β-Cell Autoimmunity in Pediatric Celiac Disease: The Case for Routine Screening?

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OBJECTIVE — To evaluate the prevalence of β-cell autoimmunity and the usefulness of a type 1 diabetes screening in patients with celiac disease.

RESEARCH DESIGN AND METHODS — We measured GAD antibodies (GADAs), insulinoma-associated protein 2 antigens (IA-2As), and insulin autoantibodies (IAAs) in 188 young Italian patients with celiac disease (66 male [35.1%]). Mean age at celiac disease diagnosis was 5.4 years (0.5–17.1), and mean celiac disease duration was 4.2 years (0–28.8). Celiac disease was diagnosed by jejunal biopsy after positivity for endomysial and tissue transglutaminase antibody was confirmed.

RESULTS — GADAs were positive in seven patients (3.7%), and IA-2As were positive in two patients. IAAs were negative in all cases. Metabolic evaluation was normal, and no patients developed diabetes during follow-up. There was no significant association among β-cell autoimmunity and sex, age, pubertal stage, family history, or coexistence of other autoimmune disorders; compliance to a gluten-free diet was confirmed.

CONCLUSIONS — Our results showed a low prevalence of β-cell autoimmunity and do not support a precocious screening for β-cell autoimmunity in young celiac disease patients.

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Celiac disease, whose prevalence in the general Western population is about 1%, is associated with other autoimmune disorders (1). Type 1 diabetes and celiac disease share a prodromic period, with autoantibodies to islet or gut antigens. Antibodies to GAD (GADAs), to insulinoma-associated protein 2 antigen (IA-2A), and anti-insulin (insulin autoantibody [IAA]) are used for type 1 diabetes screening; antiendomysial antibodies (EMAs) and endomysial tissue transglutaminase antibodies (tTGAs) are recommended for celiac disease screening (2,3). Few reports investigated β-cell autoimmunity in celiac disease patients (4,5). We evaluated the frequency of β-cell autoimmunity and the usefulness of type 1 diabetes screening in young celiac disease patients.

RESEARCH DESIGN AND METHODS

— We measured β-cell autoantibodies in 188 Italian patients with celiac disease diagnosed by jejunal biopsy according to Marsh staging criteria after confirmation of EMA and tTGA positivity and presentation of various degrees of symptoms. Gluten-free diet (GFD) compliance was evaluated by means of EMA and tTGA.

IgA tTGA was detected using enzyme-linked immunosorbent assay, and IgA EMA by indirect immunofluorescence. All samples were analyzed for GADA, IA-2A, and IAA with radiobinding assays (6). Personal and family histories for other autoimmune disorders were recorded.

Comparison of qualitative data among various groups was made by a χ^2 test or Fisher's exact test. All tests were two sided; a *P* value <0.05 was significant. Statistica (release 6; StatSoft, Tulsa, OK) was used for all of the analyses. Comparison of celiac disease duration between the two groups of patients (positive vs. negative to β-cell autoantibodies) was performed by means of the parametric Mann-Whitney *U* test because the normality assumption of the evaluable variable was not fulfilled.

RESULTS

— Characteristics of the study population are reported in Table 1. Celiac disease was diagnosed in 78.7% of children with classical symptoms, in 7.5% with atypical symptoms, and in 13.8% after the screening procedure.

We found concomitant autoimmune thyroid disease (ATD) in 5.6% of the patients. No patients had juvenile idiopathic arthritis, atrophic gastritis, Addison's disease, or vitiligo. A positive history of one or more autoimmune disorders was found in 35.6% of the families (celiac disease in 26.6, ATD in 9.6, and both type 1 diabetes and juvenile idiopathic arthritis in 2.3%).

We found positivity for diabetes-related autoantibodies in nine patients (4.8% [95% CI 2.2–8.9]): seven patients showed positivity for GADA (3.7% [1.5–7.5]) and two patients for IA-2A (1.1% [0.1–3.8]), whereas no patients presented with IAA or were positive for two autoantibodies. All nine positive patients had normal fasting plasma glucose, A1C levels, and + 120′ plasma glucose after the oral glucose tolerance test. The intravenous glucose tolerance test showed first-phase insulin response less than the first percentile only in three of nine cases. No patients developed clinical type 1 diabetes after a 3-year follow-up.

