

Should We Look for Celiac Disease among all Patients with Liver Function Test Abnormalities?

Mohammad Hassan Emami^{1,2,3}, Marzieh Hashemi², Soheila Kouhestani^{2,3}, Hajar Taheri², Somayeh Karimi²

¹Department of Gastroenterology and Hepatology, Isfahan University of Medical Sciences, ²Poursina Hakim Research Institute, ³Iranian Celiac Association, Isfahan, Iran

Correspondence to:

Dr. Mohammad Hassan Emami,
Faculty of Medicine, Isfahan University
of Medical Sciences, Isfahan, Iran.
E-mail: mh_emami@med.mui.ac.ir

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ABSTRACT

Background: Celiac disease (CD) has been found in up to 10% of the patients presenting with unexplained abnormal liver function tests (LFT). As there is no precise data from our country in this regard, we investigated the prevalence of CD in patients presenting with abnormal LFT.

Methods: From 2003 to 2008, we measured IgA anti-tissue transglutaminase (t-TG) antibody (with ELISA technique) within the first-level screening steps for all patients presenting with abnormal LFT to three outpatient gastroenterology clinics in Isfahan, IRAN. All subjects with an IgA anti-tTG antibody value of $>10 \mu\text{/ml}$ (seropositive) were undergone upper gastrointestinal endoscopy and duodenal biopsy. Histopathological changes were assessed according to the Marsh classification. CD was defined as being seropositive with Marsh I or above in histopathology and having a good response to gluten free diet (GFD).

Results: During the study, 224 patients were evaluated, out of which, 10 patients (4.4%) were seropositive for CD. Duodenal biopsies were performed in eight patients and revealed six (2.7%) cases of Marsh I or above (four Marsh IIIA, two Marsh I), all of them had good response to GFD. The overall prevalence of CD among patients with hypertransaminasemia, autoimmune hepatitis, and cryptogenic cirrhosis was determined as 10.7% (3/28), 3.4% (2/59), and 5.3% (1/19), respectively.

Conclusion: Serological screening with IgA anti-tTG antibody test should be routinely performed in patients presenting with abnormal LFT and especially those with chronic liver diseases including hypertransaminasemia, autoimmune hepatitis, and cryptogenic cirrhosis.

Keywords: Autoimmune hepatitis, celiac disease, hypertransaminasemia, liver disease, liver transplant

INTRODUCTION

The traditional concept of celiac disease (CD) is a chronic inflammatory disorder of the small intestine characterized by the clinical features of malabsorption. The characteristic

histological lesion of small intestine occurs in genetically susceptible individuals and responds to elimination of gluten from the diet.^[1,2]

Recent studies have shown elevated serum aminotransferases in 15 to 55% of patients with untreated CD. On the other hand, CD has been found in up to 10% of patients with unexplained abnormal liver function tests (LFT)^[3] and in about 3.5% of patients with non-alcoholic fatty liver disease as the only manifestation of the disease. It is also shown that some patients being investigated because of liver dysfunction have asymptomatic CD cases. In a study, 55 asymptomatic adults were investigated for the cause of raised aminotransferases, in whom, the prevalence of CD was 9%; and normalization of liver enzymes occurred with adherence to gluten exclusion.^[4]

Some investigators suggested that the possibility of CD should be investigated in patients with severe liver disorders, since dietary treatment may prevent progression to hepatic failure, even in cases in which liver transplantation is considered.^[5] Kaukinen *et al.* reported four adults being assessed for liver transplantation because of chronic liver diseases (three with cryptogenic hepatitis and one with congenital hepatic fibrosis) in whom CD was diagnosed following serological screening and gluten withdrawal led to improvement of hepatic function, eliminating the need for liver transplantation.^[6] Also, the co-existence of chronic autoimmune liver diseases including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis with CD is well recognized.^[7] Recently, a number of epidemiological studies have reported an increased prevalence of CD in patients with PBC (up to 7%) and an increased prevalence of PBC in patients with CD (up to 3%).^[8-10] This association has been so strengthened over the past decades with the estimated CD prevalence of up to 2.6% in patients with PSC, recommending screening of patients with PSC for CD.^[5,11,12] Similarly in patients with autoimmune hepatitis, the estimated prevalence of CD is as high as 3.5%.^[13] An association between hepatitis C virus (HCV) infection and CD in adults has also been reported^[14] and suggested to be the most common liver disease associated with CD.^[15]

