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Case Report

Seronegative Celiac Disease Presented with a Pronounced Abdominal Distention in a 4-Year-Old Boy- Case Report and Review of Literature

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ABSTRACT

Celiac disease is a multifactorial, autoimmune disorder that occurs in genetically susceptible individuals. Celiac disease mainly affects the small intestine, where it progressively leads to flattening of the small intestinal mucosa. The seronegative celiac disease includes a small percentage of celiac patients who display villous atrophy but are negative to specific serology. We present a 4-year-old boy who manifested an extreme abdominal distention caused by seronegative celiac disease. This form of celiac disease leads to multiple topics for discussion such as prevalence, sensitivity, and specificity of serological markers, clinical and histological features, differential diagnosis, and difficulties on monitoring and follow up. The diagnosis of seronegative celiac disease requires a careful evaluation of any symptoms because serological tests are worthless in contrast to conventional celiac disease. Genetic testing and mucosal biopsy of the small intestine are indispensable to make a correct diagnosis. A good response to a gluten-free diet is the last benchmark to confirm seronegative celiac disease.

Keywords: Celiac disease; Seronegative celiac disease; Antitransglutaminase antibodies; Endomysial antibodies

Abbreviations: CD: Celiac Disease; SNCD: Seronegative Celiac Disease; IgA: Immunoglobulin A; IgG : Immunoglobulin G; anti-DPG: Deaminated Peptide Gliadine Antibodies; anti tTG: Antitransglutaminase Antibodies; anti EMA : Anti Endomysial Antibodies; GFD: Gluten Free Diet

INTRODUCTION

Celiac disease is a multifactorial, autoimmune disorder that occurs in genetically susceptible individuals. [1] It is triggered by gluten and related prolamins present in wheat, rye, and barley. CD mainly affects the small intestine, where it progressively leads to flattening of the small intestinal mucosa. Within this definition, patients can further be defined as having symptomatic, silent, potential, or latent celiac disease [2]. In the last few decades, the identification of serological biomarkers [3] (anti-TGA; anti-EMA; anti-DGP) has reduced the role of histology in CD diagnosis. ESPGHAN guidelines recommend skipping the biopsy in symptomatic children with high titer tTGA (>10 x) and positivity for genetic CD markers HLA DQ2/DQ8(2). Although CD antibodies are detected in the vast majority of CD patients (95-98%), a minority of CD patients may test negative for serology, and in this cases the diagnosis is strictly dependent on histopathology [4,5]. In these cases, HLA DQ2/DQ8 positivity requires immediately to suspect the seronegative celiac disease. However, the definition of seronegative celiac disease has generated some confusion in the reported literature and this shows our growing understanding of this form of CD [6-9]. SNCD include a small percentage of celiac patients who display villous atrophy but are negative to specific serology. Diagnosis of this rare manifestation relies on histological response to gluten-free diet, after other enteropathy forms unrelated to gluten intake have been excluded [4,10]. In children, seronegative celiac disease studies are very limited and the discussions may demand a high level of expertise.

CASE REPORT

We present a 4 year-old-boy who has been in appointments with gastroenterologist several times because of abdominal pain. He was treated with metronidasole for giardiasis by his family doctor. According to his grandmother he has taken probiotics and enema for constipation but without any results. He was checked for celiac disease but serological test (IgA antitransglutaminase plus IgA level) was normal. He was the first child of an Albanian couple. Pregnancy and delivery was normal. Birth weight was 3,3 kg. Breast-fed till 3 years old. Supplementary foods were introduced after 6 months. He was nourished for a long time with liquid foods because his mother noticed his boy was choked frequently when he was nourished with solid foods. No history of family diseases. Four months ago his grandmother has noticed recurrent abdominal pain accompanied with anorexia, mild meteorism, and constipation. Despite a lot of

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appointments and medications, this child is hospitalized because of a severe abdominal distention. During physical examination was noticed an irritated boy. His weight was 10 kg (Weight for age=-3,84 z-score) and height was 93 cm (Height for age=-2,46 z-score). Heart rate was 110/min, normal rhythm, respiratory rate 22/min. The abdomen was totally distended without the possibility to evaluate the liver and spleen (Figure 1).

