Common Variable Immunodeficiency (CVID): A Report of Two Families

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Abstract: To recognize the genetic defects and the heterogeneity of common variable immunodeficiency (CVID), we report 4 cases with clinical information and laboratory findings in two CVID families.

Keywords: Common variable immunodeficiency (CVID), immunoglobulin deficiency.

INTRODUCTION

Common variable immune deficiency (CVID) is a heterogeneous disease associated with ineffective production of antibodies [1]. The incidence of CVID is about 1 to 10 in 100,000 [2]. It is usually diagnosed in adulthood, but a variable proportion of children develop CVID. The pathogenesis of CVID is remains incompletely understood. As the complex and heterogeneous in both genetic defect and antibody deficiency, CVID diagnosis could be challenging [3]. Here we describe two CVID families with middle-aged onset.

CLINICAL DATA

With informed consent, we collected peripheral blood from the daughters of two families for clinical test and investigated their disease developing history of the two families respectively (Pedigrees of two families are shown in Figure **1**).

Proband 1a

A 35 years old female farmer was admitted to department of rheumatology in May 2010 with 'repeated cough, expectoration and diarrhea for three years'. She had cough, expectoration and diarrhea about 2-6 times per day without abdominal pain, yellow watery stool but not bloody. Her health condition was improved with anti-infection and anti-diarrhea treatment but the symptom recurred 5-8 times yearly. Her early life and family history were normal.

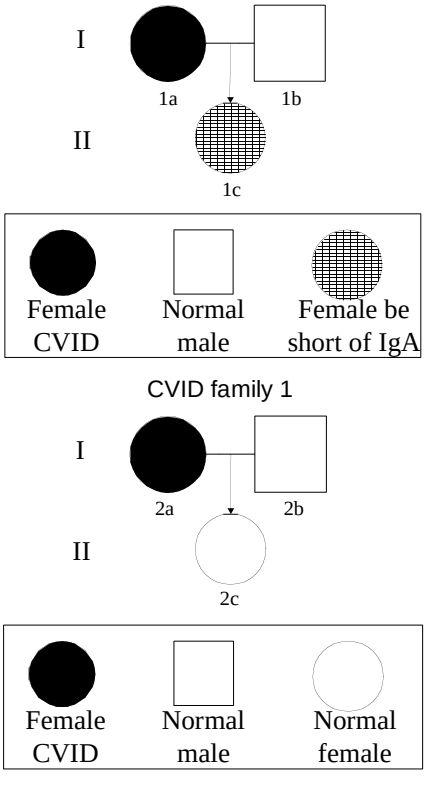

Figure 1:

Physical examination: body temperature (T) 36.5°C, pulse (P) 88 beats/min, respiratory (R) 20 times/min,

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blood pressure (BP) 11.6/7.6 KPa, weight: 33Kg, height: 150 cm. The patient appeared in emaciated and severe anemia, lucid and oriented; her bilateral breath sounds were slightly rough, liver was 2 cm below the right costal margin without haphalgesia.

Auxiliary examination: Alb 19g/L, Hb 57g/L, RBC 2.96×10^{12}/L, WBC 7.09×10^{9}/L. IgG, IgA, IgM and IgE were serious deficiency. Proportion of $CD4^+$ cells was significantly reduced with serious inversion of $CD4^+$/$CD8^+$ ratio (shown in Table **1**).

Color Doppler Imaging in the abdomen: Enlarged fatty liver and enlarged spleen, the maximum oblique diameter of right liver was 15.5 cm. The spleen was palpable 5 cm intercostal, little ascites in belly cavity. The sternum showed the increased lung makings and the lower left lung field had a little strip video; a small amount of pleural effusion showed in left. Bone marrow biopsy showed hyperplastic anemia; karyocyte proliferation was obviously active; and morphological change analysis of these three cell lines demonstrated normal.

IgG and IgM antibody of cytomegalovirus were positive, IgM antibody of rubella virus, herpes simplex virus and toxoplasma were negative.

The patient was diagnosed as CVID, who was discharged with improved health condition after treated by anti-infection and anti-virus, infusion of human immunoglobulin and potassium, but the IgA level was still significantly lower than normal (shown in Table **2**).

The Daughter of Proband 1a (1c)

A 10 years old student with normal development was referred to our clinic in November, 2010. The examination of cardiopulmonary and WBC showed normal. Her IgA was serious deficiency, and the anti-nuclear antibody (ANA) appeared suspicious (shown in Table **1**).

She had short history of repeated infection and occasional diarrhea. After other hypogammaglo-bulinemia causative factors were excluded, the patient was diagnosed as IgA deficiency.

Proband 2a

A 47 years old female farmer, was admitted to pneumology department in October 2010 with 'repeated cough, expectoration for 5 years, accompanying one year fever, and getting worse in last 4 months. The patient initially cough, expectorate

Table 1: Laboratory Findings of the Cases

Subject	Reference Ranges (unit)	Family 1		Family 2	
		1a	1c	2a	2c
IgG	8.0-15.5g/L	<0.33	19.10	<0.33	13.10
IgA	836-2900mg/L	<66.70	<66.70	<66.70	2520
IgM	700-2200mg/L	347	2250	<41.7	1760
IgE	0.1-150IU/ml	0.02	1.56	<0.01	18.97
$CD3^+$	66.90-83.10%	76.0	74.3	80.2	64.6
$CD4^+$	33.19-47.85%	8.7	30.1	20.4	29.2
$CD8^+$	20.40-34.70%	60.4	32.1	59.5	25.8
$CD4^+/CD8^+$	0.97-2.31	0.14	0.94	0.34	1.13
ANA	negative	negative	borderline	negative	negative
Anti-dsDNA	negative	negative	negative	negative	negative
Anti-Sm	negative	negative	negative	negative	negative
Anti-RNP	negative	negative	negative	negative	negative
Anti-SSa	negative	negative	negative	negative	negative
Anti-SSb	negative	negative	negative	negative	negative
Anti-Scl-70	negative	negative	negative	negative	negative
Anti-Jo-1	negative	negative	negative	negative	negative
Anti-rib	negative	negative	negative	negative	negative

ANA: antinuclear antibody.

