



Common variable immunodeficiency in an 11-year-old girl – a case report

Joanna Pawłowska^{1,A-F}, Olga Panowicz^{1,A-F}, Joanna Jerzynska^{1,A-F}

¹ Department of Paediatrics and Allergy, Medical University, Lodz, Copernicus Memorial Hospital, Korczak Paediatric Centre, Lodz., Poland

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Abstract

Common variable immunodeficiency (CVID) is one of the most prevalent, heterogenous primary immunodeficiency syndromes in children and adults. Besides impaired immunoglobulin production by B cells, abnormalities in almost all components of the immune system have been described in CVID. The clinical pictures of CVID includes acute and chronic infections, inflammatory and autoimmune diseases, and can be associated with an increased incidence of cancer and lymphoma. Due to the plurality of clinical manifestations and different ages of occurrence, diagnosis of CVID is difficult and belated in relation to primary symptoms. Patients with CVID require an integrated interprofessional team approach to minimize complications of the disease and to improve patient outcomes. The article presents the clinical case of 11-year-old girl diagnosed with CVID in day-to-day medical practice.

Key words

immunodeficiency, autoimmunity, CVID, recurrent infections

INTRODUCTION

Common variable immunodeficiency (CVID) with a calculated prevalence of 1:10,000–1:50,000 in Caucasians, and significantly less frequently in other populations, is one of the most rife symptomatic primary immunodeficiency in both adults and children [1, 2, 3, 4]. The first symptoms may occur at different age, but two peaks of incidence have been noted: in childhood (between five and ten years old) and during the second and third decade of life. For this reason, CVID can be defined as either the belated onset of hypogammaglobulinaemia, or hypogammaglobulinaemia with two occurrence peaks [5, 6]. Patients affected by CVID are prone to recurrent infections, augmented in some reports by the occurrence of autoimmune and lymphoproliferative diseases. The important issue at CVID is the variety of clinical symptoms which generates diagnostic difficulties, delays final diagnosis and thus the implementation of appropriate treatment which could protect patients from usually irreversible infectious and non-infectious complications [7]. Even though similarity concerning clinical and immunological characteristics can be observed in CVID patients, the severity and stage of progress differs remarkably among afflicted individuals [3]. Primary immunodeficiencies (PIDs) are connected with meaningful incidence and can lead to early decease if under diagnosed and untreated [8].

OBJECTIVE

The aim of this paper is to emphasize the need to perform basic laboratory tests and to determine immunoglobulin classes in clinical practice in patients with recurrent infections. The abnormalities in these widely available tests should prompt extension of the diagnosis and allow for the early detection of disorders of the immune system.

CASE REPORT

An eleven-year-old female patient, delivered by c-section from the first pregnancy and born in the 39th week of pregnancy, with a body weight of 3,750g, Apgar score – 10, breastfed up to 15 months, remained under the care of the Department of Paediatrics and Allergy from the age of three. During early childhood, her development was evaluated as proper, weight and height rated at 70 centile on growth and body weight charts. Due to the Polish obligatory vaccination schedule, all vaccines were given and no supplemental inoculations administered. At the age of three, recurrent infections of both the upper and also lower respiratory system appeared, and the patient required very frequent administration of antibiotic therapy (at least once a month). Extensive alergological, laryngological and immunological diagnostics were implemented at that time. Results of performed laboratory tests revealed significantly decreased levels (compared to normal for age) of: IgG, IgM, IgG2 and IgG3 subclasses, CD19+ lymphocytes, inhibition of granulocyte activity in Bursttest, and also decreased levels of anti-Hbs titers. Elected serum specific IgE (aeroallergens and food allergens) were negative. Laryngological examination did not indicate any abnormalities.

On the basis of the clinical picture, laboratory tests and patient's age, the girl was diagnosed with hypogamma-

Address for correspondence: Joanna Pawłowska, Department of Paediatrics and Allergy, Medical University of Lodz, Copernicus Memorial Hospital, Korczak Paediatric Centre, Lodz, Poland
E-mail: asiap06@gmail.com

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globulinaemia and cellular immunity disorders. She was qualified to the national primary immunodeficiencies treatment programme – IVIG replacement therapy. Monthly transfusions of immunoglobulins noticeably reduced the incidence of infections.