There is a lack of information on the association between liver disorders and CD in

our country. Since early detection and treatment of CD is of great importance, whether it is purely or in association with other diseases responsible for the liver abnormality, we aimed to see if it is worthy to do serologic evaluation for CD routinely in patients with abnormal LFT irrespective of clinical setting or presence of an explanation for the abnormal LFT.

METHODS

Patients and setting

This study was conducted from 2003 to 2008 on all patients presenting with abnormal LFT to Poursina Hakim Research Institute from three outpatient gastroenterology clinics in Isfahan, Iran. All patients presenting with abnormal LFT not known to be related to acute drug toxicity, ischemic attack, or other toxic liver insults (such as alcoholic liver injury) were included in the study. The ethics committee of the Isfahan University of Medical Sciences approved the study and informed consent was obtained from all patients after explaining the aims and protocol of the study.

Assessments

All patients were interviewed by a gastroenterologist to consider all possible causes of liver abnormality and to review a checklist filled by a general practitioner to detect patient's signs and symptoms along with history of the diseases known to have association with CD. Besides that, all of the following tests were done to find a possible cause for abnormal LFT: serum Cu, ceruloplasmin, Fe, TIBC, ANA, Anti-Sm antibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-trypsin level (not phenotyping since it was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liver ultrasonography.

Liver abnormalities were divided into 10 categories based on laboratory and clinicopathological findings as follows: chronic autoimmune hepatitis, PBC, PSC, chronic hepatitis B, chronic hepatitis C, Wilson's disease, non-alcoholic steato-hepatitis, liver transplant candidates, cryptogenic cirrhosis, and chronic cryptogenic hypertransaminasemia (defined as abnormal serum aminotransferases on at least

three different determinations during the previous six months).

Serological assessment for CD

The IgA anti-tTG antibody was measured for all patients using an enzyme-linked immunosorbent assay (ELISA) technique by a commercially available kit (ORG540 A, ORGENTEC Diagnostica GmbH). The upper limit of the normal range (cut-off value) for t-TG IgA antibody, as determined by the manufacturer, was 10 μ /ml and results would be reported in terms of arbitrary units (Au/ml), an IgA anti-t-TG antibody above 10 Au/ml was considered positive. If the results were very low (<5Au/ml), IgA level was measured to rule out IgA deficiency.

Pathological assessment for CD

Seropositive cases and those with IgA deficiency were recommended to undergo upper gastrointestinal endoscopy. Endoscopy was done with a standard 110 cm long video endoscope (EG 2940, Pentax EPM-3300), by a single

Table 1: Frequency of patients with abnormal liver function test in each category

Category	Liver abnormality	Frequency (%)
Autoimmune liver diseases (n=73)	Autoimmune hepatitis	59 (26.3)
	PBC	4 (1.7)
	PSC	10 (4.4)
Viral hepatitis/ metabolic disorders (n=33)	Chronic hepatitis B	22 (9.8)
	Chronic hepatitis C	10 (4.4)
Others (n=114)	Wilson's disease	1 (0.4)
	NASH	63 (28.1)
	Liver transplant candidate	4 (1.7)
	Cryptogenic cirrhosis	19 (8.4)
	Chronic cryptogenic hypertransaminasemia	28 (12.5)

PBC: Primary Biliary Cirrhosis, PSC: Primary Sclerosing Cholangitis, NASH: Non Alcoholic Steato-Hepatitis

