

Celiac-associated autoimmune thyroid disease: A study of 16 patients with overt hypothyroidism

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HJ FREEMAN. Celiac-associated autoimmune thyroid disease: A study of 16 patients with overt hypothyroidism. *Can J Gastroenterol* 1995;9(5):242-246. Previous reports have suggested that autoimmune thyroid disorders (including Hashimoto's or lymphocytic thyroiditis) may occur in patients with celiac disease. In this study, the prevalence of thyroid disease was explored in a series of 96 consecutive patients seen with biopsy-defined adult celiac disease (average age 47.3 years). Sixteen celiac patients (average age 58.1 years) were detected with hypothyroidism, including four treated with radio-iodine ablation or thyroidectomy for Grave's disease. In addition to celiac disease, almost half had dermatitis herpetiformis, a small intestinal neoplasm (particularly lymphoma) or both. Diagnosis of thyroid disease preceded diagnosis of celiac disease in 13 patients or was made concurrently in two patients. In only one patient was thyroid disease detected after celiac disease was diagnosed. This indicates that thyroid diseases occur more commonly in celiac disease than is currently appreciated, possibly due to shared embryological origins or common immunopathological features, and may be the presenting clinical manifestation in adults especially if there is coexistent dermatitis herpetiformis. Careful monitoring of this subgroup may be warranted because of the frequency of neoplastic intestinal diseases, particularly lymphoma.

Key Words: *Autoimmune thyroiditis, Celiac disease, Chronic thyroiditis, Dermatitis herpetiformis, Grave's disease, Hashimoto's thyroiditis, Hypothyroidism, Lymphocytic thyroiditis, Lymphoma*

Maladie thyroïdienne auto-immune de nature coeliaque : étude portant sur 16 patients atteints d'hypothyroïdie avérée

RÉSUMÉ : Selon des rapports antérieurs, les troubles thyroïdiens auto-immuns (y compris la maladie de Hashimoto ou la thyroïdite lymphocytaire) peuvent affecter des patients atteints d'une maladie coeliaque. Dans la présente étude, la

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OVER 100 DIFFERENT DISORDERS may occur in association with celiac disease (1) and a number of autoimmune disorders, including autoimmune thyroid diseases, have been described (2-5). In some case studies, celiac disease and hyperthyroidism have been described (2,6-10), while in others, celiac disease and hypothyroidism have been detected (11-16). In addition, some alterations in intestinal absorptive function have been detected, particularly in the presence of hyperthyroidism, but these are reported to normalize following treatment of the thyroid disease (17,18).

In a recent study from a circumscribed geographical area in Scotland (19), measurements of thyroid function and studies for thyroid autoantibodies suggested that the risk of clinically overt thyroid disease, particularly hypothyroidism, was increased in patients with celiac disease. This is not surprising because the human lymphocyte antigen (HLA) haplotypes B8 and DR3 are both more commonly detected in autoimmune thyroid disease and celiac disease patients versus the general population (20-22).

In this report, patients with biopsy-defined celiac disease were evaluated for changes in thyroid function and the presence of thyroid autoantibodies as well as other associated clinical disor-

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prévalence de la maladie thyroïdienne a été étudiée dans une série de 96 patients consécutifs porteurs d'une maladie coeliaque de l'adulte confirmée par biopsie (moyenne d'âge, 47,3 ans). Chez seize patients atteints de maladie coeliaque (moyenne d'âge, 58,1 ans) on a identifié une hypothyroïdie, y compris chez quatre sujets ayant subi une ablation radio-iodée ou une thyroïdectomie en traitement de la maladie de Grave. En plus de la maladie coeliaque, près de la moitié présentaient une dermatite herpétiforme, une néoplasie de l'intestin grêle (particulièrement sous forme de lymphome) ou les deux. Le diagnostic de maladie thyroïdienne a précédé celui de maladie coeliaque chez 13 patients, sauf chez deux sujets où les deux diagnostics ont été posés simultanément. Chez un seul patient, la maladie thyroïdienne a été décelée après que le diagnostic de maladie coeliaque ait été posé. Cela signifie que la maladie thyroïdienne accompagne plus souvent la maladie coeliaque que l'on pourrait le penser, possiblement à cause de leur origines embryologiques ou de leurs caractéristiques immunologiques communes, et qu'elle pourrait être une manifestation clinique chez les adultes, spécialement en présence de dermatite herpétiforme co-existante. Une surveillance attentive de ce sous-groupe s'impose à cause de la fréquence des néoplasies intestinales, du lymphome en particulier.

ders. The results indicate that there is high frequency of autoimmune thyroid disease in patients with celiac disease. These patients also have a high frequency of dermatitis herpetiformis and small intestinal neoplastic disease, particularly lymphoma.

