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Prevalence of coeliac disease in autoimmune liver disease and primary biliary cholangitis

Primer biliyer kolanjit ve otoimmün karaciğer hastalıklarında çölyak hastalığı prevalansı

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Abstract

Introduction: Coeliac disease (CD) is a small bowel disease, which occurs upon exposure to dietary gluten. CD is often associated with dermatitis herpetiformis, autoimmune thyroid disease, type 1 diabetes mellitus and autoimmune liver diseases. Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are the most common autoimmune liver diseases. In this study, we investigated the prevalence of CD in patients with PBC, AIH and overlapping PBC + AIH in our Hospital.

Methods: Ninety-nine patients with PBC, AIH and overlapping AIH + PBC were included in this study. Specific serum antibodies and specific duodenal biopsy results are used for diagnosis of CD.

Results: Ninety-nine patients with PBC (n=47; F: 95.7%; age: 53±10 years), AIH (n=23; F: 100%; age: 48±12 years) and overlapping AIH + PBC (n=29; F: 96.6%; age: 51±10.9 years) were included in this study. Three patients (6.4%) in the PBC group, one patient (3%) in the PBC + AIH group and two patients (8.7%) in the AIH group were serologically and histologically diagnosed with CD.

Discussion and Conclusion: Anti-gliadine antibody (AGA) positivity or anti-endomysium antibody (EMA) positivity alone was not sufficient for CD diagnosis. We suggest using both tests for CD screening to achieve more accurate results. In cases of positive CD-specific antibody results, we advise confirming the diagnosis by histopathological examination of duodenal biopsies

Keywords: Autoimmune hepatitis; coeliac disease; primary biliary cholangitis.

Özet

Amaç: Çölyak hastalığı (ÇH), glutene maruz kalındığında oluşan bir ince bağırsak hastalığıdır. ÇH, dermatitis herpetiformis, otoimmün tiroid hastalığı, tip 1 diabetes mellitus ve otoimmün karaciğer hastalıkları ile sıklıkla birliktelik gösterir. Otoimmün hepatit (OİH) ve primer biliyer kolanjit (PBK) en sık görülen otoimmün karaciğer hastalıklarıdır. Bu çalışmada, hastanemizde PBK, OİH ve PBK + OİH overlap tanılı hastalarda ÇH sıklığını araştırdık.

Gereç ve Yöntem: PBK, OİH ve OİH + PBK overlap tanılı hastalar çalışmaya dahil edilmiştir. ÇH tanısı spesifik serum antikorları ve spesifik duodenal biyopsi bulguları ile konulmuştur.

Bulgular: PBK (n=47; F: %95.7; yaş: 53±10 yıl), OİH (n=23; F: %100; yaş: 48±12 yıl) ve OİH + PBK overlap (n=29, F: %96.6, yaş: 51±10.9 yıl) tanılı toplam 99 hasta çalışmaya dahil edilmiştir. PBC grubundaki üç (%6.4), OİH grubunda 2 (%8.7), PBK+OİH overlap grubunda 1 (%3) hastaya serolojik ve histolojik bulgulara dayanarak ÇH tanısı konuluştur.

Sonuç: Tek başına anti-gliadin antikoru (AGA) pozitifliği veya tek başına anti-endomisyum antikoru (EMA) pozitifliği ÇH tanısı için yeterli değildir. Daha kesin tanı için, ÇH taramasında her 2 testin birlikte kullanılmasını ve ÇH spesifik antikorların pozitif tespit edildiği olgularda, tanının duodenum biyopsiyle desteklenmesini öneriyoruz.

Anahtar Sözcükler: Otoimmün hepatit; çölyak hastalığı; primer biliyer kolanjit.

CD (Coeliac disease) is a small bowel disorder which consists of mucosal inflammation, villous atrophy and crypt hyperplasia. CD occurs upon exposure to dietary gluten and improves after withdrawal of gluten from the diet. CD is usu-

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ally asymptomatic but may cause anaemia, diarrhea, fatigue, weight loss, abdominal pain and malabsorption. CD is often overlooked as a differential diagnosis of liver disease. The diagnosis of CD relies upon anti-gliadin (AGA), immunoglobulin A (IgA), immunoglobulin G (IgG), anti-endomysium antibody (anti-EmA) and anti-tissue transglutaminase (anti-tTG) antibodies. Duodenal biopsies (6-8 fragments) indicate villous atrophy, crypt hyperplasia and lymphocytic inflammatory infiltration. CD is associated with dermatitis herpetiformis, type 1 diabetes mellitus, thyroid and autoimmune liver diseases. AIH (Autoimmune hepatitis) is an inflammatory disease that mainly affects hepatocytes. AIH occurs due to an immunological response to normal liver cell membrane proteins and antigenic determinants on the membrane. PBC (Primary biliary cholangitis) is an autoimmune disease characterised by granulomatous and progressive destruction of small bile ducts in the liver. PBC and AIH are the most common autoimmune diseases of the liver. In different populations, many studies have shown that the frequency of coeliac disease increases in autoimmune liver diseases.[1–3]

In this study, investigated the prevalence of CD in patients with PBC, AIH and AIH + PBC.

