Coeliac disease and variable immunodeficiency. Case report

Boala celiacă şi imunodeficienţa variabilă

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Abstract

Common variable immunodeficiency syndrome affects mainly adults and rarely children. The prognosis for these patients may be favorable when they don't develop complications such as bronchiectasis, autoimmune or malignant diseases. This paper presents the clinical observation of an 11 years old girl with low levels of all classes of immunoglobulins and frequent bacterial infections, which is the main characteristic of common variable immunodeficiency. The patient had first symptoms at the age of 8 years and, after about one year, she was diagnosed with bronchiectasis. After about 3 years of follow-up she presented abdominal pains and failure to thrive. The duodenal biopsy revealed an aspect suggestive for coeliac disease type Marsh 3C. A combination of common variable immunodeficiency with atypical coeliac disease was not previously reported in Romania.

Keywords: *common variable immunodeficiency, children, coeliac disease, bronchiectasis*

Rezumat

Sindromul imunodeficienţei comune variabile afectează în principal adulţii şi mai rar copii. Prognosticul pentru aceşti pacienţi poate fi favorabil atunci când nu dezvoltă complicaţii de tipul bronşiectaziei, bolilor autoimune sau maligne. Lucrarea de faţă prezintă observaţia clinică a unei paciente în vârstă de 11 ani cu valori scăzute ale tuturor claselor de imunoglobuline şi frecvente infecţii bacteriene, principalele caracteristici ale imunodeficienţei comune variabile. Pacienta a avut debutul aparent al bolii la vârsta de 8 ani, iar la 9 ani a fost diagnosticată cu bronşiectazie. După aproximativ 3 ani de urmărire a formulat diagnosticul de boală celiacă, având aspectul histologic de Marsh 3C. O asociere a imunodeficienţei comune variabile cu boala celiacă nu a fost raportată anterior.

Cuvinte cheie: *imunodeficienţă comună variabilă, copil, boală celiacă, bronşiectazie*

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous entity characterized by an impaired ability to produce antibodies. The failure is located in partially mature B lymphocytes, though T lymphocyte abnormalities are occasionally present. This deficiency affects antibody synthesis and class switch from IgD and IgM, to IgG

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and IgA. CVID is related to selective IgA deficiency, and both abnormalities may coincide in one same family, and evolve from one to another in the same patient. The symptoms occur comonly in adults, but may be present at any age, even during infancy. The most frequent features are recurrent bacterial infections, pneumonias, gastrointestinal disorders granulomas and more rare malignancies [1]. Autoimmunity and autoinflammation may also occur in atypical phenotypes of combined immunodeficiencies usually associated with severe infectious complications [2]. CVID has been associated to insulin-dependent diabetes in children and adolescents [3, 4] and a coeliac patient with the typical DQ2 A1 0501 haplotype has been reported [5]. The incidence of CVID ranges from 1/25,000 to 1/66,000 inhabitants, though the milder cases probably go undetected [6].

Case report

A girl of 11 years and 7 months was hospitalized for the first time in the IIIrd Pediatric Clinic Cluj-Napoca at the age of 8 years (June 2007) for persistant cough and dyspnea. Family history revealed hypotrophy in brother and gastric ulcer in her father. During her first eight years of life, the girl had two episodes of urinary tract infections. About six months before her first hospitalization she had productive cough, malaise and fever. The diagnosis was acute pneumonia and she received antibiotics. In the clinical course she presented persistent cough with purulent sputum. After three months she performed a chest x-ray which showed pulmonary fibrosis secondary to pulmonary sequestration. She underwent an exploratory thoracotomy followed by the lysis of pulmonary pleural adhesions and drainage. The cough persisted after this intervention, and the patient associated fatigue and dyspnea, therefore she was admitted in our Clinic.

Physical examination on the first admission revealed severe expiratory and inspiratory dyspnea, with poor effort capacity (she stops after 2-3 steps when climbing stairs), productive cough with mucopurulent sputum, respiratory rate (RR) 22/minute, dullness of the left lower half hemithorax, normal breath sounds, bilateral crackles and some fine crackles.

