Long-term Clinical Significance of Thyroid Autoimmunity in Children with Celiac Disease

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Objective To evaluate the long-term outcome of thyroid function and autoimmunity in a large series of children with celiac disease.

Study design This longitudinal, retrospective study (duration of follow-up, 8.9 ± 4.0 years) was conducted at the Pediatric Department, University of Bologna, Italy. One hundred thirty-five consecutive patients diagnosed between June 1990 and December 2004 and followed on a gluten-free diet were examined. Inclusion criteria were good dietary compliance and duration of follow-up for at least 3 years.

Results Of 101 patients who never showed positive antithyroid titers during the follow-up, 86 remained euthyroid; 15 showed high thyroid-stimulating hormone values at diagnosis that normalized in 11 cases after 12 to 18 months of gluten withdrawal. Of 31 patients with persistently positive antibody titers, 23 (74%) remained consistently euthyroid during the follow-up and 8 (26%) had a subclinical hypothyroidism. The prevalence of cases with positive antibodies was similar in children with growth retardation or gastroenterological symptoms at diagnosis and different durations of gluten exposure.

Conclusions The presence of antithyroid antibodies in children with celiac disease has a low predictive value for the development of thyroid hypofunction during the indicated surveillance period. Longer follow-up is needed. *(J Pediatr 2010;156:292-5)*.

Previous studies have reported an increased prevalence of autoimmune thyroid disease in children with celiac disease (CD), but the clinical significance of this association is lacking. Prevalence data ranged from 14% to 41%, as related to the differences in study populations and serologic tests performed. Discordant results were also reported on the impact of gluten withdrawal in the evolution of autoimmune thyroid disease.[1-6] However, apart from a multicenter Italian study,[6] previous studies in children and adolescents with CD have included very few patients, and there are no longitudinal follow-up studies of euthyroid patients with positive antithyroid antibodies.

To evaluate the long-term outcome of thyroid function and autoimmunity, we performed a retrospective study in a large series of children with biopsy-proven CD who were diagnosed and followed up in our department.

Methods

Medical records of 135 consecutive patients (45 boys and 90 girls) diagnosed with CD in our department of pediatrics between June 1990 and December 2004 (age at diagnosis, 5.7 ± 3.9 years) and followed up for 8.9 ± 4.0 years (range, 3 to 17 years) on a gluten-free diet (GFD) were retrospectively examined. The diagnosis of CD was made according to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria.[7] Inclusion criteria were the residence in an iodine-sufficient area, good dietary compliance, and the duration of follow-up for at least 3 years. Exclusion criteria were the presence of diseases that could affect thyroid function (ie, chronic liver or renal disease or malignancy) or the use of medication known to influence serum thyroid-stimulating hormone (TSH) or fT4 (ie, dopamine, glucocorticoids, or heparin).

Initial data collection included family and clinical history, growth assessment, thyroid function, and autoimmunity tests. At diagnosis, 88 patients (65%) showed gastroenterological symptoms and 43 (32%) showed growth retardation and/or other symptoms; the clinical pattern at diagnosis was silent in 4 patients (3%). In the silent disease group, diagnosis was made through a screening program in a family study.[8]

During the follow-up, height, weight, nutritional status, and serum fT3, fT4, and TSH and antibodies against peroxidase (anti-TPO) and thyroglobulin (anti-Tg) were evaluated yearly. Thyroid ultrasound was performed in patients who showed

Ab anti-TPO	Antibodies against peroxidase
Ab anti-Tg	Antibodies against thyroglobulin
CD	Celiac disease
GFD	Gluten-free diet
TSH	Thyroid-stimulating hormone

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Table I. Anthropometric, serologic, echographic, and family history data at diagnosis in patients with CD subdivided according to final assessment

Final assessment	Cases (n)	Age (y)	Sex (% of females)	Positivity for both Ab (%)	Typical ultrasound pattern (%)	Body mass index, SDS	Weight, SDS	Height, SDS	Family history of autoimmune thyroid diseases (%)
Euthyroid patients with negative Ab	86	5.7 ± 3.9	55/86 (63.9%)	-	-	−1.0 ± 1.06	−1.0 ± 1.3	−0.9 ± 1.1	6/78 (7.7%)
Euthyroid patients with positive Ab	23	5.1 ± 3.9	18/23 (78.3%)	10/23 (43.5%)	18/23 (78%)	−0.8 ± 1.0	−0.7 ± 1.0	−0.6 ± 1.0	6/14 (42.8%)*
Subclinical hypothyroidism patients with positive Ab	8	6.0 ± 5.8	5/8 (62.5%)	6/8 (75%)	6/8 (75%)	−1.0 ± 1.04	−0.7 ± 0.7	−0.5 ± 0.7	3/7 (40%)*

*$P < .025$ vs euthyroid patients with negative Ab.

abnormal thyroid function and/or autoimmunity tests. Not all data were available for all patients.

