Original Article

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Paucity of Intrahepatic Bile Ducts in Neonates: the First Case Series from Iran

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Abstract

Objective: Paucity of interlobular bile ducts (PIBD), defined as absence or marked decrease in the number of interlobular bile ducts, is one of the causes of neonatal cholestasis. Treatment includes treating the intractable pruritus caused by persistent cholestasis. PIBD can be part of a familial syndrome of cholestasis named Alagille syndrome (AGS). We report clinical status of a case series of Iranian patients with PIBD.

Methods: In this retrospective study, patients with cholestasis admitted to the pediatric gastroenterology ward in a referral hospital in Shiraz from January 2006 to January 2010 and underwent liver biopsy were evaluated. Clinical and paraclinical status of children with the pathologic diagnosis of PIBD was assessed.

Findings: Disease was presented in all jaundiced patients with aged in average 3 days at presentation. Seven patients had the criteria of AGS. Despite medical treatment, cholestasis was not controlled in 6 (28.6%) patients. Liver transplantation led to the survival of 5 patients while the other patient who did not undergo liver transplantation died at 2 months of age. One patient underwent peritoneal dialysis due to renal insufficiency and died at 9 months of age. After 1-5 years of follow-up, the mortality rate was 9.5%.

Conclusion: In patients with intractable cholestasis, only patients that underwent liver transplantation survived. Thus, the most important criterion for liver transplantation in neonatal PIBD is intractable cholestasis. This is the first report that shows AGS can result in neonatal-onset renal insufficiency.

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Key Words: Paucity of Interlobular Bile Ducts; Alagille Syndrome; Neonates; Cholestasis

Introduction

Neonatal cholestasis is a common neonatal liver disease which results in diminished bile flow and excretion, and is defined serologically as prolonged conjugated hyperbilirubinemia in neonates[1,2]. Congenital diseases such as paucity of intrahepatic bile ducts (PIBD) can cause neonatal cholestasis[3,4]. PIBD is a pathologic diagnosis defined as loss of intrahepatic bile ducts in more than 50% of portal tracts in a specimen that contains at least 10 portal tracts. Thus, diagnosis of PIBD needs a pathologic examination on a liver biopsy[5-7].

In many patients, PIBD is associated with various disorders and anomalies in the form of a familial syndrome named Alagille syndrome (AGS) [8,9]. The features associated with BIPD in Alagille syndrome are chronic cholestasis (in approximately 90% of patients), cardiac anomalies (85 to 91%)[10-13], musculoskeletal abnormalities (39 to 87%), ocular anomalies (61-88%), and dysmorphic faces (77-95%)[10-19]. AGS is defined clinically by the presence of at least three of the five mentioned features[19] and genetically by known mutations in Jagged 1 gene on chromosome 20p12[7,20-22].

PIBD in neonates manifests with jaundice and

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conjugated hyperbilirubinemia. Besides jaundice, cholestasis can result in pruritus, xanthoma, and abnormal liver function tests. In case of AGS, manifestation of neonatal jaundice is usually associated with failure to thrive or with cardiovascular symptoms. Due to cholestasis, the concentration of bile acids in the intestine decreases, and malabsorption of dietary lipids and fat soluble vitamins results in malnutrition and severe growth retardation particularly in the first years of life. Thus, failure to thrive has been reported in 50-90% of patients[6,7,10,22,23]. In contrast to the consequences of cholestasis and cardiac involvement, the musculoskeletal and ocular features of AGS are usually asymptomatic. The most common musculoskeletal abnormality of AGS is the asymptomatic butterfly vertebrae where bodies of vertebras are split sagitally into two hemivertebrae usually diagnosed on radiologic examination. Posterior embryotoxon, the commonest ocular abnormality of AGS, is a centrally positioned ring (Schwalbe's ring) at the junction of corneal endothelium and the uveal trabecular meshwork and can only be diagnosed by an exact ophthalmologic examination[7,23]. Moreover, renal and vascular systems are involved in many patients with AGS but they are not included in the diagnostic criteria[11]. Taken together, when PIBD (syndromic or non-syndromic) is suspected, diagnostic evaluation should at least include liver biopsy, liver function tests, echocardiogram, imaging of the vertebrae, and ophthalmologic examination[11].

