Clinical and Para Clinical Findings in Children with Progressive Familial Intrahepatic Cholestasis in Iran; A Referral Center Report

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Abstract

Background

Progressive Familial Intrahepatic Cholestasis (PFIC) is a heterogeneous group of disorders with various clinical and para-clinical manifestations.

We report clinical and para-clinical findings in children with progressive familial intrahepatic cholestasis in Southern Iran.

Methods

Medical records of 102 patients aged ≤ 18 years old diagnosed with PFIC who referred to our referral center were evaluated from 2008 to 2012. Baseline and clinical characteristics, outcomes and survival of these patients were recorded.

Results

The study included 61 boys and 41 girls. Most common complaints were jaundice in 53 (51.96 %), pruritus and jaundice in 15 (14.70 %) and jaundice+elevated liver enzymes in 11 (10.78%) children. Main clinical findings in children were jaundice (51.96%), ascites (28.43%), pruritus (19.60%), fever (16.66%) and encephalopathy (14.70%). Inhomogeneous echogenicity (31.37%), splenomegaly (26.47%), hepatomegaly (17.64%), cirrhosis (9.80%) and ascites (6.86%) were the most common sonography findings among children with PFIC, respectively.

Histopathologic evaluation showed cirrhosis (34.31%), followed by fibrosis (18.62%), cholestasis (10.78%), inflammation of liver tissue (4.90%), nodule formation (2.94%), and destruction of lobular and vascular architecture (1.96%). Liver transplantation, medical therapy and biliary diversion had been performed for 67%, 13% and 11% of the patients, respectively. Mean (SD) PELD and MELD scores among children with PFIC were 7.14 ± 14.63 and 15.75 ± 7.21 , respectively. Three month mortality rate for PFIC patients with end stage liver disease was 13.1%.

Conclusion

Inhere we reported invaluable clinicopathological findings among a large series of patients with PFIC.

Introduction

Cholestasis is an alternative response to malfunctions of the liver and biliary system which may be caused by extrahepatic or intrahepatic obstruction to the bile flow (1). Cholestasis may be due to genetic, metabolic, infectious, mechanical obstruction of bile flow or functional impairment of the hepatic biliary function and bile secretion (2).

Progressive familial intrahepatic cholestasis (PFIC) is an important but relatively rare hereditary cause of cholestasis among pediatrics. PFIC was first described in an Amish kindred, then reported in families in Europe, the United States, Japan, Iran and the other parts of the world (3–7). PFIC is an inherited disorder in children with cholestasis of hepatocellular origin which presents in early infancy and childhood, progresses to cirrhosis within the first decade of life, and leads to death due to liver failure at ages ranging from infancy to childhood (3). The combined considerations of clinical, para-clinical, radiological and histological approaches, as well as specific tests for excluding other causes of childhood cholestasis aid in the diagnosis of PFIC. Diagnosis of PFIC is based on clinical and para-clinical manifestations, liver ultrasonography, liver histopathology, as well as molecular investigations (8). Medical therapy, biliary diversion and liver transplantation (LT) are three major curative modalities for treatment of the disease (5). It has been mentioned that surgical methods for treatment of PFIC such as partial external biliary diversion (PEBD) and LT are better treatment choices compared to medical therapy (9).

Multiple studies have evaluated different aspects of PFIC, however to the best of the authors' knowledge, no study with a large sample size has evaluated clinical and para-clinical features of PFIC among children. The aim of this study is to evaluate clinical and para-clinical findings of children with PFIC as well as treatment choices in southern Iran.

Materials And Methods

Study settings and patient selection

All children ≤ 18 years with signs of liver disease who referred to Namazi Hospital, affiliated to Shiraz University of Medical Sciences, since March 2008 till February 2012, were initially assessed and cases that were diagnosed with PFIC were included in the current report. Namazi Hospital is the main referral center for southern and central Iran and patients from all neighboring provinces are referred to this medical center.

Patients with recurrent episodes of cholestatic jaundice, clay colored stool, dark colored urine and pruritus were initially considered for inclusion in this study.

Variables

All medical records of children with PFIC were evaluated. Data on first clinical presentation (patients' complaint), clinical findings, sonography findings, biopsy findings as well as para-clinical data were obtained. Pediatric end-stage liver disease (PELD) score, model for end-stage liver disease score (MELD), and 3-month mortality rate were also calculated.

Through evaluation any case with anatomical and metabolic disorders of the liver other than PFIC and inborn errors of metabolism were excluded from the study.

