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Evaluation of patients with idiopathic portal hypertension: Could tissue transglutaminase antibodies predict the celiac disease?

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ABSTRACT

Idiopathic portal hypertension (IPH) traditionally has been described as a diagnosis of exclusion in patients who have presinusoidal portal hypertension. Gut- derived serologic markers in IPH are an increasing focus of attention, but there are only a few published studies on serological markers of celiac disease in patients with IPH and the results are contradictory. Furthermore, the role of tissue transglutaminase (TTG) antibodies have not been identified yet.

This study determined what proportion of IPH patients had a seropositivity of TTG antibodies and evaluated the role of TTG antibodies in IPH. Demographics and clinical data, TTG antibodies, hematologic and biochemical parameters and radiologic studies were retrospectively reviewed in all IPH patients attending our hospital.

10 clinically and biopsy-proven IPH patients (8 women and 2 men) were identified, all of them were diagnosed between 2009 and 2011. IgA and G antibodies to tissue transglutaminase were evaluated in all patients. 5 patients had a positive TTG IgA, 3 patients had a positive TTG IgG and 2 of them had negative autoantibodies. No patient was IgA deficient. 6 patients were eligible for duoenal biopsy and none of them had biopsy-proven celiac disease (CD).

Conclusions: Although the data are limited, this study suggests that seropositivity for TTG antibodies could be positive in IPH. But there was no relation between positive serologic results and CD.

Key Words: Idiopathic portal hypertension, tissue transglutaminase, Celiac Disease

Introduction

IPH is an unusual cause of portal hypertension and is still a significant problem in many countries in Asia as well as in Turkey. It is characterised by elevated portal pressure in the absence of significant parenchymal liver damage or extrahepatic portal tract obstruction. In this disease, there is an intrahepatic presinusoidal hypertension, in view of the normal HVPG.

The major manifestations of IPH are variceal bleeding and hypersplenism due to massive splenomegaly. Ascites and deterioration of liver tests are usually absent. Patient survival is often determined by variceal bleeding (1,2).

Despite no spesific findings exist in the IPH-related liver disease, the main histological features are perisinusoidal fibrosis, sinusoidal dilatation and irregulary distributed hepatic blood vessels neighboring to peripheral portal tract (3).

Etiologic factors of IPH are still unknown in vast majority of patients, although chronic exposures to arsenic (4) and vinyl chloride (5), hypervitaminosis A (6) and azathiopurine (7) have been implicated.

Despite the poisoning- medical drug theory, many factors have been proposed for the disease progression, the most important of them is postulated an increase in cytokine levels. Cytokines such as platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF) may play a role on underlying ethiology of IPH (8).

Furthermore, a number of autoimmune diseases, such as autoimmune hepatitis (9), celiac disease (10), rheumatoid artritis (11), mixed connective tissue disease (8), progressive systemic sclerosis (PSS) (12), systemic lupus erythematosus (13) and primary antiphospholipid syndrome (14) has been reported as etiologic causes.

Another proposal theory for the disease development is portal hyperantigenemia due to poor sanitation related chronic enteral infections (2,15). A major clinical argument for a pathogenic

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role of enteral infectious agents comes from the observation of the India where IPH is prevalent and enteral infectious agents are common (16).

Idiopathic portal hypertension (IPH) is uncommon in Turkey, but is common in eastern parts of Asia such as Japan (17). Few articles has been reported from Turkey (18). There have been a few reports about links between IPH and serologic markers of celiac disease. Most of them show the obscure relation is evident between the two distinct diseases (10, 19, 20). Our aim was to investigate the presence of tissue tranglutaminase antibodies in patients with IPH.

Material and methods

This was a retrospective study performed at the Gastroenterology unit of university hospital, Van, Turkey, from 1998 to 2011. IPH was confirmed with clinic, radiologic and laboratory methods as well as histopathologic studies. Ten patients, eight females and two males, with IPH were included in the study.

