Seroprevalence of celiac disease in patients with autoimmune hepatitis

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Background and aims **Prevalence data of celiac disease (CD) in patients with autoimmune hepatitis (AIH) are scarce. We investigated the relationship between AIH and CD by assessing the prevalence of IgA tissue antitransglutaminase antibodies (TGA) and antiendomysium antibodies (EMA) in a large cohort of AIH patients.**

Methods **The frequency of CD was determined by TGA antibody serology in a cohort of 460 AIH patients. In case of TGA positivity, patients were further tested for EMA serology. Retrospective data on previously diagnosed CD and patient characteristics were retrieved from computerized or written medical records. Findings were compared with archival data on the prevalence of CD in the Netherlands ($n = 1440$).**

Results **Six patients had a known history of CD and were currently in remission as determined by negative TGA serology. In addition, 10 of the 460 AIH patients (2.2%) had positive IgA TGA. Diagnosis of CD was further substantiated by positive EMA antibodies in these patients. Combined, CD was found in 3.5% of AIH patients compared with 0.35% in the general Dutch population ($P < 0.001$). When excluding patients with either a primary biliary cirrhosis or primary sclerosing cholangitis overlap, in 11 (2.8%) AIH patients, CD was found.**

Conclusion **This is the largest serological study on the association between AIH and CD and demonstrates that the presence of CD in AIH patients is more common compared with the general population; yet, it is not as high as described in some previous small studies. The possibility of concurrent CD should be considered in all AIH patients.** ***Eur J Gastroenterol Hepatol*** **26:1104–1107 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Autoimmune hepatitis (AIH) represents an uncommon chronic inflammatory disease in which loss of tolerance against hepatic tissue is presumed. AIH is characterized by a female predominance, histological features of periportal hepatitis in the absence of viral markers, hyperimmunoglobulin G, and the presence of serum autoantibodies [1].

AIH is known to be associated with other autoimmune diseases. A recent study reported as much as 40% concurrent autoimmune diseases in AIH patients [2]. Celiac disease (CD) is a permanent intolerance to gluten and leads to a malabsorption syndrome [3]. IgA tissue transglutaminase antibodies (TGA) and antiendomysium antibodies (EMA) are used as serological markers in CD because of high sensitivity and specificity. To support the diagnosis of CD, serological tests mentioned above may be combined with human leucocyte antigen (HLA)-DQ typing [4].

The serological prevalence of CD in AIH patients has so far been studied in small sample sets including a maximum of 157 patients. In these studies, the prevalence varies widely from 1.1 to 11.5% [5–9]. On the basis of these observations, it has been suggested that patients with AIH should be screened for CD [10]. *Vice versa*, liver abnormalities are frequently seen in patients with CD, and isolated hypertransaminasemia is found in up to 27% of patients [11,12].

Here, we aimed to investigate a potential association between CD and AIH by assessing the prevalence of TGA in AIH patients.

Patients and methods

Patient population

AIH patients were identified by the Dutch AIH Study group consortium (*http://www.autoimmuunhepatitis.nl*), involving the gastroenterology and hepatology departments from six academic and 21 general hospitals in the

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Netherlands. AIH patients were identified by treating physicians and by searching the database for international classification of diseases codes. The search was performed in local diagnostic registers in the departments of gastroenterology and hepatology as well as internal medicine. In all patients, clinical and biochemical parameters were assessed to exclude other etiologies such as alcohol, drugs, and metabolic disorders. Viral hepatitis was excluded by serological testing. If performed, liver biopsy was used to establish diagnosis and the presence of fibrosis and cirrhosis. We recorded manifestations of overlap syndromes with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) in the presence of AIH, if available. For PBC, these criteria consisted of antimitochondrial antibody titers higher than 1 : 80 and typical histological findings, whereas manifestations of PSC were recorded in case of typical histological and radiological findings. Diagnostic scores were determined according to the revised original International Autoimmune Hepatitis Group criteria [13]. Available data on induction and maintenance therapy, as initiated and recorded by the treating physician, were retrospectively collected from the patient hospital records. Before the initiation of the study, institutional review board approval to carry out the study was obtained in all participating centers. All participants provided written informed consent.