However, after a year, due to a renewed and increased prevalence of infections, the girl was admitted to hospitalization for further immunological evaluation. Examination of peripheral blood revealed significant deviations in immunological parameters: decreased levels of IgA and IgM in blood serum, reduced absolute count and percentage of lymphocyte B, elevated percentage of lymphocytes T, mainly CD4+, normal percent and absolute count of NK cells at evaluation of individual subpopulations of lymphocytes. IgG persisted on a satisfactory level (the patient remained on immunoglobulins replacement therapy). After evaluation of the whole clinical history and elimination of other reasons for the hypogammaglobulinaemia, the patient was diagnosed with common variable immunodeficiency. During next four years, girl remained on IVIG replacement therapy; infections occurred, but relevantly less often.

In the next couple of months, the problem of chronic cough emerged. The suspicion of developing asthma occurred, and for that reason spirometry and skin prick tests were conducted, but both turned out to be negative. The cough infections did not always require antibiotic therapy, but pneumonia and obstructive bronchitis also occurred.

The patient underwent regular checkups, at least every six months, for immunological parameters, which revealed normal IgG and IgG subclasses level (immunoglobulin therapy was continued), but absolute count of lymphocytes B still remained relevantly decreased, with concurrent normal total count and percentage of NK cells and an elevated percentage of lymphocytes T, particularly CD4+. IgA and IgM levels in blood serum were still significantly decreased, compared to age.

At the age of seven, the patient started a subcutaneous substitution of immunoglobulins, administered once a week in conditions of home therapy. Infections occurred occasionally. However, after two years, the frequency of respiratory tract infections increased – the girl needed repeated antibiotic therapy; she was admitted four times to the paediatric department due to pneumonia. Chronic antibiotic prophylaxis with amoxicillin (daily dose – 20 milligrams per kilogram per body weight) was instituted. The patient reported recurrent abdominal pain and periodically appearing diarrhoea; *Giardia lamblia* antigen was detected in faecal examination. Metronidazole was administered and after the treatment regression of symptoms was observed.

Due to the presence of recurrent dry cough, 24-hour pH monitoring with impedance was conducted. The patient was diagnosed with gastroesophageal reflux; proton-pump inhibitor and continuous gastroenterological healthcare were advised.

Due to prominently increased incidence of infections and hospitalizations, despite the immunoglobulin replacement treatment, it has been decided to perform genetic tests which, at the time of writing this article, has been in the preparation.

The patient currently remains under interdisciplinary healthcare and the treatment with subcutaneous immunoglobulin substitution administered at home is continuing.

DISCUSSION

CVID is one of the most prevalent primary immunodeficiencies (PIDs) with important morbidity and a high number of medical encounters [3, 9]. Due to clinical and immune heterogeneity, CVID has been variably defined over the years [10]. In 2016, the International Consensus Document on CVID agreed on a definition requiring IgG levels two standard deviations below the age-appropriate reference, as well as either low IgA or IgM levels, and poor antibody response to vaccination in an individual at least 4 years-old, with no secondary cause of hypoglobulinaemia [3, 11].

The European Society of Immune Deficiencies (ESID) diagnostic criteria are slightly different. To diagnose CVID, in addition to the laboratory abnormalities cited above, they require the presence of at least one of the following: increased susceptibility to infection, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, affected family member with antibody deficiency [12, 13]. In all cases, other reasons for hypogammaglobulinaemia must be carefully excluded, including immune globulin loss, medications, viral infections, known immune defects or other medical reasons for hypogammaglobulinemia [10]. Because of physiologic immaturity, which can mimic CVID in the early years, the diagnose of CVID should not be established in children under the age of four [13, 14].

CVID affected patients are at increased risk of developing serious infections, not only bacterial, but also viral, parasitic and fungal. The most common infections, often appearing as the initial symptoms of an immune defect, are recurrent infections of the upper and lower respiratory tract, and sinusitis, which is often caused by capsular bacteria – *Haemophilus influenzae* t.b, *Streptococcus pneumoniae*, or atypical bacteria, such as *Mycoplasma pneumoniae*. Chronic and recurrent airway diseases, which can lead to bronchiectasis and pulmonary fibrosis, are the main cause of frequent hospitalizations, and incidence of mortality [2, 10, 15, 16]. In CVID patients, gastrointestinal tract infections are also common, leading to recurrent or chronic diarrhea, and patients with CVID also have a higher prevalence of infections triggered by *Giardia lamblia*, *Campylobacter*, *Salmonella sp.*, *Helicobacter pylori*, *Cryptosporidium parvum*, CMV and HBV, HCV [10, 14, 17].

