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Clinical Case

Celiac Disease and Iga Deficiency - About a Clinical Case

Francisca Strecht Guimarães*, Inês Azevedo, Miguel Pinto da Costa, Cristina Rocha, Miguel Costa and Sara Freitas de Oliveira

Centro Hospitalar de Entre o Douro e Vouga, Feira, Portugal

Abstract

Celiac Disease (CD) is one of the most common diet-related chronic disease among children in Europe. The prevalence in the pediatric population has risen in recent decades. An adequate and timely diagnosis, as well as the initiation of treatment Gluten-Free Diet (GFD) reduce the complications of the disease. For this reason, it is an important topic to talk about in order to doctors to be more sensitive to this problem.

Selective IgA deficiency (SIgAD) is the most common primary immunodeficiency related to Celiac Disease (CD). The close association between both diseases has been known for a long time, what is still not definitively known is how to make the diagnosis and monitor patients with both pathologies.

We present the clinical case of a child with typical symptoms of celiac disease, in which we easily arrived at the diagnosis, but whose monitoring has proved to be a challenge, since despite the avoidance of gluten from the diet, and being asymptomatic, the antibody levels of antitissue transglutaminase (IgG anti-tTG) were progressively higher over the years.

Further studies will be needed to understand the best marker to monitor the response to the gluten-free diet in these patients.

Keywords: Autoimmunity; Celiac disease; Gluten-free diet

***Corresponding author:** Francisca Strecht Guimarães, Centro Hospitalar de Entre o Douro e Vouga, Travessa Francisco Sá Carneiro, 307 2º DTO; 4450 – 667 Matosinhos, Portugal; Phone number: +35-1912677005, E-mail: francisca.arsguimaraes@gmail.com

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Introduction

Celiac Disease (CD) is an autoimmune disease characterized by a specific serological and histological profile triggered by gluten ingestion in genetically predisposed individuals (positive for the human leukocyte antigen (HLA)-DQ2 and/or -DQ8) [1].

Gluten is a protein present in cereals such as wheat, rye, malt or barley, which together with water forms a type of gel, acting as a kind of glue, which ensures greater elasticity in foods such as bread, pasta and biscuits.

According to European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) CD is a common condition in pediatric population, reaches 1 in every 100 children in most European countries and, in some of these, it reaches 3 out of 100. However, the most remain undiagnosed.

In children, diagnose CD as soon as possible is essential to ensure a proper growth and development and minimize symptoms [2].

We can divide the clinical presentation of the disease into two types: intestinal vs. extra intestinal. The intestinal type is the most typical presentation of the pediatric age, specifically children under the age of 3 years and is characterized by diarrhea, loss of appetite, and abdominal distension. Extra intestinal clinical or laboratory signs include microcytic anemia due to iron deficiency, growth retardation and short stature, tooth enamel defects, aphthous stomatitis and hypertransaminasemia. Neurological symptoms could be present.

CD can be associated with different autoimmune diseases, such as autoimmune thyroiditis and diabetes. Selective IgA deficiency (SIgAD) is the most common primary immunodeficiency. [3-8] The close association between both diseases has been known for a long time, what is still not definitively known is how to make the diagnosis and monitor patients with both pathologies.

According to the 2012 ESPGHAN guidelines, the diagnostic criteria for CD are based on the following: symptomatic children and adolescents presenting antitissue transglutaminase (anti-tTG) serum levels over 10 times the upper limit of normal, confirmed by endomysium antibody (EMA) detection and HLA typing in subsequent blood samples, can be diagnosed as having CD without performing duodenal biopsy.

The gold standard for CD diagnosis is represented by the combination of mucosal changes, namely atrophy (detected by duodenal biopsy) and by positivity of serological tests. Actually, according to the 2020 ESPGHAN guidelines, the presence of symptoms and HLA typing are not mandatory diagnostic criteria. CD- related antibodies belong to IgA and IgG classes, but only the IgA class is specific and sensitive for diagnosis of CD. Regarding individuals with IgA deficiency, the use of anti-tTG, deamidated gliadin peptide antibodies (anti-DGP) or EMA IgG tests seems to be useful, as well as the important role of duodenal biopsy to confirm the diagnosis of CD in individuals with a positive IgG-based test [9-12].

The main question and difficulty are knowing how to monitor these patients, that is, how to monitor response to the gluten-free diet (GFD).

Then we present the clinical case of a child with typical symptoms of celiac disease, in which we easily arrived at the diagnosis, but who's monitoring has proved to be a challenge.

Case Report

A 2-year-old boy was referred to digestive pathology consultation due to a one-month history of abdominal pain, vomiting and diarrhea (without mucus or blood), and recurrent oral ulceration. Additionally, the mother, reports frequent respiratory infections. He was under iron supplementation for anemia normochromic normocytic without resolution with 6 months of therapeutic.

He was exclusively breastfed until five months of age, at which time weaning started. The introduction of gluten in the diet occurred at six months of age, without complications. Weight and height progression were adequate (between percentiles 5-15). Was denied other associated symptoms or signs, such as edema, and skin alterations. The child had no significant family history of DC.