Extremities were thin and gluteal mass was shrunk due to reduced adipose tissue (Figure 2). Lab examinations showed normal CBC and PCR. Ferritin level was 18,8 ng/mL, liver and kidney function was normal. Urine and stool analyses resulted normal. The abdominal ultrasound did not reveal anything due to abdominal overdistention. An abdominal x ray showed a severe abdominal meteorism (Figure 3) drawing attention to Hirschprung disease but barium enema did not support this diagnosis. It should be noted that all subjects above the age of 3 years were immersed in a day care setting or school environment at the time of PCR testing. Information has been provided whether or not those under the age of 3 were in daycare or had siblings in daycare. All subjects had received age-appropriate routine vaccinations based on the Center for Disease Control guidelines by age at the time of PCR testing.

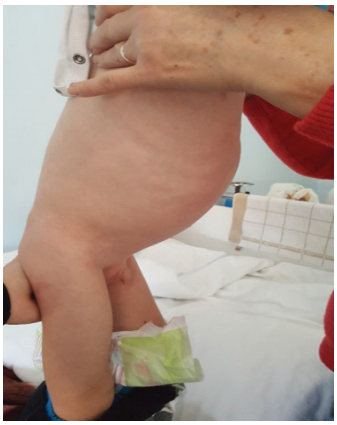

Figure 1: Image of severe abdominal distention.

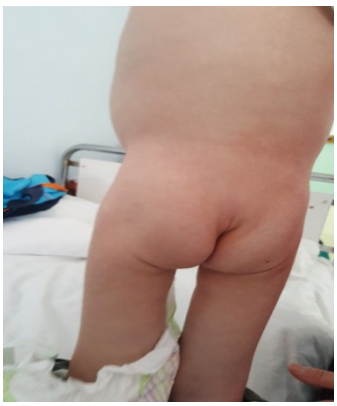

Figure 2: Image of gluteal muscle waste.

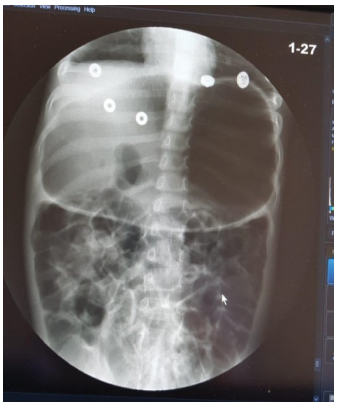

Figure 3: Abdominal X ray shows an extreme abdominal distention.

We checked again serological test for celiac disease: IgA antitransglutaninase (enzyme linked immunosorbent assay) <2 U/ml (<20 U/ml normal range); IgA-antiEMA (immunofluorescence) resulted negative. Total IgA level was normal. To exclude a seronegative celiac disease we decide to perform an upper endoscopy with duodenal biopsy and simultaneously to check HLA DQ2- DQ8.

During upper endoscopy we saw a scalloping duodenal mucosa (Figure 4) raising our suspicion about celiac disease. We took 4 duodenal biopsies (Figure 5). Waiting the result of histopathology we started gluten free diet. Before the final result of histology we had the response of genetic which confirmed HLA DQ2 positive. Histopathology images (Figure 6) confirmed villous atrophy 3a according to March Oberhuber classification.

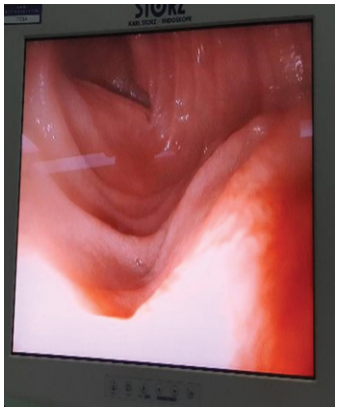

Figure 4: Images of upper endoscopy showing duodenal mucosa before biopsies.

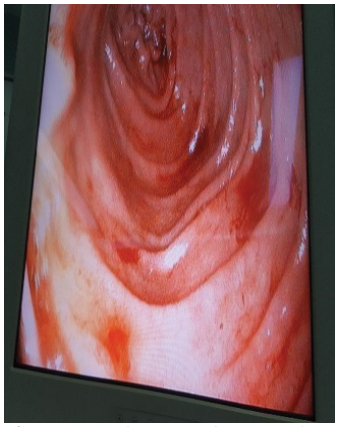

Figure 5: Images of upper endoscopy showing duodenal mucosa after biopsies.

