

# Selective Immunoglobulin A Deficiency and Celiac Disease: Let's Give Serology a Chance

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## ■ Abstract

Patients with selective immunoglobulin (Ig) A deficiency have a 10- to 20-fold increased risk of celiac disease. In these patients, serological diagnosis of celiac disease can be difficult, since specific IgA-based assays are usually negative and IgG-specific antibody tests are insufficiently reliable. We describe a girl with selective IgA deficiency who had a troublesome diagnosis of celiac disease that was established only after an unexpected positive test result for antitransglutaminase IgA and antiendomysium IgA. Our observation indicates that IgA-based serology should not be forgotten in patients with selective IgA deficiency, since positive results for antitransglutaminase IgA, antiendomysium IgA, or both can be observed at any time during diagnostic investigations.

**Key words:** Celiac disease. Immunoglobulin A deficiency. Diagnosis. Transglutaminase antibodies. Endomysial antibodies.

## ■ Resumen

Los pacientes con deficiencia selectiva de inmunoglobulina (Ig) A presentan un riesgo entre 10 y 20 veces mayor de enfermedad celíaca. En estos pacientes, el diagnóstico serológico de enfermedad celíaca puede resultar difícil, dado que los ensayos basados en IgA específica suelen ser negativos y las determinaciones de anticuerpos específicos IgG no son suficientemente fiables. Se describe a una paciente con deficiencia selectiva de IgA con diagnóstico problemático de enfermedad celíaca que solo pudo establecerse después de un resultado positivo imprevisto en la determinación de anticuerpos IgA anti-transglutaminasa e IgA anti-endomisio. Se ha observado que en pacientes con deficiencia selectiva de IgA no debe olvidarse la serología basada en IgA, dado que pueden observarse resultados positivos para anticuerpos IgA anti-transglutaminasa, IgA anti-endomisio o ambos en cualquier momento durante las pruebas diagnósticas.

**Palabras clave:** Enfermedad celíaca. Deficiencia de inmunoglobulina A. Diagnóstico. Anticuerpos anti-transglutaminasa. Anticuerpos anti-endomisio.

## Introduction

Selective immunoglobulin (Ig) A deficiency (SIgAD) is defined as very low levels of serum IgA (<0.05-0.07 g/L) in a patient older than 4 years of age with normal serum levels of IgG and IgM [1, 2]. It is the most common primitive immunodeficiency worldwide and its prevalence in Europe is 1:300 to 1:800 [2]. Patients with SIgAD have a 10- to 20-fold increased risk of celiac disease, and at least 2.6% of patients with celiac disease have SIgAD [1]. The association between the 2 diseases complicates serological testing for celiac disease. Indeed, conventional assays for the diagnosis and follow-up of celiac disease (antigliadin antibodies [AGA], tissue transglutaminase [tTG], and endomysium [EMA]) are IgA-based and are expected to be negative in IgA-deficient

patients. AGA and tTG of the IgG class can be positive in these patients, although they are much less reliable in predicting celiac disease and do not effectively prevent unnecessary biopsies from being taken.

We describe a girl with SIgAD who had a troublesome diagnosis of celiac disease that was established only after an unexpected positive test result for IgA tTG and EMA.

## Case Description

A girl was referred for the first time to our gastroenterology service at the age of 9 years with a history of recurrent abdominal pain and occasional diarrhea, selective IgA deficiency (serum IgA levels <0.05 g/L in at least 4

determinations in different laboratories, IgG 16.1 g/L, and IgM 1.31 g/L), negative IgA tTG and EMA, and a positive IgG tTG test result (14.2 U/mL, normal value <7 U/mL). Other than her presenting complaint, she was in an excellent physical health (weight, 44 kg [3-4 SD]; height 141 cm [2 SD], and body mass index 22 kg/m<sup>2</sup>). HLA genotyping showed a DQA1\*0104/0501, DQB1\*0503/0201 haplotype that contained the known HLA DQ2 haplotype (DQA1\*0501/DQB1\*0201), indicating that the patient was at risk of celiac disease. She had no family or personal history of autoimmune disease. During the previous year, her parents refused endoscopic procedures. Nevertheless, the patient had followed a gluten-free diet with evident improvement in gastrointestinal symptoms and disappearance of IgG tTG. Following the consultation, we agreed with the parents to reintroduce gluten in the diet and to perform a duodenal biopsy after at least 3 months. At her second visit, the patient had been on a full gluten-containing diet for 3 months, IgG tTG were again positive (2 to 3 times the upper limit of normal) and she reported frequent abdominal complaints. Duodenal biopsies, obtained by endoscopy, revealed histologically normal mucosa (Marsh 0). Nevertheless, the parents decided to avoid gluten-containing food and the patient remained on a gluten-free diet for about 3 years. At the age of 12, gluten was reintroduced and she remained in apparent good health for the following

