



# Common variable immunodeficiency – case report

Emina Vukas\*, Aida Dizdarević, Senka Mesihović - Dinarević, Adisa Čengić

Pediatric clinic, Clinical centre University in Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina

## ABSTRACT

Common variable immunodeficiency (CVID) or acquired hypogammaglobulinemia is the type of primary immunodeficiency. Deregulation of the immune system, leading to hypogammaglobulinemia, defective activation and proliferation of T cells and dendritic cells, and malfunction of the cytokines are observed in CVID. The clinical picture of CVID varies, any organ or system can be affected, therefore the diagnosis is often difficult and delayed and sometimes is not always possible. This article describes a twelve years old boy with all the clinical signs of immunodeficiency, as confirmed by laboratory. The main treatment consists of life-long immunoglobulin substitution in intravenous or subcutaneous form.

## INTRODUCTION

Recurrent infections are the big challenge for both pediatricians and general practitioners. Recurrent pneumonia and bronchitis, prolonged, unresponsive to standard treatment sinusitis or otitis should catch the doctor's attention and prompt him to differential diagnosis towards primary immunodeficiency disease (PIDD). Such disorders occur in clinical practice very rarely, but they shouldn't be missed considering that early diagnosis provides rapid implementation of treatment and avoidance of complications. Common variable immunodeficiency (CVID) or acquired hypogammaglobulinemia is the type of primary immunodeficiency (1). Deregulation of the immune system, leading to hypogammaglobulinemia, defective activation

and proliferation of T cells and dendritic cells, and malfunction of the cytokines are observed in CVID (2). Common variable immunodeficiency frequency varies from 1 : 10 000 to 1 : 50 000, and the diagnosis is based on a reduced level of IgG and IgA and/or IgM, which is a consequence of impaired B cell development (3). The disease manifests itself between 5 and 10 years of age and between 20 and 40 years of age (4). Genetic basis of CVID is still unknown (1). The clinical picture of CVID varies, any organ or system can be affected, therefore the diagnosis is often difficult and delayed. There is, however, a broad spectrum of clinical manifestations including recurrent infections of the respiratory tract and chronic lung disease, various autoimmune pathology, gastrointestinal disease, granulomatous infiltrative diseases, lymphoproliferative disorders and malignancies (5). It is estimated that about 78% of patients underwent lower respiratory tract infection at least once before diagnosis of CVID (6).

Recurrent infections, poorly responding to conventional antibiotics, can lead to the formation of bronchiectasis, which are particularly common medical

\*Corresponding author: Emina Vukas,  
Pediatric clinic, Clinical centre University in Sarajevo,  
Patriotske lige 83, 71000 Sarajevo, Bosnia and Herzegovina  
Phone: +3861364347  
E-mail: emina\_vs@yahoo.com

Submitted 10 June 2013 / Accepted 25 July 2013



problem, leading to frequent hospitalization and severe respiratory impairment. Early diagnosis usually protects the patient against this complication, however, development of bronchiectasis occurs even in 30% of patients, despite optimal treatment (7,8). About 20% of CVID patients developed different gastrointestinal pathology, such as inflammatory bowel disease, protein-loss enteropathy, sprue-like syndrome, chronic enteritis caused by *Giardia lamblia* or *Campylobacter* infection, celiac sprue (9,10). Here, we report a case of 12 year boy with recurrent infections of the respiratory system who was diagnosed to have CVID.

### CASE REPORT

The patient is twelve years old boy who was admitted to Department of Pediatric Allergy Immune Rheumatology with history of recurrent infections of the respiratory system, sinusitis, allergic rhinitis, allergies to nuts, conjunctivitis starting from the childhood. Bronchial asthma is diagnosed before three months. His medical history included severe swine flu two years ago, tonsillectomy, appendectomy, inflammation of the nail bed of thumbs on both legs, severe form of varicella. Every two weeks he has oral ulcers. In his family history there is no evidence of hereditary immunodeficiency or autoimmune disease. Not regularly vaccinated. On admission the general physical examination revealed remarkable pallor, fever (40°C), cough, no enlargement of liver, spleen or peripheral lymph nodes. Routine laboratory parameters were found to be normal, except markers for inflammation. Repeated hemocultures were negative. Microbiological analysis excluded some viral infections (hepatitis B, C and HIV). Standard immunological markers (ANA, AMA, ANCA, ANTI ds DNA, and rheumatoid factor) were excluded for autoimmune and rheumatoid diseases. Screening tests of serum immunoglobulin's showed decreased concentrations of three types of immunoglobulin's: IgA: in traces, IgM 0.4 g/L and IgG 4.9 g/L. Lymphocyte immunophenotypisation revealed inversed CD4+/CD8+ T cells ratio: 0.96. Switched memory B cells were decreased. Chest X ray expressed bronchiectasis. 24 h pH monitoring indicate the presence of gastro esophageal reflux disease (GERD). During the hospitalization the patient was treated with parenteral antibiotics. Re-

ceived replacement therapy with intravenous immunoglobulin at dosage 200mg/kg.

