

Original article

Primary Biliary Cirrhosis Scenario of Libyan Patients in Tripoli University Hospital

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Abstract

Background and aims. Primary biliary cirrhosis (PBC) is an autoimmune, slowly progressive, cholestatic, liver disease characterized by a triad of chronic cholestasis, circulating anti-mitochondrial antibodies (AMA), and characteristic liver biopsy.

A variant, called PBC-autoimmune hepatitis (AIH) overlap, is characterized by the above findings of PBC together with findings of elevated ALT, elevated Ig G, and ASMA. PBC is hypothesized to be related to environmental exposure in genetically vulnerable individuals. It typically occurs in middle-aged females. **The aim** of the current study is to describe the clinical and biochemical profile of adult Libyan Primary Biliary Cirrhotic patients. **Method.** This was a case series study conducted by reviewing the medical records of the 50 patients diagnosed as PBC and followed in gastro-enterology clinic in Tripoli university hospital during the study period. A relevant data obtained from the records in a preformed case sheet. **Result.** The total number of the diagnosed Primary Biliary Cirrhotic patients were 50 patients. All of them were females. Patient age during the study were from 35 to 65 years, about 90% of patients were symptomatic like gastrointestinal symptoms (jaundice in 100%, abdominal distention in 24%, and encephalopathy in 5 patients 10%), while, non- gastrointestinal symptoms like fatigue and weakness in 35 patients 70%, skin disorders(pruritis) were diagnosed in 18 patients 36%), dyslipidemia in 15 patients 30%, and osteopenia in 7 patients 14%. Serological tests(AMA) was positive in ail patients and(ASMA)in 20% of patients, biochemical profile showed that Alkaline phosphatase was raised in all patients, while, 10 patients had raised AST and ALT 20%.

Conclusion: middle-aged female patient with jaundice, fatigue and elevated alkaline phosphatase should be routinely undergoing serological testing(AMA)to check for primary biliary cirrhosis which should subsequently be verified by liver biopsy.

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Introduction

Primary biliary cirrhosis (PBC) affects predominantly women and is ten-folds more common in women than men and usually present clinically in middle age. The ready availability of diagnostic tests has revealed asymptomatic disease which can remain quiescent for years, and has shown that PBC is

a relatively common form of cirrhosis .PBC is an autoimmune, slowly progressive , cholestatic liver disease[1].A triad of chronic biochemical cholestasis, circulating anti-mitochondrial antibodies(AMA), and characteristic liver biopsy finding [2]..Development of PBC is hypothesized to be related to environmental exposure in genetically vulnerable individuals , but further studies are needed to understand its

complex etiology. PBC was first reported by Addison et al [3] in 1851, The term PBC was, however, coined by Ahrens et al [4] in 1950. Walker et al [5] first described the association between AMA seropositivity and PBC.

. There is significant geographic variation, with a much higher prevalence in the United States at 400 per million [6], or northern Europe at 200-250 per million, than in Africa, Asia, or Australia at 20 per million [7].

Environmental agents including exposure to sun light, chemicals, toxins, bacteria and viruses may differ across geographic regions and such difference may play a role in pathogenesis [8].

Genetic and familial factors play a major role in PBC. Autoimmune disorders occur more frequently in patients with PBC, including autoimmune thyroid disease, Raynaud syndrome Sjogren syndrome [9].

PBC is diagnosed provided two of the following three criteria are satisfied: (1) AMA titer>1.40, (2) alkaline phosphatase>1.5 times the upper limit of normal for >24 wk., and (3) compatible liver histology, demonstrating nonsuppurative destructive cholangitis and interlobular bile duct destruction [10].

