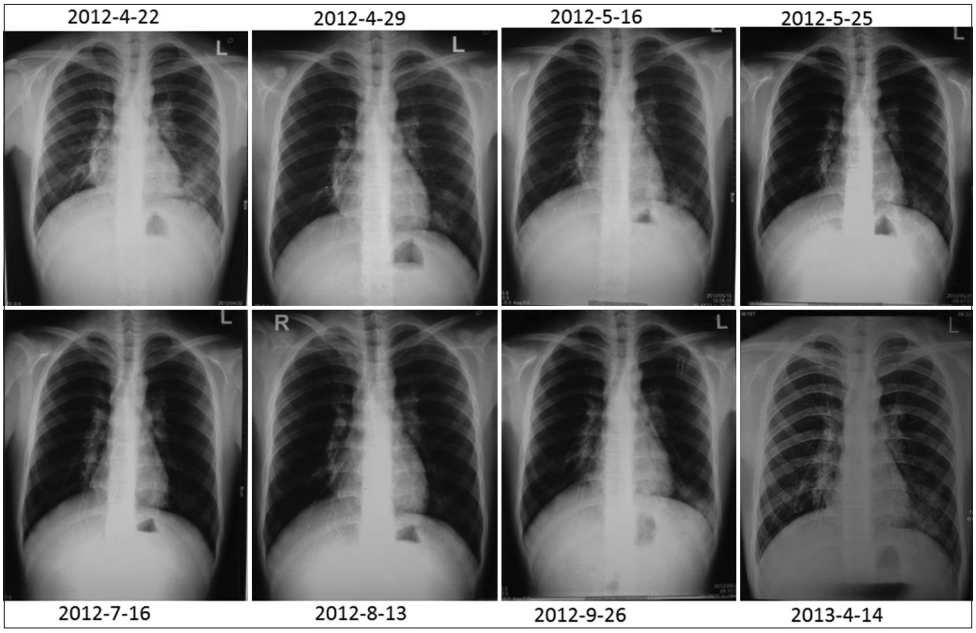

Figure 1: The chest X-ray of a patient with common variable immunodeficiency showed repeated pneumonia within 1 year.

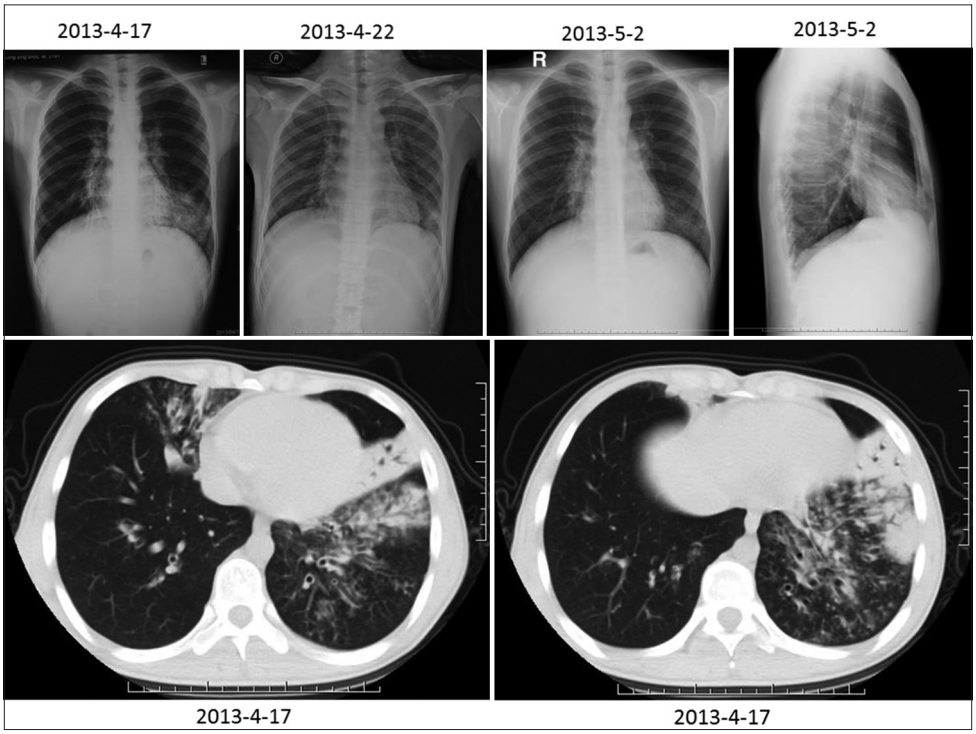

Figure 2: The chest X-ray and computed tomography of a patient with common variable immunodeficiency showed bronchiectasis with infection.