CD screening

All serological tests were determined anonymously. Serum samples were obtained from each participant, stored frozen at − 80°C, and tested in batches. The TGA-specific IgA detection in serum samples, a commercially available enzyme-linked immunosorbent assay (Diarect, Freiburg, Germany), was used according to the manufacturer's instructions.

Positive TGA samples were screened for EMA by indirect immunofluorescence assay using monkey esophagus (Bindazyme; The Binding Site Ltd, Birmingham, UK) and were genotyped for HLA DQ2 and DQ8 using Human CytoSNP 12.0 platform (Illumina, Inc., San Diego, California, USA) as described elsewere [14]. Retrospective data on previously diagnosed CD and patient characteristics were retrieved from computerized or written medical records.

Control population

Findings were compared with a control group of a study on the prevalence of CD in the Netherlands ($n = 1440$) [15].

Data analysis

Summary statistics for categorical variables are expressed as numbers (percentages). Quantitative variables are described as median with their range if not normally distributed. Statistical analysis was performed using Statistical Package for the Social Sciences, version 20 (IBM Corp., Armonk, New York, USA). Depending on the distribution, parametric and nonparametric tests, including the Mann–Whitney test, were used to test for differences within and between groups. The χ^2-test was used for the comparison between the results of the recent study and controls (adapted from Megiorni *et al.* [16]). A *P*-value less than 0.05 was considered statistically significant.

Results

The cohort consisted of 460 Dutch adult patients. The AIH cases consisted of 85 men and 375 women with a median age at diagnosis of 46 years (interquartile range: 28–61).

The median International AIH Group diagnostic score was 18 (interquartile range: 15–21) (cutoff values: ≥ 12 probable AIH; ≥ 17: definite AIH) [13]. On the basis of the antibody profile, the large majority (95%) had type 1 AIH, whereas a small minority had positive anti-LKM 1 antibodies and was thus classified as type 2 AIH (Table 1).

A total of six patients had an established diagnosis of CD. All of these tested negative for TGA, indicating strict adherence to the gluten-free diet. The screening for TGA in serum of 460 AIH patients resulted in the identification of 10 TGA-positive patients. Subsequent analysis revealed that all these samples were positive for EMA and in addition, both HLA DQ2 and DQ8 were positive in eight patients, and in two patients solitary HLA DQ2 was present. On the basis of these findings, CD was found in 3.5% of AIH patients. This number is significantly higher when compared with the prevalence of 0.35% in the Dutch population [15] ($P < 0.001$). Concurrent features of PBC were seen in 64 patients, five AIH patients with CD and 59 without. An overlap with PSC was only reported in 10 AIH patients, all without CD. When excluding patients with either a PBC or PSC overlap, in 11 (2.8%) AIH patients CD was found, still higher compared with the Dutch prevalence mentioned above.

The median alanine transaminase levels and immunoglobulin G levels at the time of diagnosis were similar in AIH patients with and in patients without concomitant CD (Table 1). Similarly, the occurrence of antinuclear antibodies, smooth muscle antibodies, and liver kidney microsomal (LKM) antibodies was not different between the two groups. Recorded liver biopsy reports at diagnosis were available in 363 patients, showing cirrhosis in 1 (6%) of the AIH patients with CD and in 36 (10%) AIH patients without CD. Fibrosis was seen in 5 (31%) AIH patients with CD and in 197 (56%) patients without. The clinical features at presentation are summarized in Table 1.

Discussion

Reports of concomitant CD in AIH were first reported in the late 1970s [17,18].

Table 1 Clinical features at presentation in TGA-positive and TGA-negative AIH patients

Characteristics	AIH patients with celiac disease ($N=16$)	AIH patients without celiac disease ($N=444$)	*N*
Age (years) [median (IQR)]	44 (33–67)	47 (28–59)	460
Pediatric patient (age < 18 years) [n (%)]	2/16 (13)	43/444 (10)	460
Female [*n* (%)]	11/16 (69)	356/444 (82)	460
IAIHG-score [median (IQR)]	18 (14–20)	18 (15–21)	460
ALT (U/L) [median (IQR)]	333 (128–596)	349 (150–817)	403
IgG (g/L) [median (IQR)]	19 (17–31)	21 (16–29)	338
SMA $\geq 1:40$ [*n* (%)]	2/12 (17)	190/422 (45)	434
ANA $\geq 1:40$ [*n* (%)]	8/12 (67)	253/422 (60)	434
LKM-1 $\geq 1:40$ [*n* (%)]	0/6 (0)	11/223 (5)	229
PBC [*n* (%)]	5/16 (31)	59/422 (14)	438
PSC [*n* (%)]	0/16 (0)	10/422 (2)	438
Fibrosis (biopsy) [*n* (%)]	5/16 (31)	197/347 (56)	363
Cirrhosis (biopsy) [*n* (%)]	1/16 (6)	36/347 (10)	363

