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Prevalence of IgG-4-associated cholangiopathy based on serum IgG-4 levels in patients with primary sclerosing cholangitis and its relationship with inflammatory bowel disease

BILIARY

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ABSTRACT

Background/Aims: Autoimmune cholangiopathy is part of a fibro-inflammatory immunoglobulin G-4 (IgG-4)-related systemic disease that causes biliary tract strictures. Its clinical presentation is quite similar to that of more common diseases such as primary sclerosing cholangitis (PSC) and pancreatobilliary malignancies. The aims of the present study were to evaluate the prevalence of IgG-4-associated cholangiopathy (IAC) in patients diagnosed with PSC and its relationship with inflammatory bowel disease (IBD).

Materials and Methods: Serum IgG-4 levels were measured in 73 patients. Laboratory data and imaging and endoscopic results were collected from their medical records. The diagnosis of PSC was based on the results of imaging and laboratory data as well as clinical presentation.

Results: Serum IgG-4 levels were elevated in 12 patients (16%); half of these patients had IBD. In the group of patients with normal serum IgG-4 levels, 39 patients (63.9%) had IBD (p=0.364). There were no significant statistical differences between PSC patients with normal and elevated serum IgG-4 levels in terms of age, smoking, presence of IBD, extension and severity of IBD, esophageal and gastric varices, Child and the model for end-stage liver disease (MELD) scores, and anatomical location of the biliary stricture (p>0.05). The prevalence of ascites was higher in patients with elevated serum IgG-4 levels (p=0.029).

Conclusion: Compared with previous reports, high serum IgG-4 levels were detected in a higher percentage of patients with a preliminary diagnosis of PSC (12% versus 16%). However, there were no clinical or imaging characteristics that could differentiate PSC patients with normal IgG-4 levels from PSC patients with higher IgG-4 levels.

Keywords: Immunoglobulin G-4-associated cholangiopathy, primary sclerosing cholangitis, inflammatory bowel disease, MELD

Original Article

INTRODUCTION

Immunoglobulin G-4 (IgG-4)-associated cholangiopathy (IAC) is a fibro-inflammatory disease that is part of an autoimmune syndrome named IgG-4-associated systemic disease (ISD). IAC can lead to inflammation, fibrosis, and narrowing of the bile ducts (1,2). Diffuse pancreatic enlargement or a pancreatic head mass associated with strictures and irregularity of the pancreatic duct are common features of IAC. However, other organ involvement such as sialoadenitis, lymphatic, renal, retroperitoneal, and mediastinal fibrosis has also been described. Occasionally, IAC presents itself as the only manifestation of ISD, involving the bile ducts (2-5). IAC is a relatively new concept (1), and the first reported cases of the disease were in 1963, where two patients with PSC along with pancreatic involvement were described in the Mayo Clinic (6). Since then, several studies have illustrated case series on biliary strictures in association with autoimmune pancreatitis (7-9). Despite the increased awareness of IAC as a distinct disorder, the pathogenesis associated with this disease has not been clearly defined (1,10,11). Two autoimmune and allergic mechanisms have been proposed in the pathogenesis of IAC. It seems that activated Th-2 lymphocyte produces cytokines, which then leads to the excessive proliferation and maturation of B cells and plasmocytes, ultimately leading to IgG-4 production (12,13).

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Patients who clinically present with evidence of jaundice, weight loss, and abdominal pain were assessed (1,2). Jaundice is mainly due to the narrowing and sclerosis of intrahepatic bile ducts or the involvement of the intrapancreatic portion of bile ducts, and in some cases, it is associated with autoimmune pancreatitis, which causes a pancreatic head mass (1,13). In most cases, because of radiographic similarities between IAC and primary sclerosing cholangitis (PSC), the diagnosis of IAC is overlooked unless concurrent pancreatic and biliary involvement are recognized (13).

Primary sclerosing cholangitis is a progressive chronic cholestatic disease with intra- and extrahepatic bile duct involvement, which causes inflammation and sclerosis around the bile ducts, which, in the long term, lead to the segmental narrowing of the bile ducts (14). At present, no effective treatment has been developed for this illness, and most patients develop cirrhosis complications within a few years. The average survival period of these patients is between 12 and 17 years, and liver transplant is the only cure for this illness. IAC, if diagnosed, has a good clinical response to corticosteroids. Patients with equivalent radiological findings with PSC and elevated serum IgG-4 levels have a more severe and progressive course, with an increased need for liver transplantation (1,11).

