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The Temporal Relationship Between the Onset of Type 1 Diabetes and Celiac Disease: A Study Based on Immunoglobulin A Antitransglutaminase Screening

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ABSTRACT. *Objective.* The association of celiac disease (CD) and type 1 diabetes is now clearly documented. Immunoglobulin A (IgA) antitransglutaminase antibodies were measured to determine the prevalence of celiac disease in a diabetic population of children and to determine the temporal relationship between type 1 diabetes onset and CD.

Methods. We measured IgA antitransglutaminase antibodies using human recombinant antigen in parallel with classical markers (IgA and IgG anti gliadin, IgA antiendomyosium) in 284 children with diabetes.

Results. In the population studied, the prevalence of CD was 3.9% (11 of 284). Two cases of CD were diagnosed before the onset of diabetes, and in 8 patients, the diagnoses of CD and diabetes were concomitant, suggesting that CD was present before the onset of diabetes. In 1 case, a girl who presented with thyroiditis, serology for CD became positive after diabetes had been diagnosed.

Conclusion. An excellent correlation was observed between IgA antiendomyosium and IgA antitransglutaminase antibodies. We therefore propose using IgA antitransglutaminase as a screening test for practical reasons. Furthermore, IgA antitransglutaminase levels and mucosa abnormalities were closely correlated. The presence of antitransglutaminase antibodies should alert pediatricians to the atypical forms of CD. This study indicates that CD is most often present before the onset of diabetes. *Pediatrics* 2004;113:e418–e422. URL: <http://www.pediatrics.org/cgi/content/full/113/5/e418>; *celiac disease, type 1 diabetes, children, screening test, antitransglutaminase autoantibodies, prevalence, autoimmune diseases.*

ABBREVIATIONS. CD, celiac disease; tTG, transglutaminase; Ig, immunoglobulin; AGA, anti gliadin antibodies; EMA, endomyosium antibodies; AU, arbitrary units; GFD, gluten-free diet.

Many studies have reported an increased prevalence of celiac disease (CD) in children with type 1 (insulin-dependent) diabetes.^{1,2} These 2 diseases both are considered autoimmune in origin and could become manifest as a result of an interaction between genetic and environmental factors. The likely explanation for the frequent simultaneous occurrence of these 2 disorders is a similar genetic background; one third of HLA DQ2 homozygous patients with type 1 diabetes express CD-associated transglutaminase (tTG) autoantibodies.³ The prevalence of this association is usually ~5% (with a range of 2.3%–7%).^{4,5} Type 1 diabetes is claimed to occur before CD in nearly all patients.⁶

Most patients who have diabetes and CD have nonclassic forms of the disease, with various symptoms such as short stature, sideropenic anemia, or hypertransaminasemia; in many cases, patients are totally symptom-free.⁷ In patients with CD, the risk of developing autoimmune diseases, malignancy, osteoporosis, infertility, and intestinal lymphomas is proportional to the time of exposure to gluten.^{8,9} Growth deficiency is also an acute issue for pediatricians. Therefore, early diagnosis is essential for the prevention of serious complications, and a diagnostic strategy must be clearly established. CD diagnostic parameters have changed substantially in the past few years. Immunoglobulin (Ig) A anti-tTG antibodies, the most recent CD markers, are extremely sensitive and reasonably specific when determination is performed using recombinant human tTG. Our aims were 1) to study the prevalence of CD by using anti-tTG antibodies as a screening method in a population of children with diabetes, 2) to determine the temporal relationship between CD and type 1 diabetes, 3) to propose an efficient and economical strategy for diagnosing CD using anti-tTG in the type 1 diabetes population.

METHODS

A total of 284 children (127 girls) with type 1 diabetes, whose age at onset of diabetes ranged from 0.3 to 16.8 years (average age: 7.5 years), were tested for CD-related markers from November 1999 to February 2002. All were diagnosed according to World Health Organization criteria. CD was diagnosed by intestinal biopsy, which showed mucosal flattening according to European Society for Pediatric Gastroenterology and Nutrition criteria. All patients were from the Rhône-Alpes region of central France.

IgA-anti gliadin antibodies (IgA-AGA), IgG-AGA, IgA antiendomyosium antibodies (anti-EMA) and IgA anti-tTG antibodies

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were determined. Intestinal biopsies were performed in children who tested positive for 2 of the 3 classes of antibodies or when symptoms were suggestive of CD. When patients were found to be positive for anti-tTG during the course of their diabetes, we tested for anti-tTG in banked serum drawn at the onset of their diabetes. This enabled us to determine whether these autoantibodies had previously been present. Informed consent was obtained from the parents before the study.

