High Rate of Spontaneous Normalization of Celiac Serology in a Cohort of 446 Children With Type1 Diabetes: A Prospective Study

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OBJECTIVE
In children with type 1 diabetes mellitus (T1DM), elevated levels of anti-tissue transglutaminase (anti-tTG) antibody may spontaneously normalize, despite continued consumption of gluten. We aimed to investigate the prevalence of spontaneous normalization of anti-tTG levels and the existence of factors predictive for this outcome.

RESEARCH DESIGN AND METHODS
All children referred from 2002 to 2012 were screened for celiac disease (CD) at diabetes onset and at specific intervals. In the presence of a high anti-tTG titer or clinical symptoms, children were offered endoscopy, and asymptomatic patients with a low anti-tTG titer were invited to a second serological test after 6 months of eating a gluten-containing diet.

RESULTS
The study included 446 children. Of these, 65 (14.5%) became positive for celiac serology: 38 (58%) had a persistently elevated anti-tTG titer and 27 (41%) fluctuating anti-tTG titer; 18 (28%) became negative. The prevalence of positive CD autoimmunity and overt CD was 14.3% (95% CI 11–17) and 8.5% (95% CI 5–10), 15- and 8-times higher than the general pediatric population, respectively. Asymptomatic children older than 9.1 years at T1DM onset had the lowest risk to develop CD.

CONCLUSIONS
Serum anti-tTG levels decreased spontaneously in 40% of children with T1DM and became negative in 20%, despite gluten consumption. This finding supports the hypothesis of a state of temporary positivity of celiac serology in children with diabetes. In absence of clinical symptoms or signs of CD, histological confirmation of the disease and the gluten-free diet should be postponed to avoid unnecessary procedures and reduce an additional psychological burden.

The prevalence of celiac disease (CD) in patients with type 1 diabetes mellitus (T1DM) is between 3 and 10%, being more than 10 times the prevalence in the general population (1). Both diseases result from a complex interplay between genetic susceptibility and environmental exposure, being associated with the major histocompatibility complex class II antigen DQ2, and share non-HLA loci (2).

Guidelines of pediatric diabetes (3) and gastroenterology societies (4) recommend screening children with T1DM for CD. From a medical perspective, numerous advantages may exist in screening asymptomatic patients with T1DM, including the...
potential of improving diabetes control and avoidance of long-term manifestations of CD (5). However, the observation that elevated levels of anti-tissue transglutaminase (anti-tTG) antibody may spontaneously normalize in children with diabetes, despite continued consumption of gluten (6) and the absence of symptoms in most of these patients (5), would suggest caution before starting a gluten-free diet (GFD) in a particularly delicate group of children already struggling with a complex chronic disease in whom the addition of a second limiting dietetic condition might be remarkably difficult in front of limited benefit (7).

Indeed, whether treating silent CD improves diabetes-related outcomes is still an open issue; to date, results suggest uncertain benefit (8), with no benefit on the control of diabetes (9) and just a slight decrease in HbA1c (10). Therefore, the benefit of early detection and treatment remains unproved and subject of continuing investigation.

The aim of the current study was to describe a large cohort of children with T1DM consecutively enrolled in a tertiary referral center for the diagnosis and follow-up of pediatric T1DM to investigate the prevalence of spontaneous normalization of tTG antibody levels and the existence of factors predictive for this outcome.

**RESEARCH DESIGN AND METHODS**

Giovanni XXII Children’s Hospital is one of the largest pediatric hospitals in Southern Italy and is the tertiary referral center for pediatric T1DM, covering an estimated population of 700,000 children with more than 800 children followed up in the diabetes clinic. San Paolo Hospital serves Giovanni XXII Hospital for pediatric gastroenterology and endoscopy. In 2002, we adopted a diagnostic protocol according to which all children with T1DM were screened for CD at onset and then annually. In presence of a high CD antibody titer or clinical symptoms (diarrhea, abdominal pain or distension, short stature, iron-deficiency anemia, constipation, vomiting, reduced BMI, diminished mass bone, delayed puberty, raised levels of transaminases), children were offered endoscopy for the histological diagnosis. Asymptomatic patients showing low CD antibody titer were invited to a second serological determination after 6 months of eating a gluten-containing diet.

