Autoimmune thyroid disorders and coeliac disease

Pekka Collin, Jorma Salmi, Olavi Hällström, Timo Reunala and Amos Pasternack
Department of Clinical Sciences, University of Tampere, Tampere, Finland

The clinical presentation of coeliac disease varies from overt gastrointestinal disease and malabsorption to atypical and even asymptomatic cases (1). IgA-class reticulin, endomysium and gliadin antibody tests can be used as a screening method in clinical practice (2–4). We have earlier noted an increased frequency of coeliac disease in type-1 diabetes (3). Coeliac disease is also associated with Addison’s disease (5). An increased frequency of thyroid abnormalities has been reported in patients with coeliac disease (6–11) and dermatitis herpetiformis (12–13) (Table 1). The occurrence of coeliac disease among thyroid patients is not well documented, and this prompted us to screen with the antibody tests a consecutive series of patients with autoimmune thyroid disorders.

Patients and methods
The study included all ambulatory patients with newly diagnosed autoimmune hypothyroidism (Hashimoto’s thyroiditis) or Graves’ disease in our hospital during the

Table 1. Studies of the occurrence of thyroid diseases in patients with coeliac disease and dermatitis herpetiformis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Disease</th>
<th>No. of patients</th>
<th>Thyroid disease in general</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
<th>Goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancaster-Smith et al. (6)</td>
<td>CD</td>
<td>57</td>
<td>5.3</td>
<td>0</td>
<td>5.3</td>
<td>—</td>
</tr>
<tr>
<td>Cooper et al. (7)</td>
<td>CD</td>
<td>314</td>
<td>3.5</td>
<td>2.3</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>Hovdenak (8)</td>
<td>CD</td>
<td>54</td>
<td>5.6</td>
<td>5.6</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Biemond et al. (9)</td>
<td>CD</td>
<td>678</td>
<td>6.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Midhagen et al. (10)</td>
<td>CD</td>
<td>139</td>
<td>10.8</td>
<td>5.8</td>
<td>5.0</td>
<td>—</td>
</tr>
<tr>
<td>Snook et al. (11)</td>
<td>CD</td>
<td>148</td>
<td>4.1</td>
<td>2.7</td>
<td>1.4</td>
<td>—</td>
</tr>
<tr>
<td>Cunningham et al. (12)</td>
<td>DH</td>
<td>50</td>
<td>30.0%</td>
<td>10.0</td>
<td>4.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Weetman et al. (13)</td>
<td>DH</td>
<td>115</td>
<td>5.2</td>
<td>3.4</td>
<td>1.7</td>
<td>—</td>
</tr>
</tbody>
</table>

*Celiac disease.
*Dermatitis herpetiformis.
*Includes two patients with benign nodules and one patient with follicular cancer.
*Data not available.
period 1990–1991. Euthyroid patients with a solitary nodule of the thyroid gland were also screened.

Patients with clinical signs of hypothyroidism, positive microsomal antithyroid antibodies and elevated serum thyroid-stimulating hormone (TSH) were considered to have Hashimoto’s thyroiditis. Criteria for Graves’ disease were clinical hyperthyroidism associated with diffuse goitre and low serum TSH. The reference value for TSH was 0.50 to 3.80 mU/l.

The patient sera were screened at dilutions of 1:5 for IgA-class reticulin and endomysium antibodies by immunofluorescent methods as described earlier (2). IgA- and IgG-class gliadin antibodies were measured using a solid-phase enzyme-linked immunosorbent assay (14); the lower limit of positivity of IgA-class was 0.2 EU/ml and that of IgG-class, 10.0 EU/ml. Patients were also screened for low values of serum iron (<8.0 μmol/l), vitamin B₁₂ (<170 pmol/l), red cell folate (<280 nmol/l), and for a selective serum immunoglobulin A deficiency (serum IgA <0.05 g/l).

For each patient with autoimmune thyroid disease, sera from three sex- and age-matched blood donors were screened for coeliac disease with the IgA-class reticulin antibody test and serum IgA. The criterion of age-matching was year of birth within three years, but this was not possible with five of the oldest patients with autoimmune thyroid disease.

