© Med Sci Monit, 2007; 13(7): CR299-306
PMID: 17599023

Received: 2006.11.03
Accepted: 2007.04.18
Published: 2007.07.01

Primary biliary cirrhosis in Lithuania: Diagnosis and clinical picture

Authors' Contribution:
A Study Design
B Data Collection
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Source of support: Departmental sources

Summary

Background: The rising detection and considerable geographical variation of primary biliary cirrhosis (PBC) in some regions demand increased awareness of the disease. The aim was to analyze the clinical, biochemical, immunological, and histological criteria of PBC patients in Lithuania and evaluate the patterns of disease presentation and histological features.

Material/Methods: One hundred thirty-one PBC patients were examined and followed in the Center of Hepatology, Gastroenterology, and Dietetics, Vilnius University Hospital. Their case records were evaluated in this retrospective record-review study.

Results: Most of the patients were women (94.6%) older than 50 years with late stages of PBC. Men were significantly older and had a threefold shorter duration from disease presentation to diagnosis (4.0±0.4 vs. 1.4±0.4 years). 29.8% of patients had asymptomatic disease at presentation and at diagnosis, were older than the symptomatic ones, and presented with significantly lower prevalence of jaundice, skin signs, and lower alkaline phosphatase (ALP) activity, but higher frequency of sicca syndrome. Antimitochondrial antibody (AMA) positivity was found in 91.7%, bile duct lesions in all patients, while the frequency of histological signs of cholestasis (except copper accumulation) was lower. No significant differences in these parameters in asymptomatic and symptomatic patients were found.

Conclusions: Most PBC patients in Lithuania were at late histological stages, with a predominance of females older than 50 years and long duration from disease presentation to diagnosis. One third of these PBC patients initially had asymptomatic course, with some differences in clinical signs and their prevalence compared with initially symptomatic patients.

key words: **primary biliary cirrhosis • diagnosis • clinical picture • symptomatic • asymptomatic • histology**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/487365

Word count: 3452
Tables: 5
Figures: 2
References: 65

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BACKGROUND

Primary biliary cirrhosis (PBC) is a progressive cholestatic liver disease frequently leading to cirrhosis and its complications. For a long time, PBC was considered a very rare disease. The widespread use of automatic biochemical screening, the introduction of AMA detection, as well as the routine taking of liver biopsies resulted in a substantial improvement in PBC diagnosis [1,2]. The rising detection of PBC in some regions, including Northern Europe, but with considerable geographical variations [3–10], obliges physicians and family doctors to increase their attention and awareness of the disease for early diagnosis and treatment. The diagnosis of PBC is based on three criteria: cholestatic liver tests, presence of AMA, and diagnostic or compatible liver biopsy. The most important criterion and hallmark of PBC is AMA positivity [11,12], although there are certain immunological and epidemiological discrepancies between AMAs and PBC development [13,14].

Patients with PBC may develop a wide range of symptoms and signs and several patterns of presentation, from the "classic type" to the absence of any disease-related symptoms. Frequency regarding asymptomatic PBC cases at presentation is controversial and ranges from 60 to 71% [15,16] and from 10 to 15% [17–19]. The diagnosis may also be difficult in patients who are negative for AMA (up to 15%) or in patients who have no conclusive liver biopsy (no florid damage of septal and interlobular bile ducts), as well as untypical or nearly normal liver function tests. Moreover, sometimes it is complicated to establish a correct diagnosis in patients with variable forms of autoimmune liver disease who show clinical features of both PBC and autoimmune hepatitis (AIH), a phenomenon called "overlap syndrome" or a mixed form of PBC and AIH [20–26]. Therefore, in spite of generally clear and distinct criteria of definite PBC, one may be confronted with certain difficulties and limitations which may result in erroneous or delayed diagnosis and treatment.

The early diagnosis of PBC is of great importance regarding treatment efficacy. Ursodeoxycholic acid (UDCA) is the current treatment of choice for patients with PBC. Although not curative when started in early stages, it significantly reduces the complications of the disease, delays histological progression, reduces mortality, and prolongs the time to liver transplantation [27–30]. Whether to treat an asymptomatic patient or not is a difficult question and more information is required on the prognosis of those patients and on the benefits and risks of their treatment. To facilitate PBC diagnosis it has been suggested [31] to differentiate between "definite" and "probable" PBC. Moreover, a scoring system for diagnosis of variant PBC forms was proposed [32].