We found no significant association among β-cell autoimmunity and sex, age at diagnosis (<10 vs. ≥ 10 years), family history of autoimmune disorders, concomitant ATD, GFD compliance, and Tanner pubertal stage. No relationships were observed between celiac disease duration and positivity to β-cell autoantibodies ($P = 0.79$).

HLA class II typing (DQ2 and DQ8 alleles) was performed in 80 of 188 celiac disease patients (42.5%). Among the nine patients with β-cell autoantibodies, HLA typing was performed in eight cases. We

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Table 1—*Clinical characteristics of celiac disease patients* (n = 188)

Sex		
Male	66 (35.1)	
Female	122 (64.9)	
Tanner pubertal stage		
I	103 (54.8)	
II	26 (13.8)	
III	18 (9.6)	
IV	10 (5.3)	
V	31 (16.5)	
Age at celiac disease diagnosis (years)	5.4 ± 4.2	4.0 (0.5–17.1)
Age at study visit (years)	10.4 ± 6.8	9.0 (1.5–48.2)
Celiac disease duration (years)	4.2 ± 5.9	2.1 (0.0–28.8)

Data are *n* (%), means ± SD, or median (minimum–maximum) unless otherwise indicated.

found HLA-DQ2 in six cases, HLA-DQ8 in one case, and HLA-DQ2/DQ8 in one case. Among the remaining 72 patients without β-cell autoantibodies, we found HLA-DQ2 in 69 cases, HLA-DQ8 in two cases, and HLA-DQ2/DQ8 in one case.

CONCLUSIONS — A low prevalence of diabetes-related antibodies was observed, as well as no association with other autoimmune disorders. In adults, celiac disease is associated with several autoimmune disorders (mostly type 1 diabetes and thyroid diseases). Otherwise, in pediatric celiac disease patients, the rate and significance of diabetes-related antibodies yielded conflicting results (7).

Di Mario et al. (8) evaluated IAAs and islet cell antibodies (ICAs) in children with newly diagnosed celiac disease on a gluten-containing diet, in those with long-standing celiac disease following GFD, and in control groups and raised the question as to whether they are predictive of subclinical diabetes or whether they are indicators of a general autoimmune diathesis. Karagiozoglou-Lampoudi et al. (9) reported no positivity for ICA in pediatric celiac disease patients. Galli-Tsinopoulou et al. (10) showed GADA and IA-2A in 23% of celiac disease patients and recommended screening for β-cell autoimmunity.

In a retrospective study of 90 young Italian patients with celiac disease, the prevalence of diabetes-related autoantibodies was 11.1% and related to gluten exposure (7). Similarly, in an Italian large case series of adult celiac disease patients, a high prevalence (9%) of one diabetes-related autoantibody (ICA, IA-2A, or GADA) was observed independently of GFD compliance (11). Despite this high rate of diabetes-related autoimmunity, no incident cases of diabetes were reported, supporting the role of common genetic susceptibility to both diseases and factors involved in gut permeability (7).

Conflicting data about prevalence of diabetes-related autoantibodies in celiac disease patients could be due to the improvement of laboratory methods, which excluded false-positive data.

In young celiac disease patients, the length of gluten exposure could influence the development of other autoimmune disorders (7). Bonamico et al. (12) reported at least one endocrine-related serum autoantibody (either ICA or antithyroid microsomal antibody) in 50% of adolescents with undiagnosed celiac disease but in only 12% of celiac disease patients on GFD, suggesting that these autoantibodies could be partly gluten dependent.

Abnormal regulation of intestinal permeability and increased autoantibody production in the setting of chronic gut inflammation are trigger factors for the development of autoimmune response (12). Recent evidence suggests that gluten-induced upregulation of zonulin, an intestinal peptide involved in the regulation of gut tight junctions, could be responsible for the aberrant increase in gut permeability otherwise found in type 1 diabetes (13). The gut immune system includes the majority of the total lymphoid tissue in humans; therefore, a detrimental response to dietary components would have repercussions throughout the organism, carried either by immune cells or immune mediators released from the gut (14).

Laadhar et al. (4) did not find differences in prevalence of β-cell autoantibodies between children with newly diagnosed celiac disease and control groups and concluded that screening for diabetes-related autoantibodies is not justified. This opinion has been shared by Fanciulli et al. (5), who did not recommend regular screening for β-cell autoimmunity in all celiac disease patients because of low prevalence of diabetes-related autoimmunity in young celiac disease patients.

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