Small bowel biopsy was performed with a Watson capsule, if any of the above tests yielded abnormal results. The biopsy was carried out by gastroscopy in patients with low vitamin B₁₂; a biopsy was also taken from the body of the stomach. Histologically, the small bowel biopsy specimens were classified into normal, mild partial, severe partial and subtotal villous atrophy, as previously described (15). Patients with severe partial or subtotal villous atrophy were considered to have coeliac disease. They were prescribed a gluten-free diet and a control biopsy was performed after six months to confirm mucosal healing.

The study protocol was approved by the ethics committee of the University Hospital of Tampere. Cross-tabulations were analysed using likelihood ratio chi-square.

Results

A total of 83 patients with autoimmune thyroid disease were screened for coeliac disease; 31 of them had Hashimoto’s thyroiditis and 52 had Graves’ disease. In addition, 25 patients with a solitary nodule of the thyroid gland were also screened. The sex and age distributions of patients are given in Table 2.

IgA-class reticulin and endomysium antibodies were both positive in 5 patients, IgA-class gliadin antibodies in 18 and IgG-class gliadin antibodies in 9 (Table 2). Five patients had iron deficiency and 6 vitamin B₁₂ deficiency. A total of 29 patients were found to be positive in the screening tests. Of these 29 patients, 28 underwent a small bowel biopsy, this being performed by gastroscopy in six patients with low serum vitamin B₁₂ and by jejunal capsule in the remainder. One patient with iron deficiency refused the biopsy.

Two patients with Graves’ disease and one with Hashimoto’s thyroiditis were found to have small bowel villous atrophy. In addition, one patient with Hashimoto’s thyroiditis had had coeliac disease diagnosed 10 years earlier and was maintaining a gluten-free diet. One patient with solitary thyroid gland nodule had small bowel villous atrophy. All patients with small bowel villous atrophy had positive IgA-class reticulin, endomysium and gliadin antibodies, and two of them had positive IgG-class gliadin antibodies; other tests were normal. One of the 249 blood donors was found to be positive in the IgA-class reticulin antibody test; small bowel biopsy confirmed that she had coeliac disease. None of these blood donors had selective IgA-deficiency.

The frequency of coeliac disease in patients with autoimmune thyroid diseases was 4.3% (4 to 83) and

Table 2. Mean age and sex distribution of patients in the present study groups and controls (blood donors). Results of screening.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of patients</th>
<th>Male/female ratio</th>
<th>Mean age (range)</th>
<th>No. of coeliac disease (%)</th>
<th>Positive findings (No. of patients with small bowel villous atrophy in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune thyroid disease</td>
<td>83</td>
<td>0.28</td>
<td>42.7 (17–77)</td>
<td>4* (4.8%)</td>
<td>ARA/EMA 4 (3) AGA I 15 (3) AGA IgA 7 (2) Signs of Malabsorption 11 (0)</td>
</tr>
<tr>
<td>Graves’</td>
<td>52</td>
<td>0.19</td>
<td>44.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hashimoto</td>
<td>31</td>
<td>0.33</td>
<td>40.4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Solitary nodule</td>
<td>25</td>
<td>0.14</td>
<td>49.0 (21–69)</td>
<td>1 (4%)</td>
<td>ARA 1 (1) AGA I 3 (1) AGA IgA 2 (0) Signs of Malabsorption 0 (0)</td>
</tr>
<tr>
<td>Blood donors</td>
<td>249</td>
<td>0.28</td>
<td>42.9 (20–68)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>

* Occurrence of coeliac disease in patients with autoimmune thyroid disease compared with blood donors (p = 0.019); in patients with solitary nodule compared with blood donors (p = 0.43).

b IgA-class reticulin and endomysium antibodies.

c IgA-class and IgG-class gliadin antibodies.

d See Patients and methods.

e In addition, one patient developed coeliac disease later.
that in blood donors 0.4% (1 to 249). The difference was statistically significant (p = 0.019). The frequency of coeliac disease in patients with solitary nodule (1 to 25) was not significantly increased when compared with blood donors (p = 0.43).

