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Original Article

Manometric assessment of esophageal motor function in patients with primary biliary cirrhosis

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ABSTRACT

Introduction/aim: Primary biliary cirrhosis is associated with other autoimmune diseases including Sjögren's syndrome, and scleroderma. Esophageal dysmotility is well known in scleroderma, and Sjögren's syndrome. The aim of this study is to investigate whether any esophageal motor dysfunction exists in patients with primary biliary cirrhosis.

Method: The study was performed in 37 patients (36 women, mean age: 56.29 ± 10.01 years) who met diagnostic criteria for primary biliary cirrhosis. Thirty-seven functional dyspepsia patients, were also included as a control group. Patients entering the study were asked to complete a symptom questionnaire. Distal esophageal contraction amplitude, and lower esophageal sphincter resting pressure were assessed.

Results: Manometric findings in primary biliary cirrhosis patients vs. controls were as follows: Median lower esophageal sphincter resting pressure (mm Hg): (24 vs 20, $p = 0.033$); median esophageal contraction amplitude (mm Hg): (71 vs 56, $p = 0.050$); mean lower esophageal sphincter relaxation duration (sc, x ± SD): (6.10 ± 1.18 vs 8.29 ± 1.92, $p < 0.001$); and median lower esophageal sphincter relaxation (%) (96 vs 98, $p = 0.019$); respectively. No significant differences were evident in median peak velocity (sc) (3.20 vs 3.02, $p = 0.778$) between patients with primary biliary cirrhosis and the functional dyspepsia patients. Esophageal dysmotility was found in 17 (45.9%) primary biliary cirrhosis patients (non-specific esophageal motor disorder in ten patients, hypomotility of esophagus in five patients, nutcracker esophagus in one patient and hypertensive lower esophageal sphincter in one patient).

Conclusion: Esophageal dysmotility was detected in 45.9% of patients. The study suggests that subclinic esophageal dysmotility is frequent in patients with primary biliary cirrhosis.

1. Introduction

Primary biliary cirrhosis is a chronic, progressive autoimmune liver disease of unknown etiology characterized by inflammatory destruction of septal and interlobular bile ducts that leads to cholestatic chronic liver disease and, eventually, to cirrhosis [1]. Primary biliary cirrhosis is associated with other autoimmune diseases such as Sjögren's syndrome, autoimmune thyroiditis, rheumatoid arthritis, ankylosing spondylitis, polymyositis, scleroderma, and thrombocytopenia [2–8]. Patients with a cholestatic biochemical pattern, positive antimitochondrial autoantibody test, and hepatic histological features compatible with primary biliary cirrhosis would generally be diagnosed as having primary biliary cirrhosis [9,10].

Primary biliary cirrhosis has been shown to be associated with primary Sjögren's syndrome [11]. Indeed, in several studies the most common autoimmune disorder associated with primary biliary cirrhosis is Sjögren's syndrome, with a reported prevalence of Sjögren's syndrome in primary biliary cirrhosis patients ranging from 50% to 81% [12,13]. Esophageal motility abnormalities are well known in progressive systemic sclerosis, Sjögren's syndrome, and some rheumatic diseases with sicca syndrome [14–16]. In a study by Parés et al., it has been demonstrated that esophageal motor disturbances existed in patients with primary biliary cirrhosis who have scleroderma and also in those with Sjögren's syndrome without scleroderma [17]. Therefore, the aims of this study were to investigate whether any esophageal motor abnormalities exist in patients with primary biliary cirrhosis and compare results with age-matched functional dyspepsia patients.

2. Patients and methods

Thirty-seven primary biliary cirrhosis patients were enrolled into the study. Thirty-six of the patients were women, with a mean age of 56.29 ± 10.01 years (range: 34–78 years). The diagnosis of primary

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biliary cirrhosis was made with combination of abnormal serum liver tests (elevation of alkaline phosphatase of liver origin for at least 6 months) and the presence of antimitochondrial autoantibody (P1:40) in serum [18]. A liver biopsy was performed to confirm the diagnosis of primary biliary cirrhosis. Histologic lesions are classically divided into four stages [19]. The presence of heartburn, dysphagia and epigastric pain was queried in patients with primary biliary cirrhosis. Thirty-seven age-matched patients with functional dyspepsia, who were diagnosed according to the Rome II criteria, were also included in the study and served as a control group [20]. None of the patients was on drugs that might alter esophageal motor function during motility testing. All patients had undergone upper gastrointestinal endoscopic examination and esophageal motility testing in two separate days. Endoscopic examinations were performed by one of the investigators using a standard video gastroscope (Fujinon, Tokyo, Japan).