In Lithuania, the situation regarding PBC is still not evaluated. Thus the aims of this study were to analyze the clinical, biochemical, immunological, and histological criteria of PBC patients, evaluate the patterns of disease presentation and histological features, and reveal possible differences compared with the data of other authors.

MATERIAL AND METHODS

Population

This is a retrospective record-review study in which the case records of 145 PBC patients from 1984–2004 were collected and analyzed. All the patients were examined thoroughly at the Center of Hepatology, Gastroenterology, and Dietetics of the Vilnius University Hospital and followed up regularly for from 1 to 15 years at the outpatient department of the Center. For a precise analysis, case records were selected of 131 patients (a) whose first symptoms and signs as well as (b) the date of first presentation and (c) the date of assessment of the correct diagnosis were recorded. Patients with serological markers of viral hepatitis B and C infection as well as those with signs of PBC-AIH "overlap" syndrome were excluded.

Clinical assessment

The complete clinical history, including drugs, alcohol consumption, blood transfusions, and symptoms and signs of the disease, was assessed at the time of diagnosis.

Laboratory investigations

Conventional laboratory tests carried out were: activity of alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (γGT), alanine and aspartate aminotransferases (ALT, AST), concentration of serum bilirubin, cholesterol, prothrombin time, and protein electrophoresis. Immunoserological tests included serum immunoglobulins IgA, IgG, IgM [33] and immunonephelometry (Dade Behring, Marburg, Germany), antimitochondrial autoantibodies (AMAs), antinuclear autoantibodies (ANAs), and smooth muscle antibodies (SMAs) by indirect immunofluorescence assay on murine tissue sections (IFA kits, the Binding Site Ltd, Birmingham, UK). Antimitochondrial M_2 was done by Western blot (Euroimmun, Lübeck, Germany). All patients were tested for anti-HCV by second-generation ELISA (Ortho Diagnostic Systems, Raritan, NJ, USA) and MEJA (HCV 3.0, Abbott Axsym System, Abbott Labs, North Chicago, IL, USA); for HBsAg (Roche Diagnostic System, Branchburg, NJ, USA) and MEJA (HBsAg 2.0, Abbott Axsym System, Abbott Labs, North Chicago, IL, USA) they underwent ultrasound examination by LOGIQ 500 PRO series (General Electric, Yokogawa Medical System, Yokogawa, Japan).

Liver histology

Ultrasound-guided liver biopsy (Hepafix needle, 12–16 gauge) was performed in 101 of the 131 patients. Samples were routinely prepared and 3- to 4-μm sections were stained with hematoxylin-eosin, collagen with picrosirius red [34], reticulin with Gordon and Sweet picrosirius (GSPS), copper with rhodanine or orsein staining [35,36] and PAS (periodic acid Schiff) [37]. Immunohistochemical staining with monoclonal antibody for cytokeratin 7 (clone OV-TL 12/30, DakoCytomation, Glostrup, Denmark) was performed to reveal the lesions of small biliary ductules and bile canaliculi epithelium. All specimens were examined at the National Center of Pathology (accredited by the Association of American Pathologists) by a single pathologist and scored according to Scheuer P. and Lefkowitch J. [38], necroinflammatory activity and histological activity index (HAI) according to Ishak et al. [39]. Evaluation of his-

Table 1. Histological stage, gender, and age at diagnosis.

Stage	Male			Female			Total		
	n	%	Age (Mean ±SE)	n	%	Age (Mean ±SE)	n	%	Age (Mean ±SE)
I	0	0	0	3	3.2	61.3±8.3	3	3.0	61.3±8.3
II	1	14.2	63	27	28.7	54.3±2.3	28	27.7	54.6±2.2
III	3	42.8	66.3±8.5	54	57.4	56.2±1.5	57	56.4	56.7±1.5
IV	3	42.8	65.7±7.2	10	10.6	61.1±3.7	13	12.9	62.2±3.1
Total	7	6.9	65.6±4.1*	94	93.1	56.4±1.2*	101	100	57.0±1.1

* p=0.0278 males vs. females.

tological stages was based on accepted criteria in terms of the most advanced lesions in each specimen.

