

Celiac disease: is it really possible to overcome duodenal biopsy?

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Summary. We report the case of a two-year-five-month-old child who underwent screening for celiac disease due to strong familiarity. During the first observation body weight and height were at 25th and 50th centile for gender and age. Physical examination did not reveal any sign of disease, but blood tests showed increased transaminases levels and antibodies research showed: tTG IgA: 100 UI/ml, tTG IgG: 36,6 UI/ml, EMA IgA: positive. HLA study revealed homozygous allelic combination DRB1*07;DQA102:01; DQB1* 02:02 with presence of a double copy of beta chain in the composition of the DQ2 heterodimer. Biopsy with histological examination did find neither mucosal alteration nor lymphocytic infiltrates (Marsh 0). During follow up with free diet the patient remained asymptomatic and all antibody titers decreased up to normalization. According to ESPGHAN guidelines the finding of hypertransaminasemia as sign of celiac hepatic inflammation, a more than 10-fold increase of tTG IgA and a high-risk HLA would permit diagnosis of celiac disease but histological examination done due to mismatch between paucity of clinical signs and a “multiple risk combination” excluded it, allowing diagnosis of potential celiac disease. We believe that this case is interesting because of its being in contrast with current literature data that suggest a linear relationship between antibodies levels and histological damage with tTG IgA at the upper reference range in case of potential celiac disease. According to guidelines we could have avoided intestinal biopsy but we would have considered as celiac a patient who is maybe just potentially affected. (www.actabiomedica.it)

Key words: celiac disease, biopsy, diagnosis

Abbreviations:

DGP: deamidated forms of gliadin peptides

EMA: endomysial antibodies

HLA: human leukocyte antigen

IgA: immune globulin A

IgG: immune globulin G

tTG: tissue transglutaminase

GFD: gluten free diet

PCD: potential celiac disease

Introduction

Celiac disease is an autoimmune enteropathy caused by gluten ingestion in genetically predisposed individuals. Population studies reported a highly vari-

able prevalence depending on geographic areas, ranging from 0,5-1% in Western Countries, to 1-2,4% in Finland, to 5,6% in Algeria (1). Pathogenesis is multi-factorial: in individuals with specific HLA haplotypes ingestion of gliadin and glutenines switch on a specific CD4 population which releases inflammatory cytokines responsible for tissue damage and systemic inflammatory response (2). Widespread clinical presentation includes intestinal and extra-intestinal manifestations that define several clinical pictures which can be differentiated through an in-depth diagnostic workup. According to recent ESPGHAN guidelines in symptomatic patients with genetical predisposition and strong positive serology (10-fold increase of anti-

tTG antibodies compared to reference range) diagnosis can be made even without bioptic demonstration of histological damage; conversely, this is required if antibodies titers are lower or in asymptomatic at risk patients. Biopsy is still the gold standard in other cases. (3). Hereafter we report a singular case of clinical-serologic mismatch in a child with familiarity for celiac disease and high risk HLA haplotype in which pathology biomarkers became negative without gluten-free diet.

Patient presentation

DMF, two-year-five-month-old male underwent screening for celiac disease due to strong familiarity. First and second degree relatives were affected by celiac disease that was associated with autoimmune thyroiditis in the father, grandmother and second degree uncles. Nothing relevant in obstetric, perinatal and physiologic history: his growth was normal, appetite was good without intestinal discomfort, no sleep or behavioral changes were referred. He did not present any recent infective gastroenteritis.

Initial diagnosis and outcome

Body weight was 12,7 kg, height was 91 cm (respectively 25th and 50th centile for gender and age). Blood exams detected hypertransaminasemia. IgA titers were regular for age. Serologic investigations performed with immune enzymatic technique showed: DGP IgA 4UA/ml, DGP IgG 36,8 U/ml, tTG IgA 100 UI/ml, tTG IgG 36,6 U/ml, positive EMA IgA. HLA study revealed that the patient presented homozygous allelic combination DRB1*07;DQA102:01;DQB1*02:02 with a double copy of the DQ2 heterodimer beta chain. Considering the presence of multiple risk factors with increased liver enzymes levels as clinical sign, despite the good weight and height growth, biopsies at D1, D2 segments and gastric antrum were performed.