PATIENTS AND METHODS

A total of 96 adults with celiac disease were seen at the University of British Columbia Hospital, Vancouver. In each patient, a small bowel biopsy diagnosis of celiac disease was established on the basis of typical histological features of a severe 'flat' lesion (23) or 'crypt hyperplastic villous atrophy' followed by a response to a strict gluten-free diet. Each patient's hospital and office records were reviewed for evidence of thyroid disease and other clinical disorders that have been previously closely linked with celiac disease, including dermatitis herpetiformis and lymphoma (24,25). For either dermatitis herpetiformis or lymphoma, a histological diagnosis was required. There were 16 patients with thyroid disease and all except one were regularly reviewed in an adult celiac disease clinic at least on an annual basis. The one patient not followed on an annual basis died of pneumonia six months following diagnosis of celiac disease. One other patient with celiac disease died with a perforated small bowel due to lymphoma (25).

Details of the clinical presentation and past medical history were recorded for each patient as were hematological (hemoglobin, white blood cell count, platelet count) and biochemical results (carotene, iron studies, folic acid, vitamin B₁₂, calcium, phosphate, total protein, albumin, prothrombin time, immunoglobulins and liver tests).

After small intestinal biopsies were done, patients were reviewed by a clinical dietitian with a special interest in celiac disease who provided specific instructions on a gluten-free diet. Patients were assessed periodically, as required, to address any concerns regarding diet treatment. Compliance and response to a prescribed strict gluten-free diet were evaluated during each clinic visit.

The 16 celiac disease patients included hypothyroid patients now on L-thyroxine with normal measurements of thyroid function; newly diagnosed thyroid disease patients; and patients with impaired thyroid gland function due to prior surgical and/or radio-iodine ablative treatment for Grave's disease. Most, but not all, of the 96 patients with celiac disease had thyroid function evaluated. Radioimmunoassays for total and/or free thyroxine and thyroid-stimulating hormone were done. Thyroid microsomal antibodies were detected by a standard agglutination technique. Hypothyroidism was diagnosed on the basis of a low

TABLE 1
Celiac disease patients with thyroid diseases

Patient/age*/sex	Other diseases
IS/68/female	Pneumonia [†]
MS/62/female	DH
WF/65/male	Pericardial effusion
WB/70/male	DH, lymphoma [†] and mesenteric lymph node cavitation [‡]
FS/60/male	DH, lymphoma, lymphocytic sclerosing cholangitis [‡]
MW/62/female	DH, ovarian cancer [‡]
DM/56/female	
DC/60/male	DH, small bowel adenocarcinoma [‡]
KB/65/female	
JM/84/male	Lymphoma [†]
BH/69/female	DH
CW/41/female	
LW/44/female	
LW/22/female	
AR/61/female	
HN/41/female	

*Age (in years) at diagnosis of celiac disease; [†]Deceased; [‡]Diagnosed after celiac disease detected; DH Dermatitis herpetiformis

thyroxine value, an increased thyroid-stimulating hormone measurement or both.

RESULTS

Patient data: All 96 patients were residents of British Columbia. Their average age at diagnosis of celiac disease was 47.3 years. Thirty-three were older than age 60 years; for the initial 30 of these elderly patients, the clinical spectrum of associated diseases was described earlier in a separate report (26). Another 63 of these 96 patients were 17 to 59 years old. Details related to the clinical features of some of these 96 patients have been documented elsewhere in earlier case report studies because of unusual or unique clinical and/or histopathological features related to the celiac disease (27-34). Sixteen of these 96 celiac disease patients had hypothyroidism detected for an overall prevalence of at least 17%; this approximates a reported prevalence of 14% for overt thyroid disease in Scottish patients with celiac disease (19) and is greater than a prevalence of 2.7% recorded in an English study (4), 5.8%