AGA (IgA and IgG) were determined using a fluorescence enzyme immunoassay (α -Gliatest IgA; α -Gliatest IgG; Eurospital-Trieste, Italy). Results are expressed in arbitrary units (AU). Antigliadin IgA values >7 AU and antigliadin IgG values >15 AU were considered positive.

Antibodies (IgA) to tissue tTG were assessed using an indirect noncompetitive enzyme immunoassay with human recombinant tTG antigen as substrate (Celikey-Pharmacia Diagnostics, Freiburg, Germany). Results >7 U/ml were considered positive.

IgA antiendomysium was screened by an indirect immunofluorescence technique on cryostat monkey esophagus sections (Bio-rad, Marnes La Coquette, France). A titer equal to 1:5 was interpreted as a positive result. Every positive serum was titrated up to 1:200. In patients with isolated positive IgG antigliadin, we measured serum levels of IgA (immunonephelometry; Immage; Beckman-Coulter, Fullerton, CA) to exclude a selective serum IgA deficiency.

Sensitivity, specificity, and positive and negative predictive values of the different antibodies were studied. Diabetic patients without detectable tTG antibodies but with digestive symptoms and normal jejunal biopsies were considered as a control group.

Patients were divided to EMA and TG values (Fig 1). Patients with positive EMA and tTG were assigned to group 1, and patients with negative EMA and tTG were assigned to group 2. It should be noted that no discordance was observed in patients' designation given the unambiguous EMA and tTG data.

RESULTS

Of the 284 children with diabetes, 11 (3.9%) tested positive for both EMA and anti-tTG (group I), 7 of whom were girls. One patient (patient 1 in Table 1) had CD for 9 years before diabetes onset. Her CD serology therefore was negative as a result of a strict gluten-free diet. The 272 remaining children tested negative for both EMA and anti-tTG (group 2).

In group 1, 45% (1-1) of the patients were AGA negative (both IgA and IgG). In group 2, 94% (group 2-1) of the patients were also AGA negative (both IgA and IgG).

A total of 18 jejunal biopsies were performed (Fig 1), with 11 patients showing atrophic mucosa on histologic analysis of intestinal biopsy specimens. Therefore, the minimum prevalence of CD among children with type 1 diabetes was 3.9%. One jejunal biopsy was normal in a girl with only slightly positive EMA and anti-tTG. The biopsies ($n = 7$) in group 2 were all normal.

In group 1, 2 patients had a diagnosis of CD before becoming diabetic. A majority of patients (8 of 12) were positive for anti-tTG at diabetes onset. One patient, completely symptom-free, had a negative serology at diabetes onset. The serology became positive later. The specificity, sensitivity, positive predictive value, and negative predictive value of the different tests are shown in Table 2. Mean HbA1c levels were elevated in 6 of 11 (HbA1c $>8.5\%$; normal: 4.5–6.0). Only 1 patient had recurrent hypoglycemia. None were IgA deficient.

DISCUSSION

The present study confirms the association between CD and type 1 diabetes in children. The prevalence of CD observed in our children with type 1 diabetes (3.9%) is higher than that reported in medical literature for the general population (0.7% and 0.3% in European and US populations, respectively)^{10–12} but similar to that reported for children with diabetes.¹³

CD is heterogeneous in both clinical presentation and pathologic expression. Atypical isolated signs or CD symptoms are the most common forms in pa-