Para-clinical variables including temperature, respiratory rate, pulse rate, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase, blood urea nitrogen

(BUN), fasting blood sugar (FBS), cholesterol, albumin, total bilirubin, direct bilirubin, prothrombin time (PT), international normalized ratio (INR), creatinine (Cr), triglyceride (TG), low-density lipoprotein (LDL) and, high-density lipoprotein (HDL) were obtained from laboratory reports. Para-clinical data of the patients were extracted from last reliable medical laboratory profile of patients.

Ethical consideration

Data on patient health identification (PHI) and any other personal data were kept safe. Research protocol was approved by the ethics committee of Shiraz University of Medical Sciences, Shiraz, Iran.

Statistical analysis

Disease manifestations including clinical findings, sonography findings and, biopsy findings were presented as frequencies (%) and parametric variables were presented as mean $\pm$ standard deviation. The data were analyzed through SPSS version 21.0. The graphs were extracted using Minitab 16.0.

Results

In this study, 102 children including 61 (59.80%) boys and 41 (40.19%) girls with PFIC were evaluated. Mean and median age of the children was 48.82 ± 48.79 SD and 30 (10, 84) IQR months. The youngest patient with PFIC was 2 months.

The most frequent complaint of patients was isolated jaundice seen among 53 (51.96%) patients, followed by pruritus and jaundice in 15 (14.70%), jaundice and elevated liver enzymes in 11 (10.78%), isolated elevated liver enzymes in 9 (8.82%), and pruritus in 9 (8.82%) cases. Overall, jaundice, pruritus and elevated liver enzymes were observed in 75, 29 and 24 cases, respectively. Most patients had more than one clinical presentation at referral.

The most frequent clinical findings of PFIC in children was jaundice (yellowish skin and sclera) seen in 53 patients (51.96%), followed by ascites (28.43%), pruritus (19.60%), fever (16.66%), encephalopathy (14.70%), diarrhea (11.76%), gastrointestinal bleeding (9.80%), clay stool (9.80%), poor feeding (6.86%), palmar erythema (5.88%), vomiting (4.90%), spontaneous bacterial peritonitis (3.92%), and ecchymosis and tea color urine (2.94%).

Abdominal sonography of patients showed inhomogeneous liver echogenicity in 32 (31.37%) children, and normal sonography findings in 31 children (30.39%). Splenomegaly (enlarged spleen) and hepatomegaly (enlarged liver) were observed in 27 (26.47%) and 18 (17.64%) cases, respectively. Moreover, liver cirrhosis was reported in 10 (9.80%) children, ascites in 7 (6.86%) cases and increased liver echogenicity in 77 (6.86%) children. Histopathology evaluation of obtained liver biopsies from patients showed cirrhosis in 35 (34.31%), fibrosis in 19 (18.62%), cholestasis in 11 (10.78%), inflammation of liver tissue in 5 (4.90%), nodule formation in 3 (2.94%) and destruction of lobular and vascular architecture in 2 (1.96%) children (Table 1).

Table 1
Clinicopathological and sonography findings among patients with
Progressive Familial Intrahepatic Cholestasis.

Variables	Statistics
First Clinical Presentation - no. (%)	
Jaundice	53 (51.96)
Pruritus + Jaundice	15 (14.70)
Jaundice + Elevated Liver Enzymes	11 (10.78)
Elevated Liver Enzymes	9 (8.82)
Pruritus	9 (8.82)
Pruritus + Jaundice + Elevated Liver Enzymes	3 (2.94)
Pruritus + Elevated Liver Enzymes	2 (1.96)
Clinical Findings - no. (%)	
Jaundice (Yellowish skin and sclera)	53 (51.96)
Ascites	29 (28.43)
Pruritus	20 (19.60)
Fever	17 (16.66)
Encephalopathy	15 (14.70)
Diarrhea	12 (11.76)
Gastrointestinal bleeding	10 (9.80)
Clay stool	10 (9.80)
Poor feeding	7 (6.86)
Palmar Erythema	6 (5.88)
Vomiting	5 (4.90)
SBP	4 (3.92)
Ecchymosis	3 (2.94)
Tea Color Urine	3 (2.94)
Sonography Findings - no. (%)	
Liver inhomogeneous echo	32 (31.37)
Normal sonography findings	31 (30.39)

Variables	Statistics
Splenomegaly (Enlarged Spleen)	27 (26.47)
Hepatomegaly (Enlarged Liver)	18 (17.64)
Cirrhosis	10 (9.80)
Ascites	7 (6.86)
Increased liver echo	7 (6.86)
Liver small size	3 (2.94)
Gall stone	2 (1.96)
Biopsy Findings - no. (%)	
Cirrhosis	35 (34.31)
Fibrosis	19 (18.62)
Cholestasis	11 (10.78)
Inflammation in liver tissue	5 (4.90)
Nodule formation	3 (2.94)
Destruction of lobular and vascular architecture	2 (1.96)

Mean AST, ALT and ALK-P in the population prior to surgery was 221.41 ± 256.16 , 141.73 ± 154.00 and 1084.30 ± 675.80 , respectively.