The presence of Sjögren's syndrome was investigated in patients with primary biliary cirrhosis and American–European Consensus Group criteria used for diagnosis of Sjögren's syndrome [21]. Esophageal manometry was performed by using a single catheter containing 8 microperfusion state pressure transducers spaced at 5 cm intervals and attached to an online computer (MMS, Medical Measurement Systems, Netherlands). Patients came to the laboratory after at least 8 h of fasting. The 8-channel catheter was lubricated and passed nasally and advanced into the stomach. A slow station pull-through was performed at 1 cm increments. Once the lower esophageal sphincter was profiled, the distal pressure transducer which included four lumens was placed in the high-pressure zone of the lower esophageal sphincter, so that the proximal pressure transducers were located 5 cm, 10 cm, 15 cm and 20 cm above the lower esophageal sphincter. A series of 10 wet swallows (with 5 mL water bolus) were given at 30 s intervals. Each contraction was recorded and then analyzed by a computerized software system (MMS, Medical Measurement Systems, Netherlands) for amplitude, contraction and velocity. The catheter assembly was then located 5 cm above the lower esophageal sphincter for assessment of the pressures from the distal part (5 cm and 10 cm) of the esophagus. Average lower esophageal sphincter resting pressure (reference 6–25 mm Hg), percentage of wet swallowing over peristaltic waves (reference N: 80%) and average esophagus corpus amplitude (reference 30–160 mm Hg) were determined. Lower esophageal sphincter relaxation and residual pressures were also recorded. The conventional classification of esophageal motility was used for diagnosis of abnormal esophageal function [22]. This classification is summarized below.

Normal

- Normal velocity
- Normal peristaltic amplitude
- ≥7 peristaltic contractions with an intact wave progression (amplitude >30 mm Hg)

Aperistalsis

- Absent or simultaneous contractions (<30 mm Hg)

Ineffective esophageal motility (IEM)

- ≥3 peristaltic contractions with failure of wave progression due to an ineffective distal contraction amplitude (>30 mm Hg) or failed peristalsis over a segment of the distal esophagus

Nutcracker esophagus

- Average peristaltic amplitude >180 mm Hg over pressure sensors 3 and 8 cm above lower esophageal sphincter

Isolated hypertensive lower esophageal sphincter

- Basal LES resting pressure greater than 45 mm Hg (mid-respiratory pressure).

The present study was approved by the Institutional Review Board of Ankara University Medical School and all patients signed informed consent before entering the study. Statistical analysis was performed with SPSS 11.5 for Windows (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation and median (min–max). Categorical variables were expressed as frequencies and percentages. Shapiro–Wilk test was used to check the normality for each group. A p value of less than 0.05 was considered significant. The differences between two groups were evaluated by Student's t test, and when the data distribution was not normal Mann–Whitney U test was used. Chi-square test and Fisher's exact test were used to evaluate categorical and continuous variables, respectively, where applicable.

3. Results

The mean age of the patients enrolled in the study (n = 37) was 56.29 ± 10.01 years. Median primary biliary cirrhosis disease duration was 74.5 months (range 3–360 months). As for symptoms, there was epigastric pain in 7 (18.9%) patients. Dysphagia in 6 (16.2%) and heartburn in 5 (13.5%) were found. Of the 37 patients who had undergone upper gastrointestinal endoscopy, 4 patients had endoscopic abnormalities which consisted of esophagitis according to the Los Angeles classification (3 grade A, 1 grade B) [23]. The clinical manifestations of primary biliary cirrhosis, and liver functions and gastrointestinal symptoms in our cases are summarized in Table 1.