**Patients**

All children referred to our unit from 2002 onward were screened for CD according to a predetermined diagnostic protocol at T1DM onset and during follow-up at 6–12-month intervals. The following data were recorded in a database: sex, mode of delivery, date of birth, duration of breastfeeding, infections or acute gastroenteritis in the first year of life (requiring admission), chronic disease, and age at onset of T1DM. Patients with major acute or chronic illnesses other than T1DM or CD were excluded from the study and handled case-by-case. The last patient enrolled in the current study was in 2012 to have a minimal follow-up of 2 years.

Weight and height data were measured at diagnosis and annually thereafter. Height was measured with a wall-mounted stadiometer (Harpenden–Holtain) and weight with a calibrated scales. Age- and sex-specific centiles were calculated according to the World Health Organization growth reference.

All children underwent the following serological determinations at the onset of T1DM and then at established intervals: a) serum levels of anti-tTG–IgA antibody, anti-endomysial antibody (EmA), and total serum IgA (for children <2 years of age serum levels of antigliadin [AGA]-IgA antibody were included); b) HLA class II antigens (in children with positive celiac serology); c) hemoglobin A1c (HbA1c) concentration; d) nutritional parameters (cholesterol, triglycerides, iron, ferritin, hemoglobin); and e) thyroid function tests (free T3, free T4, thyroid-stimulating hormone, anti-thyroid peroxidase antibodies).

Serum AGA and anti-tTG (–IgG and –IgA class) were assessed by an indirect solid-phase ELISA test (ORGENTEC Diagnostic, Mainz, Germany). The cutoff value was set for values >10 arbitrary units for both, according to the manufacturer’s instructions (11). Serological autoantibody titers were recorded as times the upper normal limit (UNL). EmA-IgA was determined by indirect immunofluorescence using monkey esophagus sections as the substrate (Euroimmun Italia Diagnostica Medica SRL, Padua, Italy). Dilutions greater than 1:10 were considered positive and then titrated. In presence of IgA deficiency, the diagnosis of CD was based on IgG class serology. All celiac serology testing was repeated twice.

Class II antigens HLA typing (HLA-DRB1* [01, 15, 16, 03, 04, 11, 12, 13, 14, 07, 08, 09, 10], HLA-DRB3*, HLA-DRB4*, HLA-DRB5*, and HLA-DQB1*[01, 02, 03]) was done by PCR sequence-specific oligonucleotide, a low-resolution molecular method, using a commercial kit (12).

Capillary HbA1c was measured by an automated immunochemical technique (DCA 2000; Bayer Diagnostics, Tarrytown, NY; normal values: 4.3–5.8%).

**Endoscopy and Histology**

Upper gastrointestinal tract endoscopy was performed by the same physician (S.C.) during the time the child was eating a gluten-containing diet. Four biopsy specimens were obtained (two from the distal and one from the proximal duodenum and bulb). A pathologist, unaware of the clinical and laboratory results, interpreted the sample according to the criteria defined by the Marsh classification (13). CD diagnosis was based on the coexistence of 1) positivity of tTG-IgA and EmA, 2) presence of positive histological evidence of villous atrophy with crypt hyperplasia and increase in intraepithelial lymphocytes, and 3) normalization of positive serum-specific antibodies on GFD.

**Group Comparison**

To compare the clinical and laboratory data of children with T1DM with and without CD, 60 children with T1DM without CD were frequency-matched for sex, age (± 1 year), and T1DM duration (± 1 year). The data presented refer to the time of first appearance of CD serology.

The institutional review board approved the study protocol. Informed consent was obtained from the parents. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

**Statistics**

 Normally distributed grouped data are expressed as the mean ± SD and were compared using paired and unpaired t tests. Nonparametric grouped data are expressed as median (95% CI) and were compared with the Mann-Whitney rank sum test (paired) or the Wilcoxon signed rank test (unpaired). Proportionate data were compared with the Fisher exact test or the χ2 test. Differences between groups were analyzed by the two-tailed Student t test for independent samples. One-way ANOVA was used to compare
means of more than two samples. \( P \) values <0.05 were regarded as significant.

