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Case Report

Early Medical Therapy May Obviate the Need the for Liver Transplant in Progressive Familial Intrahepatic Cholestasis

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Abstract

We describe a case of two-year-old boy presenting with debilitating pruritus, patchy alopecia and jaundice since the age of 6 months. On evaluation he had intrahepatic cholestasis with persistently raised serum alkaline phosphatase, normal Gamma glutamyl transferase and raised serum bile acid levels. His liver biopsy showed bland cholestasis and electron microscopy showed granular bile suggestive of Progressive familial intrahepatic cholestasis (PFIC) type I. Medical therapy with ursodeoxycholic acid, cholestyramine, and rifampicin with nutritional modification was successful in alleviating the symptoms and correcting the nutritional status. At present his liver function had stabilized at 1 year follow up and there is no need for liver transplant in him. To our knowledge this is only the twelfth case of Progressive familial intrahepatic cholestasis type reported from India. Successful medical therapy of PFIC has been rarely described in tropical countries including India. Most of the data in the literature describe poor response to medical treatment alone and need for surgical biliary diversion and liver transplant in these patients. Liver transplant has guarded prognosis in patients with PFIC I if extrahepatic manifestations are present at the onset. Recurrence of PFIC after a successful Liver transplant is a possibility due to all immunization of recipient against the effected protein. Our experience suggests that if instituted early medical therapy alone may obviate the need for liver transplant in a subset of patients with PFIC. Further molecular testing is required to identify this sub-group of patients with favorable prognosis.

ABBREVIATIONS

PFIC: Progressive Familial Intrahepatic Cholestasis; GGT: Gamma Glutamyl Transferase; UDCA: Ursodeoxycholic Acid; BSEP: Bile Salt Exporter Pump

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is a rare, heterogeneous group of cholestatic liver disorders manifesting in infancy or early childhood [1]. PFIC 1 is the subtype of this group which is characterized by intrahepatic cholestasis, intense pruritus, normal or lowGamma glutamyl transferase (GGT), and characteristic "OBylers bile" on electron microscopy [2,3]. Medical therapy alone is rarely successful and surgical biliary diversion with or without liver transplant is required in most of the patients. However certain subset of patient may respond to early medical therapy obviating the need for liver transplant. Extensive literature search revealed only handful of case reports of this rare disorder reported from India with no data available regarding the prevalence of PFIC in India. Here we discuss the diagnostic algorithm and therapeutic strategies required in managing PFIC and also review the literature regarding this rare disorder.

CASE PRESENTATION

A two-year boy, born out of a consanguineous marriage with full term normal delivery and no perinatal complications presented with history of itching which was generalized, severe and progressive associated with growth failure since the age of

six months. He also developed patchy alopecia since the age of one year. Mother noticed fluctuating jaundice since the age of one year associated with intense pruritus, without prodromal symptoms. There was no history of any hepatotoxic drug exposure, fever, hematemesis, melena, abdominal distension, abdominal pain and diarrhea.

On examination patient was < 5th percentile for his weight and height (6.5 kgs and 75 cm respectively). His pulse rate was 102 /minute, blood pressure 90 / 60 mm of Hg. He was irritable, restless with evidence of excoriated skin, lichenification, itch marks all over the body and shiny nails (Figure 1A). There were patchy areas of alopecia on scalp (Figure 1B). There was no lymphadenopathy, peripheral edema, pallor or icterus. He had mild hepatosplenomegaly. His routine blood biochemical parameters over past six months are depicted in (Table 1).

It showed mildly increased serum aminotransferase levels, mild direct hyperbilirubinemia, persistently raised alkaline phosphatase and Gamma glutamyl transferase was 28 U/L (Normal up to 75 U/L) which had not changed over six months. Blood for HBsAg and Anti-Hepatitis C virus, anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal type 1 antibody were negative. Serum Immunoglobulin and ceruloplasmin were normal. Ultrasonography showed mild hepatosplenomegaly, preserved hepatic echotexture, normal gall bladder, common bile ducts and intra hepatic biliary radicles.

Serum bile acid level was 88 mcmol/L (normal< 10 mcmol/L). Next we did liver biopsy for evaluating the cause of intra hepatic cholestasis. It revealed hepatocytes showing feathery and hydropic changes, intrahepatic cholestasis, mild periportal inflammation, unremarkable bile ducts together with no evidence of fibrosis, bile duct proliferation or giant cell hepatitis. All these features represented bland cholestasis (Figure 2).We diagnosed this case as PFIC with type I being more likely than type II in view of the liver biopsy findings. Subsequently electron microscopy from liver biopsy was done which showed distended bile canaliculi with coarse and granular bile confirming the diagnosis of PFIC I.