The clinical manifestations of CVID consist of six major categories including infections, pulmonary complications, granulomatous or polyclonal lymphocytic infiltrative diseases, autoimmunity, gastrointestinal diseases, and neoplasma.[1] First of all, over 90% of CVID patients suffer from an increased susceptibility to bacterial pathogens affecting mucous membranes of airways and to a lesser extent, of the gastrointestinal tract.[5,6] In accordance with published literatures, infection was the presenting manifestation in most of the cases in our study. The most common main complaint was fever due to infections and the symptoms associated with infections were usually cough or sputum, followed by diarrhea. It was reported that there had been a history of at least one episode of pneumonia before diagnosis in 75%–85% of the CVID patients as well as multiple episodes in many others.[7,8] Similar to that, the most frequent infection site was respiratory system, as reported previously. The frequent types of infection were pneumonia and gastrointestinal infection. Second, as to pulmonary complications, it was reported that about one-third of patients

Table 2: The data of percentage of lymphocyte subsets shown by flow cytometry (%)

Patient No.	CD19+ B (NR:5–18)	CD3+ T (NR: 50–84)	CD4+ T (NR: 27–51)	CD8+ T (NR: 14–44)	CD4+/CD8+ (NR: 0.7–2.8)	CD16+, CD56+ (NK cells, NR: 7–40)
1	3.14↓	91.40↑	13.99↓	71.90↑	0.19↓	4.91↓
2	1↓	96↑	41	56↑	0.73	3↓
3	2.10↓	90↑	37	54↑	0.69↓	11
4	3↓	86↑	39	45↑	0.87	10
5	2↓	88↑	21↓	63↑	0.33↓	12
6	–	36↓	21↓	32	0.65↓	–
7	–	35.60↓	33.30	36.20	0.92	–
8	–	63.50	47	33.30	1.41	–
9	–	89.40↑	6.80↓	49.90↑	0.10↓	–
10	3↓	86	39	45↑	0.87	–
11	–	74.40	13.40↓	57.80↑	0.20↓	–

NR: Normal range; NK: Natural killer. ↑: Above normal; ↓: Below normal.

had developed the bronchiectasis as a result of chronic and recurrent pulmonary infections.[3] Bronchiectasis was found in six patients (15%) in our study. The majority of morbidities and mortalities of CVID was associated with long-term sequelae of recurrent respiratory tract infections including bronchiectasis.[2] Third, the gastrointestinal infections were also common in CVID patients. The gastrointestinal tract was the second organ that is involved in infections in 10%–40% of the CVID cases.[1] In our study, about one-third of the cases had infections of the digestive system including severe infections such appendicular abscess, perforation, and iliac abscess. The last but not the least, the central nerve system, skin, ear, and eye could also be affected by CVID, and their involvement might be the first and only presentation of CVID in some cases.[9] Besides infection, 15% patients had autoimmune-associated disorders in our study. It was worth to note that autoimmunity could be the first manifestation in CVID and was present in about 30% of CVID patients.[2,10] The reason of high prevalence of autoimmune-associated disorders in CVID was probably the immune dysregulation due to failed or circumvented specific autoreactivity checkpoints during the B-cell development process.[11] This dysregulation culminated in the production of multiple autoantibodies against various self-antigenic targets. Autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia were the most common types of autoimmune consequences, occurring in 5%-8% of all registered CVID patients.[2,12] Moreover, CVID patients were at higher risk of neoplasma (hematological or solid tumors) compared with normal population (over 10-time the risk).[13] The most common type of malignancy was non-Hodgkin's lymphoma.[14]

