Prevalence of Autoimmune Thyroiditis in Children with Celiac Disease and Effect of Gluten Withdrawal

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Objective To study the prevalence of autoimmune thyroiditis (AT) in Sardinian children with celiac disease (CD) and the effects of a gluten-free diet (GFD) on thyroid function.

Study design Children with biopsy-proven CD (n = 324; female:male 2:1; mean age, 6.6 years) followed from 1 to 15 years, were retrospectively evaluated for AT at onset of CD and during GFD. Serum thyroid peroxidase and thyroglobulin antibodies (AbTPO, AbTG), thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), and thyroid ultrasonography were considered. Age-matched Sardinian schoolchildren (n = 8040), previously evaluated for antithyroid antibodies and thyroid function, were used as controls.

Results Thirty-four patients with CD (10.5%) developed AT (female:male 4,5:1; mean age, 10.5 years), 11 at onset of CD and 23 during GFD, with a higher prevalence than controls ($P = 2.9^{-13}$). Twenty-eight patients were euthyroid and 6 hypothyroid. AbTPO and/or AbTG persisted elevated for 2 to 9 years despite the GFD in 9 of 11 patients with AT at onset of CD.

Conclusions AT is strongly associated with CD in Sardinian children, has an age of onset of 10.5 years, and appears to be gluten-independent. In children with CD with AT, the female:male bias reported in adult AT is present before puberty. *(J Pediatr 2009;155:51-5)*.

Celiac disease (CD) is an autoimmune-mediated enteropathy triggered and maintained by the ingestion of gluten-containing cereals (wheat, rye, and barley) in genetically predisposed individuals.[1] CD is considered to be a worldwide disorder, more common in Western countries. In Europe and in the United States, the disease has been found to affect about 1 in 100 people[2]; among Sardinians with CD, it has been reported with a similar incidence.[3] Like type 1 diabetes, rheumatoid arthritis, and multiple sclerosis, CD has a strong genetic association with particular HLA class II alleles, namely the HLA genes encoding the class II DQ (α1*0501, β1*02) molecule.[4]

Sardinia is an ancient genetic isolate with a peculiar distribution of HLA class II alleles and haplotypes.[5] The CD predisposing HLA class II DQ (α1*0501, β1*02) molecule is very frequent among Sardinians (43%), and this HLA molecule is almost always encoded in *cis* by the DRB1*0301, DQA1*0501, DQB1*0201 haplotype.[6]

An increased prevalence of autoimmune disorders, including type 1 diabetes and autoimmune thyroid diseases, has been repeatedly reported in patients with CD.[7-9]

Two hypotheses have been suggested to explain this association: (1) sharing of 1 or more genes responsible for CD and for the coexpressed autoimmune disease; or (2) continued gluten exposure in untreated CD might lead to loss of the intestinal barrier function and to alterations of the systemic immune response, ultimately helping to induce other autoimmune disorders.[10]

The first concept implies that the comorbidity associated with CD is part of the individual genetic background.[11-13] On the contrary, the second concept may have important clinical implications because when the gluten induced immune reactivity and the interplay between autoimmune predisposing genes and trigger(s) is blocked, this comorbidity could be eliminated.[14,15]

In this retrospective study, a large cohort of 324 children with CD from Sardinia, followed for 1 to 15 years, was evaluated for the occurrence of autoimmune thyroiditis (AT). The aims of the study were to establish the prevalence of AT in CD and to verify if gluten exposure before the diagnosis of CD is correlated with development of thyroid autoimmunity, or vice versa if early gluten withdrawal is able to prevent the future development of AT.

AbTG	Thyroglobulin antibody
AbTPO	Thyroid peroxidase antibody
AT	Autoimmune thyroiditis
CD	Celiac disease
FT3	Free triiodothyronine
FT4	Free thyroxine
GFD	Gluten-free diet
TSH	Thyroid-stimulating hormone
US	Thyroid ultrasonography

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Methods

Patients

Children with biopsy-proven CD (n = 324) from Sardinia (223 girls; mean age at diagnosis, 6.6 years; range, 10 months to 18 years), followed between 1992 and 2007 (mean follow-up period, 8 years) at the Pediatric Gastroenterological Unit in Cagliari, Italy, were included in the study. Clinical data were collected retrospectively; affected family members of probands, patients with preexisting autoimmune conditions (type 1 diabetes, autoimmune thyroid disorders, Addison's disease), and patients with Down syndrome or Turner syndrome were excluded from the study.

