Coeliac disease and autoimmune Addison’s disease: a clinical pitfall


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Summary

Background: Coeliac disease has an increased prevalence in a number of autoimmune endocrine conditions. An association between coeliac disease and Addison’s disease has been proposed in isolated case reports, but has not been formally studied.

Aim: To investigate the extent of this association.

Design: Prospective screening of patients with confirmed Addison’s disease.

Methods: From central computerized records, we identified all living patients with a diagnosis of autoimmune Addison’s disease in the past 30 years and presently attending our affiliated hospitals. After exclusions, 44 were invited to attend for screening.

Results: Of 41 patients screened, five (12.2%) had coeliac disease: Three were previously diagnosed coeliacs and this was confirmed on review, including examination of biopsy material. A further two had positive IgA-endomysial antibodies. Histological confirmation was obtained in both cases. Neither had laboratory or clinical evidence of malabsorption.

Discussion: In this series of patients with Addison’s disease, a higher co-morbidity with coeliac disease was observed than in any previously studied endocrine condition. We recommend that coeliac serology (anti-endomysial and tissue transglutaminase antibody) testing be incorporated routinely into the autoimmune screen for other conditions in patients with Addison’s disease.

Introduction

The prevalence of coeliac disease in the West of Europe approaches 0.8%.1,2 The availability of specific and sensitive serological tests, particularly the anti-endomysial and tissue transglutaminase antibodies, has facilitated widespread screening.3,4 While the value of serological screening in the general population is not established, targeted screening of high-risk population subsets is of particular clinical importance. Individuals at risk include those with a positive family history, and those with associated autoimmune endocrinopathies.

The increased prevalence of coeliac disease in the context of autoimmune thyroid disease (5.4%) and insulin-dependent diabetes mellitus (5.0%) has received much attention.5–9 While the impact of coeliac disease on the clinical course of coexisting autoimmune conditions is unclear, a cause-and-effect relationship has recently been proposed.10 Specifically, the duration of gluten exposure has been reported to be linked to the prevalence of autoimmune disorders in coeliac patients. In those coeliacs diagnosed after the age of 10 years, the prevalence of autoimmune disorders is up to seven-fold higher than in healthy controls.10 This further strengthens the argument for early diagnosis and treatment through appropriate screening.
Addison’s disease is an endocrine condition in which co-existing coeliac disease could have serious clinical implications. Firstly, there is a crossover of symptoms between malabsorption and the vague gastrointestinal symptoms due to adrenocortical insufficiency, which may compound clinical diagnosis. Secondly, chronic steroid administration, albeit at physiological doses, may result in delayed or atypical presentation of coeliac disease. Thirdly, malabsorption associated with coeliac disease may alter steroid bioavailability in patients with Addison’s disease on replacement doses of steroids.

Scattered case reports of an association between coeliac disease and Addison’s disease can be found in the literature, but there has been no formal study to date. Our objective was to review a series of patients with autoimmune Addison’s disease and to estimate the prevalence of coeliac disease in autoimmune Addison’s disease.

Methods

From central computerized records, we identified and reviewed all patients with a diagnosis of adrenal insufficiency in the past 30 years (n = 91). The diagnosis of primary adrenal insufficiency was confirmed on the basis of recognized clinical manifestations (Table 1) accompanied by an elevated ACTH and/or a flat response to dynamic ACTH testing. Autoimmune adrenalitis was inferred by the demonstration of positive adrenal antibodies and/or the exclusion of other aetiologies, particularly infection (including tuberculosis), haemorrhage and primary or metastatic malignancy.

Of the 91 patients identified, the following exclusions were made (Table 2): 13 whose adrenal insufficiency was secondary to a pituitary tumour or surgery, four who had tuberculous adrenalitis, three who had iatrogenic disease, and another who had Sheehan’s syndrome. Seven patients had died, and a further 19 patients were excluded either because they had relocated outside this catchment area (2), or because there was insufficient information available to confirm the diagnosis of autoimmune Addison’s disease according to the above clinical or laboratory criteria (17). The remaining 44 patients, with confirmed autoimmune Addison’s disease comprised the study population.

IgA anti-endomysial and/or tissue transglutaminase antibody testing was used to screen for coeliac disease. All patients with positive serology were invited to attend for endoscopic distal duodenal biopsy. Biopsy specimens in those patients with a previous diagnosis of coeliac disease were reviewed to confirm the diagnosis. Informed consent was obtained from all participants. Approval of the study protocol was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

Results

Of the patients with autoimmune Addison’s disease, 41/44 attended for screening. (21 male, 20 female). Mean age at diagnosis was 34 years, (range 7–66 years, median 37 years). Mean duration of Addison’s disease was 10 years, (range 1–30 years, median 9 years). Adrenal antibodies were available and positive in 29/44 subjects. In the remaining 16 patients, an autoimmune aetiology was inferred by the exclusion of other causative factors.