The PBC-AIH overlap syndrome consist of a range of clinical entities of AIH together with clinical, laboratory, or histological characteristics of PBC or PSC[11], PBC generally precedes AIH by 6 months to several years[12], overlap syndrome is diagnosed when PBC is diagnosed by aforementioned criteria

Methods

Study design and setting

During the period from 2012 to 2022 in this case series study, fifty patients with symptoms of jaundice of obscure origin referred to the gastroenterology outpatient department in Tripoli university hospital as suspected liver disease, patients with different presentations and from different departments and outpatient clinics (from indoor and outdoor the hospital)

and AIH by the presence of the following criteria(1) serum alanine aminotransferase >5 upper limit of normal , serum immunoglobulin G (IgG) levels >2 upper limit of normal, or positive test for anti-smooth muscle antibodies, and (2) liver biopsy demonstrating moderate or severe periportal or periseptal lymphocytic piecemeal necrosis[13].

The most common clinical symptoms are fatigue and pruritis, jaundice in 10%-60%, xanthomas in 15%-50%, osteoporosis in 35% and dyslipidemia in>75%. No specific therapy is available, Ursodeoxycholic acid protects from cytotoxicity of hydrophobic bile acids, stimulates biliary secretion of bile acids and protects hepatocytes against bile acid -induced apoptosis, it is the only therapy approved by the United States Food and Drug Administration(FDA) [14], UDCA alone may not produce a biochemical response in patients with AIH, and such patients often require concomitant immunosuppressive therapy like corticosteroids. Budesonide reduces systemic toxicity as compared to other corticosteroids, other medications like Obetocholic, Fibrates. Clinical indications for liver transplantation in PBC include refractory ascites, recurrent spontaneous bacterial peritonitis, recurrent variceal bleeding, hepatic encephalopathy, hepatorenal syndrome type I, and hepatocellular carcinoma, subject to the Milan criteria [15]. Indications specific to PBC include refractory pruritis and chronic fatigue [16].

were included in the current study. All of them were subjected to full history of gastro-intestinal symptoms of hepatic disease apart from jaundice other symptoms like fatigue, itching, abdominal distension, altered level of consciousness and. history of hematemesis or melena, Consent form of all participants were obtained.

Data collection procedure

Clinical examination and investigations were collected, such as; complete blood picture, liver function test (total bilirubin and its types, Alkaline phosphatase, ALT and AST), prothrombin time, serum immunoglobulin G, serum albumin, vitamin D level, serum Ca²⁺ and Mg²⁺, serum urea, electrolytes and creatinine. Serological tests include anti-mitochondrial antibodies (AMA) and anti-smooth muscle antibodies (ASMA) were also screened, and all patients did an abdominal ultrasound, upper GIT endoscopy and histological finding for primary biliary cirrhosis were investigated using biopsy specimen taken from the Liver. The diagnosis was

confirmed by both serological tests and histopathological tests.

Statistical analysis

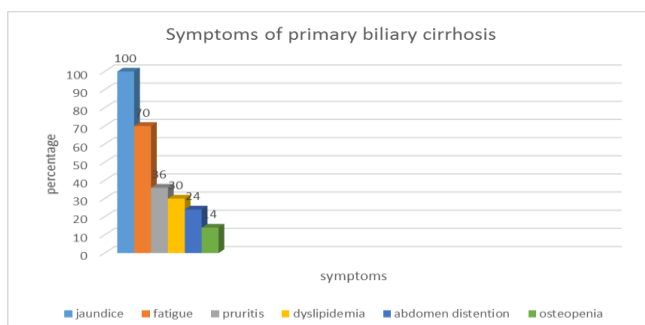
Medical records obtained from the included participants were reviewed and the relevant data for the purpose of this study were obtained in predesigned case sheet. The collected data analyzed using statistical package for the social sciences (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0, Chicago, SPSS Inc.), and descriptive statistics were used as mean, SD, and percentage. Chi square test was used to find the significance of difference between categorical variables, and p value less than 0.05 were considered significant.

RESULTS

During the period from (2012 to 2022) in this case series study, a total of 50 patients with jaundice of obscure origin with high alkaline phosphatase were diagnosed as cases of primary biliary cirrhosis in 40 patients by both serological and histopathological tests. While, 10 patients were diagnosed as a cases of Overlap syndrome (primary biliary cirrhosis and autoimmune hepatitis). All were female patients. Patient age during the study ranged from 35 years to 65 years (mean patient age 50 years), 10% of the patients were asymptomatic and 90% were symptomatic (Table 1).