Mean (SD) PELD and MELD scores among children with PFIC were 7.14 ± 14.63 and 15.75 ± 7.21 , respectively. Three month mortality rate for PFIC patients with end stage liver disease was 13.1%. Other para-clinical tests have been reported in Table 2.

Table 2
Para-clinical parameters of the children with progressive familial intrahepatic cholestasis.*

Variables	Statistics
Temperature - degrees centigrade	36.71 ± 0.48
Respiratory rate - breaths/min	27.64 ± 9.61
Pulse Rate - beats/minute	111.50 ± 17.33
Total protein - g/dL	7.22 ± 1.28
Alanine transaminase - IU/L, Mean ± SD	141.73 ± 154.00
Median and IQR	85 (53, 156)
Aspartate aminotransferase - IU/L, Mean ± SD	221.41 ± 256.16
Median and IQR	112.50 (70, 263.50)
Alkaline phosphatase - unit/L, Mean ± SD	1084.30 ± 675.80
Median and IQR	924 (605, 1495)
Blood urea nitrogen - mg/dL, Mean ± SD	12.87 ± 11.32
Median and IQR	11 (7, 15)
Fasting blood sugar - mg/dL, Mean ± SD	95.29 ± 46.53
Cholesterol - mg/dL, Mean ± SD	154.51 ± 83.70
Median and IQR	158 (92.50, 216.50)
Albumin - mg/dL, Mean ± SD	3.82 ± 0.771
Total Bilirubin - mg/dL, Mean ± SD	10.75 ± 11.28
Median and IQR	6.30 (1.90, 17.55)
Direct Bilirubin - mg/dL, Mean ± SD	4.96 ± 5.61
Median and IQR	2.95 (0.60, 7.36)
Prothrombin time, Mean ± SD	16.43 ± 7.25
International Normalized Ratio (INR), Mean ± SD	1.98 ± 2.73
Median and IQR	1.17 (1, 1.66)
Creatinine - mg/dL, Mean ± SD	0.39 ± 0.26
Triglyceride - mg/dL, Mean ± SD	168.11 ± 52.76
Low-density lipoprotein - mg/dL, Mean ± SD	88.77 ± 51.24
Median and IQR	75 (52, 144.95)

Variables	Statistics
High-density lipoprotein - mg/dL, Mean $\pm$ SD	13.17 $\pm$ 10.75
Median and IQR	8.50 (5, 23)
PELD Score, Mean $\pm$ SD	7.14 $\pm$ 14.63
MELD score, Mean $\pm$ SD	15.75 $\pm$ 7.21
3-month mortality rate (%)	
Yes	13 (13.1)
No	86 (86.9)
IQR: interquartile range; PELD: pediatric end-stage liver disease; MELD: model for end-stage liver disease	
*All plus-minus values are means and standard deviations unless stated otherwise.	

Liver transplantation was performed for 69 patients (67%); medical therapy in 13 cases (13%); biliary diversion in 11 cases (11%) and biopsy was obtained from 9% of the patients.

Discussion

PFIC diseases include a group of autosomal recessive hereditary diseases, which usually present in infancy or childhood that have cholestasis of hepatocellular origin (10). PFIC is an indications for liver transplantation in 10–15% of children (3, 10). In 1965, Clayton et al. first described this disease as Byler disease (11). The true incidence of PFIC is not precisely known, but it is considered a rare disease, with an estimated incidence of 1/50,000 to 1/100,000 among all births (12, 13).

In a referral and educational hospital such as that in our study, diseases are diagnosed by expert specialists based on patients' history, clinical and para-clinical manifestations of the disease. Cholestasis which is characterized by jaundice and pruritus, is the hallmark presentation of PFIC (3). Similarly, in our study jaundice was the most frequent clinical complaint of patients followed by pruritus and elevated liver enzymes. PFIC usually appears in the first months of patients' life and is characterized by recurrent episodes of jaundice, becoming permanent later. Age distribution of the disease in our subjects showed that the disease is mostly presented and diagnosed in early periods of children's life.

Extrahepatic manifestations of PFIC includes persistent poor growth, short stature, sensorineural deafness, watery diarrhea, pancreatitis, elevated sweat electrolyte concentration, liver steatosis, gastrointestinal bleeding and cirrhosis (14). In our cases, the most frequent clinical signs were ascites, pruritus, fever, encephalopathy, diarrhea, gastrointestinal bleeding, clay stool, poor feeding and, palmar erythema. Vomiting, spontaneous bacterial peritonitis (SBP), ecchymosis and tea color urine were other clinical findings in children with PFIC.