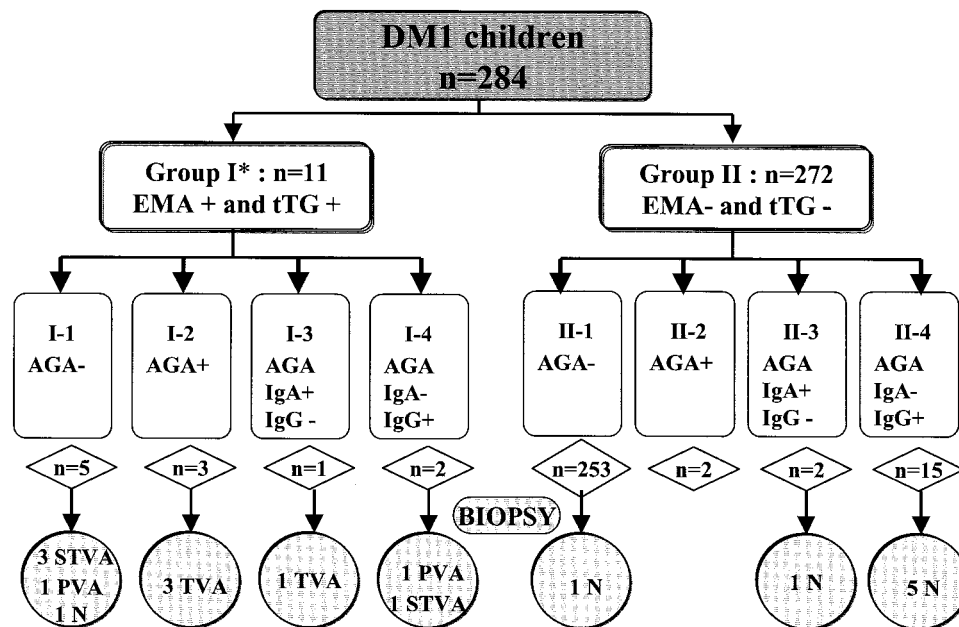


Fig 1. Serology and biopsy results for children with type 1 diabetes. Results of the screening tests with EMA, tTG, and AGA in 284 children with diabetes and results of intestinal biopsies. DO, diabetes onset; N, normal biopsy; PVA, partial villous atrophy; STVA, subtotal villous atrophy; TVA, total villous atrophy. Group I*: One CD patient was excluded from this group because she had CD and GFD before DO and her celiac serology was negative.

TABLE 1. Diabetic Patients With Positive Anti-tTG Antibodies

| Patient | Gender | Age at Diabetes Onset (Years) | Signs or Symptoms Suggestive of CD at Diabetes Onset | Serology at Diabetes Onset | | | | Histology | |
|--|--------|-------------------------------|---|----------------------------|----------|---------|---------------------|-------------|--------|
| | | | | Antigliadin | | EMA IgA | Anti-tTG IgA (U/mL) | Age (Years) | Result |
| | | | | IgA (AU) | IgG (AU) | | | | |
| CD diagnosed before diabetes | | | | | | | | | |
| 1 | F | 10.9 | Typical form, GFD for 9 y | Serology negative (GFD) | | | | 1.3 | TVA |
| 2 | F | 1.4 | Typical form, GFD for 3 mo | 16.5 | 77 | 100 | >100 | 1.1 | TVA |
| Positive serology at diabetes onset | | | | | | | | | |
| 3 | M | 15 | Typical form undiagnosed: poor growth, abdominal pains, delayed puberty | 8.5 | 16.8 | >200 | >100 | 15 | TVA |
| 4 | F | 8.4 | Typical form undiagnosed: poor growth, anorexia, abdominal pains, zinc and iron deficiency, uncontrolled diabetes | 12 | Neg | 200 | >100 | 8.4 | TVA |
| 5 | F | 7 | Poor growth, zinc deficiency | 7 | 27.2 | >200 | >100 | 10.3 | TVA |
| 6 | F | 8 | Poor growth, abdominal pains, abdominal distension, recurrent hypoglycemia, thyroiditis | Neg | Neg | 200 | >100 | 13 | STVA |
| 7 | M | 11.3 | Abdominal pains, uncontrolled diabetes, migraine | Neg | Neg | 100 | 70 | 12.4 | STVA |
| 8 | M | 2.8 | Poor growth, abdominal pains, constipation, iron deficiency | Neg | 40 | >200 | 97 | 8 | PVA |
| 9 | M | 4 | Abdominal pains | Neg | Neg | >200 | >100 | 5.8 | STVA |
| 10 | F | 9 | Poor growth, uncontrolled diabetes, depression | Neg | Neg | 100 | 41 | 14.8 | STVA |
| Serology turned positive during the course of diabetes | | | | | | | | | |
| 11 | F | 7 | Symptom-free, uncontrolled diabetes, thyroiditis | Neg | Neg | Neg | Neg | 15 | PVA |
| 12 | F | 7 | Poor growth, abdominal pains, uncontrolled diabetes | Neg | Neg | 26 | >100 | 17 | Normal |

Neg indicates negative; PVA, partial villous atrophy; STVA, subtotal villous atrophy; TVA, total villous atrophy.