### DISCUSSION

CVID is essentially a diagnosis of exclusion, as other causes of hypogammaglobulinemia, including known gene defects, medications, protein loss, or malignancy, must be excluded (1). Correct diagnosis of immune deficiency is not easy, and sometimes is not always possible (1,2). It often requires quite detailed studies that are not available in routine diagnostics. However, the initial suspicion of immunodeficiency in a patient (Table 1) is possible at the level of every general practitioner (3). A careful investigation of past medical history is the first step in the diagnosis. Past medical history should include the presence of allergic diseases. Also very important is the knowledge of the possible occurrence of immunodeficiency in relatives. It should be established when the first symptoms of immunodeficiency such as persistent, recurrent infections occur. Children up to 6 month of age possess maternally derived antibodies, therefore, in accordance with European Society for the Immunodeficiency's (ESID) criteria (Table 2) CVID can be recognized after 2 years of age (1,3). In addition to infections such as sinusitis, otitis media, bronchitis, pneumonia, or gastrointestinal disorder, the nutritional status of the patient should be evaluated. Unexplained weight loss is relatively common symptom in CVID. Besides recurrent infections, CVID patients have an increased tendency to develop autoimmunity, lymph-proliferative disease and malignancies (2). Although these

**TABLE 1.** Problems suggesting immune deficiency disorders in children (for suspected immunodeficiency just one of the following)

Eight or more infections per year
Two or more serious sinus infections within 1 year
Antibiotic therapy lasting two months or more without a clear improvement
Two or more pneumonias within 1 year
Growth and weight failure in infant
Recurrent deep skin or organ abscesses
Persistent thrush in mouth or fungal skin infection
Need for intravenous antibiotics to clear infections
Two or more deep-seated infections including: encephalitis, osteomyelitis, dermatitis, sepsis.
A family history of PID

**TABLE 2.** European Society for the Immunodeficiency's (ESID) Criteria for the diagnosis of CVID

<b>Probable</b>
Male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria: 1) Onset of immunodeficiency at greater than 2 years of age 2) Absent isohemagglutinins and/or poor response to vaccines 3) Defined causes of hypogammaglobulinemia have been excluded
<b>Possible</b>
Male or female patient who has a marked decrease (at least 2 SD below the mean for age) in one of the major isotypes (IgM, IgG and IgA) and fulfills all of the following criteria: 1) Onset of immunodeficiency at greater than 2 years of age 2) Absent isohemagglutinins and/or poor response to vaccines 3) Defined causes of hypogammaglobulinemia have been excluded

disease complications cause severe morbidity, the enormous heterogeneity in the clinical presentation of CVID. Failure to make a diagnosis at the early stage can result in complications of recurrent infections particularly those of the chest (8). The clinical relevance of under diagnosing this disorder is that it precludes appropriate management by the use of intravenous immunoglobulin (IVIG). The primary treatment of CVID is replacement of antibody by either an intravenous or subcutaneous route, usually in doses of 400 to 600 mg/kg body weight per month (1). Our patient is receiving a lower dose because still produces some immunoglobulin's. This dose is usually divided into once or twice a week, or every 2 weeks (for the subcutaneous route) or every 3 or 4 weeks (for the intravenous route). Although expensive, the use of IVIG can allow patients to lead a near normal life and perform productive work.

## CONCLUSION

This case highlights the importance of increasing awareness among primary care doctors for suspecting and confirming a diagnosis of CVID and to emphasize the need to perform basic laboratory tests and to determine immunoglobulin classes in clinical practice in patients with recurrent infections. Although IVIG provides improvement in these patients, early diagnosis is the key to preventing significant morbidity and mortality and improving prognosis.

## REFERENCES

1. Cunningham-Rundles C. How I treat common variable immune deficiency. *Blood* 2010;116:7-15.
2. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. *Curr Allergy Asthma Rep* 2009;9:347-352.
3. Geha RS, Notarangelo LD, Casanova JL, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol* 2007;120: 776-794.
4. Cunningham-Rundles C, Lieberman P, Hellman G, et al. Non-Hodgkin lymphoma in common variable immunodeficiency. *Am J Hematol* 1991;37:69-74.
5. Piqueras B, Lavenu-Bombléd C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, et al. Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. *J Clin Immunol.* 2003;23:385-400.
6. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92: 34-48.
7. Kainulainen L, Nikoskelainen J, Vuorinen T, et al. Viruses and bacteria in bronchial samples from patients with primary hypogammaglobulinemia. *Am J Respir Crit Care Med* 1999;159: 1199-1204.
8. de Gracia J, Vendrell M, Alvarez A, et al. Immunoglobulin therapy to control lung damage with common variable immunodeficiency. *Int Immunopharmacol* 2004;4:745-753.
9. Zullo A, Romiti A, Rinaldi V, Vecchione A, Tomao S, Aiuti F, et al. Gastric pathology in patients with common variable immunodeficiency. *Gut.* 1999;45:77-81.
10. Kalha I, Sellin JH. Common variable immunodeficiency and the gastrointestinal tract. *Curr Gastroenterol Rep* 2004;6:377-383.