Table 2: Celiac cases in patients with liver function test abnormality

Case number	Sex	Age (year)	Liver abnormality	IgA anti-tTG (U/mL)	Intestinal biopsy
1	Female	21	Autoimmune hepatitis	10.1	Marsh IIIA
2	Female	23	Autoimmune hepatitis	45	Marsh IIIA
3	Male	30	Hypertransaminasemia	18.5	Marsh IIIA
4	Male	58	Hypertransaminasemia	13.4	Marsh IIIA
5	Male	53	Hypertransaminasemia	36	Marsh I
6	Female	70	Cryptogenic cirrhosis	20.7	Marsh I

gastroenterologist, during which four biopsy specimens were obtained from the distal part of the second portion of duodenum. The specimens were processed and stained with HandE and studied under light microscopy by a gastrointestinal oriented pathologist. Histopathology was reported according to the Marsh classification (1992), considering intestinal "infiltrative" phase with more than 30 lymphocytes per 100 epithelial cells, defining as Marsh type I, "infiltrative/hyperplastic" phase as Marsh II and "partial, subtotal, or total villous atrophy" as Marsh IIIA, IIIB, and IIIC, respectively. Seropositive patients found to have at least Marsh I with an expected good response to gluten free diet (GFD) was considered to have CD.

RESULTS

During the study, 224 patients with abnormal LFT were evaluated; 131 were male (mean age = 39.6 years, SE = 1.2) and 93 were female (mean age = 38.5 years, SE = 1.4). Population of patients in each category is shown in [Table 1].

Ten patients (4.4%) had positive IgA anti-tTG and nobody was found to be IgA deficient. One of the seropositive patients refused any further investigation, and unfortunately, one another patient with cryptogenic cirrhosis who was candidate for liver transplantation died with advanced liver failure before further investigations. Finally, duodenal biopsies were performed in eight cases. Six patients had at least Marsh I in histopathology; all of them had good response to GFD [Table 2]. Accordingly, 4.4% (10/224) of all patients were seropositive for CD and at least 2.7% (6/224) of the cases were diagnosed to be definite CD cases.

Clinical and paraclinical findings in CD cases are shown in [Table 2]. Among patients with hypertransaminasemia, not having any other

explanation for the abnormality, 10.7% (3/28) had CD and out of 59 cases with autoimmune hepatitis, two patients (3.4%) had CD; none of the CD cases had PBC or PSC. One of the patients with CD had cryptogenic cirrhosis and so the prevalence of CD among patients with cryptogenic cirrhosis was determined as 5.3% (1/19). The underlying disorder in four candidates of liver transplant were as follows; hepatitis C, PSC, autoimmune hepatitis, and cryptogenic cirrhosis.

Four patients with Marsh IIA and two with Marsh I started the GFD and was followed every month for a period of six months to evaluate the response. Gluten withdrawal led to improvement of hepatic function in all cases and decline in transaminases within about eight weeks [Table 3].

DISCUSSION

The aim of this study was to investigate if it is worthy to screen patients with abnormal LFT for CD. Our study results demonstrated that there is at least double increase in risk of CD in patients presenting with abnormal LFT compared with general population (2.7% vs. ~1%). The prevalence of CD among Iranian populations (healthy Iranian blood donors) is reported to be 1:104,^[16] but its prevalence among western European populations is thought to be about one per 100-300.^[17,18] One of the reasons underlying the discordant data on prevalence is related to severity of clinical presentation and duodenal histological changes as shown by our previous study that sensitivity of serological tests is highly related to it.^[17,18] However, this high prevalence of CD in patients with

abnormal LFT suggests that serological screening should be considered routinely in such patients by IgA anti-endomysial or anti-tTG antibody.

