Original Article

Primary biliary cirrhosis In a sample of Iraqi patients

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Abstract

Background: Primary biliary cirrhosis(PBC) is an autoimmune liver disease that generally affects middle aged women and it is the most common chronic cholestatic liver disease in adult .There are a few studies described this disease in Iraq .

Aim of the study: The aim of this study is to evaluate a sample of Iraqi patients with primary biliary cirrhosis regarding the clinical presentation, investigations and associated diseases.

Setting: Gastroenterology and Hepatology teaching hospital-Baghdad-Iraq

Result: Thirty-two patients involved in this study (mean age 45.9 year), most of patients were female .All patients presented with itching, and most of them with jaundice, about two thirds of patients complained of fatiguability and more than half of them had abdominal pain. Eighty-seven percent of patients were younger than 60 years old. Fifty percent of them had serum bilirubin less than 6 mg/dl, 39.3% had serum bilirubin more than 6 mg/dl .One-third of them had prolong prothrombin time, while serum alkaline phosphatase is elevated in all patients, and about 80% of patients had elevated liver enzymes .About 75% of patients had positive AMA, while ANA was positive in 21 .9% of patients .Liver biopsy was compatible with PBC in 56.3% of patients . Primary biliary cirrhosis associated with many diseases .In this study 28.1% of patients had PBC associated with arthralgia, Sicca syndrome found in 12.5% of patients, 6.3% had full-blown picture of scleroderma, thyroid disease mentioned in 6.3 % of patients .Gall bladder stones reported in 9.4 % of patients.

Conclusion:

1. All patients presented with itching, so any patient complain of itching should draw a special attention in a diagnosis and early treatment.
2. All patients had high serum level of alkaline phosphatase so this test can be used as a screening test for PBC in patients with itching. 3. One forth of patients had AMA negative variant so this test will be unreliable as a screening test in Iraq.
4. One-third of patients candidate for liver transplant so we need to develop a liver transplant center in Iraq. Keywords: PBC primary biliary cirrhosis

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Introduction:

Primary biliary cirrhosis (PBC) is an autoimmune liver disease that generally affects middle aged women and it is the most common chronic cholestatic liver disease in adult .PBC characterized by ongoing inflammatory destruction of intralobular and septal bile ducts that lead to chronic cholestasis and biliary cirrhosis with subsequent complications such as portal hypertension and liver failure. [1, 2].Primary biliary cirrhosis occur world wide and predominant in women with female to male ratio of 9:1 .Median age of onset is approximately 50 year with range of 21-91 year.PBC has been documented in children

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and adolescent.[10]It accounts for0.6 to 2.0 % of death from cirrhosis world wide.[10]

Clinical features. Fatigue ,although relatively non specific in PBC ,it is the most common symptoms found in about two-third of patients ,it generally become worse as PBC progress[10] .The fatigue of PBC must be differentiated from other causes of tiredness that may presented in any patient ,these include depression ,unrecognized thyroid diseases or adrenal diseases or side effect of medications ,in particular antihistamines give for itching [10].Pruritus may first occur during pregnancy and may be mistaken for pruritus of pregnancy ,however the pruritus of pregnancy resolve in post partum period ,whereas that due to PBC persist .Once pruritus occurs ,it is unusual for the itching to disappears spontaneously,the same is true for jaundice ,itching worse at night ,under constricting, coarse garments,in association with dry skin ,and in hot humid weather .Pruritus is often not recognized as a sign of cholestasis and many patients are referred to dermatologist [15]Unexplained right upper quadrant (RUQ) discomfort was reported in 8% of patients in one study[16]

.Jaundice occur later in the course of the disease and it is usually persistent and associated with poor prognosis .Many patients with PBC do not have jaundice at the time of diagnosis .Symptoms may be related to fat-soluble vitamin deficiency ,bone pain with or with out spontaneous fractures,symptoms of advanced liver disease ,such as ascites ,bleeding from gastrointestinal varices and encephalopathy ,usually occur late in the course of PBC[10,15]

The finding on physical examination vary widely and depend on the stage of the disease at the time of presentation .The physical examination is often normal in asymptomatic patients .The skin is initially normal, but excoriations sever enough to cause bleeding. Xanthomas are a late manifestation. Striking hepatic enlargement is often found occasionally in asymptomatic patients ,hepatomegaly becomes more common with progressive disease and it is found eventually in approximately 70% of patients[10,15].Splenomegaly is found at presentation in 15% of patients .Jaundice is a later manifestation but in some patients it may be seen at presentation in only10% of patients [10,15] Spider nevi, muscles wasting, ascites, and edema are all late manifestation of the disease [15]

Associated diseases:

These summarized in table (1)[10]