The histological lesions found in PBC patients were divided into diagnostic (having specific histological features), compatible (without specific histological findings), and atypical (neither diagnostic nor compatible) [31].

Those patients who did not undergo liver biopsy (30 patients of the 131, because of contraindications or because the patient refused biopsy) but who were AMA positive and presented cholestatic liver enzymes and typical clinical symptoms were classified into four clinical stages according to Schaffner and Popper [40], stages I–IV being asymptomatic, oligosymptomatic, symptomatic anicteric, and icteric stage (precirrhotic and cirrhotic), respectively.

Furthermore, all patients were divided into two groups, asymptomatic and symptomatic, according to the first presentation. Asymptomatic patients did not have any specific symptom or sign of liver disease at disease presentation (itching, jaundice, hepatomegaly, ascites, edema, variceal bleeding, or portosystemic encephalopathy).

Those patients who met the conventional criteria of PBC after evaluation of symptoms, biochemical and immunological tests, and histology were divided into two groups: definite and probable PBC [31]. The triad for definite PBC was defined as: cholestatic liver tests, positive AMA (i.e. AMA-M_2 titer ⩾1:40), and diagnostic or compatible liver histology. Probable PBC was defined as: positive AMA, cholestatic liver tests, and histology neither diagnostic nor compatible for PBC (variant 1); positive AMA, untypical or nearly normal liver tests, and diagnostic or compatible liver histology (variant 2); and AMA negative, cholestatic liver tests, and diagnostic or compatible liver histology (variant 3). In patients with probable PBC, the following additional criteria for diagnosis were used: itching, jaundice, skin hyperpigmentation, presence of xanthelasmas, and associated diseases, e.g. Sjögren's syndrome, calcinosis cutis, Raynaud's syndrome, polymyalgia rheumatica, thyroid diseases, etc.

Statistical methods

Descriptive data are presented as the percentage or the mean ±standard error (*SE*). The distribution of quantitative variables was evaluated by the Kolmogorov-Smirnov test. Analysis of variables was performed by Student's *t*-test (SPSS software for Windows). Differences were considered significant if $p \leqslant 0.05$.

Results

Patients' characteristics

There were 124 (94.6%) women with ages ranging from 26 to 81 years: 72 (58.1%) were 51-70 years old, 6 (4.5%) were younger than 50 and 17 (13%) older than 70. The age of men ranged from 53 to 80 years and they were significantly older than the women at disease presentation (i.e. occurrence of the first symptoms or signs of the disease, p=0.0124) and at diagnosis (Table 1).

At the time of diagnosis, most of the PBC patients were in the late stages of the disease (histologically and/or clinically) and presented with evident symptoms, while the early stages (I and II) were the minority (Table 1). Thirty (66.6%) patients in whom a biopsy was not performed at the time of diagnosis also showed clear symptoms of cirrhosis, in 15 (50%) of them complicated by portal hypertension. Only 5 (16.6%) of these patients were oligosymptomatic (clinical stage II) and 5 (16.6%) symptomatic (clinical stage III). Asymptomatic patients, including women, were significantly older than symptomatic ones (Table 2). No statistical differences in the prevalence of early and late stages of PBC in asymptomatic and symptomatic patients were found.

Clinical symptoms and signs of PBC

The mean duration from the first symptoms to correct diagnosis of the disease was 4.0±0.4 years in women and 1.4±0.4 years in men (p<0.0001), with 3.7±0.3 years for symptomatic and 4.4±0.7 years for asymptomatic patients. Asymptomatic patients were older than symptomatic ones (Table 2).

In symptomatic patients the most common and typical "liver-related" symptom at disease presentation was itching, which occurred as the first symptom of the disease in 39.9% of patients, while in the others were simultaneous or later than occurrence of jaundice and fatigue (Table 3). The other presenting symptoms and signs, also at diagnosis, are shown in the same table. Almost one third of PBC

Table 2. Histological stage, gender, and age at diagnosis in asymptomatic and symptomatic patients.