Risk models were developed using a decision tree. Briefly, a decision tree is a flowchart-like structure in which the internal node represents a test on an attribute, each branch represents the outcome of the test, and each leaf node represents a class label (decision taken after computing all attributes). To investigate the presence of attributes with predictive power, the algorithm builds a tree in a stepwise fashion analyzing potential predictors and possible cut points (if continuous). Two models were developed: one to predict the onset of CD in children with T1DM and the second to predict those children with positive celiac serology who became seronegative. The data set included 444 patients with 38 overt CD cases. The following attributes were studied: 1) presence or absence of CD (class label attribute); 2) age at diagnosis of T1DM; 3) sex; 4) breast-feeding duration (0–12 months; 5) infection in the first year of life (yes or no); 6) acute gastroenteritis in the first year of life (yes or no); 7) anti-tTG level (expressed as multiple of the UNL); and 8) EmA (positive or negative). Precision rate, sensitivity, specificity, and positive and negative predictive values of the decision tree were calculated.

The relationship of several risk factors to outcome (serological evidence of CD, diagnosis of CD, transient CD) was evaluated using logistic regression. The statistical analysis was performed using SPSS 13.0 software (SPSS Inc, Chicago, IL).

RESULTS
A total of 446 children (200 girls [44.8%]) were diagnosed during the study period; of these, 272 (61%) were born by vaginal delivery, 380 (85%) received breast milk for at least 4 months, and 76 (17%) had an infection in the first year of life (21 acute gastroenteritis). The median age at T1DM onset was 8.5 ± 4.1 years (95% CI 4.2–12.5). Two children had a diagnosis of CD before T1DM onset, and none had positive serological evidence for CD (anti-tTG-A and/or EmA) at T1DM onset. During follow-up, 65 children (14.5%) became serologically positive for CD (anti-tTG-IgA and/or EmA). Of these, 38 (58.4%) had persistently elevated anti-tTG antibody and EmA levels, whereas 27 (41.5%) showed a fluctuating titer of anti-tTG antibody levels (9 EmA positive) and therefore entered a serological follow-up while eating a gluten-containing diet. Overall, 47 children were EmA and anti-tTG-IgA positive, whereas 18 children were anti-tTG-IgA positive and EmA negative; we never found EmA positivity in anti-tTG-IgA negative cases. A progressive decline of celiac serology titer was achieved in 9 of 27 (13.8%) and complete negativity (anti-tTG-A and EmA) in 18 (27.6%); during follow-up, 3 became subsequently positive. The evolution of the cohort is reported in Fig. 1.

Our cohort is therefore composed of three groups of children with diabetes: a) 381 without CD (T1DM-only); b) 38 with CD (T1DM-CD); and c) 27 with
fluctuating (spontaneous decline or negativity) CD serology (T1DM-FCS). The main clinical characteristics of the three groups are reported in Table 1.

Prevalence of CD in Children With T1DM

Overall, the prevalence of positive CD autoimmunity and overt CD in children with T1DM is 14.3% (95% CI 10.8–17.5) and 8.5% (95% CI 5.2–10.3), respectively. Considering that the reported highest prevalence of CD in a large sample of the Italian pediatric population is 1.0% (35 of 3,188) (14), children with T1DM have an 8-times higher risk of overt CD (odds ratio 8.39; CI 95% 5.2–13.4; P < 0.0001) and a 15-times higher risk of positive celiac serology (odds ratio 15.36; CI 95% 10–23.5; P < 0.0001) compared with the general pediatric population. Female sex (P < 0.03) and younger age at onset of T1DM (P < 0.0001; Fig. 2) were associated with a higher risk for developing overt and CD autoimmunity, respectively. No role was found for mode of delivery, infection or acute gastroenteritis in the first year of life, or duration of breast-feeding (Table 1).

Prevalence of CD in Children With T1DM

Overall, the prevalence of positive CD autoimmunity and overt CD in children with T1DM is 14.3%.

Histology

Among the 45 children who underwent endoscopy, only 7 children were among those with spontaneous decline/normalization of CD serology. We found an atrophic lesion in all of the 38 children classified as T1DM-CD, whereas among the 7 T1DM-FCS children, 2 had entirely normal mucosa and 5 had an infiltrative lesion.