There was no significant difference between mean age 56.29 ± 10.01 years (range: 34–78 years) vs 44.25 ± 11.35 years (range: 23–73), p = 0.576 in patients with primary biliary cirrhosis compared to the control group. As for manometric findings, median lower esophageal sphincter resting pressure (mm Hg) (24 vs 20, p = 0.033), and median esophagus contraction amplitude (mm Hg) were significantly higher (71 vs 56, p = 0.050); median lower esophageal sphincter relaxation (%) (96 vs 98, p = 0.019), and mean lower esophageal sphincter relaxation duration (sc) were significantly lower (6.10 ± 1.18 vs 8.29 ± 1.92, p < 0.001), in patients with primary biliary cirrhosis compared to functional dyspepsia patients. There were no significant differences between median peak velocity (sc) (3.20 vs 3.02, p = 0.778) in patients with primary biliary cirrhosis compared to functional dyspepsia patients (Table 2). Esophageal dysmotility was detected in 17 of 37 patients (45.9%) with primary biliary cirrhosis, whereas none of the functional dyspepsia patients had any abnormality. Individual analysis of the esophageal motility studies showed different patterns of esophageal dysfunction:

1. Hypertensive lower esophageal sphincter in one patient.
2. Nutcracker esophagus one patient.
3. Hypomotility of esophagus in five patients.
4. Non-specific esophageal motor disorder in ten patients.

Of the 17 patients, 12 of them had at least one of the findings such as dysphagia, heartburn and esophagitis. Esophageal dysmotility was detected in 3 of 6 patients suffering from dysphagia symptoms.

Table 1
The characteristics of primary biliary cirrhosis patients.

	PBC n = 37, (%)	SS (+) n = 21, (%)	SS (−) n = 16, (%)	p
Age (mean ± SD)	56.3 ± 10.0	60.1 ± 8.3	51.3 ± 10.1	0.006[a]
Symptoms				
• Pruritus	19 (51.3%)	12 (57.1%)	7 (43.7%)	0.535[b]
• Weakness	19 (51.3%)	14 (66.7%)	5 (31.3%)	0.048[b]
• Heartburn	5 (13.5%)	5 (23.8%)	0	0.062[c]
• Dysphagia	6 (16.2%)	4 (19.0%)	2 (12.5%)	1.000[c]
• Epigastric pain	7 (18.9%)	7 (33.3%)	0	0.027[c]
• Esophagitis	4 (10.8%)	3 (14.2%)	1 (6.3%)	1.000[c]
• Jaundice	1 (2.7%)	1 (4.8%)	0	1.000[c]

SD: standard deviation.
[a] Student's t test.
[b] Chi-square test.
[c] Fisher's exact test.

Table 2
The comparison of manometric findings between PBC patients and control groups.

	PBC group (n = 37) Mean ± SD Median (min–max)	Control group (n = 37) Mean ± SD Median (min–max)	p
LES resting pressure (mm Hg)	24.56 ± 9.69 24 (11–51)	20.24 ± 7.93 20 (10–53)	0.033[a]
LES relaxation (%)	93.68 ± 5.91 96 (76–100)	95.78 ± 5.60 98 (80–100)	0.019[a]
LES relaxation duration (sc)	6.10 ± 1.18 6 (3.70–9.10)	8.29 ± 1.92 8.40 (4.60–12.0)	<0.001[b]
Esophagus contraction amplitude (mm Hg)	76.18 ± 39.55 71 (13–202)	60.95 ± 23.91 56 (21–150)	0.050[a]
Peak velocity (sc)	4.27 ± 4.87 3.20 (−0.73–28.64)	3.46 ± 1.62 3.02 (0.99–8.71)	0.778[a]

SD: standard deviation, min: minimum, max: maximum.
[a] Mann–Whitney U test.
[b] Student's t test.

Twenty-one patients met clinical criteria for Sjögren's syndrome. The mean age, epigastric pain, heartburn, and weakness symptoms were significantly higher in patients with Sjögren's syndrome compared to patients without Sjögren's syndrome (60.09 ± 8.34 vs 51.31 ± 10.07, p = 0.006; 33.3% vs. 0.0%; 23.8% vs. 0.0%; 66.7% vs 31.3%, p = 0.048 respectively). There were no significant differences between jaundice (%) (4.8 vs 0.0), dysphagia (%) (19.0 vs 12.5 p = 1.000), and esophagitis (%) (14.2 vs 6.3 p = 1.000) in patients with Sjögren's syndrome positive compared to Sjögren's syndrome negative patients.