12 months. At age 13, her body mass index was 25 kg/m<sup>2</sup>, she had no gastrointestinal disturbances but IgA tTG (14 U/mL, normal value <5 U/mL) and EMA tests became unexpectedly positive. Serum IgA levels were undetectable, IgG (12.9 g/L), IgM (1.2 g/L), hemoglobin (13.5 g/dL), serum iron (55 µg/dL), transferrin (2.62 g/L), and transaminases were all in the normal range. She underwent a second endoscopic procedure, and the biopsy revealed subtotal villous atrophy of the mucosa, with increased intraepithelial lymphocytes and IgA-secreting cells within the lamina propria (Marsh 3b) (Figure). The diagnosis of celiac disease was thus established and a gluten-free diet definitively prescribed.

## Discussion

The case of our girl is remarkable for 2 reasons. First, it summarizes the multiple difficulties encountered in diagnosing celiac disease in patients with IgA deficiency. IgA-based serology is not usually of diagnostic value in these patients, and IgG tTG and IgG AGA do not indicate which patients should be further investigated with intestinal biopsy. Antibodies to

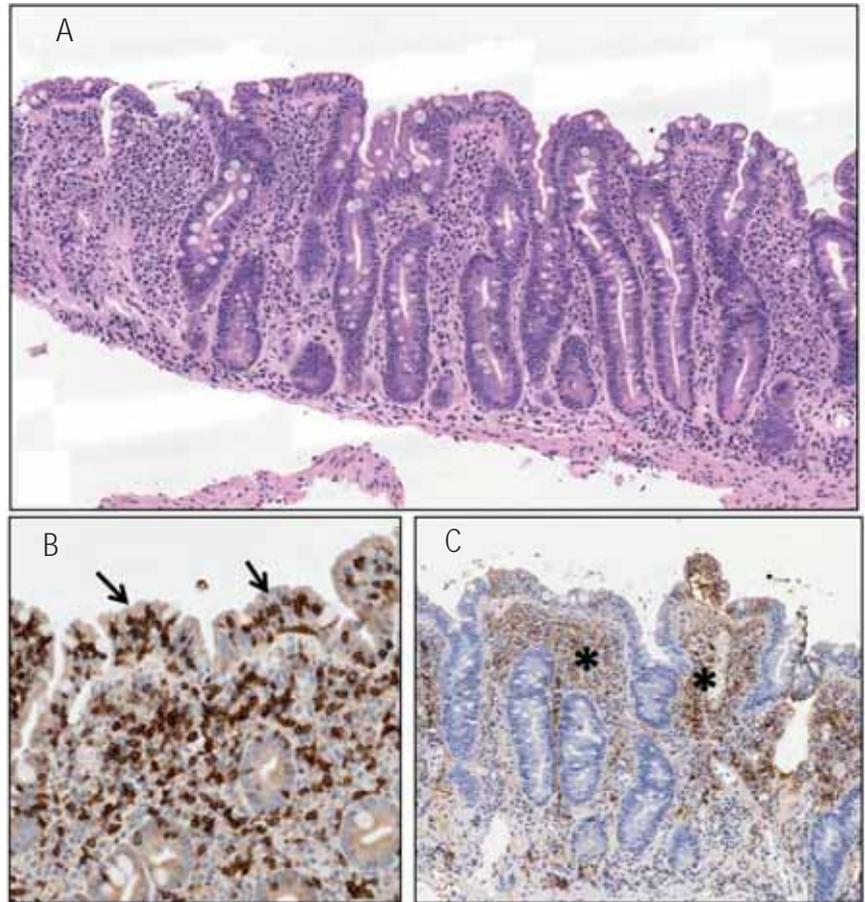


Figure. Histology and immunohistochemistry of the duodenal mucosa. A, Partial villous atrophy and crypt hyperplasia ( $\times 10$ ). B, CD3+ intraepithelial lymphocyte infiltration (arrows)( $\times 20$ ). C, Immunoglobulin A-secreting cells in the lamina propria (asterisks)( $\times 10$ ).

