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

Alessandra Cassio, MD, Giampaolo Ricci, MD, Federico Baronio, MD, Angela Miniaci, MD, Milva Bal, MD, Barbara Bigucci, MD, Veronica Conti, MD, and Alessandro Cicognani, MD

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...
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/m²) 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 hypoecho- genic 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-re- lated 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 di- lution 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 indi- cated otherwise. All statistical analyses were performed using SPSS version 12.01 (SPSS Inc., Chicago, Illinois) for all calculations. Data were analyzed using the χ² test for differences in frequencies and Student t test for comparison of means. A 2-tailed P value <.05 was considered statistically significant.

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

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

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

Results

At diagnosis, negative antithyroid antibody titers were ob- served 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 diagno- sis, 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 auto- immune hypothyroidism (15/135, 11% vs 2/135, 1.5%; P < .0001). Of 2 patients with autoimmune subclinical hypo- thyroidism 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 normal- ization, 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 ultra- sound pattern was found. Therefore, overall positive antithy-roid 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...
who had hypothyroidism needed substitutive therapy at different times during the follow-up (in 1 patient at diagnosis); 4 patients showed consistently borderline TSH values (range, 4.7 to 5.5 mU/L) without ultrasound signs of goiter and were followed up without therapy. As shown in Table I, all patients with persistently positive antibodies showed a greater frequency of positive family history for autoimmune thyroid diseases. However, none of the variables examined was significantly different in the subjects in whom subclinical hypothyroidism would develop. The percentage of cases with positivity for both anti-TPO and anti-Tg antibodies was higher in the group that had development of hypothyroidism, but this difference was not significant.

Table II shows thyroid function and autoimmunity outcome in children with CD according to the symptoms at diagnosis. The age at diagnosis and the duration of gluten exposure was significantly higher in the group diagnosed on the basis of growth retardation, but at the final assessment the prevalence of cases with persistently positive antibodies was similar in both groups.

**Table II.** Final assessment of hormonal and autoimmune thyroid function in patients with CD according to symptoms at diagnosis

<table>
<thead>
<tr>
<th>Clinical pattern at diagnosis</th>
<th>Cases, n</th>
<th>Age at diagnosis (y)</th>
<th>Euthyroid patients with negative Ab, n (%)</th>
<th>Euthyroid patients with positive Ab, n (%)</th>
<th>Subclinical hypothyroidism patients with positive Ab, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth retardation</td>
<td>32</td>
<td>8.0 ± 2.8</td>
<td>25 (71.8%)</td>
<td>4 (12.5%)</td>
<td>2 (6.2%)</td>
</tr>
<tr>
<td>Gastroenterological symptoms</td>
<td>88</td>
<td>4.1 ± 3.0*</td>
<td>68 (69.3%)</td>
<td>13 (14.7%)</td>
<td>5 (5.7%)</td>
</tr>
</tbody>
</table>

*P < .0001 vs patients with growth retardation.

Discussion

CD has been associated with many different autoimmune endocrine diseases and a common immunogenetic basis, possibly related to major human histocompatibility complex (HLA), has been considered for this association. In particular, the high prevalence of thyroid autoimmunity both in pediatric and adult patients with CD has been reported in previous studies, but data about the clinical and prognostic significance of this association is lacking.

We conducted a longitudinal long-term follow-up of thyroid function and autoimmunity in a pediatric population with CD. The reliability of the results should not be affected by the retrospective character of the investigation because diagnosis and follow-up criteria were homogeneous in all patients examined in the same pediatric department.

The results of our longitudinal long-term study are in agreement with the multicenter cross-sectional study of Ansaldo et al that reported positive antibody titers in 24% of 256 children examined on a GFD at a mean age of 9 years, with a prevalence of autoimmune hypothyroidism of 7% in patients with CD. These findings suggest that thyroid autoimmune in our patients with CD should be considered a possible common immunologic mechanism with an independent course for the two diseases.

Previous studies, both longitudinal and cross-sectional in adult patients, strongly support this hypothesis. In particular, Sategna-Guidetti et al found a prevalence of autoimmune hypothyroidism (6.4% of cases) in 128 patients examined at a mean age of 30 years within 12 months from gluten withdrawal. These data are comparable with our findings in adolescent patients at the final assessment. In accordance with our data, Hadithi et al reported 21% of positive thyroid serology in a group of adult Dutch patients with CD. However, in contrast with all literature data, they also found overt hypothyroidism in 12% of the cases.

Besides possible differences in ethnic origin, this greater prevalence of hypothyroidism may be related, at least in part, to the older mean age of patients examined (53 years) and the high percentage (42%) of patients newly diagnosed with CD and untreated. Our data, in agreement with data reported by other authors, suggest that the main etiological factor of hypothyroidism at diagnosis may be attributed to a decreased thyroid hormone synthesis as a consequence of isolated malnutrition, and the normalization of thyroid function was obtained by means of gluten withdrawal alone. Moreover, we must point out that the absorption of dietary iodide in the small intestine is the first step in iodide utilization and thyroid hormone synthesis. Recently, Nicola et al reported that Na+/I- symporter was functionally expressed at the apical surface of rat and mouse enterocytes, where it mediated active iodide accumulation. Therefore, iodide malabsorption could strongly contribute to the etiology of nonautoimmune hypothyroidism in CD.

The relationship between GFD and autoimmunity remains controversial; conflicting results have been reported as to the role of age at diagnosis and the duration of gluten exposure as risk factors for increasing the occurrence of thyroid autoimmune disorders.

Because of the limited number of observations and the study design, our longitudinal evaluation may not definitively clarify this issue. However, some results of our study do not seem to confirm the role of gluten exposure as a risk factor for thyroid autoimmunity. In fact, the final outcome of thyroid function and autoimmunity was comparable in subjects with different ages at diagnosis, and the development of autoimmune thyroid impairment may occur in some patients even after 4 years of GFD. Probably the conflicting data reported in literature can be explained, at least in part, by the possibility of a spontaneous fluctuation of antibodies over time and a transitory normalization that may occur in
some cases. Only a longer follow-up will be able to emphasize these phenomena.

Finally, our data, in agreement with Radetti et al.\textsuperscript{19} confirm that autoimmune thyroiditis in children and adolescents shows a very low cytotoxic activity with a tendency to develop overt hypothyroidism only in 12% (4/31) of the cases. We searched for reliable prognostic factors to predict disease evolution, but we could not find any sure markers of deteriorating thyroid function at diagnosis. Therefore, we suggest that a regular screening for thyroid function should be performed in all patients with CD who have positive antithyroid antibody titers.

In conclusion, we suggest that the presence of positive antithyroid antibody titers in children and adolescents with CD has a low predictive value for the development of thyroid hypofunction, at least during the surveillance period considered. A longer follow-up is indicated to demonstrate that thyroid function is not deteriorating.

References