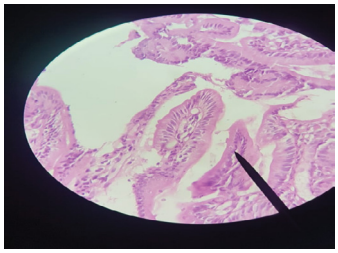

Figure 6: Histopatological view of Marsh 3a in duodenal biopsy.

A week later on the gluten-free diet this boy started some signs of improvement such as less abdominal pain, milder meteorism, and more appetite. He was discharged and in two months he gained 1,3 kg. We followed up in 6 months and improvement on a strictly gluten-free diet was spectacular.

DISCUSSION

Theoretically, SNCD includes patients with villous atrophy who shows the response to GFD but without IGA/IGG endomysial and IGA/IGG tissue antitransglutaminase antibodies. CD remains a polymorphic disease with variability of symptoms and forms. A lot of CD patients today are misdiagnosed because of mild or absent signs. Even more, SNCD remains very difficult in diagnostic because the serological tests which are the cornerstone of diagnosis are missing. The most common question which comes out is how is the prevalence of SNCD. The first prevalence of SNCD dates back to 15 years ago and showed that SNCD accounted upto 10%-20% of all untreated CD patients [11-13]. This historical data does not reflect the contemporary serological markers such as tissue antitransglutaminase and endomysial antibodies [4]. The higher sensitivities of the serological markers result in a low prevalence of SNCD. According to Schiepatti et al. [8], The prevalence of SNCD is 3%-5% but two other recent Italian articles reported a prevalence of 2 % of their total celiac disease population [7,9]. According to S.U. Goebel et al [14] seronegative celiac disease has been reported in 6.4-9.1% of patients with normal IgA serum concentrations; however, these patients are either elderly or have severe disease.

Another interesting point of discussion is the quality of serological markers in the diagnostic of CD. The sensitivity and specificity of IgA anti tGT are reported between 81 to 100% and 97 to 99% respectively [15]. It is of interest that a negative predictive value of 99.6% would conclude that a negative serology test would allow the physician to exclude the diagnosis of CD. The sensitivity and specificity of anti-EMA are between 74 to 100% and 99 to 100% respectively [16]. The sensitivity and specificity of serology markers depend on laboratory standardization [17].

In our case, we missed some months before the final diagnosis. Firstly because our boy initially had mild symptoms and secondly the serological tests for CD were negative. A high suspicion about SNCD should demand a genetic test despite the cost. If the genetic test is positive such as in our case the final step should be histological evaluation. According to Volta et al (7) SNCD has a higher frequency of total villous atrophy. Villous atrophy can be the result of other gastrointestinal conditions such parasitic infections, autoimmune enteropathies, small bowel bacterial overgrowth, medicament-related enteropathies, Crohn disease, etc [18]. If HLA DQ2/DQ8 result negative possibility to have villous atrophy caused by another disease is very high.

Data about clinical features of SNCD in children are very scarce. Interestingly a publication of 12 case series of SNCD by EV. J. Bernardo et al [19] noticed that in 12 patients (children and adults) diagnosed with SNCD the most prominent sign was increased abdominal circumference. Regarding our case who suffered for several months abdominal distention arriving at an extreme point we think that this common sign of celiac disease must remain in our memory for a diagnostic of SNCD moreover when other possible causes are excluded.

Another questionable issue is how to monitor an SNCD patient. Usage of serological antibodies during follow-up of SNCD patients is worthless but other examinations should be performed strictly as every other CD patient. Resolution of clinical signs on GFD associated with normalization of biochemical abnormalities should be the best indicator for monitoring SNCD.

CONCLUSION

The diagnosis of SNCD requires a careful evaluation of any symptoms because serological tests are worthless in contrast to conventional celiac disease. Genetic testing and mucosal biopsy of the small intestine are indispensable to make a correct diagnosis. A good response to GFD is the last benchmark to confirm SNCD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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