Table (1) Diseases associated with primary biliary cirrhosis

Disease associated with PBC Frequency%	
Keratoconjuctivitis sicca	72-100
Arthritis /Arthropathy	4-42
Scleroderma and Variants	15-20
Scleroderma	3-4
CREST or any of its components	7
Raynaud's disease	8
Autoimmune thyroditis	15-20
Cutaneouse disorder (lichen-planus,discoid lupus,pemphigoid)	11
RTA proximal or distal*	50-60
Gall stone	33

*RTA=renaltubular acidosis ,HCC= hpatocellular carcinoma

Diagnosis:

Biochemical tests: the liver biochemical tests show a cholestatic picture .Almost all patients have increased serum level of alkaline phosphatase (ALP) (3-4 times normal) (1) and it is of hepatic origin. The serum levels of aminotransferases may be normal or slightly elevated (usually less than three times normal) marked elevation are distinctly unusual and may suggest PBC -autoimmune hepatitis overlap syndrome or coexisting viral hepatitis (7) .The serum bilirubin concentration is usually normal early in the course of the disease ,but becomes elevated in most of patients as the disease progress, both direct and indirect fractions are increased(8).Level of immunoglobulin especially IgM,serum bile acid are all increased .Serum cholesterol level are elevated in at least 50 % of patients (8).

Serological diagnosis:

Antimitochonderial antibodies (AMA) are serologic hallmark of PBC .Thus , an AMA test should be performed whenever the presence of PBC is suspected (5) ,AMAs are presented in 90% to 95% of patients with PBC (4).Other autoantibodies found in patients with PBC are RF (70%),ASMA(66%),antithyroid antibodies (41%),and ANA (35%)(1).

Liver biopsy:

The initial lesions on liver biopsy specimens is damage to epithelial cells of the small bile ducts .The most important and only diagnostic clue in many cases is ductopenia defined as the absence of interlobular bile ducts in more than 50% of portal tracts .The florid duct lesions, in which the epithelium of the interlobular and segmental bile ducts degenerates sequentially with the formations of poorly defined non caseating epitheloid granulomas is nearly diagnostic of PBC but it is found in a relatively small number of cases mainly in the early stages(10)

Aim of the study:

To study the clinical presentation, liver biochemistry, and liver biopsy in a sample of Iraqi patients with PBC

Patients and methods:

During the study period (September 2002 - January 2004) thirty-two patients involved in the study (31 female, one patient male) mean age 46.4 year. All patients were referred to Gastroenterology and Hepatology teaching hospital for suspected PBC or as a case of chronic liver disease. The diagnosis of PBC is established by biochemical tests that are consistent with cholestasis and presence of AMA and liver biopsy which either compatible (ductopenia ,the florid duct lesions in which the epithelium of the interlobular and segmental bile ducts degenerations sequentially , with the formation of poorly defined non caseating epitheloid granulomas) or cirrhosis (1,4,9). Ptients divided into two groups , those less than 60 years old who had total serum bilirubin (TSB)≤6mg/dl (100umol/L)and those patients more than 60 years old with TSB >6 mg/dl ,because liver transplant is curative and should be consider for those patients younger than 60 years old and TSB≤6mg/dl(10)

Result:

Thirty-two patients involved in this study .Mean age was 45.9 year; most of patients were female (96.9%)while male only one patient (3.1%)

All patients presented with itching although it varies with severity. Most of the patients presented with jaundice (90.6%).Fatiguability described in 68.8% of patients. RUQ pain found in 59.4% of them .Encephalopathy diagnosed in 15.6% of patients as a complication of chronic liver disease, three of them died. .Fifteen percent presented with upper gastrointestinal tract bleeding, twenty-five percent of patients had esophageal varices, twenty-eight percent of patients had ascites and 34.4% of patients had skin pigmentation.(Table2). Patients less than 60 years old were 28 (87.5%) patients , 53.6% of them had TSB≤6 mg/dl. 39.3% had TSB more than 6 mg/dl and 7.1 % of them had normal TSB. (Table 3)Coagulation abnormalities represented by prolong PT was found in 31.3% of patients.(Table 4).

Regarding the liver biochemistry, it was found that all patients had elevated ALP (mean 3.9 folds). 81% of patients had elevated liver enzyme ALT and AST (mean of 3.7 folds and 3.6 folds respectively). Fifty percent of patients had hypoalbominemia.

Three-quarter of patients had AMA positive and 25 % had negative result, ANA was positive in 21.9% ASMA was positive in 6.3% of patients. (Table 4)

Liver biopsy was compatible with PBC in 56.3% of patients; others had liver biopsy showed advance liver cirrhosis. (Table 4).