Management of PIBD (syndromic and non-syndromic) is a conservative medical management that focuses on treating individual diseases of each organ system[8,24]. In some cases, especially older and larger patients, biliary diversion is used to manage the debilitating pruritus[6,22,25].

Despite the medical treatments, end stage liver disease can occur due to persistent cholestasis[12]. These patients with end stage liver disease are amenable to liver transplantation[26]. Other criteria of liver transplantation in patients with PIBD include intractable pruritus despite medical management which affects quality of life, intractable failure to thrive despite enteric nutritional support, and osteodystrophy[12,15,26]. Taken together, liver transplantation is required in 21-31% of patients with AGS and PIBD[11,27] so that 5-10% of all pediatric liver transplantations are done in these patients[22].

The two main prognostic factors of patient's outcome are severity of liver disease and cardiac involvement. Presence of congenital heart disease causes a higher mortality rate.

Here, we present a descriptive report on the first case series of Iranian PIBD neonates with regard to clinical, laboratory, and treatment variables to see if Iranian patients show similar characteristics as other patients.

Subjects and Methods

In a retrospective study, patients with cholestasis admitted to the pediatric gastroenterology ward in a referral hospital in Shiraz, southern Iran, from January 2006 to January 2010 who underwent liver biopsy were evaluated. From these patients, children with the pathologic diagnosis of PIBD were enrolled in this study after obtaining informed written consent from the parents.

Firstly, all the biopsies were reviewed by the same pathologist to confirm the pathologic diagnosis. If PIBD was confirmed, the medical record of patients was used to fill the questionnaire of the study. The questionnaire contained questions about onset age of the clinical presentation, family history, clinical and laboratory markers of involvement of different systems and organs (including hepatobiliary, cardiac, ocular, renal, and musculoskeletal systems), presence of failure to thrive (FTT), syndromic or non-syndromic nature of the disease, performed treatments, and final outcome of the patients. Involvement of hepatobiliary system was evaluated through assessing signs and symptoms such as jaundice, pruritus, hepatosplenomegaly, and laboratory tests of liver function. Cardiac involvement was assessed through evaluations done by a cardiologist (including echocardiograms). Ocular disease was assessed through ophthalmologic examinations. Renal involvement was assessed through urine analysis, laboratory tests, and occasionally by

FTT was defined as presence of any of following criteria: 1) Weight below the 2nd percentile for

gestation-corrected age and sex on more than one occasion; 2) Weight less than 80 percent of ideal weight for age, using a standard growth chart; 3) Depressed weight for length; 4) A low rate of weight gain that causes a decrease in two or more major percentile lines (90th, 75th, 50th, 25th, 10th, and 5th) over time. Finally to assess the survival, the patients were called between January 2011 and February 2011.

Univariate analysis of syndromic versus non-syndromic PIBD using variables of family history, FTT, disease of hepatobiliary system was done using chi-square or Fisher's exact test. The analyses were done by SPSS software (version 19).

Findings

During the period of January 2006 to January 2010, 21 patients were identified with the pathologic diagnosis of PIBD. Five (23.8%) of the patients had a history of familial liver disease. Parents of 18 (85.7 %) patients including all the 5 patients with family history of liver disease were consanguineous.

The median (interquartile range) age at onset of clinical signs and symptoms was 3 days (3 to 9 days). The clinical presentation was before 2 months of age in 20 patients and at 6 months of age in one patient. Symptoms of hepatobiliary systems included jaundice and hyperbilirubinemia in all patients. Pruritus was present in 18 (85.7 %) patients. In physical examination of hepatobiliary system, hepatomegaly was obvious in all patients while only 18 (85.7%) patients had splenomegaly. One (4.8%) patient had skin xanthoma. In laboratory tests, serum aspartate transaminase (AST) and alanine transaminase (ALT) levels were high in all patients while alkaline phosphatase (ALP) was not high in one of them. Among the 20 patients with high ALP, gamma-glutamyl transpeptidase (GGTP) was not high in 2 of them. Prothrombin Time (PT) was abnormal in 5 patients (23.8%). All patients consumed Ursodiol and phenobarbital. Rifampin was administered in 6 (28.6%) patients. The disease was not controlled by these medications in 6 (28.6%) patients. In 5 of these 6 patients (23.8 % of all patients) liver transplantation was done from which one patient was also subject to biliary diversion surgery.