Another common complication in CVID is autoimmunity (e.g. autoimmune thyroid disease or inflammatory bowel disease), affecting at least 25% of patients. Curiously, although not typical, this may be the first manifestation of an immune defect in an occasional patient who has never experienced significant clinical infection [10, 16, 17, 18, 19].

Antibody-mediated cytopenia predominate in such cases, most often immune mediated thrombocytopenia (ITP), less frequently, haemolytic anaemia, or rarely, autoimmune neutropenia [10]. These patients are also significantly more likely to have one or more of other CVID-associated non-infectious complication, including lymphoproliferation, granulomatous disease, lymphoma, hepatic disease, interstitial lung diseases or enteropathy, as well as lymphadenopathy and splenomegaly [5, 10, 17].

Patients with CVID also have an increased incidence of allergic diseases, with deteriorations and worse response to treatment, compared to individuals without PIDs (20).

A large number of CVID patients present a clinical history which may suggest allergic respiratory disease. There are

studies which evaluate respiratory comorbidities in CVID-affected individuals indicating the prevalence of asthma at the level of 15%. Nevertheless, the role which is assigned to atopy in CVID-affected patients has not been determined unequivocally, because the total IgE serum level or specific IgE level are frequently not elevated. In these patients, it is possible that reports of asthma may be confused with a history of remittent respiratory system infections. There may also be difficulties in the evaluation of asthma in CVID patients, some of whom manifest respiratory symptoms as a cause of infectious complications, or may in fact be presentations of respiratory allergy [21].

Patients affected by CVID are susceptible to malignancy and have increased risk of developing cancers. The most frequent malignancy is non-Hodgkin lymphoma, although other malignancies such as colorectal, breast and uterine cancer have been reported [5, 10, 17, 22].

The 11-year-old patient in this case report entirely fulfilled the diagnostic criteria for CVID, both laboratory – IgG, IgA and IgM <2SD of the normal levels for the age; poor response to vaccines, and clinical – increased susceptibility to infections and its recurrence and severity, gastroentero problems. There were no clinical signs, neither of autoimmunity nor lymphoproliferation and neoplastic disease, but the patient remains under multi-specialistic care to monitor potential symptoms and complications.

The treatment of humoral immune defect in CVID is based on immunoglobulin replacement therapy, at a dose 0.4 – 0.8 g/kg intravenous once monthly [5, 23, 24, 25], or subcutaneous in an equivalent divided dose, with an interval of one to two weeks. Such treatment was also introduced in the presented case, initially intravenously then, after training the parents, by the subcutaneous route. Both routes of administration are efficacious, safe and widely available, being on the World Health Organization Essential Medicines Lists for adults and children [3]. Long-term administration of immunoglobulins protects against recurrence of severe and frequent infections [6], and was also effective in the presented case. Since enormous progress has been made in the genetic diagnosis of primary immunodeficiencies, the results are awaited of the genetic test in this patient.

CVID occurs very rarely in clinical practice, but it should not be missed as early diagnosis allows for rapid implementation of treatment, improvement in the clinical and quality-of-life outcomes, and avoidance of complications. Unfortunately, the average time from occurrence of the first symptoms until making an accurate diagnose is estimated at 4.4 years [1, 26]. Reducing diagnostic delay, therefore, is crucial, and approaches include improved education and awareness, particularly regarding the onset and presentation of variable non-infectious of clinicians in both primary and secondary care. For that reason, it is especially important for paediatric general practitioners to have in mind, so called '10 warning signs of a primary immunodeficiency in children' (Tab. 1), which may suggest a primary immunodeficiency [27].

It is essential to determine if there is a family history of PID, draw attention to the current course and the rate of infection, effectiveness of their treatment, and evaluation of the physical and psychological development of the child.

Patients with CVID require an integrated inter-professional team approach to improve short-term and long-term patient outcomes. The main goal of therapeutic management in children with CVID is to decrease the morbidity and mortality

Table 1. If a paediatric patient is affected by at least 2 signs mentioned in the Table, there is a possible presence of an underlying primary immunodeficiency and the patient should be consulted with an immunologist

≥4 ear infections in one year	≥2 deep-seated infections, including septicaemia
≥2 serious sinus infections in one year	failure of an infant to gain weight or grow normally
≥2 pneumonias in one year	family history of primary immuno-deficiency
recurrent, deep skin or organ abscesses	persistent thrush in mouth or fungal infection on skin

associated with recurrent infections. The consensus among paediatric immunologists is that close clinical monitoring and appropriate IgG replacement can ultimately extend the life expectancy of these young patients so that it approaches that of the general population [3].

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