Decision Tree Analysis

Two decision trees were built to predict the best characteristics to identify children with diabetes who will show positive celiac serology/disease and became negative after a positive celiac serology test.

The result of the first decision tree analysis for prediction of CD is shown in Fig. 3A. The lowest risk to develop CD was assigned to asymptomatic children with T1DM onset at more than 9.1 years. This tree correctly classified 421 of 445 children (72.1%), with a sensitivity of 0.35, specificity of 0.87, positive predictive value of 0.7, and negative predictive value of 0.28. A logistic regression analysis confirmed a statistically significant positive association between CD and a) being asymptomatic (67% vs. 12%; P < 0.0001) and b) lower age at T1DM onset (6.3 ± 3.6 vs. 8.9 ± 4.1 years; P < 0.0001) and duration of breast milk of less than 4 months (8.1% vs. 18.4%; P < 0.02). A trend for an increased risk was found in girls (55% vs. 45%; P < 0.06).

The result of the second decision tree analysis for prediction of CD serology becoming negative is shown in Fig. 3B. The highest chance was assigned to children with EmA negativity, tTG values lower than 7.8-fold the UNL, and asymptomatic. This tree correctly classified 56 of 64 children (87.5%), with sensitivity of 0.50, specificity of 1.0, positive predictive value of 1.0, and negative predictive value of 0.24. A logistic regression analysis confirmed that the likelihood of becoming serologically negative was associated with: a) EmA negativity (100% vs. 12%; P < 0.0001), b) lower levels of tTG (2.3 ± 2.1 vs. 7.4 ± 2.9 UNL; P < 0.0001), c) being asymptomatic (100% vs. 49%; P < 0.0001), and d) older age at first CD serological positivity (10.1 ± 4.5 vs. 7.4 ± 4.6 years; P < 0.009).

Profile of Children With T1DM-FCS

Older age at onset of CD autoimmunity (10.1 ± 4.5 [95% CI 8.3–11.9] vs. 7.4 ± 3.6 [95% CI 6.2–8.6] years; P < 0.02) and lower titer of anti-tTG–IgA (3.1 ± 3.3 [95% CI 1.8–4.4] vs. 7.9 ± 5.1 [95% CI 5.9–10.1] UNL; P < 0.02) were associated

Table 1—The main clinical characteristics of the three groups of children: those with T1DM only, those with T1DM-CD, and those with T1DM-FCS

<table>
<thead>
<tr>
<th></th>
<th>T1DM only</th>
<th>T1DM-CD</th>
<th>T1DM-FCS</th>
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<tbody>
<tr>
<td></td>
<td>n = 381</td>
<td>n = 38</td>
<td>n = 27</td>
</tr>
<tr>
<td>Female sex</td>
<td>164 (42)*</td>
<td>23 (60)*</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>137 (38)</td>
<td>15 (39)</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Breast milk (≥4 months)</td>
<td>206 (58)</td>
<td>29 (78)</td>
<td>16 (72)</td>
</tr>
<tr>
<td>Infections in the first year</td>
<td>60 (17)</td>
<td>5 (13)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Acute gastroenteritis in the first year</td>
<td>17 (4.4)</td>
<td>2 (5.2)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Age of T1DM onset (years)</td>
<td>9.8 ± 4</td>
<td>7.4 ± 3.6</td>
<td>10.1 ± 4.5</td>
</tr>
<tr>
<td>Age of CD onset (years)</td>
<td>—</td>
<td>7.5 ± 3.1</td>
<td>6.8 ± 3.7</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>7.5 ± 4</td>
<td>7.8 ± 2.7</td>
<td>6.8 ± 3.7</td>
</tr>
</tbody>
</table>

Data are shown as number (%) or as mean ± SD. NS, not significant. *P < 0.05.

Figure 2—Age at onset of T1DM in the three groups of children with T1DM, T1DM/CD, and T1DM-FCS. Horizontal line, median top and bottom borders of box = interquartile range; NS, not significant; whiskers = 95% CI.
with the higher chance of a fluctuating CD phenotype. The 27 children in the T1DM-FCS group were monitored periodically for anti-tTG antibody levels for a mean of 3.7 ± 2.3 years (95% CI 3.1–4.5). Endoscopy was performed in 7 of 27 children (26%), and histologic analysis showed the absence of atrophic lesions (Table 2). The median time to normalization of anti-tTG antibody was 1.3 ± 1.1 years (95% CI 0.8–1.8).