Table 1: Laboratory parameters of the patient in last six months.

Parameters (Normal values)	6 months ago (June 2015)	On presentation (December 2015)
Hb (11.5-14.5gm %)	12 .2gm%	12 .4gm%
TLC(4000-12000/ cumm)	5,500 cu mm	4,500 cu mm
Platelets (1.5 L- 4.5L/ cumm)	5,00,000 cu mm	4,50,000 cu mm
AST (0-50U/L)	62 IU/L	65 IU/L
ALT (0-50U/L)	55 IU/L	62 IU/L
TB (≤ 1.00mg/dl)	2.5 mg/dl	1.9 mg/dl
DB (0.0-0.3mg/dl)	1.5 mg/dl	1.4 mg/dl
ALP (149-369 U/L)	538 U/L	592 U/L
TP (>6.5 gm/dl)	7.5 gm%	7.2 gm%
Albumin (3-5gm/dl)	4 gm%	3.9 gm%
PT (11-13 seconds)	13 seconds	14 seconds

Hb: Hemoglobin; TLC: Total Leucocyte Counts; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; TB: Total Bilirubin; DB: Direct Bilirubin; TP: Total Protein; PT-Prothrombin Time.

Figure 1 Figure (A) shows a restless child with intense itching, excoriated and dry skin and Figure (B) shows patch of hair loss on scalp before starting treatment. Figure (C) shows significant improvement in skin texture with only few pigmented spots seen in both upper and lower limbs and Figure (D) show recovery of alopecia after two months of treatment.

He was given adequate sunlight exposure, moisturizing lotions, nutritional supplement of vitamin A, D, E and K. He was given total calorie intake of 125 % of recommended dietary allowance. Initially Ursodeoxycholic acid (UDCA) in dose of 12 mg/kg/day in 3 divided dose, and Cholestyramine 2gm/day in 4 divided doses was given. However, there was only partial relief of symptoms. Subsequently Rifampicin 2.5 mg/kg/day in 2 divided doses was added. Combined therapy was successful in alleviating his pruritus and hair loss by the end of two months (Figure 1 C,D). At present his liver function is stabilized on 1 year follow up. Biliary diversion was not offered as he responded to medical therapy. Parents were counseled for the need of liver transplant in future if end-stage liver disease occurs.

DISCUSSION

PFIC is an autosomal recessive disease occurring equally in both sexes. Though the Western data suggests an incidence of 1 per 50,000 to 1 per 100,000 births, no data is available regarding its prevalence from India [3].

PFIC is divided into three types: 1, 2 and 3.PFIC1 is associated with defects in ATP8B1 gene on chromosome 18 (18q21-22) which encodes for familial intrahepatic cholestasis 1 protein. The intense pruritus involving the extremities and scalp results in marked thickening, lichenification, excoriation, hyperpigmentation of skin, shiny nails and occasionally cicastrical alopecia [4]. Cirrhosis with portal hypertension and decompensation develops earlier in the first year of life in PFIC type 2 as compared to early childhood in PFIC type 1 [5].

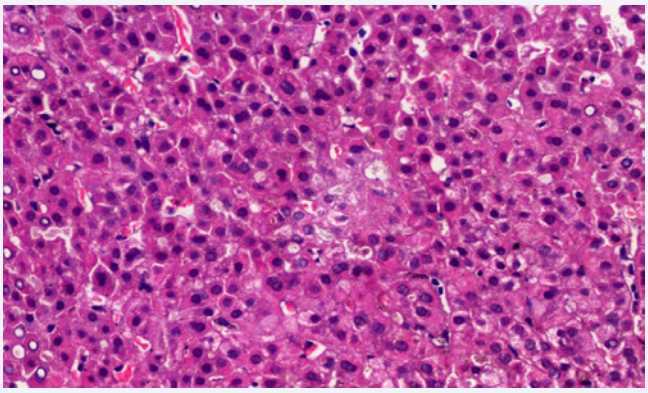

Figure 2 Haematoxylin and eosin stain of the liver biopsy specimen shows hepatocytes with feathery and hydropic changes, intrahepatic cholestasis, mild periportal inflammation, suggestive of bland cholestasis.

Table 2: Summarizing the case reports/case series of PFIC reported from India.

