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Three Children with Failure to Thrive and Recurrent Infections

TF ***LEUNG***, CK ***LI***, MMK ***SHING***, KW ***CHIK***, PMP ***YUEN***

Abstract We report three young children with common variable immunodeficiency that presented with failure to thrive as well as recurrent viral, bacterial or fungal infections. They had abnormal humoral and cellular immune functions as well as altered functions of granulocytes and natural killer cells. Our oldest boy died from severe pneumonia whereas the other two patients are free from serious infection on follow-up. Although common variable immunodeficiency typically affects young adults, this diagnosis should also be considered in infants and young children who suffered from atypical or recurrent infections. Thorough immunological investigations should be performed in these patients.

Key words Children; Common variable immunodeficiency; Outcome; Primary immunodeficiencies

Introduction

Common variable immunodeficiency (CVID) is a conglomeration of as yet undifferentiated syndromes that are characterized by recurrent pyogenic infections. Defective antibody formation is the *sine qua non* for diagnosis of CVID.[1] However, CVID is a diagnosis of exclusion. It is also one of the most frequent of the primary immunodeficiency diseases (PID). In a local single-centre review, CVID constitutes 7 of 99 children with PID and 20% of patients with predominant humoral immunodeficiency.[2] The usual age of presentation for this entity is the second or third decade of life.[3] CVID rarely occurs in the paediatric age group. In addition to recurrent infections, patients with CVID are prone to a variety of autoimmune disorders and malignancies due to dysregulated and uncontrolled activation of the immune system.[1] We describe three children with early onset CVID who have different combinations of underlying immune defects and clinical outcomes.

Department of Paediatrics, 6/F, Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T., Hong Kong, China

TF **LEUNG**	*MBChB(CUHK), MRCP(UK), FHKAM (Paed)*
CK **LI**	*MBBS(HKU), FRCP(Edin), FRCPCH*
MMK **SHING**	*MBBS(HKU), FRCP(Edin & Glas)*
KW **CHIK**	*MBChB(CUHK), MRCP(UK), FHKAM (Paed)*
PMP **YUEN**	*MD(Sask), FRCPC, DABPaed*

Correspondence to: Dr TF **LEUNG**

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Case Reports

Case 1

A 5-year-old Chinese boy of non-consanguineous parents presented with adenovirus pneumonia at five months of age. Laboratory investigations showed panhypogammaglobulinaemia (IgG 0.4 g/L; IgA < 0.1 g/L; IgM 0.1 g/L). Two doses of intravenous immunoglobulin (IVIg) were then given 6 weeks apart. Following this episode of severe infection, he failed to gain weight and suffered from another attack of severe pneumonia by influenza virus type A four months later. He required mechanical ventilation during both attacks. Further immunological assessment was then performed at 10 months old and results are summarized in Table 1. His serum Ig levels were still markedly diminished. Besides, he had reduced numbers of natural killer (NK) cells (82 cells/μL; 1.4% of peripheral blood lymphocytes, PBL) and mature B lymphocytes (13 cells/μL; 0.2% of PBL). Lymphoproliferative response of PBL *in vitro* to phytohaemagglutinin (PHA) was normal whereas those to concanavalin A (ConA) and pokeweed mitogen (PWM) were diminished, with stimulation indices of 49 and 30 respectively. Microcytotoxicity assays using NK cells from this patient revealed response rates of 3.2% on 1:5 (ratio of target to NK cells), 8% on 1:20 and 19.2% on 1:80, with the corresponding normal ranges being 12-34, 28-61 and 49-76. These results indicated that his NK cells were functionally defective. The diagnosis of CVID was made because this patient had persistently low serum Ig as well as abnormal numbers and functions of PBL and NK cells. He was started on regular IVIg replacement and

prophylactic cotrimoxazole. High-resolution computerized tomography (HRCT) of his lungs performed at 4 years old revealed bilateral interstitial pulmonary disease. He continued to have intermittent wheezing episodes but free from serious infection on follow-up.