Physical examination at admission showed discolored mucous membranes and oropharynx with multiple oral ulceration, without other particularities.

Findings from the initial laboratory workup were as follows: hemoglobin 11.1 g/dL (normocytic/normochromic); sedimentation rate (28 mm/1h) and C-reactive protein (2.4 mg/L); normal liver and renal functions, with no electrolyte imbalances. Serum albumin and protein were within the normal range. Serum Total IgA levels were undetectable (< 6 mg/dl), therefore the anti-transglutaminase IgA and anti-gliadin IgA antibodies were negative. Therefore, the test of the other antibodies revealed normal anti-transglutaminase IgG antibody levels (2.7 U/mL, for a normal of < 7) and high anti-gliadin IgG antibody levels (33 U/mL, for a normal of < 7). Additionally, bacteriological and parasitological stool exams were negative. A duodenal biopsy was performed, showing total villous atrophy and transepithelial lymphocytic infiltrate compatible with celiac disease (Marsh 3C).

Diagnosis of CD was determined at 3 years old, and a gluten-free diet was started, with significant symptomatology improvement.

Two years after the diagnosis, the child presented newness positive values of anti-transglutaminase IgG (295 U/mL). Subsequently, at four and eight years after the diagnosis, he presented values of 242 U/mL and > 600 U/mL (exceeding the measurement range), respectively. The levels of anti-gliadin IgG antibody became persistently negative after the initial diagnosis. However, the anti-endomysia IgG antibody became positive. The parents referred correct implementation of the gluten-free diet and the child was asymptomatic. The information given by the parents seemed to have a high degree of reliability and was evaluated in a nutrition consultation, which confirmed the clinical impression that there was good adherence.

Peptide measurement was not used to monitor adherence to the diet, as we do not have this analysis available in our hospital.

At 12 years of age, despite remaining asymptomatic, and with good growth in height and weight, due to the persistent high values of IgG tTG (> 600 U/mL), and for the study/evaluation of the case, it was decided together with the parents to performed a duodenal biopsy that revealed no alterations.

Discussion

The procedures for diagnosing and monitoring CD in patients with SIgAD still require careful review. The only established consensus seems to be the determination of anti-tTG IgA and total serum IgA as an initial screening for all patients with suspected CD.

The case presented above raises the question of what tools do we have for monitoring these patients, other than just using methods as invasive as biopsy.

Once the presence of SIgAD has been demonstrated, the choice of an IgG-based test necessary to continue the diagnostic investigation remains open. There is no strong evidence on which should be the most sensitive and useful IgG marker for both diagnosis and follow-up, given the great heterogeneity of IgG serology in this field.

Although initially it appeared that the persistence of specific IgG antibodies was more pronounced in patients who did not follow a strict gluten-free diet than in those on a strict gluten-free diet, several authors have demonstrated that anti-tTG, anti-DGP and EMA IgG often persist in the serum of affected patients, despite treatment with GFD, even for a long period of time. Several mechanisms have been proposed to explain this phenomenon; whether they are diet quality or genetic factors, (it has been associated with the HLA haplotype B8-DR3-DQ2). Furthermore, the persistence of specific IgG antibodies and the high frequency of concomitant autoimmune diseases observed in IgA-deficient CD patients may be linked to compensatory stimuli acting on B cells.

Even so, some studies have identified anti-tTG IgG as a more reliable marker for monitoring than anti-DGP IgG for CD in patients with SIgAD, which is the opposite of what we verified with this case.

However, we have to bear in mind the possibility of anti-tTG IgG levels remaining high even in a patient who adheres to a GFD, and as such, this antibody does not constitute a very reliable method of monitoring these patients (as regards whether or not they comply with the therapy).

From basic Immunology we know that different antibody classes exhibit different, class specific, behavior: IgM antibody presence is frequently linked with acute, ongoing or recent exposure to an antigen (be it from a pathogen, an allergen or even an autoantigen) and disappears shortly after the removal of said antigen; on the other hand, IgG antibody presence tends to linger in time long after the antigen stimuli has been removed, which is even a very useful feature of this antibody class as it allows clinicians to document past exposure to a given antigen. Perhaps that is what happened in the presented case: as we were forced to try to monitor disease activity with IgG class antibodies (due to the SIgAD), we ended up documenting the patient's Immune maturation by Immunoglobulin class switching to IgG (even after the removal of the triggering antigen). Albeit a curious finding, ultimately proved useless as a CD monitoring tool.

More studies will be necessary and useful to understand the time of disappearance of specific IgG antibodies, as well as to evaluate the long-term implications of their persistence in the bloodstream; thus, they will help to improve the monitoring of IgA-deficient CD patients undergoing GFD treatment.

Conclusion

Finally, a serum marker capable of identifying intestinal damage would be desirable as a useful additional tool to fully monitor CD without subjecting patients to multiple duodenal biopsies.

Statements

Statement of Ethics: Consent was obtained from the parents of the child in the clinical case to write the case.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Data Availability Statement: All data generated or analyzed during this study are included.

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