Manometric investigation was abnormal in 10 primary biliary cirrhosis with Sjögren's syndrome patients (non-specific esophageal motor disorder in 6 patients, esophageal hypomotility in 3 patients, and hypertensive lower esophageal sphincter in 1 patient). Five cases suffered from reflux symptoms in which endoscopy showed grade A esophagitis in 3 cases. Esophageal motor abnormalities were detected in 43.8% (7/16) of Sjögren's syndrome negative patients with manometric studies (non-specific esophageal motor disorder in 4, esophageal hypomotility in 2, and nutcracker esophagus in 1 patient). Median lower esophageal sphincter resting pressure (mm Hg), mean lower esophageal sphincter relaxation duration (sc), median contraction amplitude (mm Hg), median velocity (sc), and median lower esophageal sphincter relaxation (%) were not statistically different in primary biliary cirrhosis with Sjögren's syndrome patients compared to primary biliary cirrhosis without Sjögren's syndrome patients (24 (11–51) vs. 24.5 (12–37), p = 0.892; 6.03 ± 1.03 vs 6.20 ± 1.38, p = 0.697; 80 (13–144) vs. 67.5 (13–202), p = 0.534; 3.14 vs 3.26, p = 0.306; and 96 vs 93, p = 0.354 respectively) (Table 3). There was no correlation between esophageal dysmotility and stage of liver disease.

4. Discussion

Primary biliary cirrhosis is a chronic autoimmune cholestatic liver disease characterized by destruction of medium and small caliber intrahepatic bile ducts and by the presence of antimitochondrial autoantibodies in around 95% of sufferers [1]. The etiology of primary biliary cirrhosis is uncertain but is likely to include both genetic and environmental components whilst the genetic basis of primary biliary cirrhosis has been studied extensively, for example in twin concordance, family history and human leucocyte antigen genotyping studies [24–27]. Environmental risk factors are less clear. Several groups have suggested roles for a variety of infectious agents, smoking and hair dye [28–30].

Primary biliary cirrhosis is associated with other autoimmune diseases such as Sjögren's syndrome, autoimmune thyroiditis, rheumatoid arthritis, ankylosing spondylitis, polymyositis, scleroderma, and thrombocytopenia [2–8]. Esophageal motility abnormalities are well known in progressive systemic sclerosis (scleroderma), Sjögren's syndrome, and some rheumatic diseases with sicca syndrome [14–16]. However there is not enough data about esophageal dysmotility in patients with primary biliary cirrhosis.

Esophageal manometry is a procedure in which intraluminal pressures are measured at different sites along the length of the esophagus including the upper and lower esophageal sphincters. The pattern of observed pressures (including the amplitudes, duration and peristaltic properties) provides information about possible diseases affecting the esophagus. Conventional manometry assemblies detect pressure using a catheter with several water-perfused sideholes and with or without the addition of a, so called, sleeve sensor or solid state pressure transducers [31]. Conventional manometry uses catheters with 4 to 8 pressure sensors, whereas high-resolution manometry catheters have a higher number of pressure sensors (available in 20–36 channels) separated by shorter intervals [32].

In the present study, conventional manometry was used for evaluation of esophageal function.

In this study esophageal dysmotility was detected in 17 of 37 patients (45.9%) with primary biliary cirrhosis, whereas none of the functional dyspepsia patients had any abnormality. Median lower esophageal sphincter resting pressure, median lower esophageal sphincter relaxation (%), mean duration of lower esophageal sphincter relaxation, and median esophagus contraction amplitude were significantly higher in patients with primary biliary cirrhosis compared to the functional dyspepsia group. Our study is the second study about esophageal dysmotility in primary biliary cirrhosis patients. In the first study reported by Parés et al., they showed esophageal motility dysfunction in patients with primary biliary cirrhosis. They performed esophageal manometry in 18 patients with primary biliary cirrhosis and in a control group of 18 subjects matched by age and sex. All patients were screened for clinical manifestations of scleroderma and for the presence of Sjögren's syndrome. Four patients had scleroderma (all of them with Sjögren's syndrome), nine had Sjögren's syndrome without scleroderma and five had neither Sjögren's syndrome nor scleroderma. Esophageal motor disturbances were observed in the four patients with scleroderma. All had decreased lower esophageal sphincter resting pressure and three had aperistalsis. Five of the nine patients with Sjögren's syndrome without scleroderma also had esophageal motor abnormalities manifested by reduced lower esophageal sphincter resting pressure (two cases) and decreased distal esophagus

Table 3
The comparison of manometric findings between in patients with PBC with SS groups compared to PBC without SS group.