**Follow-up of Children With T1DM-CD**

The 38 children in T1DM-CD group underwent endoscopy and histology, which showed an atrophic lesion (Marsh 3) in all. The adherence to the GFD was followed by a progressive resolution of symptoms and normalization of anti-tTG antibodies.

**Comparison of Children in the Three Groups**

At the time of the first appearance of positive CD serology, we found that children with T1DM-CD had lower levels of blood triglycerides than those with T1DM-only and T1DM-FCS (109 ± 149 mg/dL vs. 59 ± 35 mg/dL vs. 88 ± 39 mg/dL; P < 0.01). No differences were found for nutritional, hormonal, and other biochemical parameters.

**CONCLUSIONS**

This prospective study, to the best of our knowledge, is the first to describe the occurrence of fluctuating celiac serology in a large population of children and adolescents with T1DM, evaluated from the onset of the disease. Our study demonstrates that serum anti-tTG antibody levels decrease spontaneously in 40% and become persistently negative in at least 20% while eating a gluten-containing diet. Moreover, we confirm that the prevalence of overt CD and positive CD autoimmunity are significantly higher than in the general pediatric population (15,16). This finding suggests that in children with T1DM there may be a state of temporary positivity of celiac serology. Consequently, in the absence of clinical symptoms or signs of CD, the histological confirmation of the disease and the GFD should be postponed to avoid unnecessary procedures and reduce the psychological burden that a GFD would add, further affecting quality of life (17).

Although CD is considered a life-long disorder, transient or fluctuating anti-tTG–IgA seropositivity has been observed in children with T1DM eating a gluten-containing diet. Barera et al. (18) reported that 30% of EmA-positive children with diabetes became negative during follow-up and concluded that these patients have either a transient false-positive test, as described for anti-reticulin antibodies (19) and EmA (20) or a form of CD that has not yet manifested in significant mucosal injury. In our study, the false positivity of CD serology was unlikely, mainly because we used anti-tTG antibodies, an automatized and not operator-dependent ELISA test. Furthermore, although the Barera et al. (18) study described a single EmA positivity, our study shows a...
persistent (at least twice) positivity of celiac autoimmunity and HLA typing consistent with CD predisposition. A more recent retrospective study of 738 children with T1DM reported anti-tTG antibody levels normalized in 35% of children consuming a gluten-containing diet (6).

The clinical significance of transient or fluctuating tTG-IgA autoantibodies while eating a gluten-containing diet remains obscure; however, it is remarkable that in our cohort of 27 children with fluctuating anti-tTG levels, the spontaneous loss of serum CD autoimmunity (anti-tTG antibodies and EmA) was the most frequent outcome, occurring in 67% of cases, although overt CD developed in three children during follow-up. Serology is becoming increasingly relevant for the identification of CD among children with T1DM younger than 9 years were the strongest predictors of positive CD serology, whereas being EmA positive and having an IgA-tTG antibody level greater than the seven- to eightfold ULN value were the strongest predictors of an overt CD diagnosis. We first demonstrated the existence of a path in the decision tree that brings together the data presented in previous articles: the presence of symptoms in family-risk infants (23) and the age at onset of T1DM (24,25) as a strong predictor of overt CD.

Presence of CD symptoms and age at onset of T1DM younger than 9 years were the strongest predictors of positive CD serology, whereas being EmA positive and having an IgA-tTG antibody level greater than the seven- to eightfold ULN value were the strongest predictors of an overt CD diagnosis. We first demonstrated the existence of a path in the decision tree that brings together the data presented in previous articles: the presence of symptoms in family-risk infants (23) and the age at onset of T1DM (24,25) as a strong predictor of overt CD.