Laboratory investigations showed: $satO_2$ 92-95%, negative CRP, ESR 28 mm in 1 hour, α1antitrypsine 204 mg/dl (NV 90-200) and low values of serum immunglobulins: IgG 277 mg/dl (NV 577-1410), IgA 0 mg/dl (NV 65-210), IgM 34 mg/dl (NV 60-175). Sweating test was within normal limits, chlorine of 36mEq/L. Stains of sputum examination in May-Grunwald-Giemsa and Ziehl-Nielsen were negative for pathogens and sputum culture revealed *Streptococcus viridans*.

Bronchoscopy examination showed pneumonia accompanied by atelectasis. Abdominal ultrasound was normal.

Pulmonary function tests (FlowScreen II Jaeger spirometer) revealed a severe restrictive syndrome (FVC 0.68 L = 36% of predictive) with mild obstruction (FEV1 0.64 L = 41% of predictive) and mixed ventilatory dysfunction. She started therapy with repeated courses of antibiotics associated with nebulised mucolytics (acethylcysteine, normal saline) and physiotherapy with the Flutter.

In July 2007, a second right thoracotomy was carried out. It revealed loose adhesions on both the coastal and mediastinal sides, pulmonary parenchyma with tough and fibrous condensations, which occupied the left lower lobe and partly lingula, homogeneous hepatization without focal lesions of parenchyma. Pulmonary biopsy from the fifth segment and from lingula presented aspects of follicular bronchiolitis, probably secondary to an infection.

In September 2007, the patient had acute respiratory infections that exacerbated cough and dyspnea. Laboratory examinations showed CRP 12.5 mg/dl and urinary tract infection with *E. coli*. She received treatment with ceftazidime.

In October 2007 in the context of maintaining low serum immunglobulins (*Table 1*),

Table 1. Serum immunglobulins evolution at the time of diagnosis

Period	Serum immunoglobulins, mg/dl		
	IgG	IgA	IgM
VI.2007	277	0	34
VII.2007	277	25	40
X.2007	259	7	34
XII.2007	2770	9	40

substitution treatment with intravenous immunoglobulines G (IVIG) was initiated. We used monthly Octagam, and since March 2008 weekly Pentaglobin. Between 2007 and 2009 she had a steady weight.

Between April and July 2009 she had burning epigastric pains without radiation, associated with heartburn and bitter taste. Symptoms occured daily, both before and after meals. Antacids administrations improved clinical condition of patient. On July 2009 we performed an upper gastrointestinal endoscopy with *duodenal biopsy*. The pathology exam revealed: two pieces of mucosa with completely flattened villous and hyperplastic crypts, intense and diffuse lymphocytic infiltrate of the chorion. The fragments presented lymphoid chorionic follicles, and inflammatory infiltrate with nuclear cells, numerous eosinophils and rare polymorphonuclear cells. The surface of epithelium and the brush border was preserved, but the cells are flattened and discontinuous. In the thickness of the surface and cryptic epithelium, a pathological intense exocytosis could be observed. Pathology diagnosis was Marsh 3C coeliac disease, and acute duodenitis. Since the patient's brother presented also failure to thrive, we performed a serological assessment which showed normal levels of serum immunglobulins: IgG 980 mg/dl, IgA 149 mg/dl, IgM 101 mg/dl and negative values of IgA tissue transglutaminase antibodies (IgA-TgA).

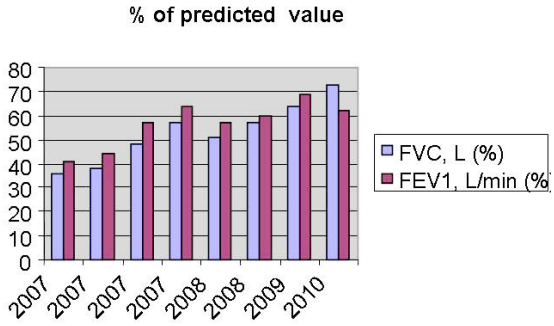

Figure 1. The value of respiratory functional tests in evolution

After the diagnosis of coeliac disease, our patient started a strict gluten free diet. During July 2009 - March 2010 she had a good clinical course (*Figure 1*), without other significant infections, weight gain of approximately 6 kg within 9 months. Serological evaluation of the patient one year after gluten-free diet showed negative values for IgA-TgA.