The diagnosis of IPH was based on the clinical, endoscopic, histopathological and radiographic findings according to the criteria issued by the APASL (21).

A detailed medical history was obtained and a physical examination as well as laboratory studies were performed in all patients. Diagnostic procedure included abdominal ultrasonography, thoracoabdominal tomography and portal vein doppler ultrasonography. Percutanous liver biopsy was also performed for all patients in order to detect IPH.

Serum samples were obtained from all patients and tissue transglutaminase antibodies were assessed by automatic ELISA triturus analyzer (Grifols-USA) in microbiology laboratory.

To determine whether the patients have true celiac disease, 10 of 5 patients with histologically proven IPH underwent duodenoscopy and biopsy was taken from the second part of duodenum. 5 case were unavaible for endoscopic biopsy because of severe thrombocytopenia.

Data were recorded on SPSS program. Statistical analysis was performed using SPSS and significance determined by independent samples t-test.

Results

80% of patients were women (n=8); median age was 30.2 years (SD ± 9.9). Almost all patients were residents of rural areas of the Van prefecture.

All patients were born in their villages without a medical stuff and there were more than five family members in their homes. Medical history for PICA (eating unpalatable things such as sand) was reported in 7 patients. Only two patients have experienced a variceal bleeding. Other associated diagnoses were as follows: micrognatia, megasisterna magna and famial mediterranean fever.

Moderate to severe splenomegaly in association with splenic vein enlargement was detected in all patients. Mean splenic vein diameter was 13.4 mm (SD±3.2) and average splenic size was 226 mm (SD±69). Mean portal vein diameter was calculated as 15.5 mm (SD±5).

All of the patients had anemia, 7 of them had microcytic or iron deficiency anemia. Thrombocytopenia was prominent in all cases. Mild prolonged prothrombine time was detected in 8 patients.

Liver-related transaminases were mildly elevated in 3 patients. Alkaline phosphatase level was elevated in 7 patients and GGT level was elevated in 3 patients. Policlonal hyperglobulinemia was observed in 4 patients. ANA (Antinuclear antibody) seropositivity was detected in three patients.

All liver biopsy specimens revealed perisinusoidal or periportal fibrosis with sinusoidal dilatation and lack of cirrhosis.

Among the 10 patients with IPH, 5 (50%) had TTG IGA positive, 2 (20%) had TTG IgG positive and the remaining 3 (10%) had no antibodies.

Upper endoscopy with duodenal biopsies was performed in patients with positive serologic tests and none of them had celiac disease.

Gastroesophageal varices were also evident on endoscopy in all of the patients. Endoscopic band ligation was performed in four cases. No death was identified at follow-up program.

Discussion

IPH is classified as a cause of noncirrhotic portal hypertension with obscure etiology and characterised by periportal fibrosis with turmoil of small and medium branches of the portal vein. Diagnosis of IPH is made by a combination of clinical, laboratory, radiologic and histopathologic studies. As a rule, lack of cirrhosis in connection

with well- preserved hepatic paranchymal microarchitecture in a patient with portal hypertension and no established ethiology of other liver diseases may suggestive for the disease as well (17).

Epidemiologic studies show that the disease more prevalent in eastern parts of the world than in the western countries. Furthermore, low socioeconomic status and chronic enteric infections are related to the disease. IPH is more common among women than men (2).

In the current study 8 (80%) patients were female. All of them were living in rural areas of the city and had a lower socioeconomic status. PICA (eating of unpalatable things) was also a striking finding which was rarely reported in previous studies.

Almost always, liver tests remain in near-normal ranges in patients with IPH. Classical findings of the disease include hepatosplenomegaly, anemia, trombocytopenia, esophageal varices, lack of evidence of liver cirrhosis in liver biopsy specimens. Elevated levels of cholestasis enzymes and prolonged PT are usually seen in patients with IPH (3, 22, 23).