TABLE 2
Thyroid database

Patient/age*/sex	Current thyroid state
IS [†] /68/female	Age 40: partial thyroidectomy for thyroid adenoma Age 68: euthyroid during terminal hospitalization on L-thyroxine. Thyroid microsomal antibodies positive, 1:6400
MS/62/female	Age 44: thyroidectomy for hyperthyroidism Age 72: euthyroid on L-thyroxine. Thyroid microsomal antibodies positive, 1:100
WF/65/male	Age 48: hypothyroidism diagnosed after presentation with pericarditis and pericardial effusion Age 65: euthyroid on L-thyroxine. Thyroid microsomal antibodies, not done
WB [†] /70/male	Age 70: hypothyroidism (low free T4 and high TSH). Thyroid microsomal antibodies positive, 1:25,600 Age 73: euthyroid on L-thyroxine during terminal hospitalization. Mother had 'goiter'
FS/60/male	Age 58: biochemical hypothyroidism (low free T4 and high TSH). Thyroid microsomal antibodies positive, 1:6400 Age 64: euthyroid on L-thyroxine
MW/62/female	Age 62: biochemical hypothyroidism (low free T4 and high TSH). Thyroid microsomal antibodies positive, 1:25,600. Daughter, autoimmune thyroiditis
DM/56/female	Age 34: hypothyroidism diagnosed Age 56: euthyroid on L-thyroxine. Thyroid microsomal antibodies, not done
DC/60/male	Age 65: hypothyroidism diagnosed (low T4 and high TSH). Thyroid microsomal antibodies positive, 1:1600 Age 67: euthyroid on L-thyroxine
KB/65/female	Age 42: Grave's disease and thyroidectomy Age 69: euthyroid on L-thyroxine. Thyroid microsomal antibodies, not done
JM/84/male	Age 80: biochemical hypothyroidism (low free T4 and high TSH). Thyroid microsomal antibodies positive, 1:6400 Age 84: euthyroid on L-thyroxine
BH/69/female	Age 55: hypothyroidism (low T4 and high TSH) Age 69: euthyroid on L-thyroxine. Thyroid microsomal antibodies positive, 1:6400
CW/37/female	Age 32: hypothyroidism (low T4 and high TSH) Age 42: euthyroid on L-thyroxine. Thyroid microsomal antibodies positive, 1:400
LW/44/female	Age 36: Grave's disease diagnosed, elevated radio-iodine uptake (70% at 24 h) and radio-iodine treatment; exophthalmos. Age 68: euthyroid on L-thyroxine
LW/22/female	Age 21: Grave's disease diagnosed and radio-iodine treatment Age 35: euthyroid. Thyroid antibodies positive, 1:1600
AR/61/female	Age 41: hypothyroidism diagnosed Age 65: euthyroid on replacement L-thyroxine. Thyroid microsomal antibodies positive, 1:3200
HN/41/female	Age 34: hypothyroidism diagnosed (low T4 and high TSH). Thyroid microsomal antibodies positive, 1:4600 Age 43: euthyroid on L-thyroxine

*Age (in years) at diagnosis of celiac disease; [†]Deceased; TSH Thyroid-stimulating hormone

in a Swedish population (5) and 5.4% in a Finnish report (35).

There were 70 females and 26 males for an overall female:male ratio of 2.7:1. These findings are similar to the age and sex distribution for celiac disease patients reported by investigators elsewhere (36) and recorded earlier in a separate report describing clinical fea-

tures in elderly biopsy-defined celiac disease patients (26). In the 16 patients with thyroid disease reported here, there were 11 females and five males for a female:male ratio of 2.2:1.

All 16 patients with thyroid disease were Caucasian and no patient had a known family history of celiac disease. However, two patients had an apparent

family history of thyroid disease: a 70-year-old male reported that his mother had a 'goiter' and a 62-year-old female had a daughter with autoimmune (Hashimoto's) thyroiditis and hypothyroidism. The average age at diagnosis of celiac disease for these 16 patients (with both celiac and thyroid diseases) was 58.1 years (compared with the group average of 47.3 years).

Related clinical disorders: Table 1 lists related disorders that were identified in each patient. In the 16 patients with thyroid disease described in the present report, dermatitis herpetiformis was diagnosed in six patients (38%) and five (31%) had a neoplastic disorder. These included small intestinal lymphoma in three patients and a small intestinal adenocarcinoma in one. Although the relationship among celiac disease, lymphoma and dermatitis herpetiformis has been well established (24), thyroid disease has not previously been recognized in association with this triad of related clinical disorders. None of these 16 thyroid disease patients had any other endocrine disorder detected, including insulin-dependent diabetes.