Screening for Celiac Disease

The diagnosis of CD was based on the revised criteria of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition,[16] for example, clinical history, positivity of IgA antiendomysial antibody, typical histological features on small intestinal biopsy, and clinical response to the gluten-free diet (GFD) (Table I).[17] All patients were typed for anti-gliadin antibody (AGA, both IgA and IgG) and antiendomysial antibody (EMA); most patients were also typed for anti-tissue transglutaminase antibody IgA (tTG-IgA) and anti-actin antibody IgA (AAA-IgA). The latter has been previously associated with the severity of intestinal damage.[18] Mucosal atrophy has been graded according to the Marsh classification,[19] modified by Oberhuber in type 3a, 3b, and 3c.[20] After diagnosis of CD, all patients followed a GFD, and the dietary compliance was evaluated by assessment of AGA, EMA, and tTG every 12 months.

Thyroid Function Assessment

Screening for thyroid peroxidase antibody (AbTPO) and thyroid globulin antibody (AbTG) was performed in all 324 patients at the onset of CD and once per year after the institution of the GFD. When abnormal values were detected, a complete thyroid evaluation, including serum-free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and thyroid ultrasonography, was performed.

Thyroid autoantibody serum titers were detected using competitive radioimmunoassay (RIA Medical System; Genoa, Italy) with coated-tube technique thyroperoxidase antibodies (AbTPO, normal values <50 IU/mL), RIA-immunoradiometric assay (IRMA, Medical System; Genoa, Italy) with solid-phase technique antithyroglobulin (Ab TG, normal values <100 IU/mL). Serum FT3 and FT4 were detected by RIA (Medical System; Genoa, Italy) using commercial kits (normal values, 0.8 to 2 ng/mL for FT4; 1.40 to 4.2 pg/mL for FT3), whereas serum TSH was measured by a chemiluminescent method (Medical System; Genoa, Italy), with normal values ranging between 0.3 and 5 μU/mL.

Ultrasonography of the thyroid gland was performed with a 7.5-MHz linear probe. Thyroid echographic images were classified and graded in 4 patterns according to Sostre et al[21] and Marcocci et al.[22] We restricted the diagnosis of AT to patients with high titers of AbTPO and/or AbTG associated with an abnormal thyroid echographic pattern. Therefore, patients with mild elevation of AbTPO and/or AbTG were eliminated from the statistical analysis to avoid possible overestimates. Thyroid function was classified according to the American Thyroid Association Guidelines.[23]

Table I. Clinical manifestations and serological markers of CD in 324 Sardinian children

	Patients (%)
Clinical form	
Classic symptoms	39
Nonclassic symptoms	56
Iron deficiency anemia	22
Failure to thrive	18
Abdominal pain	5
Pubertal delay	4
Vomiting	3
Diarrhea	2
Chronic constipation	2
Silent	5
Serological markers	
AGA IgA	73
AGA IgG	88
tTG-IgA	95
EMA	99
AAA-IgA	64

Control Subjects

We compared the frequency of AT among patients with CD with the prevalence of antithyroid antibodies (ATA) in an age-matched Sardinian background population also evaluated for thyroid function.[24]

In this cohort of 8040 schoolchildren (4194 boys, 3846 girls, ages 6 to 15 years) ATA were detected in 235 children (2.92%).

Statistical Analysis

Data were evaluated by χ^2 test with Yates corrections, or by the Wilcoxon test, setting the level of significance at .05.

Results

Clinical data of patients with CD with AT are summarized in Table II (available at www.jpeds.com).

Overall AT was found in 34 (28 girls, 6 boys) of 324 patients with CD; 23 were on GFD when AT was diagnosed (Table III). Considered as a whole, a high prevalence of AT among children with CD (10.5%), compared with the Sardinian pediatric background population (2.92%), was found ($P = 2.9^{-13}$). This prevalence is similar to or even lower than that reported in other studies conducted in adults and children.[12,25] Euthyroidism was observed in 28 of 34 patients (82.4%), and 6 were hypothyroid. In 3, hypothyroidism preceded diagnosis of CD, and the other 3 patients developed hypothyroidism during GFD (Table II).

The thyroid ultrasonography showed an abnormal pattern with varying severity, suggestive of an autoimmune infiltrate