	PBC (n = 37) Mean ± SD Median (min-max)	SS positive (n = 21) Mean ± SD Median (min-max)	SS negative (n = 16) Mean ± SD Median (min-max)	p
LES resting pressure (mmHg)	24.56 ± 9.59 24 (11-51)	24.62 ± 10.99 24 (11-51)	24.50 ± 7.72 24.5 (12-37)	0.892[b]
LES relaxation (%)	93. 68 ± 5.91 96 (76-100)	94.67 ± 4.92 96(83-99)	92.38 ± 6.95 93(76-100)	0.354[b]
LES relaxation duration (sc)	6.10 ± 1.18 6 (3.7-9.10)	6.03 ± 1.03 6.1 (3.7-7.5)	6.20 ± 1.38 5.90 (4.50-9.10)	0.697 [a]
Esophagus contraction amplitude (mmHg)	76.18 ± 39.55 71 (13-202)	77.52 ± 37.68 80 (13-144)	74.43 ± 43.07 67.5 (13-202)	0.534[b]
Peak velocity (sc)	4.27 ± 4.87 3.20(-0.73–28.64)	5.25 ± 6.09 3.14(1.97-28.64)	2.86 ± 1.56 3.26(-0.73–5.32)	0.306[b]

SD: Standard Deviation, [a] : Student's t test, [b] :Mann Whitney U test

mean wave pressure in the remaining three cases. However, they did not show esophageal abnormality in primary biliary cirrhosis patients without Sjögren's syndrome [17].

Primary biliary cirrhosis has been shown to be associated with primary Sjögren's syndrome [11]. Indeed, in several studies the most common autoimmune disorder associated with primary biliary cirrhosis is Sjögren's syndrome, with a reported prevalence of Sjögren's syndrome in primary biliary cirrhosis patients ranging from 69% to 81% [12,13]. In the present study, 21 patients (56.7%) met clinical criteria for Sjögren's syndrome. Primary Sjögren's syndrome is an autoimmune disease affecting the exocrine glands, resulting in diminished or absent glandular secretion and mucosal dryness. In addition, various non-exocrine organs may be involved in the disease, including the gastrointestinal and nervous systems. Dysphagia is a common gastrointestinal complaint in primary Sjögren's syndrome and has been reported to affect 33–92% of primary Sjögren's syndrome patients [14–16,33,34]. In previous studies these symptoms have been attributed to either lack of saliva, esophageal dysmotility or esophageal webs [15,34–37]. In this study, dysphagia was seen from 19% of primary Sjögren's syndrome patients.

Esophageal manometry in primary Sjögren's syndrome patients has shown that about one-third of the patients display varying degrees of esophageal dysmotility [14,36–38]. Esophageal peristalsis and exocrine secretion are both influenced by the autonomic nervous system and autonomic nervous system signaling is affected in primary Sjögren's syndrome [39–43]. Therefore, dysphagia and esophageal dysmotility may be due to impaired autonomic nervous function, as reported in other diseases with gastrointestinal symptoms such as systemic sclerosis, diabetes mellitus, gastro-esophageal reflux disease and non-specific esophageal motility disorder [44–48]. In the present study, manometric investigation was abnormal in 10 primary biliary cirrhosis with Sjögren's syndrome patients (non-specific esophageal motor disorder in 6 patients, esophageal hypomotility in 3 patients, and hypertensive lower esophageal sphincter in 1 patient). Seven of the 16 patients with primary biliary cirrhosis without Sjögren's syndrome had esophageal disturbances. Four of them had non-specific esophageal motor disorder, 2 patients had esophageal hypomotility and 1 patient had nutcracker esophagus. When the manometric evaluation of primary biliary cirrhosis with Sjögren's syndrome patients was compared with primary biliary cirrhosis without Sjögren's syndrome patients, there was no statistical significance. Turk et al., performed esophageal manometry in 40 patients with primary Sjögren's syndrome, 15 with rheumatoid arthritis, 15 with rheumatoid arthritis and secondary Sjögren's syndrome, and 21 healthy volunteers. Median lower esophageal sphincter resting pressures were found significantly higher in primary Sjögren's syndrome patients than with healthy controls and rheumatoid arthritis patients with or without Sjögren's syndrome ($p < 0.05$). Esophageal dysmotility was detected in 14 of 40 patients (35%) with primary Sjögren's syndrome, whereas none of the healthy volunteers had any abnormality. In conclusion, they suggested that various esophageal motility disorders can be found in patients with primary Sjögren's syndrome which could be related to increased lower esophageal sphincter pressure [15].