TABLE 2. Sensitivity, Specificity, and Predictive Value of Various Tests Compared With Biopsy for 18 Children

| | IgA AGA (%) | IgG AGA (%) | EMA (%) | tTG (%) |
|-------------|-------------|-------------|---------|---------|
| Sensitivity | 40 | 40 | 100 | 100 |
| Specificity | 88 | 38 | 88 | 88 |
| PPV | 80 | 44 | 91 | 91 |
| NPV | 54 | 33 | 100 | 100 |

PPV indicates positive predictive value; NPV, negative predictive value.

tients with type 1 diabetes.⁵ Most of our 11 patients with type 1 diabetes and a biopsy showing atrophic mucosa had, in fact, evocative symptoms of CD (Table 1). Only 4 of 11 had a typical form associated with gastrointestinal symptoms and weight loss with growth retardation. Among the patients who had a positive biopsy, only 1 of 11 was totally symptom-free, which is less than the 22% reported in a previous study.⁷ It is important to specify that atypical symptoms were clearly noted before CD diagnosis, thereby excluding a possible bias of the aforementioned symptoms. Controversy exists regarding the role of a gluten-free diet (GFD) in diabetes control. Children with coexisting type 1 diabetes and CD have equivalent diabetes control compared with matched type 1 diabetes control subjects.^{14,15} In our study, the mean HbA1c level was higher than 8.5% in half of our CD patients. These results are similar to

those of other non-CD type 1 diabetes patients in our clinic population (data not shown). However, children with both type 1 diabetes and asymptomatic CD may be at an increased risk of hypoglycemia up to 12 months before and 6 months after the diagnosis.^{16,17} In our cohort, we found only 1 patient with recurrent hypoglycemia. Our results confirm that GFD has little effect on the metabolic control of children who have type 1 diabetes with CD. However, it is important to note that dietary compliance with the GFD is only 30% to 50% in children with type 1 diabetes.^{14,18}

Nevertheless, the only patient who was EMA and anti-tTG positive but who had a normal biopsy (patient 12) presented with abdominal pains, weight stagnation, and uncontrolled diabetes. This patient had a low positive anti-tTG level compared with the other 10 patients with proven atrophic mucosa (17 AU vs 100 U/ml) and an EMA titer that was only slightly positive (5 vs 200). Additional clinical follow-up is needed to determine whether this patient will develop symptomatic CD over the next few years.

tTG and EMA antibodies have a high sensitivity and specificity (100% and 88%, respectively) in our population such as it is described in a normal population.¹⁹ In our study, IgA and IgG AGA have lower sensitivity and specificity than previously reported in children,²⁰ but our results are closer to the sensi-

tivity and specificity demonstrated in the general population of adults (IgA AGA sensitivity: 68%–100%; IgA AGA specificity: 65%–100%; IgG AGA sensitivity: 65%–100%; IgG AGA specificity: 50%–100%). The majority of patients with diabetes are older than 2 years and have a majority of atypical forms of CD such as in general population. Thus, these results confirm that tTG is an efficient test for children with diabetes.

Finally, we set out to determine which comes first: CD or type 1 diabetes. Several studies show that CD only occasionally precedes the onset of type 1 diabetes. More often, CD is diagnosed shortly after or sometimes years after the onset of type 1 diabetes.^{5,21–23} To determine the temporal relationship between the onset of type 1 diabetes and CD, we tested for anti-tTG in the initial serum taken at the onset of diabetes using our serum library. The retroactive screening showed that only 1 of 11 patients (patient 11)—the one with a positive jejunal biopsy—was anti-tTG negative at the onset of the type 1 diabetes. One of the 2 patients who initially had received a diagnosis of CD before type 1 diabetes became diabetic just 3 months later. This finding indicates that diabetes autoantibodies were probably already present at that time. Among the patients who were tTG positive at type 1 diabetes onset, most (6 of 8) received a diagnosis of CD after an average of just 4.3 years. In a prospective study, the median time after the onset of type 1 diabetes to the diagnosis of asymptomatic CD detected by screening was 13 months, but the serology did not use anti-tTG (IgA-AGA and IgA-antireticulin).²⁴ This result seems to demonstrate that CD occurs after type 1 diabetes, but in fact in our study, tTG serology was already positive at type 1 diabetes onset. The atypical form of CD explains this late diagnosis. Furthermore, IgA-tTG antibodies could be detectable earlier, as suggested by the Saukkonen study,²⁴ in which 9 patients with proven CD were negative for IgA-AGA and IgA-antireticulin when type 1 diabetes was diagnosed but became positive for these antibodies within 24 months. A similar chronology is reported by Williams et al²⁵ for a patient who had type 1 diabetes and only a positive anti-tTG level at the onset of type 1 diabetes. This increased 3 years later accompanied with the development of EMA, which initially had been negative. An increased prevalence of celiac autoimmunity has been found in the children of parents with type 1 diabetes,²⁵ and 19% of nondiabetic first-degree relatives have a high level of both tTG and EMA compared with none from a comparative group of schoolchildren.²⁵ The later appearance of type 1 diabetes in these relatives could be a strong argument for this hypothesis.