IgG-4-associated cholangiopathy also should be differentiated from other diseases such as cholangiocarcinoma and pancreatic malignancies. Misdiagnosis may lead to unnecessary treatment and even surgical intervention. Therefore, the early diagnosis and treatment of IAC are important in the prognosis of these patients (1). However, because of the fact that patients with IAC show no signs of the illness, except for abnormal liver tests, under some circumstances, we had two aims in this study: to measure the prevalence of IAC on the basis of serum IgG-4 levels in patients with PSC and to evaluate its relationship with the frequency and severity of IBD.

MATERIALS AND METHODS

Ethical statement

The protocol of the present study was approved by the Ethical Committee of Shiraz University of Medical Sciences, Shiraz, Iran. Also, our study followed the Helsinki Declaration of 1975, as revised in 2000 (available at http://www.wma.net/e/policy/17-c_e.html). The patients were thoroughly briefed on the detailed procedures and filled out the relevant questionnaire; their consents were obtained and arrangements were made for their blood samples to be taken for further analysis.

Sample, inclusion and exclusion criteria

In this cross-sectional study, patients with a preliminary diagnosis of PSC attending Motahari Transplant Clinic affiliated to Shiraz University of Medical Sciences, Shiraz, Iran and who were on a waiting list for liver transplantation were enrolled in the study. The diagnosis of PSC was based on the following criteria:

- Clinical observations of cholestasis, jaundice, and itching;
- Laboratory data demonstrating abnormal elevated alkaline phosphatase and gamma glutamyl transferase activities not related to other causes of cholestasis;
- Sufficient evidence, such as pancreatic and bile duct involvement, in magnetic resonance cholangiopancreatography (MRCP) or in endoscopic retrograde cholangiopancreatography (ERCP);
- Exclusion of secondary cholestasis;
- As the last resort where the above information did not deliver sufficiently clear results, a histological examination by liver biopsy was carried out on a small numbers of patients.

Our inclusion criteria were patients aged between 18 and 70 years old, who were referred to the clinic between September 2014 and August 2015. Patients suspected of having cholangiocarcinoma and overlap syndromes with autoimmune hepatitis were excluded.

Demographic information

A questionnaire concerning demographic information, history of smoking, and the presence of clinical complaints was completed by each patient. MRCP, ultrasound, and colonoscopy results were extracted from each patient's medical records. Based on the biochemical results and other obtained information, the Child score and the model for end-stage liver disease (MELD) score were calculated.

The patients' colonoscopy results were divided into different categories in which the intensity of bowel involvement was defined as mild, moderate, or severe. In term of disease extension, the categories of proctitis, left side colitis, extensive colitis, or patchy involvement were defined. The intensity of bowel involvement in endoscopy was based on the division defined by the Mayo score as follows:

- Mild: mucosal erythema and slight brittleness, reduce vascularity;
- Moderate: mucosal erythema and fragility, noticeable loss of vascular pattern, the presence of erosions;
- Sever: ulceration and spontaneous bleeding.

MRCP was performed for all patients, including patients who had ERCP. Bile duct and pancreatic involvement were diagnosed based on MRCP and/or ERCP. The endoscopy results were reviewed to check for the presence of gastric or esophageal varices, while ultrasound and, if available, abdominal CT scans were reviewed for the presence of ascites.

Serum IgG-4 measurement

Serum IgG-4 was evaluated by nephelometry method using the MININEPH PLUS device as a semi-automatic efficient system to determine the levels of several blood plasma proteins at low volumes in terms of mg/L. The normal limit of test is 62–1127 mg/L and the kit is designed to measure and detect an abnormal metabolism of IgG-4. When the obtained values were higher than the recommended range of the kit, re-measurement was performed at a dilution level of 1:5. Furthermore, serum IgG-4 levels equal to or more than 135 mg/dL were considered as abnormal elevated IgG-4.

Statistical analysis

Data were presented as the frequency and percentage for qualitative variables and the mean and SD for quantitative variables. All the data were analyzed by SPSS version 19 using Chi-square tests and independent samples T- tests to find significant relationships and differences at $p<0.05$.

RESULTS

Data were collected from 73 patients, of whom 26 were female (35.6%). The demographic information of these patients based on normal or elevated serum IgG-4 levels is presented in Table 1.

