ORIGINAL ARTICLE

Progressive Familial Intrahepatic Cholestasis in Malaysian Patients – A Report of Five Cases

W S Lee, FRCPCH*, P F Chai, MRCPCH*, L M Looi, FRCPath**

*Departments of Paediatrics, and **Pathology, University of Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia

SUMMARY

Progressive familial intrahepatic cholestasis (PFIC) is characterized by early onset cholestasis, progressive liver cirrhosis, pruritus, poor growth and inexorable progression to liver cirrhosis in early childhood. The serum level of gamma-glutamyl transferase is low or normal, which is discordant with severe cholestasis. Five Malaysian patients with PFIC, who all had typical features of PFIC with early onset of severe and progressive cholestasis, pruritus, cirrhosis and liver failure, were described. Three patients died as a result of the disease, while another one died due to post-liver transplant complication. The only survivor has compensated liver cirrhosis. Patients with severe cholestasis but has spuriously low γGT should be suspected of having PFIC. Liver transplant, which is life-saving in a majority of patients with PFIC, should be considered in all patients with PFIC.

KEY WORDS:
Progressive familial intrahepatic cholestasis, Mortality

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is an autosomal recessive disorder of intrahepatic cholestasis characterized by early onset cholestasis, progressive liver cirrhosis, and hepatic failure in early childhood[1]. It was originally described as `Byler disease' in Amish descendants of Jacob Byler[2]. Affected children had pruritus, steatorrhoea, poor growth and inexorable progression to cirrhosis[2]. A prominent finding of PFIC, which has since been described in children of non-Amish origin,[1,3,4] is a low or normal serum gamma-glutamyl transferase (γGT), which is discordant with the severe cholestasis[3, 4]. To date, PFIC have mostly been reported in the Caucasians children[1, 3]. The present case note describes five cases of PFIC from a multi-ethnic Southeast Asian country.

CASE REPORT

Five infants with PFIC were seen at the Department of Paediatrics, University of Malaya Medical Centre (UMMC), Kuala Lumpur, from November 1996 to May 2004. The diagnostic criteria of PFIC were: chronic unremitting cholestasis with onset in infancy, exclusion of anatomical and metabolic aetiologies after a thorough clinical, laboratory and radiological evaluation, typical biochemical markers of cholestasis, including increased levels of conjugated bilirubins and alkaline phosphatase (ALP) but low to normal levels of serum γGT[1]. A positive family history was a necessary additional diagnostic criterion if the γGT was raised[5]. As no genetic studies were carried out for the purpose of the present study, no attempt was made to differentiate PFIC1 (FIC1) from PFIC2 (BSEP) disorders. Patients with raised γGT were considered as having PFIC3 (MDR3 deficiency).

The patients' usual degree of pruritus was recorded as 0 – 4+, as described by Whitington *et al*:[6] none = 0; rubbing or mild scratching when not distracted = +1; active scratching without evident skin abrasions = +2; abrasions evident = +3; cutaneous mutilation, haemorrhage and scarring evident = +4.

Of the five patients (four males, one female; three Chinese, two Malays) with PFIC in the present study, four cases of PFIC 1 / PFIC 2 and one case of PFIC 3 (Case no. 3) were diagnosed (Table I). There was no history of consanguinity in any of the patients. The elder brother of Case no. 3, who had jaundice since birth died at age of one year due to progressive cholestatic jaundice. An exploratory laparotomy performed at another hospital showed a patent extrahepatic biliary duct. No similar family history was noted in other patients.

All patients were term infants (birth weight from 2.4 to 3.5 kg). All had neonatal jaundice within the first week of life which was subsequently persistent. No patients had any facial dysmorphic facial features. At initial presentation, all had moderate to severe jaundice. Stools were pale in four patients and slightly pigmented in one. All patients had enlarged liver (3 – 8cm), while three patients had splenomegaly.

One patient (Case 5) had developmental delay. A magnetic resonance scan of the brain and peripheral nerve conduction study were all normal. The remaining four patients were all normal neurologically and developmentally. No abnormalities of cardiovascular or respiratory systems were noted in any of the patients. No patient had long standing diarrhoea during infancy or subsequently. Significant pruritus was noted in four patients (grade 3+ or 4+), despite adequate therapy with anti-histamines and rifampicin. All infants had significant failure to thrive.

All five patients had cholestatic jaundice upon first presentation, with markedly raised serum conjugated bilirubin levels. γGT were low in the four patients, and remained low in three patients throughout their course of disease.

