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Nonspecific Symptoms in Celiac Disease- Case Report

Valentina Sas[1], Camelia I. Bud[2,*], Ioana Fodor[2], Sorin C. Man[1]

[1]Mother and Child Department, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2]Third Pediatric Clinic, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania
*Corresponding author: cami_bud01pd@yahoo.com

Abstract Celiac disease is an immune-mediated systemic disorder with a genetic predisposition. The availability of more specific serology tests showed that celiac disease is more common than previously suspected and that many patients do not demonstrate specific clinical or even histological sings. We present a case of celiac disease with the unset at 5 years, with recurrent episodes of diarrhea, weight loss and anemia. The serology tests showed a high level of IgA tissue transglutaminase antibodies, exceeding 10 times the upper limit but the intestinal biopsy showed normal size villi, intact surface epithelium and a lymphoplasmacytic infiltrate at chorionic level (Marsh 1). The diagnosis of celiac disease was confirmed by resolution of symptoms and normal tissue transglutaminase antibodies level, six month after starting the gluten free diet.

Keywords: *celiac disease, children, diagnosis, challenge*

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1. Introduction

Celiac disease (CD) is considered now a common multiorgan disease with a strong genetic predisposition, rather than a rare, uncommon enteropathy as believed in the past [1]. The pathogenesis was clarified after demonstrating the gluten-reactive small- bowel T cell activity that specifically recognize gliadin peptides, in predisposed patients presenting HLA-DQ2 and HLA-DQ8 haplotypes [2]. The discovery of specific antibodies like tissue transglutaminase type 2 (TG2) antibodies demonstrated the immune nature of this disorder and improved the diagnosis process [3].

The prevalence of CD is increasing because of westernization of diet and improvement of serological testing. In Unites States the prevalence is estimated at 0.71% and in European countries between 0.6 and 1%, a single study performed in Romania in 2003 showed a prevalence of 2.2% [4,5,6].

CD has a high variability regarding the clinical manifestations, from asymptomatic patients to signs and symptoms that highly suggest CD. ESPGHAN 2012 guideline recommends testing of two groups of patients: children or adolescents with symptoms or signs suggestive of CD (including atypical symptoms) and asymptomatic children or adolescents with CD associated conditions: T1DM, autoimmune thyroid disease, Turner syndrome and selective IgA deficiency [1]. The diagnosis is made by clinical and serological aspects, presence of HLA-DQ2 and HLA-DQ8 and histology findings in correlation with a normal gluten intake. HLA testing should be performed in cases of uncertain diagnosis. High TG2 antibodies (>10 times upper limit) measured by a qualified laboratory have a high diagnosis accuracy and correlates with villous atrophy [9]. The diagnosis is confirmed by amelioration of symptoms and decreased antibodies levels after introduction of the gluten free diet.

The gluten free diet is the only lasting treatment of CD, adherence to this diet is important in preventing chronic complications of malabsorption and in achieving a good quality life for the patients.

2. Case Presentation

Patient SA, aged 5, presented to our service in September 2015, for diarrheic stool. The onset of the symptoms was 4 weeks before with 3-6 watery stools/day, no mucus or blood. She received probiotics and racecadotril at home, with persistence of diarrhea (3-4 stools/day). The stools appeared most frequently during the night. Further she developed abdominal pain and weight loses 1.5 kg in 2 weeks. At that moment she was evaluated in our clinic, the laboratory findings showed microcytic hypochromic anemia, no inflammatory syndrome, normal liver and kidney function, the stool exam was negative and the abdominal ultrasound was normal. The case was interpreted as postenteritic syndrome and she received probiotic treatment. At home she continued to have recurrent episodes of diarrhea mostly during the night, lasting for 1-2 days, with 1 week between the episodes. The mother put her on a lactose free diet but the symptoms persisted. She was admitted for further investigation in October 2015.

She has no significant past medical history and from the family medical history we found out that she has an uncle (mother's brother) with chronic digestive problem who was recently diagnose with CD at the age of 30.

Physical examination at admission showed a good general condition, weight 19 kg (30th percentile), height

144 cm (47th percentile), body mass index 14.6 kg/m^2, pale skin, reduced adipose tissue, respiratory rate 20/min, heart rate 90/min, normal lungs and heart sound, no abdominal distension or sensibility, normal neurologic exam.

Laboratory tests showed the absence of inflammatory syndrome, ESR and CRP were in normal range, microcytic hypochromic anemia, liver and renal functions were normal, no electrolytes disorders. Serum albumin level and immunoglobulins (including IgA) were in normal range. Stool cultures were negative and there was no blood or parasites in stool. At this stage we exclude an infectious cause of diarrhea and we suspected a food intolerance/allergy, CD or inflammatory bowel disease. Screening for CD showed high levels of IgA TG2 antibodies (194.7 U/ml; normal values < 20 U/ml) and positive antiendomysial antibodies on immunofluorescence methods.

Upper digestive endoscopy was performed before starting a gluten free diet. There were no macroscopic changes and several biopsies were taken from the duodenal bulb and D2 segment of the duodenum. The biopsy result showed duodenal mucosa with normal size villi, intact surface epithelium and a lymphoplasmacytic infiltrate at chorionic level (Marsh 1), cryptic exocytosis was abnormal.