In this trial, all patients had anemia and thrombocyopenia due to hypersplenism. Mildly elevated liver-related transaminases were evident in 4 (40%) patients. Raised levels of alchaline phosphatase were seen in 6 (60%) patients. Three patients had also elevated GGT levels. Almost all patients had a mild to moderate prolonged PT.

Many immunological alterations have been reported among patients diagnosed with IPH, including policlonal hypergammaglobulinemia, evidence of antinuclear and anti-smooth muscle antibodies (24).

In our study, 4 (40%) patients were found to have hypergammaglobulinemia. The remainder of the major abnormality consisted of a positive ANA in 3 (30%) patients.

Abdominal ultrasound examination is revealed the IPH- related changes such as splenomegaly, enlarged splenic and portal veins, collateral veins as well as thickening of portal vein at the level of portal hilus. Splenoportography may use as a dignostic tool to detect dilated portal vein at the hepatic hilum which is a characteristic finding for the disease (2).

All of our patients had portal hypertension associated radiologic findings such as splenomegaly and enlargement of portal and splenic veins. Splenoportography was performed on three patients as an additional procedure.

Esophageal varices due to enlarged portal and splenic veins are also prominent in patients with IPH. So, the most devastating complication of the disease is variceal bleeding. Therefore, palliative treatment of IPH must always include the portal pressure lowering agents such as propranolol. Endoscopic sclerotherapy and band ligation are used in case of acut variceal bleeding. Clinical course is almost undeteriorated for a long time (25).

We identified esophageal varices, by means of the panendoscopy, in all patients. Three of them had also additional gastric varices. No major variceal bleeding was reported. We may propose that deathly esophageal variceal bleeding was not a significant problem in our cases.

CD is a chronic autoimmune disorder of small intestinal mucosa and caused by gluten sensitivity related mucosal damage. A massive infiltration of the lamina propria with lymphocytes in the small bowel biopsy samples is hallmark of the CD. Partial or total atrophy of intestinal villi occur as a result of the disease. In patients with CD, histocompatibility antigen HLA-DQ2, which is related with autoimmun diseases, is found in majority of the cases (26).

The classical features of celiac disease include anemia, chronic diarrhea and weight loss. Raised levels of antibody to gliadin of both the IgG and IgA are the main cornerstones of serologic diagnosis. If a selective IgA deficiency is not evident, TTG IgA has a sensitivity of 93% and a specifity of 95%. These antibodies should be used only in support of the diagnosis and should not be replaced to duodenal biopsy (27).

We have still little knowledge on whether CD is prominent in IPH or whether the autoantibodies are found incidentally.

TTG antibodies but not anti-endomysium antibodies may be found in a wide range of extraintestinal circumstances. One of them has been reported as hepatic diseases. However, patients with liver disease are found at particular risk of false positive results for CD despite the positive serum TTG antibodies (28).

Furthermore, an Italian study frankly indicated that serum TTG IgA ELISA determination based on TTG from guinea pig liver as the target antigen has a low sensitivity and specifity in screening patients with chronic liver disease for CD (29).

A few studies have shown that celiac disease may coexist with IPH (10,19). In a recently published British study showed that 16% of patients with IPH found to have concomitant CD (30). But in

this study, it is unclear whether the CD were responsible for the ethiology of IPH, because disease resolution was not reported following gluten-free diet.

Our study results demonstrated that existence of celiac autoantibodies were seen in vast majority of patients with IPH. Interestingly, the positive results of serologic tests failed to predict the diagnosis of CD. This may indicate that enteral disturbances have a significant impact in the pathogenesis of IPH or the serologic tests based on tTG from guinea pig liver as the target antigen has higher false positive results in patients with IPH.

Obviously, our preliminary findings need to be confirmed in prospective trials with larger series, evaluating serologic markers for diagnosis of IPH. Furthermore, new-concept serologic tests may help to detect the disease in near future. Finally, tissue transglutaminase antibodies should not be used as a screening test for CD particularly in patients with liver diesase.

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