The patient in whom the disease was not controlled by the drugs and did not underwent transplantation, died at 2 months of age.

Disorders of cardiac system and ocular system (in form of posterior embryotoxon) was present in 10 (47.6%) patients and 8 (38.1%) patients,

Table 1: Univariate analysis of syndromic versus non-syndromic PIBD using variables of family history, failure to thrive, and disease of hepatobiliary system

Variable	Alagille Syndrome (n=7) Frequency (%)	Non-Syndromic PIBD (n=14) Frequency (%)	*P* value*
Family history of liver disease	1 (14.3)	4 (28.6)	0.624
Parents consanguinity	6 (85.7)	12 (85.7)	1
Jaundice	7 (100)	14 (100)	-
Pruritus	5 (71.4)	13 (92.8)	0.247
Xanthoma	1 (14.3)	0	0.333
Hepatomegaly	7 (100)	14 (100)	-
Splenomegaly	6 (85.7)	10 (71.4)	0.624
Failure to Thrive	6 (85.7)	8 (57.1)	0.337
Aspartate Transaminase	7 (100)	14 (100)	-
Alanine Transaminase	7 (100)	14 (100)	-
Alkaline Phosphatase	7 (100)	13 (92.8)	1
Gamma-glutamyl Transpeptidase	6 (85.7)	12 (85.7)	1
Direct bilirubin	7 (100)	13 (92.8)	1
Prothrombin time	2 (28.6)	3 (21.4)	1
Control of cholestasis with medical treatment	5 (71.4)	10 (71.4)	1
Liver transplantation	2 (28.6)	3 (21.4)	1

* Fisher's Exact Test; PIBD: Paucity of Intrahepatic Bile Ducts

respectively. Dysmorphic face was obvious in 5 (23.8%) patients. In chest X-ray of 5 (23.8%) patients, signs of butterfly vertebrae or hemivertebrae were present. Renal involvement was present in 2 (9.5%) patients. Azotemia and high serum creatinine was present in only one of them (4.8% of all patients) who was the only one that underwent peritoneal dialysis. This patient died at 9 months of age. In the other laboratory tests, high serum triglyceride and high serum cholesterol level was present in 4 (19%) patients and 20 (95.2%) patients, respectively. Lipid lowering agents were administered in one (4.8%) patient who consumed lovastatin.

In the whole assessment, the syndromic type (AGS) of disease was found in 7 patients (one third of the patients). From the 5 clinical diagnostic features of AGS, cholestasis, cardiac disease and posterior embryotoxon were present in all patients with AGS. Six (85.7%) of them had musculoskeletal anomalies and only 5 (71.4%) had dysmorphic faces. As shown in Table 1, none of variables of hepatobiliary involvement and family history were different in syndromic and non-syndromic presentation of PIBD.

During the follow up period, only 2 patients died; one patient with non-syndromic PIBD whose hepatobiliary disease was not controlled by medications and did not undergo liver transplantation, and another patient with AGS who had undergone peritoneal dialysis due to renal insufficiency.

Discussion

Although BIPD seems to be the main and the most constant feature in AGS, it is only found in 80-85% of patients. In fact, pathologic picture of AGS progresses in a continuum based on age. BIPD is not found in most infants less than 6 months of age but the intralobular ducts evolve over time so that BIPD occurs with increasing age[7,22,24]. Thus, low rate of neonates with PIBD have AGS. Similarly, in our study only 33% of neonatal PIBD patients had AGS.