Stage	Male			Female			Total		
	n	%	Age (Mean ±SE)	n	%	Age (Mean ±SE)	n	%	Age (Mean ±SE)
Asymptomatic									
I	0	0	0	1	3.6	47	1	3.3	47
II	0	0	0	6	21.4	59.5±4.5	6	20.0	59.5±4.5
III	1	50.0	81	17	60.7	59.4±2.6	18	60.0	60.6±2.7
IV	1	50.0	62	4	14.3	65.5±4.2	5	16.7	64.8±3.4
Total	2	6.7	71.5	28	93.3	59.9±2.0**	30	100	60.6±2.0*
Symptomatic									
I	0	0	0	2	3.0	68.5	2	2.8	68.5
II	1	20.0	63	21	31.8	52.2±2.4	22	31.0	52.7±2.3
III	2	40.0	59	38	57.6	55.5±2.0	40	56.3	55.7±1.9
IV	2	40.0	67.5	5	7.6	55.6±5.1	7	9.9	59.0±4.5
Total	5	7.0	63.2±3.7	66	93.0	54.9±1.5**	71	100	55.5±1.4*

* p=0.0357 symptomatic vs. asymptomatic pts; ** p=0.0455 symptomatic vs. asymptomatic females.

patients were asymptomatic and the disease was diagnosed accidentally or after abnormal biochemical liver test findings when examined because of unspecific symptoms and signs, or on routine check-up before surgery. The most frequent nonspecific symptoms and signs reported by asymptomatic patients were pain and discomfort in the abdomen, dyspeptic complaints, hepatomegaly, or splenomegaly accidentally found during conventional examination. On follow-up, 29 (74.4%) initially asymptomatic patients showed specific symptoms and signs developing in the course of about 4.3 years (range: 1–16 years).

At diagnosis the asymptomatic patients presented with a lower frequency of jaundice (33.3% vs. 64.1%, p<0.0001), skin signs (43.4% vs. 89.1%, p<0.0001), and weight loss (7.7% vs. 25%, tendency to statistical significance: p=0.07), but a higher frequency of sicca syndrome (28.2% vs. 4.4%, p=0.009).

The most common associated diseases in PBC patients at diagnosis were thyroid diseases (mostly thyroiditis) in 21 (16%), followed by arthropathy in 18 (13.7%), Sjögren's syndrome in 15 (11.4%), and scleroderma in 3 (2.3%). Gallstones were diagnosed in 47 (35.8%) PBC patients and cholecystectomy was performed in 19 (14.5%) of them.

Laboratory tests

Biochemical parameters

The mean values of ALT and AST activity were mildly elevated and exceeded the upper normal limits (UNL) by about threefold (Figure 1). The increases in the cholestatic liver enzymes ALP and γGT were significant and exceeded UNL by 6 and 14 times, respectively. Only 3 (2.3%) patients had normal ALP and one (0.8%) normal γGT activity. The concentrations of total and conjugated bilirubin at diagnosis were elevated in 99 (78.5%) and 94 (98.9%) patients and were 4 and 9 times higher than the UNL. No differences in ALT, AST, and γGT activity in symptomatic compared with asymptomatic patients were found. The mean values of ALP activity (616.9±71.1 vs. 834.2±54.5 IU/l, p=0.0164) and the concentrations of total and conjugated bilirubin were significantly lower in asymptomatic patients (Figure 2).

Immunological parameters

Elevation of IgM concentration was found in 96 patients (80%), IgG in 89 (74.2%), and IgA in 35 (29.2%). Mean values of serum IgA, IgG, and IgM concentration were significantly increased (Ig A: 3.3±0.18 g/l, p<0.0001; IgG: 17.7±0.61 g/l, p<0.001; IgM: 5.34±0.4 g/l, p<0.0001), but did not differ significantly in symptomatic and asymptomatic as well as in AMA-positive and -negative patients.

Serum AMAs were found in 111 (91.7%) patients at titers of 1:40–1:800. In 61 (50.4%) patients, AMAs were the only immunological marker (at titers of 1:100–1:320 in 50/82%). In the other 42 (34.7%) patients, AMAs were detected together with ANAs (titers 1:40–1:320) having different patterns: multiple nuclear dots, nuclear rim, speckled, and centromere. Only in 4 patients were AMAs found together with SMAs (titers 1:20–1:100) and in 4 with ANAs and SMAs. Ten patients (8.3%) were AMA negative: 3 of them did not have any autoantibody, 4 presented ANAs of different patterns, and two patients had SMAs (titer 1:100).