Numbers within parentheses are in percentages for proportional variables and interquartile range for continuous variables.
AIH, autoimmune hepatitis; ALT, alanine transaminase; ANA, antinuclear antibodies; IAIHG, International Autoimmune Hepatitis Group; IgG, immunoglobulin G; IQR, interquartile range; LKM-1, liver kidney microsomal antibodies; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibodies; TGA, antitransglutaminase antibodies.
$P > 0.05$ for all characteristics, with the exception of PBC; $P = 0.02$.

However, systematic large-scale studies on the association between AIH and CD have not been reported. In 1998, Volta *et al.* [9] studied the sera of 157 type 1 AIH and 24 type 2 Italian and American AIH patients; CD was found in both types of AIH, and EMA was identified in 8 (4%) patients.

In a later study in Italy, 47 AIH patients were studied; the prevalence of CD in patients with AIH was 6.4% [8]. In previous studies from Greece and Iran, an association between CD and AIH was reported; however, it was executed in a small patient population, 117 and 59 individuals, respectively. Prevalence of CD in these studies ranged from 3.4 to 6.0% [6,7,10]. A study in native Egyptian AIH children reported a higher prevalence of CD of 11.5% [5]. In contrast, one study from Sweden has shown no association between CD and chronic liver disease [19]. Some of these studies were hampered by the lack of uniform diagnostic criteria and small sample size or were executed in either single centers or tertiary referral hospitals. The present study is the largest study on the seroprevalence of CD in AIH in a homogeneous population with a well-defined prevalence of CD [15]. We demonstrate that the presence of CD in AIH patients is more common compared with the general population; yet, it is not as high as reported in some previous studies.

It should be noted that many of the AIH patients included in this study were treated with steroids. It has been described that steroids can occasionally restore villous architecture and result in false-negative antibody results [20]. In addition, occasional CD patients already on a gluten-free diet (GFD) may have been missed in this retrospective cohort, as information on GFD diet was not specifically collected. Finally, it is well established that IgA deficiency is more common in patients with CD, and this was not specifically tested for in this study. Consequently, the real prevalence of CD in treated patients (corticosteroids or GFD) might be slightly higher in this cohort of patient.

In a previous study, an older age, ANA positivity, increased levels of alkaline phosphatase, and the presence of cirrhosis were found independently associated with TGA positivity [6]. Our study does not confirm these associations. The relationship between CD and PBC is well documented.

In a large registry from the UK, PBC was identified in 6% of CD patients [21]. This association was confirmed by two large population-based studies from Danish and Swedish cohorts. In these studies, EMA tests were positive in 11% of PBC patients [22]. In addition, in the current study, significantly more AIH patients with PBC overlap were diagnosed with CD. Interestingly, a recent genome-wide association study has identified a single nucleotide polymorphism in the *SH2B3* gene as the first genetic risk factor for AIH outside the MHC region. This single nucleotide polymorphism has also been implicated in the genetic susceptibility to PBC and CD and may explain, in part, the increased co-occurrence of these diseases [14].

It has been shown that timely recognition of silent CD and the subsequent introduction of GFD can reduce the risk of developing CD-associated complications, including osteoporosis and intestinal lymphoma. Olsson *et al.* [23] showed that chronic active hepatitis may have a more serious outcome in patients with concomitant CD than in patients with normal short bowel villous architecture.

It is important to bear in mind that the elevated liver enzymes can normalize as a result of GFD. Kaukinen and colleagues described four patients with advanced liver disease who were found to have CD. The liver disease improved significantly after adapting a GFD [24]; however, another study did not observe this beneficial effect [25].

In conclusion, the results of this study show around 10 times higher prevalence of CD in AIH patients compared

with the general Dutch population. Awareness of the possibility of a concomitant CD in this patient category is therefore warranted, and screening for CD in AIH patients should be considered.

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Conflicts of interest

There are no conflicts of interest.

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