Based on clinical symptoms, high levels of IgA TG2 antibodies and the minimal changes on intestinal biopsy, a final diagnosis of CD was made and a gluten free diet was recommended.

Other investigations were performed to exclude autoimmune diseases, associated to gluten- sensitive enteropathy: autoimmune thyroiditis, IgA nephropathy, type I diabetes.

The gluten free diet was started in November 2015, with resolution of symptoms. At two months evaluation the girl gained weight (500g), she had no diarrhea episodes and blood test showed significant decrease levels of IgA TG2 antibodies (from 194.7 U/ml to 18.7 U/ml). At six month after the gluten free diet was started the IgA TG2 antibodies were negative. The clinical and serological improvement supports the diagnosis of CD.

3. Discussions

CD is characterized by the presence of a variable combination of gluten dependent clinical manifestations, CD specific antibodies: IgA anti- endomysial antibodies (EMA), tissue transglutaminase type 2 and deamidated gliadin peptides (DGP), presence of HLA-DQ2 or HLADQ8 haplotypes and enteropathy. ESPHGAN guideline for CD 2012 recognize two major clinical situation: gastrointestinal symptoms and sings like chronic diarrhea, vomiting, constipation, and extra intestinal symptoms and sings like failure to thrive, anemia, neuropathy, alteration of liver function tests, and decrease bone density, increase risk of bone fractures [1]. The nutritional status depends on the time of diagnosis and the extension of intestinal damage. The onset for our patient was gradually, with digestive symptoms, recurrent episodes of diarrhea and diffuse abdominal pain, lasting 1-2 day with watery stools, mostly during the night, appearing at 1 week interval. Chronic diarrhea is defined as increased in frequency, volume and fluidity of stools that last more than 14 days; for our patient, none of the episodes lasted more than 48 hours, and the stools were more watery than steatorrheic. She also presented weigh loss (1.5 kg in 2 weeks), being at the 30th percentile for weight and also for BMI. Laboratory findings showed microcytic hypochromic anemia as a result of decreased iron absorption. The malabsorption syndrome present in CD can also include fat-soluble vitamins, calcium and folic acid deficiencies [7].

The serology testing include EMA who have the highest specificity and positive like hood ration for CD diagnosis. The specificity and positive predictive value of TG2 antibodies is lower than positive EMA [8, 9].

The improvements in serology testing have changed the diagnosis algorithm for CD in children. If the TG2 antibodies exceed 10 times the upper limit than there is an increased risk of villous atrophy [9, 10]. Correlating this high TG2 antibodies level with suggestive clinical features, positive EMA and positive HLA testing, allows the option of omitting the confirmatory biopsy [1]. Contradictory with these findings in the literature, our patient had an increased level TG2 antibodies exceeding 10 times the upper limit (194 U/ml, normal range < 20) but the biopsy showed no villous atrophy with Marsh score 1.

HLA testing is recommended when the diagnosis is uncertain, negative serology tests, Marsh score 0-1. Negative results render CD highly unlikely in these children [1]. HLA testing was not performed for our patient because of financial aspects. Regarding the genetic predisposition of CD it is well known the presence of this disease to grade 1 relatives. Our patient had only a grade 2 relative who was recently diagnose with CD at the age of 30 years, because of chronic digestive symptoms. This raises the question about other members of the family having an asymptomatic form of CD?

The histological findings in CD are not specific, they can be also found in cow's milk or soy protein hypersensitivity, intractable diarrhea of infancy, heavy infestation with Giardia lamblia, immunodeficiency, tropical sprue, and bacterial overgrowth [11]. The histologic findings in CD can be characterized by patchiness of the lesions, which may be present only at duodenal bulb level [12]. The most common histopathologic change in CD is the so-called severe "flat" mucosal lesion. Villi are absent or rudimentary. The surface epithelium appears more cuboidal and there is increased lamina propria lymphoid cell elements and increased intraepithelial lymphocytes. Crypt cell hyperplasia with an increase in the crypt epithelial cell mitotic index is present [13].

The histological findings must be correlated with clinical and serological aspects. Recurrent biopsies and gluten challenge is necessary only in patient with an uncertain diagnosis.

ESPGAHN 2012 guideline presents a score of diagnosis in CD. The scoring takes into account 4 items: symptoms, antibodies, HLA, and biopsy findings. To make the diagnosis, a sum of 4 points is required, for our patient these score was 4, presenting malabsorption syndrome and high levels of TG2 antibodies [1].

Diagnosis of CD can be confirmed by resolution of symptoms, decreased TG2 antibody level and regeneration of intestinal epithelium, after exclusion of gluten from the diet. Clinical improvement is expected in 2 weeks to 6

month, histologic findings improve in 2 to 3 months, but it can be incomplete in 50% of patients. The TG2 antibody level can achieve normal levels in 3 to 12 month and can be a useful tool in monitoring the therapy although these practice is controversial [14].

4. Conclusions

Despite the progresses made in understanding the pathogenesis of CD and also in increasing the accuracy of serologic testing, the diagnosis of CD remains a challenge for the clinicians. Early diagnosis and treatment is important especially in children because of the impact of this disease on growth and development. Symptoms of CD can be absent or nonspecific. Like in the case presented above, the histological findings can be minimal with normal villi size, supporting the concept that the diagnosis of CD is made by correlating the clinical, serological, genetic and histological findings.

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