Histological findings

The most important histological alteration of PBC, inflammatory bile duct lesions, were found in all PBC patients who underwent liver biopsy, while the prevalence of histological signs of cholestasis (except copper accumulation) and cho-

Table 3. Main symptoms and physical signs at PBC presentation and at diagnosis.

Symptoms and signs	At disease presentation		At diagnosis	
	n	%	n	%
Liver related				
Itching	80	61.1	109	83.2
Jaundice	36	27.5	72	55.0
Variceal bleeding	1	0.8	2	1.5
Hepatomegaly	4	3.0	46	35.1
Unspecific gastrointestinal				
Abdominal pain	6	4.6	8	6.1
Discomfort in right upper abdomen	9	6.9	43	32.8
Dyspepsia or nausea	5	3.8	21	16.0
Anorexia	4	3.0	5	3.8
Weight loss	6	4.6	26	19.8
Inconstant stool and flatulence	2	1.5	19	14.5
Other				
Fatigue	16	12.2	72	55.0
Xantelasma	3	2.3	9	6.9
Subfebrility	2	1.5	1	0.8
Skin signs (dryness, hyperpigmentation, thickness, excoriations)	10	7.6	97	74.0
Abnormal liver tests	19	14.5	64	48.8
Elevated erythrocyte sedimentation rate	8	6.1	61	46.5
Arthralgia and myalgia	8	6.1	22	16.8
Sicca syndrome	0	0	15	11.4

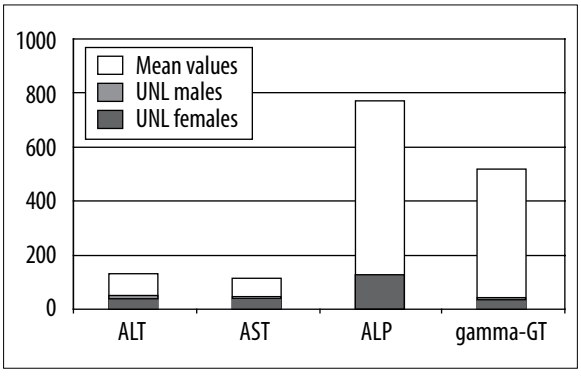

Figure 1. Liver enzyme activity (IU/l) in PBC patients at diagnosis.

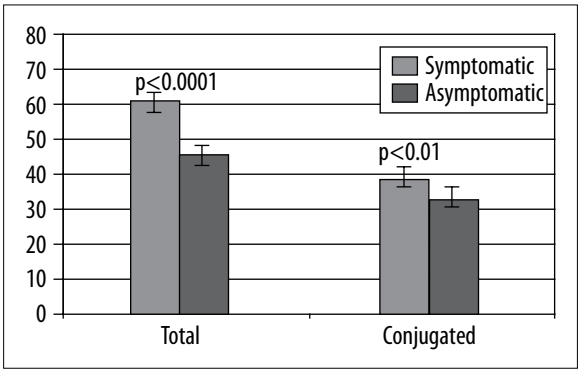

Figure 2. Concentrations of total and conjugated bilirubin (µmol/l) in symptomatic and asymptomatic PBC patients.

latostasis was lower (Table 4). We did not find significant differences in histological findings when comparing symptomatic and asymptomatic patients (probably because of the small number of asymptomatic patients). Nevertheless, some histological signs of cholestasis, were less frequent in asymptomatic than in symptomatic patients (e.g. canalicular cholestasis – twice, intracellular cholestasis – 1,7 times.

Different stages of fibrosis were found in all patients, with a high prevalence of advanced fibrosis (stages III and IV) (Table 5). Mild histological activity (HAI 4–8) prevailed in 54.5% of the patients. The HAI depended on the stage of the disease and was significantly higher in patients with PBC stages II, III, and IV compared with stage I (Table 5). HAI did not differ significantly in asymptomatic and symptomatic patients, neither when comparing mean values of HAI overall, nor depending on PBC stage.