No histological changes were detected, villi showed regular height and architecture, with regular villi/crypts ratio and regular number of intraepithelial lymphocytes (inferior to 25%). In light of a potential

celiac disease hypothesis a gluten free diet was not prescribed and the child kept on receiving a free and varied diet.

Subsequent follow up showed a general stability of growth speed for the whole observation duration and a progressive decreasing in antibody titers: after 6 months DGP IGA 0,7 UA/ml, DGP IGG 8,8 U/ml, tTG IgA 32,2 UI/ml, tTG IgG 10 U/ml, EMA IgA positive; after 12 months: tTG IgA 16,5 UI/ml, EMA IgA persisting positive.

Discussion

In 2012 ESPGHAN published new guidelines for diagnosis of celiac disease in pediatric population, according to which the disease should be suspected in children with clinical manifestations suggestive for disease and in children and adolescents at risk for positive familiarity for the disease or other autoimmune disorders. Serologic investigations have high sensitivity and specificity and can be used as a diagnostic tool in patients complaining symptoms and signs of pathology with high risk HLA haplotype, in which duodenal biopsy can be bypassed (3).

On the other side, according to American guidelines, duodenal biopsy is still the gold standard for diagnosis and cannot be replaced by a serologic test that can have variable specificity and sensitivity depending in different laboratories (4).

On the basis of current available evidences, the presence in our patient of high genetic risk, positive familiarity for the disease and other autoimmune manifestations, finding of hypertransaminasemia as sign of hepatic celiac inflammation and a very strong serology, diagnosis of celiac disease would have been possible without histological confirmation necessity (3).

Several studies, in fact, demonstrated that anti-tTG antibodies have a high sensitivity and specificity and villous damage is positively correlated to the value of the antibody titer (6).

In fact, a linear correlation between anti-tTG IgA antibodies titer and the degree of intestinal lesion has been documented (7).

Similar trend was observed with EMA titers, as reported by Kruppa et al.: in their study of 2012 they

reported small bowel and crypt hyperplasia in 85% of EMA positive patients despite age of presentation (8).

However the mismatch between the paucity of clinical signs and symptoms and the laboratory data (high levels of tTG IgA and contemporary increased levels of EMA and DGP IgG) pushed us to complete the diagnostic workup with bioptic investigation that, although invasive, allows to exclude the disease in uncertain cases.

Absence of architectural alterations and lymphocytic infiltrate (Marsh 0) confirmed our suspect, leading us to classify the patient as affected by potential celiac disease.

This condition is characterized by the presence of anti-tTG IgA antibodies only at the upper reference limits (9) and compatible HLA with absence of duodenal villi atrophy (10).

It is not an infrequent condition, also before 2012 ESPGHAN guidelines publication Tosco et al. detected the possibility of fluctuation or negativization of antibodies titers in patient with PCD, but all the patients who showed a fluctuation or negativization of serology presented at the moment of the first evaluation levels of tTG IgA lower than our case; moreover, in the same study the titers of the patients who came to negativization were statistically lower than those of patients who showed a persistent positive serology (10).

Reviewing more recent literature we verified that our case is partially overlapping with Lionetti et al. findings: comparing overt CD versus potential CD, they considered lack of symptomatology, but levels of tTG IgA lower than 10 fold the ULN strong predictors of potential celiac disease (7) and detected a lower rate of familiarity and genetic risk (despite statistically not significant) in the group of potential celiac patients than in whom with a clear diagnosis.

We found also a similar clinical case described by Schirru et al., in which a gastroenteritis in the pathological story of the patients could justify increased levels of liver enzymes (12).

In a new prospective study the authors detected a correlation between high antibodies titers and symptomatology and an higher risk of persistence of high antibodies levels in children carrying two copies of HLA DR3-DQ2 compared to those with one copy (13). That allows us to underline the peculiarity of

our case in which a patient with important serological findings had as only clinical sign hypertransaminasemia and, despite he was genetically at high risk, came to complete serological remission without a GFD in 18 months.

Following European guidelines we could have avoided intestinal biopsy (3) but we would have considered as celiac a patient that maybe is just potentially affected. On the basis of current evidences it is not possible to foresee the evolution of this condition, the possibility that it stays stable with antibodies titers fluctuations is high (14) and a tight clinical and laboratory follow up is needed to define its development.

We wish to stress that the decision to perform or avoid duodenal biopsy in cases of difficult or uncertain interpretation should be exclusively performed by reference centers with a specific experience in the field.

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