Gastrointestinal bleeding can occur in older children or young adults due to cirrhosis and portal hypertension (15). Sun et al. (16) mentioned that diagnosis of PFIC should be suspected in patients with a clinical history of cholestasis of unknown origin after exclusion of other common cause of cholestasis (20). Both genders are usually equally affected (8). Affected children have a poor quality of life secondary to growth retardation, intractable pruritus and severe rickets (3, 10, 17).

Biochemical analysis of PFIC patients shows alteration in liver function test. Para-clinical and biochemical analysis of children with PFIC showed elevated levels of liver enzymes such as ALT, AST and alkaline phosphatase. Prolonged international normalized ratio (INR) is common and correctable with injectable vitamin K in early stages of the disease (15). In our study, INR was prolonged compared with normal ranges of healthy children.

There is various ultrasound finding in children with PFIC such as hepatomegaly, splenomegaly and increased echogenicity of the liver (18, 19). Abdominal sonography findings of our subjects showed liver inhomogeneous echo, splenomegaly (enlarged spleen), hepatomegaly (enlarged liver), cirrhosis, ascites, increased liver echogenicity and, and a small sized liver (in cirrhotic patients). Normal ultrasound findings were also considerable in our study.

Histopathological findings in liver specimen biopsies of PFIC patients were also in favor of cirrhosis, fibrosis, cholestasis, and inflammation of liver tissue, destruction of lobular and vascular architecture which was similar with the results of studies reported by Morotti et al. and (2), Alonso et al. (20) .

Different treatment modalities are considered in treatment of PFIC including liver transplantation, medical therapy and biliary diversion (6). Medical treatment with ursodeoxycholic acid may improve the pruritus and the biochemical tests in 10–50% of the patients (21). Indications for liver transplantation in PFIC patients are severe intractable pruritus, not responding to medical treatment, growth failure despite adequate nutritional support and severe rickets unresponsive to treatment (22, 23). In our study, liver transplantation was performed for 67% of patients, medical therapy in 13% and biliary diversion in 11% of the cases. Twelve patients died during the study period. Hereditary liver diseases such as PFIC can cause mortality in infants and children (24). In one study, 1-year mortality after liver transplantation for PFIC was reported ranging from 5–15% (25). In our study, 13.1% of the children with PFIC died during the study period.

Antenatal diagnosis may be proposed for affected families in which a mutation has been identified. As well as Ursodeoxycholic acid (UDCA) therapy, biliary diversion may also be effective. However, most PFIC patients are ultimately candidates for liver transplantation.

The study did have some limitations. One of the limitations of the study was lack of molecular investigation data for determination of PFIC type. So, we didn't have any information with regard to PFIC type. As this was a referral center based study we were not able to have an estimate on prevalence of the disease and this would require population based national registries to be established. On the other hand the heterogeneity of our patients makes this study a good representative of the Iranian population.

Moreover, we evaluated different aspects of PFIC patients including clinical and para-clinical variables as well as sonography and liver biopsy analysis in a considerable sample size of patients.

More detailed studies with molecular investigations with longer follow-ups are suggested.

Conclusion

PFIC is one of the main indications for pediatric liver transplantation presenting with various clinical and para-clinical features and detailed evaluation of children for PFIC is necessary for choosing an appropriate treatment prognosis.

List Of Abbreviations

Ursodeoxycholic acid (UDCA), spontaneous bacterial peritonitis (SBP), patient health identification (PHI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase, blood urea nitrogen (BUN), fasting blood sugar (FBS), cholesterol, albumin, total bilirubin, direct bilirubin, prothrombin time (PT), international normalized ratio (INR), creatinine (Cr), triglyceride (TG), low-density lipoprotein (LDL) and, high-density lipoprotein (HDL), Progressive Familial Intrahepatic Cholestasis (PFIC), pediatric end-stage liver disease (PELD), model for end-stage liver disease (MELD)

Declarations

Ethics approval and consent to participate

Patients filled the informed consent form of participating in study. The study protocol was approved by research ethical committee of Shiraz University of Medical Sciences by the code of IR.SUMS.REC.93.7346.

Consent for publication

No individual person's data are present in this manuscript.

Competing interests

There is no Competing interests for this study.

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Authors' contributions

MZ, and SMD had designed the study. MZ, FE, MRF, and RK collected data. MZ, SMBT, and AD performed data analysis. MF and MZ wrote the draft manuscript. All authors contributed in revisions.

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Availability of data and materials

All data related to this article are available in the manuscript and there is no further data.

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