After summarizing the results of the three most important findings (ALP and γGT activity, presence of AMA, and liver histology findings) all PBC patients who underwent liver biopsy (n=101) were divided into 2 groups: definite PBC (all three parameters of the triad were present) was diagnosed in 80 (79.2%), and probable PBC (when one of the triad parameters was absent) in 27 (20.8%) patients. The first vari-

Table 4. Histological findings in symptomatic and asymptomatic PBC patients.

Histological findings	Symptomatic (n=73)		Asymptomatic (n=28)		Overall	
	n	%	n	%	n	%
Bile ducts lesion	100	100.0	28	100.0	101	100.0
Ductopenia	53	72.6	17	60.7	70	69.3
Ductular proliferation	57	78.1	20	71.4	77	76.3
Canalicular cholestasis	21	28.8	4	14.3	25	24.8
Intracellular cholestasis	43	58.9	10	35.7	53	52.5
Foamy degeneration	35	47.9	10	35.7	45	44.6
Mallory bodies	13	17.8	6	21.4	13	12.9
Copper accumulation	63	86.3	22	78.6	85	84.2
Lymphoid aggregates	17	23.3	8	28.6	25	24.8
Granulomas	40	54.7	15	53.4	55	54.2
Portal inflammation	71	97.3	28	100.0	99	98.0
Lobular necrosis	58	79.5	21	75.0	79	78.2

Table 5. HAI in PBC patients according to histological stage.

Stage	n	%	Mean ±SE (HAI score)	*p*
I	3	3.0	3.7±0.1	
II	28	27.7	6.1±0.7	0.0007
III	57	56.4	7.0±0.4	<0.0001
IV	13	12.9	8.3±1.0	<0.0001
Overall	101	100.0	6.9±0.3	

p – statistical significance in PBC stages II, III, IV vs. stage I.

ant of probable PBC, i.e. patients who had nonspecific and non-compatible liver histology (nonspecific portal and periportal infiltration with fibrosis and minimal or no bile duct damage and no signs of cholestasis), was found in 4 (4%). The second variant, patients who had normal activity of cholestatic enzymes, was considered in 5 (5.0%), and the third variant, patients who had negative AMA, in 10 (9.9%).

Discussion

Early reports on PBC described it as an almost universally severe but rare disorder. The current data on PBC have been reviewed and have changed our understanding of its epidemiology, clinical features, diagnostic possibilities, and management [41]. The data on PBC patients in Lithuania showed them having typical and common clinical features of this disease, but also revealed some peculiarities and differences compared with the findings of other investigators. Our results regarding gender and age of PBC patients and the women-to-men ratio (19:1) are higher than in published data [42–47], while the finding of men being older than women at PBC presentation and diagnosis was not reported earlier [48].

Of the patients, 70.2% were symptomatic and 29.8% asymptomatic at presentation and at diagnosis. In 74.4% of the initially asymptomatic patients, specific symptoms and signs developed in the course of about 4.3 years. Asymptomatic patients at the time of diagnosis were significantly older than symptomatic ones and presented lower frequency of jaundice, skin signs, and weight loss, but a higher prevalence of sicca syndrome. Previous studies found asymptomatic patients having milder severity of PBC [41], lower prevalence of jaundice, hyperpigmentation, hepatomegaly, and splenomegaly [19], as well as serum bilirubin and cholesterol levels. The data regarding the age of asymptomatic patients are controversial [16,43,49].

The prevalence of asymptomatic PBC patients according to different investigators comprised 13–70%, mostly about 50–60% [7,16,19,20,42,49]. During the last decades it has significantly increased in Western Europe countries. It is assumed that the widespread use of diagnostic tests such as antibody screens and increased awareness of the disease among doctors has led to an increasing rate of PBC diagnosis and improved recognition of asymptomatic cases.

The reasons for the rather low prevalence of asymptomatic PBC in Lithuania are not clear, but could possibly be explained by regional differences (in Estonia the prevalence of asymptomatic PBC was 13%) or partly by under-diagnosing of asymptomatic PBC cases in the past (the study included patients from the year 1984). The rather long time from the early symptoms and signs of the disease to correct diagnosis (4.4±0.7 years) as well as the high prevalence of advanced stages (III and IV) in 66.2% of patients may be in favor of this assumption [7]. In the meantime, the diagnosis of PBC at early stages of disease is very important, because those patients might benefit most from early therapeutic intervention [15].