Case 2

A 15-year-old Chinese boy of non-consanguineous parents had history of frequent oral ulcers, skin abscesses and failure to thrive since infancy. He was seen in our unit for assessment of frequent infections at 3 years of age. This patient was found to have cyclic neutropaenia on serial monitoring of his complete blood counts. Bone marrow examination revealed maturation arrest at the promyelocyte and myelocyte stages. Subsequently, he developed an episode of pneumonia and gastrointestinal bleeding at five years old. Immunological investigations at that time revealed that his serum IgG was 1 g/L (normal 3.7-15.8) whereas IgA and IgM concentrations were normal (Table 1). He had normal serum isohaemagglutinins on subsequent testing (1:8 for anti-A and 1:64 for anti-B). The numbers of his PBL subsets were normal. Lymphoproliferative responses of PBL to PHA, ConA and PWM were normal. However, his PBL showed markedly reduced proliferation to OKT3 (a T cell stimulant), with a response of 4000 as compared to 46000 in healthy control. Neutrophil candida killing (17%, normal 19-38) and chemotaxis in the presence of N-formyl-methionyl-leucyl-phenylalanine (FMLP; 395μ, normal 759-1250) were also diminished. In view of frequent pneumonia, diminished IgG level as well as subnormal functions of his neutrophils and T lymphocytes, this patient was diagnosed as having CVID and treated with monthly IVIg replacement. Multiple antibiotics, anti-viral and anti-fungal agents were given for infection prophylaxis. His cyclic neutropaenia recovered spontaneously after 6 years old. Despite this haematological improvement, this patient subsequently had an attack of *Penicillium marneffei* lymphadenitis and another one with severe herpetic tracheitis that required permanent tracheostomy. HRCT of his chest revealed bilateral bronchiectatic changes. He acquired chronic hepatitis B virus infection from regular IVIg infusions since 10 years old. This patient ran a progressive downhill course, and developed end-stage renal failure due to chronic interstitial nephritis and early membranous nephropathy. He finally succumbed at the age of 15 years following an attack of severe pneumonia.

Case 3

An 8-year-old Chinese girl of non-consanguineous parents had problem of recurrent skin abscesses since young infancy. She developed failure to thrive with frequent pneumonia since four years old. No positive bacterial, fungal or viral culture could be isolated from any of these pneumonic episodes. This patient also had extensive icthyosis and recurrent herpetic gingivostomatitis. She suffered from an attack of herpes zoster involving her right fifth cervical dermatome at 5 years of age. Immunological investigations were first done when she was 6 years old and were summarized in Table 1. She had lymphopaenia (302 cells/μL; 13% of total leukocytes), IgA deficiency (0.56 g/L, normal 0.63-2.34) and abnormal concentrations of IgG3 and IgG4 subclasses (IgG3 1.08 g/L, normal 0.02-0.88; IgG4 level undetectable). Besides, she did not produce antibodies against poliovirus, mumps, measles, rubella and hepatitis B surface antigen despite the history of previous immunizations. Anti-B IgM isohaemagglutinin could be detected in her serum. Lymphocyte proliferation *in vitro* to PHA and PWM were subnormal (stimulation indices of 84 and 18 respectively). Nitroblue tetrazolium test to

Table 1 Summary of immunological investigations in our three patients*

Immune functions	Case 1	Case 2	Case 3
Humoral immunity			
Serum immunoglobulins	↓ IgG / IgM / IgA	↓ IgG	↓ IgA
IgG subclass concentrations	ND	ND	↓ IgG4; ↑ IgG3
PBL total and subset numbers as	↓ $CD19^+$ (B)	Lymphocytosis	Lymphopaenia
measured by flow cytometer	↓ $CD16/56^+$ (NK)	Normal subsets	Normal subsets
Lymphoproliferative responses of PBL	↓ ConA / PWM	↓ OKT3 / candida	↓ PHA / PWM
Functions of natural killer (NK) cells	Abnormal MCA	ND	ND
Granulocyte functions	ND	↓ candida killing	↓ NBT to *E.coli*
		↓ chemotaxis	↓ candida killing/chemotaxis

B: B lymphocytes; ConA: concanavalin A; MCA: microcytotoxicity assay; NBT: nitroblue tetrazolium test; ND: not done; OKT3: T cell antigen; PBL: peripheral blood lymphocytes; PHA: phytohaemagglutinin; PWM: pokeweed mitogen

* Detailed results for individual, abnormal immunological investigations are provided in the text.

E. coli endotoxin was 8% (normal >40). Ability of her neutrophils to kill candida was 18% (normal 19-38) whereas neutrophil chemotaxis in the presence of FMLP was 652 μ (normal 759-1250). HRCT of her chest showed multilobar bronchiectasis. The diagnosis of CVID was made from her defective *in vivo* specific antibody responses to previous immunizations, imbalance in IgG subclass levels, peripheral blood lymphopaenia as well as abnormal functions of her PBL and neutrophils. She was then started on regular IVIg replacement and prophylactic cotrimoxazole, and was free from serious infection on follow-up.