As shown, 61 patients (83.6%) had normal serum IgG-4 levels, with a mean age of 38.56±10.72 years old, while 12 patients (16.4%) had high serum IgG-4 levels, with a mean age of 34.58±8.63 years old. No significant difference was detected related to the MELD score between the two groups (14.28±5.65 vs. 15.42±8.69 in PSC patients with normal and elevated serum IgG-4 levels, respectively, p=0.85). Most of the patients in both the normal and elevated serum IgG-4 groups had a Child B score (31 patients (50.8%) in PSC patients with normal serum IgG-4 levels and 7 patients (58.3%) in PSC patients with elevated serum IgG-4 levels). In the group with high levels of serum IgG-4, 11 patients (91.7%) had jaundice and itching symptoms, while in the group with normal levels of serum IgG-4, 59 patients (96%) were symptomatic (p=0.42). In the normal serum IgG-4 group, 39 patients (63.9%) had IBD, while in the high serum IgG-4 group, only 6 patients (50%) had IBD (p=0.364). In the high serum IgG-4, 1 patient (16.7%) had proctitis, 1 patient (16.7%) had left side involvement, and 4 patients (66.7%) had extensive involvement (p=0.79).

DISCUSSION

The differences in clinical observations and the intensity of the liver disease and bowel involvement in PSC patients with normal and high serum IgG-4 levels were investigated. We found that with the exception of ascites, which had a significantly higher frequency in elevated serum IgG-4 patients, no significant differences existed in terms of other variables between PSC patients with normal and high serum IgG-4 levels.

Table 1. Mean±SD and frequency (percentage) of demographic information in IgG4 normal and abnormal groups

	IgG4 (normal)	IgG4 (elevated)	p
Age (mean±SD, years)	38.56±10.72	34.58±8.63	0.231
MELD	14.28±5.65	15.42±8.69	0.85
Gender			0.99
Male	39 (63.9)	8 (66.7)	
Female	22 (36.1)	4 (33.3)	
Symptoms			0.42
Yes	59 (96.7)	11 (91.7)	
No	2 (33)	1 (8.3)	
Child score			0.74
Child A	22 (36.1)	3 (25)	
Child B	31 (50.8)	7 (58.3)	
Child C	8 (13.1)	2 (16.7)	
Smoking			0.18
Yes	3 (4.9)	2 (16.7)	
No	58 (95.1)	10 (83.3)	
Colonoscopy			0.51
Normal	22 (36.1)	6 (50)	
Abnormal	39 (63.9)	6 (50)	
Liver MRCP			0.18
Intrahepatic bile duct	28 (45.9)	3 (25)	
Intra- and extrahepatic bile duct	33 (54.1)	9 (75)	
Pancreatic MRCP			0.99
Normal	59 (96.7)	12 (100)	
Abnormal	2 (3.3)	0 (0)	
Sonography ascites			0.04
Yes	16 (26.2)	7 (58.3)	
No	45 (73.8)	5 (41.7)	
Varices endoscopy			0.49
Yes	32 (52.5)	5 (41.7)	
No	29 (47.5)	7 (58.3)	
Colonoscopy severity			0.81
Mild	25 (64.1)	5 (83.3)	
Moderate	7 (17.9)	0 (0)	
Sever	7 (17.9)	1 (16.7)	
Colonoscopy extension			0.79
Proctitis	4 (10.3)	1 (16.7)	
Left side colitis	4 (10.3)	1 (16.7)	
Extensive	27 (69.2)	4 (66.7)	
Patchy involvement	4 (10.3)	0 (0)	

SD: standart deviation; IgG4: immunoglobulin G-4; MELD: model for end-stage liver disease; MRCP: magnetic resonance cholangiopancreatography

IgG-4-associated cholangiopathy diagnosis is based on histology, imaging, serology, other organ involvement, and the response to corticosteroid therapy (HISORt) criteria provided by the Mayo Clinic (1). Type 2 IAC with both intra- and extrahepatic involvements is very similar to PSC (13, 15). Patients with both diseases have similar clinical symptoms, but a sudden onset of obstructive jaundice is more visible in patients with IAC than with PSC (75% versus 4%) (16). Both PSC and IAC are more common in men than women. IAC patients are mostly older men with an average age of 60 years old, while patients with PSC are young or middle-aged patients with an average age of 40 years old (13,15). Nakazava et al. (17) evaluated the cholangiographics findings of biliary involvement in patients with IAC. They reported that in IAC patients, the cholangiographics findings comprised a long segmental stenosis and prestenotic dilatation of the distal common bile duct, while in PSC patients, stenosis was more likely to appear as a Rosary bead, band shaped or as a pruned tree. In a large cohort study conducted by Mendes et al. (18), high levels of serum IgG-4 were detected in 9% of PSC patients, and these patients with elevated serum IgG-4 levels had a higher rate of liver cirrhosis.