Table & Figure 1. Clinical features of Libyan patients with Primary biliary cirrhosis (Tripoli University hospital 2012-2022)

Character	No. (%)
Asymptomatic	10 (10%)
Jaundice	100 (100%)
Fatigue and weakness	35 (70%)
Pruritis	18 (36%)
Dyslipidemia	15 (30%)
Abdominal distention	12 (24%)
Osteopenia and bone fracture	7 (14%)



In table 1 & 2, all symptomatic patients present with symptoms of jaundice (like yellowish sclera, yellow dark skin and darkened urine), associated with general fatigue and weakness in 70%, other gastrointestinal symptoms (abdominal distention in 24%, altered level of consciousness in 10%, and none of them presented with hematemesis or melena). Non-gastrointestinal symptoms like skin disorders in the form of itching in 18 patients, dyslipidemia & xanthomas in 15 patients and osteopenia with history of bone fracture in 7 patients. All patients had high bilirubin and high alkaline phosphatase while, raised immunoglobulin G, AST and ALT in 10 patients, and 3% of patients had prolonged PT. Osteopenia was reported in 7 patients (low vitamin D and low serum Ca⁺² and Mg⁺²). Non suppurative destructive cholangitis and inter lobular bile duct destruction was the commonest (80%) histopathological feature in our PBC subjects. While, periportal and periseptal piecemeal necrosis was noted in 20% subjects.

There was a significant relation between middle aged female patients having jaundice (Tot. bilirubin ≥ 2 mg/dl) and fatigue in PBC patients, the chi square test was applied to test

if there is any relation between fatigue in middle aged female patient having jaundice with Total bilirubin ≥ 2 mg/dl, (p= 0.019). Moreover, there was significant correlation in PBC middle aged female patients having jaundice with Tot. Bilirubin ≥ 2 mg/dl and fatigue.

Table & Figure 2. Biochemical and Serological features of Libyan patient with Primary biliary cirrhosis (Tripoli University hospital 2012-2022)

Character	No. (%)
Total bilirubin ≥ 2 gm\dl	50 (100%)
High Alkaline phosphatase	50 (100%)
Raised AST&ALT& Ig G	10 (20%)
Raised serum cholesterol & TG	15 (30%)
Low Vitamin D &Ca ⁺² &Mg ⁺²	7 (14%)
AMA	50(100%)
ASMA	10(20%)

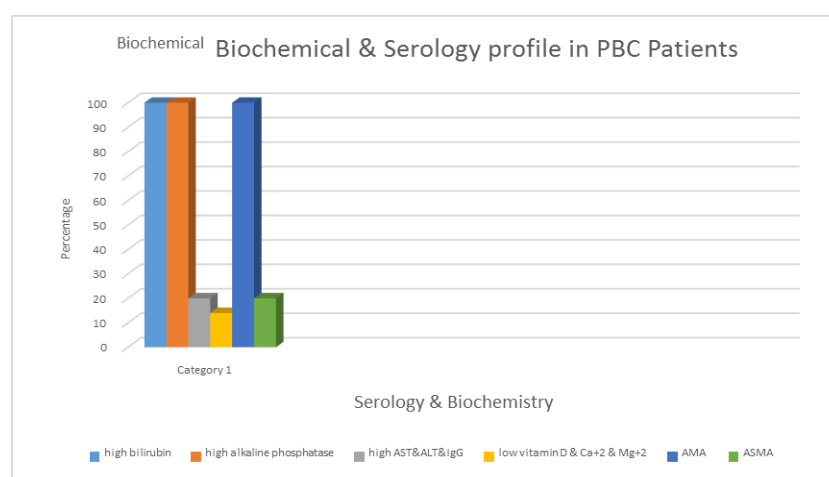
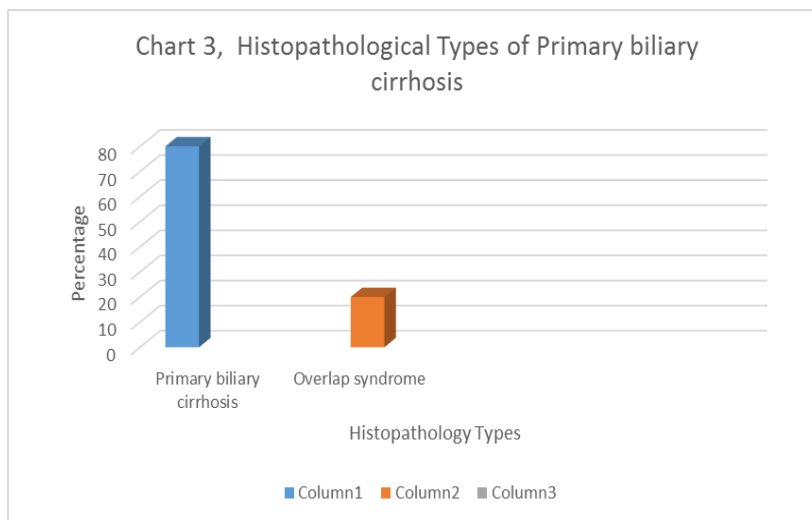