At each examination, height was evaluated with a Harpenden stadiometer (mean of 3 measurements) and nutritional status was evaluated by calculating the body mass index (kg/m^2) SDS, according to the Italian cross-sectional growth charts.[9,10]

Free thyroid hormone and TSH serum levels were measured by commercial kits. Thyroid autoimmunity was investigated by evaluating anti-TPO and anti-Tg antibodies, using commercial kits. To compare the data during a long-term follow-up, antibody positivity was defined as titer increase >50% above the upper normal limit for our laboratory in the period considered.

Thyroid function was classified using the American Thyroid Association guidelines.[11] A inhomogeneous hypoechogenic ultrasound pattern with or without enlarged gland was considered typical of autoimmune thyroid disease.[12,13]

The dietary compliance was assayed by means of CD-related serology. Anti-endomysial antibodies were detected by indirect immunofluorescence in the same certified immunology reference laboratory, and we considered as negative titer the absence of the immunofluorescence in sera tested at a dilution of 1:5.[14] The dietary compliance was also assayed by the evaluation of biochemical parameters of malabsorption.

Statistical Analysis

Data are reported as mean ± standard deviation, unless indicated otherwise. All statistical analyses were performed using SPSS version 12.01 (SPSS Inc., Chicago, Illinois) for all calculations. Data were analyzed using the χ^2 test for differences in frequencies and Student t test for comparison of means. A 2-tailed P value <.05 was considered statistically significant.

Results

At diagnosis, negative antithyroid antibody titers were observed in 119 of 135 patients (88%) and positive antibody titers in 16 of 135 patients (12%).

Of 119 patients who tested negative at diagnosis, 104 (87%) were euthyroid and 15 (13%) showed TSH values above the upper normal limit (TSH range, 4.6 to 29.7 mU/L). TSH values normalized after 12 to 18 months of GFD in 11 of 15 cases, whereas subclinical hypothyroidism was confirmed in 4 cases. In these 4 patients, ultrasound examination showed an ectopic thyroid gland in 1 case (TSH at diagnosis, 29.7 mU/L) and a normal gland in situ in the other 3 cases (TSH at diagnosis, 4.8, 6.4, and 4.9 mU/L, respectively). None of these 15 cases had thyroid autoimmunity during the follow-up. Of 104 euthyroid patients who tested negative at diagnosis, 86 never showed positive antibody titers during the follow-up, whereas 18 had thyroid autoimmunity after 1 to 4 years of GFD (3 of 18 patients shifted toward autoimmune subclinical hypothyroidism during the follow-up).

Of 16 patients who tested positive at diagnosis, 14 (87.5%) were euthyroid and 2 (12.5%) showed TSH values above the upper normal limit (15.2 mU/L and 7.3 mU/L, respectively). At diagnosis, the frequency of subclinical hypothyroidism with negative antibodies was significantly higher than autoimmune hypothyroidism (15/135, 11% vs 2/135, 1.5%; $P < .0001$). Of 2 patients with autoimmune subclinical hypothyroidism at diagnosis, TSH values normalized in 1 case (TSH at diagnosis, 7.3 mU/L) but remained unchanged in the other case. Of 14 euthyroid patients who tested positive at diagnosis, 7 remained euthyroid with positive antibodies, 4 shifted toward autoimmune subclinical hypothyroidism, and 3 showed a normalization of antithyroid antibody titers after 1 year of GFD. In 3 other cases, after an initial normalization, positive antibody titers reappeared in the following tests and remained until the end of the follow-up. In the 3 cases that had normalized antibody titers, a normal ultrasound pattern was found. Therefore, overall positive antithyroid antibody titers were observed in at least 1 test in 34 of 135 patients (25%); 16 of these patients (47%) had positive titers at diagnosis and 18 (53%) had thyroid autoimmunity after 1 to 4 years of GFD. Thirty-one percent of the cases tested positive for AbTPO, 24% for AbTg, and 45% for both. Positive antibody titers were found in 7 of 45 (15.5%) boys and in 27 of 90 (30%) girls.

At the final assessment, negative antithyroid antibody titers were observed in 104 of 135 patients (77%) and positive antibody titers in 31 of 135 patients (23%).

Of 31 patients with persistently positive antibody titers, 74% (23 cases; 17% of patients with CD) remained euthyroid during the follow-up and 26% (8 cases; 6 % of patients with CD) shifted toward a subclinical hypothyroidism that was concomitant with CD diagnosis in 1 case. Four of 8 patients