There are different opinions regarding asymptomatic PBC. Some investigators consider it an early form of symptomatic PBC [50], while others a distinct presentation of the disease.

Some authors reported that the prognosis of asymptomatic patients appears to be better and their median survival longer than of symptomatic patients [17,19,42,51,52]. According to contrary data, asymptomatic PBC patients have similar survival as symptomatic ones, although it is reduced compared with the survival of the general population [41,53,54]. Further investigations are needed to determine the survival of asymptomatic patients in our country and to specify existing controversies.

The suspicion of PBC is usually based on its clinical symptoms. The classic pattern of disease presentation may facilitate the diagnosis of PBC and shorten the duration from disease presentation to diagnosis. Symptomatic patients showed several patterns of disease presentation, with a prevalence of the classic mode (with predominant itching, followed by jaundice, fatigue, abdominal pain, and discomfort in the right upper abdomen). These observations correspond to the data of several other studies [44–48,55], although the prevalence of jaundice in our patients (27–55%) at presentation and diagnosis was slightly higher than reported previously [42,46,56,57]. In spite of the typical pattern of symptomatic PBC presentation, the median duration from the first symptoms to diagnosis was long (3.7±0.3 years) and advanced stages of the disease prevailed (in 76.7%). These data did not differ from those of asymptomatic patients.

Our data confirmed the high diagnostic significance of the three PBC criteria: cholestatic liver enzymes, presence of AMA, and diagnostic or compatible liver biopsy [31]. Marked elevation of ALP and γGT was found in almost all patients, but asymptomatic PBC patients presented a significantly lower elevation of ALP and concentrations of total and conjugated bilirubin than symptomatic, i.e. they had less severe elevations of biochemical parameters of cholestasis. Our data partially correspond to the findings of other investigators who also found lower ALP, ALT, and bilirubin in asymptomatic patients [16,58]. AMAs were found in 91.7% of our patients as the only marker in 50.4%, simultaneously with ANAs in 34.7%, which correspond to the data presented in other studies [60–63].

The biopsy of PBC patients is usually confirmative rather than diagnostic, but it also provides information about the stage of the disease and prognosis. Moreover, different histological PBC patterns which may have impact on PBC progression were reported recently [58]. The histological hallmark of PBC is florid bile duct lesions [64,65]. Bile duct damage and different grades of portal inflammation with piecemeal necrosis were found in all our PBC patients who underwent liver biopsy, while the prevalence of cholestasis (except copper accumulation) was lower. No statistically significant differences in histological findings were found between symptomatic and asymptomatic patients (probably because of the small number of asymptomatic patients). Nevertheless, a lower prevalence of some signs of cholestasis, i.e. canalicular and cellular cholestasis and ductopenia, was observed in the latter group.

The mean values of HAI depended on the stage of the disease, gradually increased with disease progression, and did not differ significantly in symptomatic and asymptomatic patients.

On the basis of three main investigations – AMA, histological changes, and activity of cholestatic liver enzymes – "definite" PBC was diagnosed in 2/3 and "probable" PBC in 1/3 of the patients.

Further investigations are needed to specify regional differences of PBC distribution in Lithuania and to study asymptomatic PBC patients more precisely in order to specify their prognosis, survival, and treatment benefits.

Conclusions

Our study shows that most PBC patients in Lithuania at diagnosis were at late (III and IV) histological and clinical stages of the disease, with the significant predominance of females older than 50 years (19:1) and with a rather long duration to correct diagnosis. Males with PBC were significantly older than females and had almost a three times shorter duration from disease presentation to correct diagnosis. Approximately 30% of PBC patients had asymptomatic disease at presentation and at diagnosis and were older than symptomatic patients. They presented lower prevalence of jaundice, skin signs, and weight loss, but a higher frequency of sicca syndrome. They also showed significantly lower elevation of some biochemical parameters of cholestasis, but the same stages of fibrosis and HAI as symptomatic ones. The triad of liver tests (AMA positivity, presence of cholestatic liver enzymes, and compatible or diagnostic liver histology) is a valuable and informative tool for PBC diagnosis: "definite" PBC was found in 80.2% of patients and "probable" in 19.8%.

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