Figure 3. Histological types of Primary biliary cirrhosis



Discussion

During the study period (from 2012 to 2020), a total of 50 patients with jaundice of obscure origin referred to the gastroenterology outpatient department in Tripoli university hospital as suspected liver disease patients with different presentations and from different departments and outpatient clinics. These patients present to outpatient department with symptoms and signs of jaundice as (yellow sclera, dark yellow skin and darkened urine), nearly two third of patient were complaining of malaise, general fatigue. While, itching in one third. Other symptoms like xanthomas was present in 15 patients, abdominal distention in 12 patients, altered level of consciousness in 5 patients and none of them had hematemesis or melena, and investigation sent as CBC, complete LFT (with bilirubin and its types, AST, ALT, Alkaline phosphatase, Ig G, Serum albumin, and PT), lipid profile (serum cholesterol, TG, HDL, LDL, VLDL), U/E/C, vitamin D level, and serum Ca^{+2} & Mg^{+2} . Serological tests AMA and ASMA were also screened with results: AMA was positive in all PBC patients and ASMA was positive only in 10 patients, an abdominal ultrasonography and upper GIT endoscopy were done for all patients and grade I Esophageal Varices was found in 24 patients. Liver biopsies was done under aseptic

precaution under ultrasound guide and a histopathological result showed: Non suppurative destructive cholangitis with inter lobular bile duct destruction in 40 patients, while, periportal and periseptal lymphocytic piecemeal necrosis was noted in 10 patients.

All our patients were middle aged females. Similar study result showed that PBC is ten-fold more common in women than men. The reason for this is unknown, but a relatively recent study revealed that X chromosome monosomy was more common in women with PBC. This finding suggests that genes related to X-linked immunodeficiency can lead to granuloma formation and elevated IgM levels, both of which occur in PBC [17]. The median age of diagnosis is about 50 years [18].

Fatigue was presenting symptom in 70% of our PBC Patients. Other studies showed that fatigue was the presenting symptom in about 70% and this is due to excessive manganese deposits in Globus pallidum and elevated inflammatory cytokines[19], jaundice in 60% of patients due to cholestasis[20], pruritis in 75% due to cholestasis and increased opiodergic tone, dyslipidemia due to reduction in biliary secretion of cholesterol and toxic effects of unconjugated bilirubin which may leads to Xanthomas and osteoporosis in 35% due to

disturbance of bone remodeling due to metabolic changes.

Primary biliary cirrhosis is most often diagnosed when routine investigations reveal an increase in alkaline phosphatase, AMA, the serological hallmark of PBC and presents in about 95% of the patients, but in less than 1% of healthy adults [21]. High alkaline phosphatase in conjunction with the presence of AMA is sufficient to diagnose the disorder. Liver biopsy is not necessary for diagnosis but can be useful in the absence of AMA or in the presence of overlap syndrome.

Conclusion And Recommendation

There is significant correlation between middle-aged female patients having jaundice and / or fatigue to be primary biliary cirrhosis.

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