In our study, positive IgA-tTG was detected with a significantly increased frequency compared to data from our general population (0.96% according to Akbari *et al.* study vs. 4.4% in our study; OR=4.583).^[16] Other investigators have also recommended regular LFT checkups in patients with CD.^[3] Our results are consistent with data from Italy^[3] and Spain,^[13] suggesting that screening for CD should be considered in patients suffering from chronic liver diseases. In contrast to our study, some reports from Sweden^[19] and Greece^[10] have shown no association between CD and chronic liver diseases. The possible explanation relevant to these controversies could be the methodological differences in detecting and defining CD, like the different serological tests used for screening, the degree of intestinal damage defined to include as CD, or genetic variations in different geographic areas making variability of CD complications.

Our study has shown that the prevalence of CD (seropositive) among liver transplant candidates is 25% (1:4), but the patient died before further investigations and we couldn't evaluate his response to GFD. Even though four cases of liver transplant candidates are not enough for a definite conclusion, another study also suggests that transplant candidates would require an evaluation for CD.^[6] Kaukinen *et al.* reported four adults being assessed for liver transplantation because of chronic liver disease (three with cryptogenic hepatitis and one with congenital hepatic fibrosis) in whom CD was diagnosed following serological screening. The authors reported that gluten withdrawal led to the improvement of hepatic function and transplantation was avoided.^[6] Likewise, Ojetti *et al.*^[20] reported a 28-year-old woman with acute liver failure of unknown etiology that turned out to be a case of CD through the transplantation program and after the initiation of GFD, a significant improvement in the liver function ensued. Currently, her liver disease is in remission with a GFD being her only therapy omitting the need for liver transplantation.^[8] Although according to Vivas *et al.* study,^[21] the prevalence of CD in patients with cryptogenic hypertransaminasemia is 9%, 18 times higher than their general population,

Table 3: Level of transaminases in patients with chronic liver disease before and after GFD

Case number	Before GFD		After GFD	
	AST (U/ml)	ALT (U/ml)	AST (U/ml)	ALT (U/ml)
1	69	50	37	24
2	55	40	29	25
3	118	85	35	38
4	1281	620	29	40
5	35	107	36	34
6	78	96	28	12

GFD: Gluten free diet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

but its prevalence among our patients was 10.7% which is about 10 times higher than our general population. One study reported a firm link of CD with autoimmune cholangitis, recommending screening for CD in patients with these disorders and vice versa (screening for PBC and/or PSC in patients with CD).^[19] But none of the patients with autoimmune cholangitis had CD in our study. Similarly, Chatzicostas *et al.*^[11] showed no relationship between CD and autoimmune cholangitis. Therefore, there have been no efforts to evaluate patients with autoimmune cholangitis for CD, presumably because this disorder represents a rare form of chronic cholestatic liver disease.

In our study, CD was found in 3.4% of patients with autoimmune hepatitis which is in agreement with a study from Crete, Greece.^[10] In contrast to our study, an increased prevalence of CD in HCV/HBV positive patients has been reported recently. In such patients, CD might arise as a part of the multiple autoimmune conditions triggered by HCV.^[14,15] CD should be detected in patients with hypo-albuminemia and ascites, but otherwise well-preserved liver function. If necessary, a GFD should be implemented, as this may improve the overall condition of the patient.^[6] The best screening methods for large number of individuals are based on non-invasive serological tests^[22-24] and we used anti-tTG compared with the classical anti-gliadin or anti-endomysium antibodies. According to Iacono *et al.*,^[3] the best screening test to estimate the prevalence of CD in patients with unexplained liver damage was IgA anti-tTG and the confirmation of disease in isolated borderline values was done by IgA anti-endomysium before performing duodenal biopsy.

CONCLUSION

According to high prevalence of CD among patients presenting with abnormal LFT, we recommend that serological screening by IgA anti-tTG test should be routinely performed in these patients as well as in patients with chronic liver diseases such as autoimmune hepatitis, cryptogenic cirrhosis, hypertransaminasemia, and also in liver transplant candidates. Early detection of possible CD cases would help to prevent progression of chronic liver disease to hepatic failure. More

studies should be done to find the prevalence of CD in different ethnic groups with liver diseases and to determine diagnostic value of various serological tests in different underlying diseases and clinical settings.

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