Studies conducted by Boonstra et al. (19) on PSC patients showed that 15% of them had high serum IgG-4 levels. The positive predictive value in relation to IAC in patients who had serum IgG-4 levels between 1 and 2 times higher than the normal levels was 28%. A study by Björnsson et al. (20) conducted on 285 patients with PSC found that 12% of patients had higher than normal serum IgG-4 levels and of these, 4 patients (17%) had pancreatic involvement. The use of serum IgG-4 in the diagnosis of IAC from PSC is helpful, but should not be used as the sole factor for the diagnosis of IAC (1,11). In this respect, a positive anti-neutrophil cytoplasmic antibody (ANCA) will be beneficial for the diagnosis of PSC (13,15). In preliminary studies, a higher serum IgG-4 level was introduced as a highly sensitive and specific marker of IAC disease. However, in subsequent studies, it has become clear that an increase in the serum level of IgG-4 can be observed in allergic diseases too, such as asthma and atopic dermatitis, as well as in autoimmune diseases, such as pemphigus vulgaris, myasthenia gravis, vasculitis including systemic lupus erythematous, and in malignancy of the bile ducts and pancreas (11,12). The exact serum IgG-4 level that is sensitive for IAC diagnosis has not yet been clearly defined. However, a serum IgG-4 level equal to or more than 135 mg/dL is regarded as an acceptable level for detection of IAC. However, it has been reported that a 2-fold increase compared to the normal value would provide a considerably higher rate of IAC detection and differentiation of PSC and cholangiocarcinoma (11,12,21). In our study, 12 of 73 PSC patients (16%) had elevated serum IgG-4 levels, which indicated a slightly higher percentage than reported in other studies.

It must be considered that 92.5% of IAC patients suffer from autoimmune pancreatitis but the lack of pancreatic involvement should not deter the physician from an IAC diagnosis. Therefore, the assessment of other organs involvement is critical in IAC diagnosis in such circumstances (1). Ghazale et al. (1) reported that 7.5% of cholangitis due to IAC had no evidence of autoimmune pancreatitis. Also, a number of patients had been wrongly diagnosed with biliary or pancreatic cancer and had undergone surgery respectively. In that study, the sensitivity of serum IgG-4 levels was 74% for the identification of autoimmune cholangiopathy; however, the positive and negative predictive factors were not identified. The positive predictive value of serum IgG-4 in patients with autoimmune pancreatitis in another study carried out by Ghazale et al. (22) was about 36%. In another multi-center study conducted in Japan on 388 PSC patients, it was revealed that 28 patients (7%) had suffered from autoimmune pancreatitis (23).

Our findings indicated that none of the patients in the elevated IgG-4 level group showed any pancreatic involvement, and pancreatic involvement as chronic pancreatitis was detected only in 2 patients in the normal serum IgG-4 level group. The MRCP findings indicated that one in two patients suffered from beading of the pancreatic duct, which may justify pancreatic involvement in PSC and, in the long term, may have led to chronic pancreatitis. Although PSC is commonly associated with IBD, whereas IBD is diagnosed in 70% to 80% of patients with PSC, the instances of IBD have not been clearly associated with IAC. In certain studies, the incidence of IBD has been reported to be low in patients with IAC (24). However, the lack of IBD existence should not be considered as a criterion for the diagnosis of IAC because 30% of patients suffering from PSC show no evidence regarding the presence of IBD. In a study by Ghazale et al. (1), 6% of patients with IAC suffered from IBD at the same time and in patients suffering from PSC, this number increased to 70%. In our study, the presence of IBD in PSC patients with normal and elevated levels of serum IgG-4 was 63.9% and 50%, respectively. The only similar study conducted in our country was carried out at Shahid Beheshti University, Tehran, on 35 patients with PSC. This study showed that 26.5% of PSC patients had high serum IgG-4 levels (12), which is a higher percentage than that in our research.

Our study suffers from certain limitations. Due to the small number of patients and sample size, significant statistical results in many variables could not have been obtained. In addition, our targeted patients were referrals to the liver transplant clinic; most of these included cases that had advanced stages of liver disease. Therefore, a liver biopsy assessment was not possible as part of this study. Therefore, the percentage of patients with high serum IgG-4 levels and who suffered from IAC could not be ascertained in this preliminary study.

Conclusion

The diagnosis of IAC requires high clinical suspicion. Based on the recommended guidelines in AASLD 2010, any patient who has stricture of the bile ducts and is suspected of having PSC should have his/her serum IgG-4 level checked in order to evaluate the presence of autoimmune cholangiopathy (25). A high serum IgG-4 level, as observed in 33 patients (16%) in this study, supports the implementation of this test. Research on the prevalence of autoimmune cholangiopathy in Iran is new and is therefore incomplete and negligible. Hence, the diagnosis of patients in the early stages of the disease as a precautionary measure will result in fewer risks for performing liver biopsy and will lead to a more accurate diagnosis of IAC, which has a good clinical response to corticosteroids.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Shiraz University of Medical Sciences, Shiraz, Iran.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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