deamidated gliadin peptides (DGP-AGA) of the IgG and IgA class have only recently been introduced in clinical practice as a much more reliable test result to confirm a positive IgA tTG test or to assist in the follow-up of patients on a gluten-free diet. IgG DGP-AGA seem to offer better diagnostic accuracy than previous IgG-based tests and they are likely to play a greater role in the serological approach to diagnosis of celiac disease in IgA-deficient patients [3]. Unfortunately, at the time our patient presented, DGP-AGA were not yet available in our laboratory and, despite a positive IgG tTG test result, the first duodenal biopsy did not allow us to make a definitive diagnosis of celiac disease. The initial refusal to undergo duodenal biopsy and the arbitrary decision to exclude gluten from the diet delayed the diagnosis.

The second and probably more interesting aspect of our report was the unexpected appearance of high serum levels of IgA tTG and EMA despite persistently undetectable circulating levels of IgA. There is evidence that partial IgA deficiency (ie, serum IgA concentrations below 2 SD of normal values for age) may not interfere with the diagnostic reliability of IgA tTG and EMA test results [4,5]. Partial IgA deficiency can be viewed as a maturative delay of the IgA system, and the residual capacity

of antigen-specific IgA response in patients with celiac disease has been described [4,5]. On the other hand, there are very few reports of an antitransglutaminase IgA response in patients with SIgAD. Donaldson et al [6] recently described 2 cases of IgA deficiency (Marsh 0 and Marsh 3) and positive IgA tTG, EMA, or both. Korponay-Szabó et al [7] described an IgA-deficient patient with celiac disease (aged 3 years) with positive IgA tTG levels and 3 additional IgA-deficient celiac patients with negative IgA tTG at diagnosis who regained normal serum IgA levels while on a gluten-free diet. Regulation of the IgA system is heavily influenced by mucosal antigens, cytokines, and transforming growth factor  $\beta$ , one of the prominent regulators of the IgA class switch, which seems to be impaired in the celiac mucosa [8]. Gluten avoidance and healing of the mucosa might have a positive effect on the mechanisms of IgA synthesis in infancy. However, prolonged elimination of gluten-containing food did not modify total serum IgA levels in our patient. McGowan et al [9] reported 2 children (7 and 9 years old) with IgA deficiency, strongly positive IgA EMA test results (1:320, 1:1280), and histologically confirmed celiac disease (Marsh 3c). In both patients, serum IgA concentrations remained undetectable after 12 months of gluten-free diet.

SIgAD does not exclude a residual capacity to mount an IgA antibody response; it simply indicates the lower limit (0.05 g/L) under which serum IgA concentrations become undetectable by most laboratory assays. In our patient, tTG and EMA tests revealed a specific serum IgA response, even if total IgA levels were undetectable. In fact, more than 95% of IgA in the dimeric form is produced locally in the gastrointestinal system, and individuals diagnosed with SIgAD may still synthesize IgA in the mucosa [2]. Methods to detect IgA AGA, tTG, and EMA in salivary secretions have recently been proposed [10], although salivary IgA antibodies are not invariably associated with the intestinal secretory IgA response, and this can compromise the eventual reliability of the results [11]. In our patient, the antibody response to gliadin or transglutaminase was not measured in mucosal secretions, but the capacity of local IgA synthesis was evidenced by the presence of IgA-secreting cells in the lamina propria. Our observation indicates that IgA-based serology should not be abandoned in patients with selective IgA deficiency, since positive tTG and/or EMA results can eventually occur at any time during diagnostic investigations.

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