The positive diagnosis in this patient was: common variable immunodeficiency, chronic obstructive bronchitis, bronchiectasis, chronic respiratory failure, coeliac disease.

Discussion

The main complain of our patient was dyspnea and persistent cough suggestive for chronic respiratory failure after a pneumonia. Gastrointestinal symptoms, which occurred about two years after the diagnosis of CVID suggested gastritis or gastric ulcer. This was the main reason for which we performed upper gastrointestinal endoscopy. Except the failure to thrive, she had no clinical clue for the diagnosis of coeliac disease. The awareness for the possible clinically silent or atypical disease course

might be significant in order to investigate these patients [7, 8]. Duodenal villous atrophy is very frequent in symptomatic CVID patients, with relevant clinical and immunological implications [9], but the relationship between primary immunodeficiency syndromes and gastrointestinal manifestations is not yet well defined.

In a group of 32 children with common immunodeficiency, Urschel et al. [10] described its variability using retrospective questionnaires. A variety of infections were present in these patients: recurrent or chronic respiratory infections (88%), sinusitis (78%), otitis media (78%), as well as other infections, like intestinal tract infections (34%), mainly with encapsulated bacteria, meningitis (25%), sepsis (16%), or pyelonephritis in 16% of patients. About 34% of patients develop bronchiectasis and 13% may have lymphoid proliferative disease. Poliomyelitis after vaccination occurred in two patients and opportunistic infections. Allergic disorders were also present at 38% and autoimmune disease in 31% of patients. Because of recurrent infections, about 80% of patients underwent surgical procedures. Growth retardation was observed in 28% of patients, while 16% had mental retardation. Our patient presented bronchiectasis and underwent two surgical procedures. She also had failure to thrive which is caused by the associated coeliac disease. The pathological findings patognomonic for coeliac disease were surprising. By that time we could not perfom serological tests for confirmation of the diagnosis. The gluten-free diet improved signifficantly the weight gain in our patient. In the mentioned study group, the mean time between symptoms and the start of replacement therapy with immunoglobulin was 5.8 years (between 0.2 to 14.3 years). The diagnosis in our patient was established at the age of 8 years and replacement treatment was started after about 4 months.

In a retrospective study on 57 patients with variable immunodeficiency syndrome, Diez et al. [11] showed that digestive symptoms were found in 74% of patients, and diarrhea is the most common. About 46% of these patients underwent endoscopy and biopsy, which contributed to the diagnosis of coeliac disease, chronic atrophic gastritis, ulcerative colitis or Crohn's disease. In IgA deficits, the most common digestive disease was chronic gastritis, mainly due to *Helicobacter pylori* infection. Therefore, the presence of gastrointestinal disorders in patients with humoral immunodeficiency was recognized, and recommendations for their management were reviewed [12].

In conclusion**,** chronic immune deficiency syndrome is an entity which should be considered in patients with recurrent infections. When associated with marked hypotrophy, coeliac disease is a possible co-morbidity. The aspect of Marsh 3C coeliac disease found in our patient had not been reported before in Romania.

Abbreviations list

α1AT - alpha 1-antitrypsin;
BMI - body mass index;
CRP - C reactive protein;
CVID - common variable immunodeficiency;
ESR - erythrocyte sedimentation rate;
FEV1 = peak expiratory flow in first second;
FVC / FEV 1 = Tiffneaud index;
FVC = forced vital capacity;
IgA - immunglubulin A;
IgA-TgA – IgA tissue tranglutaminase antibodies;
IgD - immunoglobulin D;
IgG - immunoglobulin G;
IgM - immunoglobulin M;
IVIG - G immunoglobulines intravenously;
NaHCO3 - Sodium bicarbonate;
RR - respiratory rate;
$satO_2$ - oxygen saturation;
T – height.

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