Some studies showed that lower esophageal sphincter resting pressure is significantly higher in patients with primary Sjögren's syndrome than in controls [15,49]. Turk et al., found that the mean lower esophageal sphincter resting pressures were significantly higher in primary Sjögren's syndrome patients than healthy controls and rheumatoid arthritis patients with or without Sjögren's syndrome. In our study median lower esophageal sphincter resting pressure was significantly higher in patients with primary biliary cirrhosis compared to the functional dyspepsia group. But there was no statistical difference between median lower esophageal sphincter resting pressure in primary biliary cirrhosis patients with Sjögren's syndrome and primary biliary cirrhosis patients without Sjögren's syndrome.

In patients with cirrhosis, esophageal varices may affect esophageal functions [50]. Chen et al., compared cirrhotic patients with healthy individuals and observed no change in lower esophageal sphincter resting pressure. However, 5 and 10 cm above the lower esophageal sphincter, contraction amplitudes decreased and tertiary waves in the body of the esophagus increased [51]. Pathogenesis of dysfunction of the esophageal function is unknown but one possibility is that cirrhosis itself causes neuromuscular disorders with the development of peristaltic abnormality [52]. Endoscopic injection sclerotherapy and endoscopic variceal ligation are two popular endoscopic methods used to treat esophageal variceal hemorrhage. Anatomical esophageal alterations including ulceration and stricture formation occur commonly following endoscopic injection sclerotherapy. Endoscopic injection sclerotherapy led to changes in esophageal motility in the forms of reduction in basal lower esophageal sphincter resting pressure, slowing of propagation of primary contraction waves along the esophageal body and abnormal contraction waves in the distal esophagus. The long-term changes in esophageal motility, which may be related to the submucosal fibrosis in the esophageal wall, have been shown in the autopsy studies [53]. However, endoscopic variceal ligation had limited effect on the mucosal and submucosal layers and appears to have little impact on esophageal motility. Viazis et al., compared variceal ligation with sclerotherapy in 60 cirrhotic patients in terms of esophageal motility and occurrence of gastro-esophageal reflux. Their results showed a decrease in the esophageal peristaltic contraction amplitude and increase in simultaneous contractions with the percentage of time with $pH < 4$ in the sclerotherapy group. However, they did not find changes in these parameters in the ligation group [54]. In this study, esophageal varices were not seen in any of the patients. There was no correlation seen between esophageal dysmotility and stage of liver disease or liver functions.

In conclusion, we have demonstrated that 45.9% of patients with primary biliary cirrhosis have esophageal motor dysfunction compared to functional dyspepsia subjects. Altered esophageal motility may help to explain a part of unexplained upper gastrointestinal symptoms in patients with primary biliary cirrhosis that may be clinically helpful in managing patients with primary biliary cirrhosis with upper gastrointestinal symptoms. Esophageal motor dysfunction in patients with primary biliary cirrhosis is independent of stage of liver disease. This study suggests that subclinic esophageal dysmotility is frequent in patients with primary biliary cirrhosis and presence of Sjögren's syndrome had no impact on manometric findings. Therefore, further prospective, well-designed studies are needed to assess the clinical relevance of our findings.

Conflict of interests

None of the authors have any conflict of interest to disclose.
None of the authors have any pharmaceutical and industry support.

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