Materials and Method

Ninety-nine patients with PBC, AIH and overlapping syndromes attending the hepatology outpatient clinic of Ege University hospital from January 2001 to December 2012 were included in this study.

All participating patients were informed about the study, and their written consent was obtained.

The PBC diagnosis was based upon the Paris criteria as follows: (1) serum alkaline phosphatase (ALP) >2 times upper limit of normal (ULN) or gamma-glutamyl transpeptidase (GGT) >5 times ULN; (2) a positive test for AMA; and (3) a florid bile duct lesion liver biopsy result.[4,5]

The diagnosis of autoimmune hepatitis was made according to Simplified scoring system recommended by the international autoimmune hepatitis group and liver biopsy results.[6]

Patients with histological features of autoimmune hepatitis, but with serological PBC findings (i.e. anti-mitochondrial antibodies (AMA)) and histologically confirmed cholangitis in liver biopsies were diagnosed as overlapping AIH + PBC syndromes.[7,8]

All patients were asked if they had any of the common CD symptoms. AST, ALT, ALP, GGT, albumin, T. bilirubin and complete blood count (CBC) test results were evaluated. The diagnosis of CD is usually based on the presence of serum antibodies (against deamidated gliadin, endomysium or anti-tissue transglutaminase) and duodenal biopsy results (the presence of intraepithelial lymphocytosis or villous atrophy and crypt hyperplasia of the small-bowel mucosa). Histopathological classification of coeliac disease was made using modified Marsh criteria.[9,10]

Venous blood samples were collected for the detection of EMA-AGA IgA and TTG-AGA IgA and sent to the Paediatric Immunology Laboratory (a tertiary reference laboratory).Blood samples were taken after an overnight fast and allowed to clot at room temperature. Serum was obtained following centrifugation, and aliquots were frozen at -20°C until assay. Samples were analysed by immunofluorescence (IF) and enzyme-linked immunosorbent assay (ELISA).

The presence of human IgA antibodies against endomysium (EmA) and deaminated gliadin (AGA) peptides in serum was detected by IIFT (Euroimmun, Lubeck, Germany). Slides which were coated with monkey liver tissue and deaminated gliadin peptides were used for in vitro determination of antibodies. The determination of EmA on classical tissue sections plays an important role in the confirmation of the coeliac disease diagnosis. According to test procedure serum samples diluted to 1:10 with PBS were applied on the slides and incubated for 30 minutes at room temperature. Slides were rinsed with a flush of PBS and immersed in PBS for 5 minutes, and then incubated for 30 minutes after applying fluorescein labelled anti human IgA. Slides were rinsed with a flush of PBS and immersed in PBS for 5 minutes again. A cover glass was placed on the slides after drying. Two paediatric immunologists examined the slides on a (Eurostar™) fluorescence microscope in a double-blind setting (each immunologist examined the samples separately, with no knowledge of the other's results or patient information). Quality control was ensured by using negative and positive controls with known antibody titres for each assay. Autoantibodies against endomysium react with many types of tissue. In the case of a positive sample filamentous linings of the intralobular sinusoids of monkey liver tissue shows a fluorescent reaction. And if the gliadin-specific antibodies present in the serum, green circular fluorescent areas fluoresce against a dark background. In qualitative determination, the initial 1:10 sample dilution factor was taken as cut off value for defining positive reactions for anti-EMA IgA and anti-AGA IgA antibodies in serum.

At least six samples were taken from the distal duodenal mucosa of patients by upper gastrointestinal system endoscopy when one or both of the antibody tests (AGA, EmA) were positive. Biopsies were evaluated by pathologists specialised in gastrointestinal tract pathology.

Ethics

The study was planned and completed in accordance with the Helsinki Declaration. The study protocol was approved by the local ethics committee.

Statistical analyses

Quantitative characteristics of three subgroups (PBC, AIC, PBC + AIC) were compared by one-way analysis of variance using mean and standard deviation.

For the two subgroups (CD and others), the distribution of the frequencies in the groups was heterogeneous, and the quantitative characteristics were compared using the Mann-Whitney

Table 1. Duodenal biopsy and antibody results

	Coeliac antibodies	n	%	Duodenal biopsy	n	%
PBC	AGA(+)	3	6.4	(MARSH I)	3	6.4
AIH	AGA(+)	1	4	(1 MARSH II) (1 MARSH III)	2	8.7
PBC+OIH	AGA (+) & EmA (+)	5	17	(MARSH I)	1	3
	AGA (+)	1	3			
	EmA (+)	1	3			

PBC: Primary biliary cholangitis; AGA: Anti-gliadine antibody; AIH: Autoimmune hepatitis.

U test with the mean, standard deviation and median.

Categorical distributions were evaluated by Chi-square or Fisher's exact test.

Analyses were performed using IBM SPSS version 19. The significance limit was accepted as $p < 0.05$ for all tests.

Results

Of 99 patients, 47 (F: 95.7%, age: 53±10 years) patients were diagnosed with PBC. Of the remaining patients, 29 had AIH and PBC (F: 96.6%, age: 51±10.9 years) and 23 had AIH (F: 100%, age: 48±12 years).