Discussion

The incidence of CVID is estimated to be 1:50000 to 1:200000.[1] There is no sexual preponderance. A small proportion of patients with CVID had family history of IgA deficiency or CVID. Schroeder et al showed that the occurrences of these two diseases are linked to the susceptibility loci HLA-DR3, B8 and A1.[4] CVID is a heterogeneous group of diseases characterized by recurrent infections as well as hypogammaglobulinaemia and impaired specific antibody responses. Other known causes of humoral immune defects, such as X-linked agammaglobulinaemia and hyperIgM syndrome, should also be excluded. Although abnormal humoral immunity is the commonest laboratory abnormality in CVID, dysfunctions in T lymphocytes, natural killer cells and granulocytes can also occur. All our three patients had diminished total serum Ig or IgG subclass levels but with different combinations of the above immunological abnormalities. They were also symptomatic with frequent infections since infancy, which is among the youngest cases reported in the literature.[3] A high index of suspicion and comprehensive immunological investigations is required in these young children with recurrent infections and failure to thrive in order to make a correct diagnosis.

Earlier studies demonstrated that B lymphocytes from CVID patients had diminished ability to produce Ig *in vitro*.[5] On the other hand, most patients had normal T lymphocyte subsets in their peripheral blood although a subgroup had increased $CD8^+$ cells and normal or decreased $CD4^+$ lymphocytes. Cellular immunodeficiency occurred in half of the patients with CVID and worsened with increasing age.[3] T lymphocytes from these patients showed subnormal proliferation to keyhole limpet haemocyanin which is a T cell-specific antigen.[6] About 40% of these patients were shown to have defective expression of CD40 ligand on activated T lymphocytes.[7,8] This molecule is responsible for mediating efficient intercellular signaling between T and B cells that results in isotype switch and differentiation of mature B lymphocytes into Ig-secreting plasma cells. Thus, recent evidences support the hypothesis that CVID is caused by primary T cell defects that result in abnormal interaction between T and B lymphocytes. Defects in cytokine secretion and adhesion molecule expression are also found in patients with CVID.[9,10]

Regular IVIg replacement at dosage of 400 to 800 mg/kg/month is the treatment of choice for CVID in view of common defect in the production of specific antibodies.[1] Our first two patients required IVIg replacement because of frequent infections and persistently low serum Ig concentrations. The last patient required this treatment in view of her recurrent skin and sinopulmonary infections and inability to produce protective antibodies to previous immunizations *in vivo*. The prevalence of IgA deficiency in the Caucasian population was estimated to be about 1 in 500. Patients with selective IgA deficiency frequently have anti-IgA antibodies in their serum. Administration of IVIg should be avoided in these patients because the infused IgA molecules may combine with the existing anti-IgA antibodies in patients' serum and result in serious anaphylactic reaction.[11]

Apart from regular IVIg replacement, prophylactic cotrimoxazole is also indicated in infection prophylaxis against bacteria and *Pneumocystis carinii*. Despite the frequent use of these two treatments, patients with CVID are still susceptible to recurrent opportunistic infections as illustrated in our patients. A high index of suspicion and aggressive treatment of acute infections with broad-spectrum antimicrobial agents should also be achieved. Steroids and other immunosuppressive agents should only be used in short courses in those patients who develop significant autoimmune diseases. Recombinant human interleukin-2 is currently only an experimental therapy.[12] There are anecdotal reports of successful haematopoietic stem cell transplantation in treating these patients. However, this treatment should be offered as rescue therapy in view of frequent treatment-related morbidity and mortality.

The long-term outcome for CVID is still unclear. Johnson et al reported that hypogammaglobulinaemia resolved in only one of their 68 patients with CVID.[13] Our oldest child died of severe infection and end-stage renal failure due to membranous nephropathy following chronic hepatitis B virus infection as well as interstitial nephritis secondary to prior prolonged use of amphotericin B. In the largest cohort published by Cunningham-Rundles, male patients die at an earlier age than females (29 years compared to 55 years). The common causes of death in these patients are chronic lung diseases, liver failure due to viral hepatitis, chronic gut damage with malabsorption and malignancies.[3]

In conclusion, our patients illustrated that CVID can occur in young children. A high index of suspicion and thorough immunological investigations should be performed in those infants and children who have failure to thrive and recurrent infections in order to make the diagnosis early. Newer and specific therapies are necessary to improve the prognosis in these patients.

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