The most common clinical manifestation of cholestasis in neonatal BIPD and AGS is reported to be jaundice[7,10,22,23]. When cholestasis becomes chronic, it manifests by pruritus. Pruritus usually becomes present at age 4 to 6 months so that it becomes a major problem in the first decade of life[11,23]. On the other hand, symptoms like xanthoma are only present when cholestasis is severe so that xanthoma is present in only 40% of patients[7,22,23]. Similarly in our study most patients (more than 80%) suffered from jaundice and pruritus while only one patient (less than 5%) had xanthoma. Laboratory tests of patients with PIBD are mostly indicative of cholestasis with elevation of serum bilirubin, alkaline phosphatase, bile acids and increase of gamma-glutamyl transpeptidase (GGTP). As the function of hepatocytes are preserved, serum aminotransferases are elevated up to 10-fold. Also in our patients, laboratory studies were indicative of cholestasis in almost all patients and serum aminotransferases were elevated in all patients[6,7,16].

Since cholestasis is the major component of PIBD that needs treatment, all patients were treated for cholestasis using Ursodiol and phenobarbital and some patients consumed phenobarbital. However, cholestasis was not controlled in 6 patients (2 patients with AGS and 4 patients with non-syndromic PIBD). As mentioned previously, intractable cholestasis is a criterion for liver transplantation in PIBD[12,15,26]. Thus, 5 patients underwent liver transplantation. All these patients survived until the end of the study. However, only one patient with an intractable cholestasis did not undergo liver transplantation and died in 2 months of age. This data can suggest that liver transplantation is vital for intractable cholestasis so that it seems to be the only way for the survival of patients with PIBD along with intractable cholestasis. Similarly, previous studies have shown that intractable cholestasis is the most frequent indicator of liver transplantation in these patients[6,12]. Mortality rate was less than 10% (9.52%) in our study. As 23.8 % of patients were transplanted, this low mortality rate can show the importance of performing liver transplantation when indicated. Maybe the other 5 patients with intractable cholestasis would have died if they had not undergone liver transplantation.

As shown in Table 1, there was no difference in family history and hepatobiliary variables between patients with AGS and patients with non-

syndromic PIBD. Thus, maybe they are both familial diseases[6,8]. Since the hepatobiliary parameters were not different between the two groups, one may suggest that these diseases have the same mechanism which may indicate the same genetic abnormality. Thus, well-designed studies are needed to compare the genetic differences of syndromic and non-syndromic PIBD.

As mentioned previously, neonatal jaundice in AGS is usually associated with failure to thrive or with cardiovascular symptoms. In the same way, all patients with AGS in our study had cardiac involvement and only one patient was free from FTT. In our study, rate of the 5 associated clinical features of AGS were not different from previous studies[10-19].

Renal anomalies of AGS, found in 15-50 percent of patients, are of large variety including solitary and ectopic kidney, multicystic and dysplastic kidneys, bifid pelvis, reduplicated ureters, tubulointerstitial nephropathy, renal tubular acidosis, and mesangiolipidosis. However, almost always, they are mild anomalies so that the serious cases cause a mild malformation or dysfunction. In fact, renal insufficiency in adult patients with AGS is only reported in a few cases[7,10,14,28]. However, here we report the first case of neonatal-onset renal insufficiency in a patient with AGS who died at 9 months of age. This case suggests the probability of underestimation of renal diseases in these patients. Maybe renal function is not the main focus in medical management of children and infants with PIBD and AGS. Thus, the hazards of renal abnormalities are not attended and they are all attributed to severe hepatic malfunction. In the same way, renal abnormalities are not included in the diagnostic criteria of AGS. Thus, maybe a more detailed evaluation of renal system is needed in management of patients with PIBD and AGS.

Conclusion

Patients with intractable cholestasis, only those that underwent liver transplantation survived. Thus, the most important criterion for liver transplantation in neonatal PIBD is intractable cholestasis. This study was the first report that shows AGS can result in neonatal-onset renal insufficiency.

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Conflict of Interest: None

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