There were no significant differences in age and gender between groups.

Three patients (6.4%) in the PBC group, one patient (3%) in the PBC + AIH overlap group and two patients (8.7%) in the AIH group were serologically and histologically diagnosed with CD.

Antibody (AGA, EmA) and duodenal biopsy results are presented in Table 1.

Biochemical parameters and haemoglobin values were compared between the CD-diagnosed and CD-free patients, but no significant differences were found.

Discussion

CD is a primary small bowel disease that causes malnutrition. Moderate elevations in transaminases can be seen in CD (AST: 29–80 IU/dl, ALT: 60–130 IU/dl).[11,12] In a meta-analysis, CD-specific antibodies were found in 6% of patients with cryptogenic hypertransaminasemia and 4% of patients had a duodenal biopsy consistent with CD. In the same meta-analysis, hypertransaminasemia was detected in 27% of newly diagnosed Coeliac patients, and transaminase levels returned to normal within one year in 60–90% of patients on a gluten-free diet.[13]

CD is often associated with autoimmune liver diseases. AIH and PBC are the most common autoimmune liver diseases. In our study, CD was detected in 6.4% of patients with PBC, 8.7% of patients with AIH and 3% of patients with overlapping PBC and AIH. These values are higher than the current prevalence of CD in our study which is estimated to be 1.3% based on a study of healthy blood donors.[14,15] The prevalence of CD in AIH is 3–6%.[16–18] In one study, 157 type 1 and 24 type 2 AIH patients were investigated, CD serology was positive in 4.4%, CD-compatible duodenal biopsy findings were present in 2.8% and 75% of the patients were reported to be asymptomatic.[17] CD prevalence was 6.4% in a study of 47 AIH patients in Italy.[18] Our rate was slightly higher, and the CD prevalence was 8.7% in patients with AIH. In a Dutch cohort of 460 patients with AIH, 3.5% were diagnosed with CD, which was 10-fold greater than the general population. Most of the patients were of type 1 AIH and CD was diagnosed by the presence of positive anti-tissue transglutaminase IGA antibodies.[19] In a meta-analysis involving a total of 2049 paediatric patients and nine studies, the CD prevalence was 6.3% (95% CI 3.87–11.7) in children with AIH.[20] In another study, patients with AIH and CD who were treated with a gluten-restricted diet remained in remission longer than non-CD AIH patients. As CD leads to malabsorption, early diagnosis of CD may positively affect the prognosis of the disease in AIH patients.[21]

In an Italian study, the prevalence of CD in patients with AIH and PBC was 3.5% (14/281) and 5% (12/327), respectively.[22] In a multicentre study involving Italy, Sweden, France and Turkey, CD prevalence was 4.2% in patients with AIH/PBC overlap.[23] In our study, Coeliac disease was found in 3% of patients with overlap syndrome and appeared in similar proportions. In 1998, Kingham et al. found a CD prevalence of 6% (4/67) in PBC and many studies have found similar results.[24–26] In our study, CD was detected in 6.4% of the patients with PBC.

In both PBC and AIH groups, all patients with CD were anti-gliadin and anti-endomysium positive, but only one of the five patients with overlap syndrome was histopathologically positive for CD. In addition, CD was not detected histopathologically in any of the patients who were only positive for anti-gliadin. The frequency of coeliac disease in autoimmune liver diseases has increased. There was no significant association between the recommended screening criteria for CD (elevated transaminase levels, anemia, abdominal pain and complaints such as diarrhoea) and CD diagnosis.

In patients with AIH alone, low-titre anti-gliadin antibody positivity was not found to be suitable for CD screening. In addition, in some patients with overlap syndrome, CD was not supported by duodenal biopsy, although both antibodies (AGA and EMA) were positive. This result is thought to be due to the high levels of autoimmunity in these patients.

The incidence of myopathy and osteoporosis may increase due to vitamin D deficiency in combination with PBC and CD. When diagnosed, myopathy and osteoporosis treatment is simple, and results are satisfactory. CD patients with high cholestatic liver enzymes may be screened using anti-mitochondrial antibodies for PBC.

Low number of patients and absence of a control group were the major limitations of the study. Only patients with antibody positivity underwent endoscopy. Performing endoscopy to all participants would be better. Nowadays, more sensitive and specific methods than AGA are used in CD screening. We have used this study since AGA is already present in the database of study patients.

In our study, single AGA or EmA positivity was not sufficient for CD diagnosis. We believe that the combined use of two tests in CD screening will give more accurate results.Despite the low number of patients in our study, while investigating CD frequency in three different autoimmune diseases, the use of endoscopic duodenal biopsies proved to be useful in addition to autoantibody positivity. We suggest that autoimmune hepatitis markers and anti-mitochondrial antibodies should be evaluated in coeliac patients with liver enzyme elevation at outpatient clinics. In patients with PBC or AIH, it may be advisable to confirm the CD diagnosis with duodenal biopsy.

Conflict of interest: There are no relevant conflicts of interest to disclose.

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