This article was accepted: 19 August 2009
Corresponding Author: Lee Way Seah, Departments of Paediatrics, University of Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia
Email: leews@um.edu.my

Table I: Clinical and laboratory features of 5 infants with progressive familial intrahepatic cholestasis

Case No.	Age at Onset (days)	Stools	Size of liver (cm) [a]	Pruritus [b]	Growth [c]			TB (μmol/L)	γGT (IU/L)	ALT (IU/L)	ALP (IU/L)	Total chol	PTR	aPTT
					Age in	Wt in kg	Ht in cm	3-17	15-85	30-65	<400	3.6-5.2	1-1.2	33-41
1.	3	slightly pale	4	3+	7	7.8 (25th)	64.5 (3rd)	281	61	156	308	ND	1.30	46.2
2.	4	pale	3	3+	43	10 (< 3rd)	78 (< 3rd)	382	16	77	506	2.4	0.85	34.9
3.	3	pale	4	4+	14	6.8 (< 3rd)	69 (< 3rd)	166	215	90	568	3.6	0.94	37.8
4.	3	pale	8	1+	7	6.6 (< 3rd)	65.5 (3rd)	438	25	372	388	1.2	1.65	47.5
5.	3	pale	5	3+	36	13.7 (25th)	90.2 (5-10th)	309	51	193	1291	3.1	1.84	58.5

Wt: weight, Ht: height
a.Size of liver was parameter obtained upon first admission. The size of liver was measured in cm below the right costal margin.
b.Pruritus was recorded as 0-4+ according to criteria described by Whitington et al (1988): none = 0; rubbing or mild scratching when not distracted = +1; active scratching without evident skin abrasions = +2; abrasions evident = +3; cutaneous mutilation, haemorrhage and scarring evident = +4.
c.Growth recorded were the parameters obtained at the latest follow-up (age in months)

TB – total bilirubin
ALT – alanine transaminase
PTR – prothrombin ratio
ND – not done
γGT – gamma glutamyl transpeptidase
ALP – alkaline phosphatase
aPTT – activated partial thromboplastin time

Table II: Management and outcome of 5 infants with progressive familial intrahepatic cholestasis

Case No.	Age at liver biopsy (days)	Histology of liver biopsy	Management	Outcome	Cause of death
1.	46	Giant cell hepatitis marked cholestasis	UDCA, lipid-soluble vitamins anti-histamine, rifampicin	Death, 18 m	Cirrhosis, liver failure
2.	60	Mild stasis, mild hepatitis	UDCA, lipid-soluble vitamins, anti-histamine, rifampicin	Death, 51 m	Cirrhosis, liver fialure
3.	45	Giant cell hepatitis, marked cholestasis	UDCA, lipid-soluble vitamins, anti-histamine, rifampicin	Death, 22 m*	Died of sepsis after liver transplant
4.	150	Giant cell hepatitis, cirrhotic nodules	UDCA, lipid-soluble vitamins anti-histamine	Death, 9 m	Coagulopathy, massive upper GI bleed
5.	95	Marked giant cell hepatitis early cirrhosis	UDCA, lipid-soluble vitamins, anti-histamine, rifampicin	Alive at 41 m	

* Patient no. 3 succumbed to sepsis one week after receiving a living-related liver transplant performed at age of 22 months.
GI: gastrointestinal, UDCA: ursodeoxycholic acid lipid-soluble vitamins: vitamins A, D, E, and K .

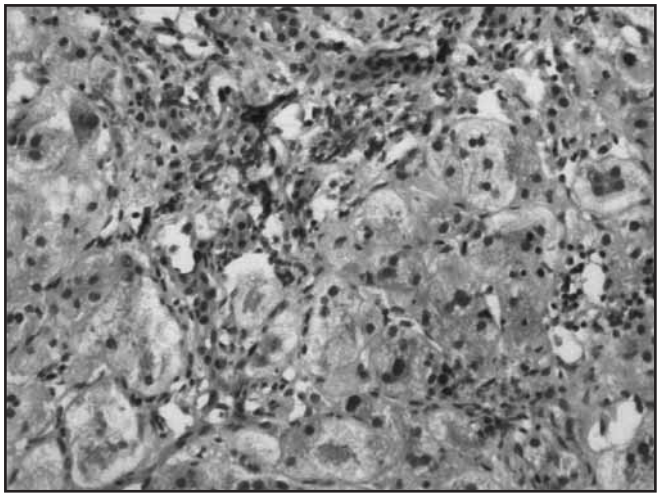

Fig. 1: Photomicrograph of liver biopsy in a patient with PFIC (Case no. 5)
Legend: There was florid giant cell transformation (haemotoxylin and eosin stain, original magnification x 200)

Four of the five patients had ^{99m}Tc-mebrofenin IDA hepatobiliary scintigraphic examination which was non-excretory. Four of the five patients had laparotomy which showed patent extrahepatic biliary ducts.

All patients had liver biopsies. Marked giant cell hepatitis was common and was seen in four cases (Table II, Fig. 1). Cholestasis was another common feature. Absence of bile duct proliferation was a feature noted in patients who had liver biopsy obtained early in life (Case 1 at day 46, Case 3 at day 45). Liver cirrhosis was noted in two cases in whose liver biopsies were performed late (Case 5 at day 95, Case 4 at 150).