Our long-term data show that children with diabetes with a spontaneous decline or normalization of CD serology have no hidden signs of malabsorption and have normal values of nutritional, biochemical, and growth parameters, whereas children with overt CD have some abnormality of triglyceride that reverses after a GFD. The benefits of the adherence to a GFD in patients with T1DM regarding growth parameters, Hba1c levels, and hypoglycemic episodes are still debated (26–28). The discordant findings among studies, the small numbers of patients, and the lack of distinction between symptomatic and asymptomatic patients make it difficult to comment on the real effect of adherence to a GFD in patients with T1DM. Recent studies suggest that no significant adverse outcomes take place in anti-tTG–positive children with T1DM who delay starting a GFD for 2 years (29) and that positive antibodies are insufficient to cause a noticeable effect on important outcomes (microvascular complications, neuropathy) for which coexisting enteropathy is required (30).

The main limitation of our study is that only seven children among those with spontaneous decline or normalization of CD serology (26%) underwent endoscopy and histology: the mucosa was entirely normal in two, and an infiltrative lesion was present in seven; therefore, the absence of an atrophic lesion in this subgroup of patients is still questionable.

In conclusion, we have shown that children with T1DM symptomatic for CD and with a high anti-tTG titer are at high risk of having overt CD and need a GFD (26,27), and we propose that the absence of CD symptoms, the negativity of EmA, and a low anti-tTG level should induce serologic testing to be repeated on a gluten-containing diet rather than to go for an immediate intestinal biopsy considering that benefit of early GFD is limited (7,8,31). Nevertheless, we suggest adoption of the recommendation of the International Society for Pediatric and Adolescent Diabetes that all children diagnosed with T1DM be screened for CD at the time of diagnosis, and every 1–2 years thereafter (32).

Finally, considering that patients with T1DM can show minimal lesions of intestinal mucosa as an expression of their autoimmune condition without the coexistence of CD (5), being very cautious before prescribing a GFD is mandatory. In practice, a diagnosis of intraepithelial lymphocytosis with normal villous architecture should be accompanied by a

### Table 2—Serological, genetic, and histological data of children with T1DM-CD or with T1DM-FCS

<table>
<thead>
<tr>
<th></th>
<th>T1DM-CD</th>
<th>T1DM-FCS</th>
<th>P</th>
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<tbody>
<tr>
<td>Anti-tTG–IgA* (UNL)</td>
<td>7.9 ± 5.1 (5.9–10.1)</td>
<td>3.1 ± 3.3 (1.8–4.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>EmA positivity</td>
<td>38 (100)</td>
<td>22 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>170 ± 34 (157–183)</td>
<td>151 ± 26 (137–166)</td>
<td>0.06</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>71 ± 56 (49–92)</td>
<td>50 ± 14 (42–59)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspartate aminotransferase (units/L)</td>
<td>22 ± 5 (20–24)</td>
<td>24 ± 5 (21–27)</td>
<td>NS</td>
</tr>
<tr>
<td>Iron (μg/dL)</td>
<td>76 ± 25 (66–87)</td>
<td>88 ± 24 (74–102)</td>
<td>NS</td>
</tr>
<tr>
<td>Free T3 (pg/dL)</td>
<td>3.8 ± 0.6 (3.6–3.9)</td>
<td>4 ± 1.2 (3.3–4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Free T4 (pg/dL)</td>
<td>1.6 ± 2.1 (1–2.3)</td>
<td>1.7 ± 0.7 (1.2–2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (mIU/L)</td>
<td>4 ± 6.2 (2.1–5.9)</td>
<td>2.6 ± 1.7 (1.6–3.6)</td>
<td>NS</td>
</tr>
<tr>
<td>HLA DQ2</td>
<td>32 (84)</td>
<td>23 (85)</td>
<td>NS</td>
</tr>
<tr>
<td>HLA DQ8</td>
<td>6 (16)</td>
<td>4 (15)</td>
<td>NS</td>
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<tr>
<td>Marsh lesion</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>—</td>
<td>2 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>4 (57)</td>
<td>NS</td>
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<tr>
<td>2</td>
<td>—</td>
<td>1 (14)</td>
<td>NS</td>
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<tr>
<td>3a</td>
<td>3 (8)</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>3b</td>
<td>9 (24)</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>3c</td>
<td>26 (68)</td>
<td>—</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are reported as median ± SD (95% CI) or as number (%). NS, not significant. *Anti-tTG–IgA antibody titer reported as times the UNL.
comment emphasizing the nonspecific nature of this finding (33), and patients should be left on a gluten-containing diet with a clear indication to attend a careful serological and histological follow-up.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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