Thyroid disease data: Details related to thyroid disease of each of the 16 patients are provided in Table 2. The average age for diagnosis of thyroid disease in this group was 47.6 years. In contrast, in the same group the average age at celiac disease diagnosis was 58.1 years, over a decade later. This age difference in diagnosis for the two disorders may reflect a sexual difference in expression of thyroid and celiac diseases. In females, average age at diagnosis of the thyroid and celiac diseases was 40.1 and 53.4 years, respectively; in males, however, the average age was 64.2 and 67.8 years, respectively, which indicates a similar age at diagnosis for both disorders in males. In these 16 patients, 13 had thyroid disease detected before celiac disease diagnosis, two had both conditions detected concurrently and only one patient had celiac disease detected about 10 years before the diagnosis of thyroid disease.

In 11 patients, the clinical and laboratory features were very typical of autoimmune hypothyroidism with biochemical features of thyroid hypofunc-

tion and, in nine patients, of positive thyroid microsomal antibodies. In four patients, hypothyroidism followed prior surgical or radio-iodine treatment for hyperthyroidism; in another patient a partial thyroidectomy for a thyroid adenoma was done. Thyroid microsomal antibodies were also detected in three of these patients. The titres of the thyroid antibodies detected in this series varied from dilutions of 1:100 to 1:25,600; interestingly, the high titres were found in the only two patients in this series with family histories of thyroid disease. All 14 surviving patients are euthyroid with normal thyroid function measurements, and, in most instances, the patients are now receiving replacement L-thyroxine therapy.

DISCUSSION

The present report indicates that autoimmune thyroid diseases are common in patients with celiac disease and may occur more often than has been previously recognized. In this study, 16 of 96 celiac disease patients (17%) had overt thyroid disease and, in most, this was associated with impaired thyroid function. It is possible that the prevalence was even higher because thyroid function was assessed in most, but could not be examined prospectively in all 96 patients in a systematic fashion. The association is not entirely unexpected, however, because the thyroid gland shares a common embryonic origin during fetal development, derived from the pharyngeal gut on the 17th day (37). In addition, patients with autoimmune thyroid disease and celiac disease both have increased frequen-

cies of the HLA haplotypes B8 and DR3 (20-22). Finally, HLA DR antigen expression both occurs in the small bowel of patients with celiac disease and has been detected in epithelial glandular structures of patients with other autoimmune diseases (eg, salivary glands in Sjögren's syndrome) (38,39).

The 16 patients with both thyroid and celiac disease were much older than the average age of the 96 celiac patients in this series. Possibly this reflects the reported tendency to an increased prevalence of hypothyroidism with increasing age (40). Or elderly celiac disease patients, being untreated for prolonged periods before diagnosis, may be more likely to develop autoimmune thyroid or other diseases. Greater small intestinal permeability in celiac disease patients may permit excessive amounts of antigen to enter the circulation and cross-react with other tissues, including the thyroid gland (19).

In the present study, thyroid disease was detected before celiac disease in most patients, and only one patient had treatment with a gluten-free diet before detection of thyroid disease. As suggested elsewhere (19), it would be of particular interest to assess the prevalence of thyroid diseases in adult celiac patients treated with a gluten-free diet from childhood.

This study also explored clinical disorders that are already known to be strongly linked with celiac disease. Almost half of the patients in the present study also had dermatitis herpetiformis, small intestinal lymphoma or both. While this 'triad' has been previously recognized and linked with celiac disease (24), detection of altered thyroid

function may lead to recognition of a clinical setting that carries an increased risk of neoplastic disease. In addition, earlier studies, especially in animal models, have suggested a critical role for thyroid hormones in altering the normal pattern of epithelial cell renewal and epithelial proliferation rates in the small intestine (41,42). Studies are needed to elucidate more precisely the role of altered levels of circulating molecules, including hormones, in the development of malignant complications in this clinical setting of adult celiac disease.

The association of celiac disease with autoimmune thyroid disease may be important to recognize from a clinical perspective as the two disorders share several common features, such as anemia, altered bowel habit and impaired absorption, especially in hyperthyroidism. Failure to diagnose both conditions might result in a limited, or even an apparent lack of, response to a treatment regimen. Alternatively, hypothyroidism might mask the clinical features of celiac disease, such as weight loss and diarrhea. Thus, it may be important to exclude thyroid disease in all celiac disease patients, especially if there is an apparent failure to respond to a gluten-free diet. Conversely, hypothyroid patients failing to respond to oral L-thyroxine treatment may have undiagnosed or occult celiac disease. Prospective studies are needed to define further this intriguing relationship of celiac disease with autoimmune endocrine, including thyroid, diseases.

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