CVID is a complex, multifocal disease. The molecular basis, both immunologically and genetically, of CVID remains unclear despite huge amounts of evaluation in this filed in the past decades. The origins of CVID seem to be partially understood. Patients with CVID have a marked reduction in serum levels of IgG and usually IgA, with reductions in serum IgM in about half of all cases. With the loss of antibody, patients have a high incidence of infectious disease. The main immunological defect in CVID is reported to be the failure of B-cell Ig production, although abnormalities have been described in all other components of the immune system.[15,16] An inexpensive, quantitative determination of serum Igs is the first and most important step in the diagnosis of CVID. Required for the diagnosis of CVID is the diminution of at least two isotypes (IgG and IgA or IgM). IgG is typically decreased, and IgA is markedly reduced or not detectable in most patients. IgM is also below the normal range in up to 80% patients.[17] The next stage of diagnosis is flow cytometric analysis of lymphocyte subpopulations. Numerous immunological studies have demonstrated phenotypic and functional abnormalities of lymphocytes. Abnormalities in peripheral blood B-cell subsets have been identified in CVID patients. The total number of peripheral B-cells is slightly reduced in about 40%–50% of CVID patients and in only about 10% of CVID patients are B-cells dramatically reduced or absent. Disease progression tends to be more rapid and severe in this patient.[17] We analyzed the lymphocyte subsets expressed as a percentage of total lymphocytes by flow cytometry. Six patients had complete data about the number of total B-cells, and there was a significant reduction in total B-cells for all of them, in keeping with the published literatures. The classification of CVID patients with the separation of B-cell subpopulations is reserved for specialized immunodeficiency centers. Bone marrow biopsy should be performed in patients with low B-cell numbers (<1%) and if lymphoma or myelodysplasia is suspected.

Advances have been made in the management of CVID to improve outcomes in the patients. Current therapy of CVID includes the following: regular and sufficient substitution with Igs (IgG trough levels >7.0 g/L); targeted antibiotic treatment of infections; adequate treatment of complications; and in selected patients with severe hematological changes, secondary malignancies, and suspected combined immunodeficiency, allogeneic peripheral stem cell transplantation is being considered in experienced centers.[18] The Ig replacement therapy is the mainstay of therapy, and 90% of CVID patients are on either intravenous (IVIG) or subcutaneous treatment. The current standard dosage when administered intravenously is 400–600

mg/kg every 3–4 weeks.[19] For subcutaneous administration, this corresponds to 100–150 mg·kg^{-1}·week^{-1}.[20,21] In CVID patients with pulmonary diseases, new therapeutic approaches focus on interleukin-2 therapy, short- and long-acting inhaled β2-agonists in bronchiectasis and leukotriene receptor antagonists.[1]

The life expectancy of CVID patients has considerably improved from initially 12 years to currently over 50 years over the past 30 years.[2,5,22] For patients with non-infectious complications such as lymphoma, chronic hepatitis, structural lung disease, and chronic gastrointestinal disease, the risk of death was much higher.[23] The age at diagnosis, lower baseline IgG and fewer peripheral B-cells were significantly associated with reduced survival.[17]

In conclusion, infection is the most frequent presentation at onset of CVID. Diagnosis delay may lead to bronchiectasis or other damage of organs due to repeated infections. The early diagnosis and suitable treatment of CVID are important for a favorable outcome. Our CVID analysis presents with comparable symptoms and disorders as previously reported. To avoid delay in diagnosis or misdiagnosis, early recognition of the clinical manifestations of CVID followed by suitable auxiliary examinations including serum Ig test and lymphocyte subset analysis and further analysis is of great importance. We call for more study about the clinical features as well as the mechanism of CVID for better and earlier diagnosis and treatment of this relatively rare disease in Chinese.

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Received: 07-04-2014 **Edited by:** De Wang
How to cite this article: Lin LJ, Wang YC, Liu XM. Clinical and Immunological Features of Common Variable Immunodeficiency in China. Chin Med J 2015;128:310-5.

Source of Support: This work was supported by a grant from National Natural Science Foundation of China (No. 81141001 and No.81270114).
Conflict of Interest: None declared.