Primary biliary cirrhosis associated with many diseases .In our study 28.1% of patients had PBC associated with arthralgia, Sicca syndrome found in 12.5%, and 6.3% had full-blown features of scleroderma, thyroid disease mentioned in 6.3 % of patients .Gall bladder stones reported in 9.4% of patients.(Table5)

Tables:

Table (2) presentations of patients with Primarybiliary cirrhosis

features	Fatigue (%)	Pruritus (%)	RUQ Pain (%)	Jaundice (%)	Bleeding (%)	Encephalopathy (%)	Hepatomegaly (%)	Splenomegaly (%)	O.V.* (%)	Ascites (%)	Skin Pigmentation (%)	
present	22 (68.8)	32 (100)	19 (59.4)	29 (90.6)	5 (15.6)	5 (15.6)	28 (87.5)	26 (81.3)	8 (25)	9 (28)	11 (34.4)	
absent	10 (31.2)	0	13 (40.6)	3 (9.4)	27 (84.4)	27 (84.4)	4 (12.5)	6 (18.7)	24 (75)	23 (72)	21 (65.6)	

*esophagealvarices

Table (3) Distribution of patients who have jaundice according to age

Age year	NO.(%)	TSB* >6mg NO.(%)	TSB <6mg NO.(%)	Normal TSB NO.(%)
>60	28 of 32 (87.5)	15 of 28 (53.6)	11 of 28 (39.3)	2 of 28 (7.1)
<60	4 of 32 (12.5)	3 of 4 (75)	0	1 of 4 (25)

*TSB= Total serum billirubin

Table (4)results of the investigations in patients with PB C

Types	AMA*		ANA**		ASMA***		PT****		ALP*****		ALT*!		AST*!!		Alb.*!!!		LIVER BIOPSY	
	+	–	+	–	+	–	%	N	%	N	%	N	%	N	%	N	+1	-2
NO.	24	8	7	25	2	30	10	22	32	0	26	6	26	6	16	16	18	14
%	75	25	21.9	78.1	6.3	93.7	31.3	68.7	100	0	81.2	18.8	81.2	18.8	50	50	56.3	43.7

*AMA =Anti mitochondrial antibody, **ANA= Antinuclear antibody, ***ASMA= Anti smoothmuscle antibody, * **PT=Prothrombin-time, ****ALP=Alkaline-phosphatase, *!ALT= Alanine aminotransferase , *!!AST=Aspartate aminotransferase ,*!!!Alb= serum albumin, +1 compatible, -2 cirrhosis

Table (5) diseases associated with PB C

NO.	4	1	2	1	9	3	2	1
%	12.5	3.1	6.3	3.1	28.1	9.4	6.3	3.1

Discussion:

Our study showed that all patients presented with itching, most of them presented with jaundice, fatigability more than half of the patients had RUQ pain and some of them presented with encephalopathy ,this consistent with Puri .A.S.,Kumar.N,Gondal .R.,et al found that the PBC rare in India ,they study 5 patients they found pruritus ,jaundice ,and fatigability were the most common initial symptoms, hepatomegaly was seen in 4 of 5 and associated autoimmune disease were present in 2 patients ,all patients presented with mild hyperbilirubinemia ? 6 mg/dl with raised serum alkaline phosphatase level (11).While in our patients 53.6% of patients less than 60 year old had TSB > 6 mg/dl .In Indian experience 4 of 5 patients had AMA positive ,while in our study ,AMA positive in 75% of patients .(11)

W.Ray Kim,Keith D.Lindor,G.Richard Locke et al.found that the majority of patients were women 89% ,the median age at diagnosis was 52 years.(12) In our study most of patients were women 96.9% and diagnosed at a younger age (mean 45.9 year). They found that AMA positive in 89%.(12)while in our study the AMA positive in 75% of patients.

W.Ray Kim,Keith D.Lindor,G.Richard Locke et al. found that pruritus and jaundice were present in only 9 patients (20%) .(12) This is inconsistent with our finding, jaundice described in 90.6% of patients and pruritus in all patients.

About 70% of patients presented with fatigue, this is consistent with Sherlock.S,Scheuer,PJ .and Long .RG ,Scheuer.P.J,Sherloch S.they found that up to 78% of patients had fatigue at presentation.(13,14)

We found that 12.5% of patients had PBC associated with Sicca syndrome, while Culp. KS,Fleming .CR,Duffy.J ,et al found 40 to 65 % of patients have dry eyes and dry mouth,5-15% had scleroderma (15),this is consistent with our finding 6.3% of patients had scleroderma .

All patients in our study had elevated level of ALP (mean 3.9 folds), ALT and AST elevated in 81.2% of patients; this is consistent with many studies which showed that ALP almost always elevated in PBC and serum level of aminotrasferases rarely increased more than five -fold above normal. (16,17)

Conclusion

1.All patients presented with itching,so any patient complain of itching should drow a special attention in a diagnosis and early treatment .

2.All patients had high serum level of Alkaline phosphatase so this test can be used as a screening test in patients with itching . 3. One forth of patients had AMA negative variant so this test will be unreliable as a screening test in Iraq.

4. One-third of patients candidate for liver transplant so we need to develop a liver transplant center in Iraq.

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