Case report/ Series	Age of onset (months) and sex	Presenting features	PFIC subtype	Method of diagnosis	Treatment
Ganesh R et al. [7].	6 months, boy	Persistent jaundice Pruritus, alopecia, growth failure,	PFIC I	Liver biopsy and electron microscopy	PIBD (cholecystojejunocolic anastomosis)
Sharma et al. [8]	1 month, girl	Neonatal cholestasis	PFIC II	Liver biopsy and mutational analysis for ABCB 11 (done from outside India)	PEBD (cholecystoappendicostomy)
Koshy A et al. [9]	30 months, male	Pruritus, jaundice	PFIC I/II	Liver biopsy	PEBD
Kaur S et al. [10] (series of seven patients)	6 months –36 months, 4 boys, 3 girls	Pruritus, jaundice in 3 patients Decompensated liver disease in 4 patients	PFIC I/II- 3 patients. PFIC II – 2 patients PFIC III- 2 patients	Liver biopsy and electron microscopy	Liver transplant in 3 patients. Biliary diversion in 2 patients Medical therapy in 1 patient
Zaki SA et al. [11]	8 months, girl	Pruritus, jaundice	PFIC III	Liver biopsy	Medical therapy
Present case	6 months, boy	Debilitating pruritus, alopecia, growth failure	PFIC I	Liver biopsy and electron microscopy	Medical therapy

PFIC: Progressive Familial Intrahepatic Cholestasis; PIBD: Partial Internal Biliary Drainage; PEBD: Partial External Biliary Drainage.

History of consanguinity in parents with evidence of intrahepatic cholestasis, predominant pruritus, normal GGT, raised serum bile acid level; bland cholestasis on biopsy suggested the diagnosis of PFIC 1 in our patient. Other factors that helped in distinguishing PFIC 1 from PFIC 2 in our patient included presence of growth failure, absence of evidence of portal hypertension, and only mild increase in amino transferase levels. Liver biopsy also favored PFIC 1 as there was absence of giant cell hepatitis, significant portal inflammation and fibrosis all of which are seen more commonly in PFIC 2. Lastly electron microscopy was the key in our patient demonstrating the characteristic granular bile ("O Bylers" bile) seen classically in PFIC 1 as compared to amorphous bile seen in PFIC 2.

Genetic testing is gold standard for confirmation of diagnosis as prognosis and definitive management of patients differ between PFIC 1 and 2 [6]. Patients suspected to have PFIC 1 or 2 should undergo immunohistochemistry staining with BSEP protein. Those who are negative for BSEP staining should undergo mutational analysis for ABCB 11 (for PFIC 2), whereas those who are positive should undergo analysis for ATP8B1 (for PFIC 1). Though genetic tests are not available in India and could not be done in our case, the diagnosis was made on clinical, histological, electron microscopy findings and response to treatment.

Literature search revealed only four case reports and one case series of seven patients of PFIC reported from India. Table (2) summarizes the presenting feature, mode of confirming the diagnosis and management strategies in each of them. Genetic analysis was possible in only one case done from overseas [8]. Four cases could not be differentiated between PFIC I or II. Biliary diversion was used in five patients for relieving jaundice and pruritus [7-10]. Medical therapy was successful in one patient. Three patients underwent live donor liver transplant for decompensate liver disease out of which one died [10].

Our patient successfully responded to medical therapy

comprising of UDCA, cholestyramine and rifampicin. There was no indication of biliary diversion at this stage as his pruritus had resolved and there was no significant jaundice. Liver transplant is indicated in patients with end stage liver disease or hepatocellular carcinoma or those with poor quality of life due to pruritus despite medical therapy and biliary diversion. Liver transplant has guarded prognosis in patients with PFIC I if extrahepatic manifestations are present at the onset [3]. Recurrence of PFIC after a successful Liver transplant is a possibility due to alloimmunization of recipient against the effected protein (FIC 1, MDR 3 or BSEP) [12].

Prognosis in PFIC is variable. In a series of 33 patients with PFIC I/II only seven patients where older than 16 years on their last follow up [13]. A series of 62 children with PFIC I/II showed that 87 % patients were alive at median age of 10.5 years with therapy involving biliary diversion and/or liver transplant [13]. Genetic testing as well as genetic counseling of parents and prenatal diagnosis of PFIC is still at a premature stage in India whereas it has become a standard of care in managing patients of PFIC in the West.

Early recognition and prompt referral to higher center for biliary diversion and/ or Liver transplant in cases of failure of medical therapy is crucial in managing PFIC patients. More reports and long term follow up data on PFIC is required from India.

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