None of the four patients with thyroid disease and villous atrophy had abdominal symptoms suggestive of coeliac disease. However, under gluten-free regimen the villous architecture recovered in all these patients within six months, confirming the diagnosis of coeliac disease. The patient with Hashimoto’s thyroiditis was treated with thyrroxin, patients with Graves’ disease first with antithyroid drugs and thereafter with radioidine. The patient with solitary nodule was operated. Treatment results were good in all patients (Table 3).

The only patient with positive reticulin antibody titre and normal jejunal biopsy was later seen to develop coeliac disease: a new biopsy 14 months later showed subtotal villous atrophy.

Three of the six patients with low serum vitamin B12 were found to have chronic atrophic gastritis of the body of the stomach.

Discussion

There are several studies describing the occurrence of thyroid diseases in patients with coeliac disease and dermatitis herpetiformis (Table 1). On the other hand, there are few reporting the frequency of coeliac disease in patients with thyroid diseases. Siurala et al. (16) examined small intestine mucosal lesions in patients with hyperthyroidism. Biopsies were performed on 32 patients but no villous atrophy was detected. In another study they carried out jejunal biopsies on 32 patients with various endocrinologic disorders, and found five cases of subtotal and one partial villous atrophy, all of them patients who had thyroid disease (17). In contrast to the present study, there was no response to a gluten-free diet, and the writers concluded that the villous alterations were possibly induced by “intestinal myxedema” or general autoimmune phenomena and were not due to gluten intolerance.

Coeliac disease and autoimmune thyroid disease have similarities in pathogenesis. Coeliac disease is known to be associated with HLA DR3 antigen (18), and such an association has also been demonstrated in Graves’ disease (19) and in Hashimoto’s thyroiditis (20). The activation of T cells, which results in expression of major histocompatibility type II antigens, has been described in both coeliac disease and autoimmune thyroid diseases (21, 22).

By reason of the asymptomatic cases which often remain undetected, the true prevalence of coeliac disease is not known. Prevalence figures of 1:1000 have been reported for symptomatic disease (10). Asymptomatic cases, for their part, can be found only by screening methods. Hällström (23), in Finland, screened IgA-class reticulin antibodies and Hed et al. (24), in Sweden, screened IgA-class gliadin antibodies in blood donors and found coeliac disease frequencies of 1 in 304 and 1 in 267, respectively. It has been concluded that the prevalence is close to 1 in 300 when the population is screened for coeliac disease (25), a proportion comparable with the frequency of coeliac disease (1 in 249) in the blood donors in the present study. In the present study, the frequency of coeliac disease in patients with autoimmune thyroid disease was 1 in 20 and thus at least tenfold increased.

Early diagnosis of coeliac disease is important: patients run an increased risk of malignant lymphoma and treatment with a gluten-free diet can prevent the development of malignancy (26). IgA-class reticulin, endomysium and gliadin antibody tests detected all new cases of coeliac disease in the present study. The significance of false positive reticulin, endomysium or gliadin antibody tests is obscure. Some of these patients, especially patients positive in IgA-class reticulin and endomysium antibody tests, may later contract coeliac disease (27). In the present study, the only patient with positive reticulin and endomysium antibody tests but normal villous architecture had such latent coeliac disease: he was later found to develop coeliac disease. Laboratory tests indicating malabsorption were of no use in detecting asymptomatic coeliac disease in the present...
series. Low vitamin B12 levels in these patients would imply atrophic gastritis rather than coeliac disease.

In conclusion, asymptomatic coeliac disease occurs in increased frequency in patients with autoimmune thyroid disease. Serologic screening with reticulin or endomysium antibody tests is recommended to detect these patients.

Acknowledgments. This study was supported by grants from the Yrjö Jahnsson and Emil Aaltonen Foundations.

References


Received February 18th, 1993
Accepted September 8th, 1993