Table 3 summarizes the results. Five patients (5/41, 12.2%) had a new or confirmed diagnosis of coeliac disease (95%CI 3–21%). Three of these (A, B, C) were known coeliacs prior to the study. A further two patients (D, E) were found to have positive endomysial antibodies on screening, and endoscopic small-bowel biopsy subsequently confirmed coeliac disease. One of these patients had...
a mild increase in intraepithelial lymphocytes and blunting of villi, the other had severe partial villous atrophy. In no patient were the diagnoses made simultaneously; the interval between diagnoses was 1–30 years.

One of the patients (D) with previously unrecognized coeliac disease reported non-specific abdominal pain and nausea; the other (E) was asymptomatic at the time of screening, and on review of her medical records, there had been no gastrointestinal symptoms predating the diagnosis of Addison’s disease. There were no haematological or biochemical abnormalities. Steroid replacement doses were within the standard range in both patients.

**Discussion**

This is the largest reported series of patients with coeliac disease and autoimmune Addison’s disease to date. No cases of Addison’s disease are likely to have been missed for the period of assessment, as all such patients are followed at hospital-based endocrine clinics within the region. The strength of association between these two conditions (12.2% in this series) is higher than any other previously reported endocrine condition. Although a control group was not studied, the background prevalence of coeliac disease in the Irish population is ~1%.1

A similar immunogenetic background is one explanation for the link between these conditions. The HLA association of coeliac disease is well characterized. Approximately 95% of patients possess the (HLA)-DQ (A1*0501, B1*0201) heterodimer, compared to 20–30% of controls.18 The inherited susceptibility to autoimmune Addison’s disease is strongly associated with (HLA)-DR3 and DR4 alleles.19 The genotype HLA DQA1*0501 is significantly more common in Addison’s disease (70%) than in controls (43%).20

It is likely that one or more genes at an HLA-unlinked locus are a stronger determinant of susceptibility to coeliac disease than HLA.18 The CTLA-4 molecule has been assessed as a potential candidate for this role. The CTLA4 gene exon 1 polymorphism (49 A/G) has recently been demonstrated to predispose to coeliac disease.21 In patients with Addison’s disease, those carrying the susceptibility marker, HLA DQA1*0501, have also been shown to be significantly more likely to have this polymorphism than controls with the same DQA1 allele.22

The recent demonstration of a relation between the duration of exposure to gluten and the prevalence of autoimmune disorders in coeliac disease is also of significance in this study.10 The mean age at diagnosis of coeliac disease in this group was 57 years with a range of 21–48 years. Two of the five patients had a second autoimmune disorder (Table 3).

Autoimmune Addison’s disease is relatively rare, with an estimated prevalence of approximately 39 to 60 per million.17 Its association with coeliac disease is potentially clinically important, having both diagnostic and therapeutic implications. From a clinical standpoint, chronic adrenal insufficiency is often difficult to diagnose. Its onset is insidious and symptoms can be vague. Typical complaints include chronic malaise, fatigue and generalized weakness. Gastrointestinal manifestations are present in more than 50% of these patients, and include lower abdominal cramps, anorexia, weight loss and nausea.23 Other features common to coeliac disease include pigmentation, reduced bone mineral density, amenorrhoea, anaemia and an association with other endocrine conditions.

There have been reports in the literature of an unmasking of coeliac disease in patients discontinuing chronic steroid therapy24,25 and steroids have a well-recognized therapeutic role in the management of refractory coeliac disease. In a treated Addison’s patient, physiological doses of steroids, through partial treatment of the mucosal lesion, may mitigate symptoms and partially suppress the immune response.
As a corollary, institution of a gluten-free diet and subsequent reversal of mucosal abnormalities has implications for optimal treatment of Addison’s disease. In patients with unrecognized and untreated coeliac disease, the pharmacokinetics of steroids may be altered; in particular, those with hypoalbuminaemia may have an increased volume of distribution and reduced protein binding. Correction of hypoalbuminaemia may therefore necessitate a reduction in the maintenance dose of steroids.

In conclusion, of the previously reported autoimmune endocrinopathies, Addison’s disease has the strongest association with coeliac disease. This is likely to be related to their similar genetic backgrounds, although a cause-and-effect relationship between gluten exposure and autoimmunity has been raised. We recommend that coeliac serology be incorporated into the routine screen for autoimmune conditions in patients with autoimmune Addison’s disease.

References