Table 2: Immunoglobulin Reevaluation

Subject	Reference Ranges (unit)	Proband 1a		Proband 2a	
		Admission test	Discharge test	Admission test	Discharge test
IgG	8.0-15.5g/L	<0.33	19.10	<0.33	13.10
IgA	836-2900mg/L	<66.70	<66.70	<66.70	2520
IgM	700-2200mg/L	347	2250	<41.7	1760

without obvious incentive, and her condition was improved after anti-infection treatment. Her symptoms were recurrent, and exacerbated in autumn and winter. Her early life and family history were normal.

Physical examination: T 38°C, P 114/min, R 21/min, BP 13.06/7.33Kpa. The patient appeared to be chronic tolerance, anemia, and conscious. The bilateral breath sounds were rough and the left lung diffused moist rales. Spleen was 2cm below ribs.

Auxiliary examination: Alb 29.2g/L, Hb 89g/L, RBC 3.81×10^{12}/L, WBC 6.97×10^{9}/L. IgG, IgA, IgM and IgE were serious deficiency. Proportion of $CD4^+$ cells was significantly reduced with serious inversion of $CD4^+$/$CD8^+$ ratio (shown in Table **1**).

IgG antibody of mycoplasma pneumoniae and chlamydia were positive. Color Doppler Imaging found an enlarged spleen. This patient was diagnosed as CVID, she was discharged with improved health condition after treated with thymosin α1, fat emulsion, amino acid and infusion of human immunoglobulin, her IgG, IgA and IgM were appeared normal (shown in Table **2**).

The Daughter of Proband 2a (2c)

A 20 years old student with normal development, she had a short history of repeated infection. The examination of cardiopulmonary and WBC showed normal. Immunoglobulin, cytoimmunity and autoantibody data were negative (shown in Table **1**). Physical examination showed no abnormalities.

DISCUSSION

CVID is a clinical syndrome caused by antibody deficiency with low or lack immune response to antigens. The syndrome is a common immunodeficiency disease with clinical heterogeneity, pathogenesis of CVID is complex and not yet fully understood.

Familial aggregation defect in IgA played an important role in the pathogenesis of CVID [4]. In our study, admission test showed that the immunoglobulin (including IgG, IgA, IgM and IgE) of two probands were serious deficiency; and the daughter of proband 1a (1c) who has not yet manifested severe clinical symptoms was diagnosed as IgA deficiency according to her significantly decreased IgA level. Linkage and haplotype analysis have indicated CVID susceptibility loci on 4p, 5p, 6p, 12p and14q [5]. Recently, a genome-wide case-control study revealed several significant SNPs of genes including: MHC, ADAM7, ADAM28, ADAMDEC1, STC1, SDK1, FLJ32784, UBXN10, FGGY and FLJ16124 [6].

Data in Table **1** shows that $CD4^+$ cells in four cases of two families are significantly reduced, particularly, immunoglobulin deficiency with serious inversion of $CD4^+$/$CD8^+$ ratio in two probands. $CD4^+$ T cells can benefit of B cell maturation and antibody secretion [7]. Reduction of $CD4^+$ T cells could cause a reduction even loss of humoral immune function. To further understand the causes of $CD4^+$ cell reduction, we should find the intrinsic genetic defects and related risk environmental factors interaction with.

Hypoimmunity of CVID with immunoglobulin deficiency, the patients could have complicated clinical features which manifestation of cough, diarrhea, fever and other symptoms, including recurrent pulmonary infection [8]. Both probands are middle-aged onset, the daughter of the proband 1a (1c) who had IgA deficiency with young age of onset, this stage may be an early manifestation of developing a further immunoglobulin deficiency in her later life. In addition, presenting of ANA usually is expected a high risk of the autoimmune diseases [9]. As shown in Table **2**, the IgA level of proband 1a was still significantly lower than normal after treatment, which indicated the patient still have a poor immunity and should be protected from deterioration. In order to control disease progression and provide experimental evidence for disease prognosis, the patients and susceptibles should be taken a regularly clinical following up, monitoring the level of immunoglobulin and the variation of autoantibodies.

Furthermore CVID may be more accurate to use absolute numbers of B lymphocyte subpopulations in studies of CVID phenotypes [10]. Our data shows that CD4 +/CD8 + ratio may be the index of CVID, the children of the proband should be monitored for immunoglobulin and diagnosed early.

As a poor prognosis expected for CVID patients, therapy for this two families were taken mainly to improve symptoms by anti-infection, nutrition and immunoglobulin replacement. Furthermore, hematopoietic stem cell transplantation has been successfully applied for CVID patients [11] and it has shed light in our future CVID therapy.

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