Our results show that CD and type 1 diabetes can be detected simultaneously. In most cases, CD may precede the onset of type 1 diabetes. These results differ from those of previous studies and can be explained by the higher sensitivity and/or earlier positivity of anti-tTG antibodies. More widespread screening, using anti-tTG, could avoid underdiagnosis. Of note is that all of the specimens were maintained at -80°C , which might adequately preserve

the quality of sera and did not affect tTG serology results.

Previous studies suggested that type 1 diabetes might exert an independent trigger effect on the development of CD.²⁶ Immunoregulatory disturbances in type 1 diabetes could trigger the reaction to gliadin in susceptible individuals.⁵ However, we speculate that CD occurs first and that abnormal intestinal mucosa enhances the absorption of foreign antigens, inducing an immune response in patients who are genetically predisposed to type 1 diabetes. Type 1 diabetes could then develop in patients with silent, nontreated CD through gluten-mediated immune activation against other organs.²² Recently, a study identified a first candidate diabetes-related wheat protein, the Glb1 protein. This wheat protein is not only antigenic in diabetic rats and human patients but also closely linked with the autoimmune aggression in the pancreas.²⁷ These results raise the possibility that wheat may also be involved in the pathogenesis of human type 1 diabetes. Our data support this hypothesis.

CONCLUSION

Among our population of children with diabetes, the minimum prevalence of CD is 3.9%. The most interesting finding of this study is that 82% of them were already positive for anti-tTG antibodies at type 1 diabetes onset.

Atypical isolated signs or lack of serious CD symptoms are the most common clinical presentation in our type 1 diabetes population. However, patients who are totally symptom-free are rare (10%).

Anti-tTG and EMA are concordant in all of our cases with high sensitivity when using recombinant human tTG (10 of 11 patients who were EMA and tTG positive had an abnormal biopsy) and specificity (no patient who was EMA or tTG negative had atrophic mucosa). Of course, different tTG serologic assays were used by various investigators, which can explain dissimilarities relative to specificity and sensitivity among studies. The presence of impurities in guinea pig-anti-tTG test, especially in patients with other autoimmune disease such as type 1 diabetes, explains the high false-negative or false-positive rate.²⁸ The use of highly purified human anti-tTG as antigen improves the quality and the specificity of this test. Results can be even better than those obtained from EMA detection by immunofluorescence.²⁹ Our results confirm this result. Nevertheless, screening for atypical CD in diabetes still attracts some controversy.³⁰ On the one hand, risk of complications (eg, short-term growth failure, delayed puberty, osteopenia, anemia), diagnosis difficulties, and absence of data allowing the elimination of possible malignancy development in subclinical disease support active screening CD. On the other hand, there are important difficulties associated with GFD toward the uncertainties of the complications in asymptomatic patients, which may suggest that screening for CD in all children with diabetes is not justified. In our experience, after analyzing the financial advantages (cost ~ 10 \$ US per sample), quick results, and safety of a standardized anti-tTG com-

pared with EMA, we suggest more widespread screening of patients with diabetes using only human anti-tTG antibodies after verification of normal serum levels of IgA. If anti-tTG are positive, then EMA testing, which is still to date the “gold standard” for serologic testing, should be used before performing a biopsy to confirm CD. In a prospective 6-year study on children who had diabetes and CD, no patients were found to develop CD >4 years after diabetes onset.²³ Therefore, we suggest that screening for CD should be performed annually on patients with negative CD serology at diabetes onset for a minimal duration of 4 years. This strategy should be evaluated in prospective studies to confirm that anti-tTG limited testing is a cost-effective method to identify CD.

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