All patients were managed conservatively initially with lipid-soluble vitamins supplement, ursodeoxycholic acid, and caloric supplements. The cholestasis was persistent and progressive in all patients. Three of the five patients, who all had progressive liver cirrhosis and liver failure died, without liver transplant at 18, 22 and 51 months of age, respectively.

Patient no. 4 developed clinical rickets, ascites, portal hypertension and gross ascites at nine months of age. The patient had been on vitamins D and K supplement and was also prescribed spironolactone. However, the parents were not regular with follow-up. At nine month of age, gross derangement of coagulation (PTR 6.4, aPTT > 200) was noted. The parents insisted on discharge against medical advice and the patient died of massive upper gastrointestinal bleeding at the local hospital few days later.

Patient no. 5 is still alive with liver cirrhosis, hepatosplenomegaly, and delayed development. There was an episode of haemetemesis at two years of age, but upper gastrointestinal endoscopy showed no oesophageal varices. The serum albumin level and coagulation were normal at latest follow-up.

DISCUSSION

The present study is the first description of PFIC in Malaysian infants. The mortality of PFIC in the present study was high. Four of the five patients died due to the disease. The only survivor has compensated liver cirrhosis.

All the patients were prescribed ursodeoxycholic acid, which has been shown to improve the clinical status in PFIC[7]. In the present study, no significant improvement in disease progression has been shown in any of the patients who had ursodeoxycholic acid, although the number of patients studied was small.

Biliary diversion surgery, considered to be effective in some forms of PFIC, was not performed in the present study[8]. This could be a potential area of exploration in the future, as liver transplantation is limited in Malaysia. However, the outcome of external biliary diversion is not universally favourable[9]. Often, liver transplantation is necessary in children with PFIC.

No genetic study to delineate the underlying mutations was performed for the present study. Increasingly, PFIC diseases are defined on genetic rather than clinical criteria[10]. Mutations in three canalicular membrane proteins have been identified that result in cholestasis and progress to chronic liver disease[5]. PFIC are disorders caused by mutations in the genes coding for familial intrahepatic cholestasis 1 protein (FIC1), the bile salt export pump (BSEP) and the phospholipid translocase (MDR3), respectively. FIC1, BSEP and MDR3 are now the preferred nomenclature over PFIC as PFIC is considered to be inaccurate since not all patients with PFIC has a positive family history.

FIC1 is characterized by progressive jaundice, pruritus, diarrhoea, failure to thrive and a low γGT in the first several months[10]. The gene ATP8B1, has been found to code for the protein FIC1[10]. Patients with BSEP mutation have fewer extrahepatic abnormalities. The gene mutated in BSEP patients is *ABCB11* coding for bile salt export pump (BSEP), an ATP binding cassette (ABC) transporter found in the canalicular membrane of the liver[11]. MDR3 is clinically similar to FIC1 and BSEP, but with an elevated γGT level[5]. The gene causing MDR3 is ABCB4, which is located on chromosome 7q21, codes for MDR3, an ABC transporter protein[12].

In conclusion, the present study demonstrates that Malaysian patients with PFIC have clinical features and disease progression which is similar to those reported in the literature. The outcome is poor because liver transplantation is not commonly available in Malaysia.

REFERENCES

1. Whitington PF, Freese DK, Alonso EM, Schwarzenberg SJ, Sharp HL. Clinical and biochemical findings in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutri 1994; 18: 134-41.
2. Clayton RJ, Iber FL, Ruebner BH, McCusick VA. Byler disease: fatal familial cholestasis in an Amish kindred. Am J Dis Child 1969; 117: 112-24.
3. Maggiore G, Bernard O, Riely CA, Hadchouel M, Lemonnier A, Alagille D. Normal serum Á-glutamyl-transpeptidase activity identifies groups of infants with idiopathic cholestasis with poor prognosis. J Pediatr 1987; 111: 251-2.

4. Knisely AS. Progressive familial intrahepatic cholestasis: a personal perspective. Pediatr Develop Pathol 2000; 3: 113-25.
5. Harris MJ, Le Couteur DG, Arias IM. Progressive familial intrahepatic cholestasis: genetic disorders of biliary transporters. J Gastroenterol Hepatol 2005; 20: 807-17.
6. Whitington PF, Whitington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. Gastroenterology 1988; 95: 130-6.
7. Jacquemin E, Hermans D, Myara A, *et al*. Ursodeoxycholic acid therapy in pediatric patients with progressive familial intrahepatic cholestasis. Hepatology 1997; 25: 519-23.
8. Emond JC, Whitington PF. Selective surgical management of progressive familial intrahepatic cholestasis (Byler's disease). J Pediatr Surg 1985; 30: 1635-41.
9. Wanty C, Joomye R, Van Hoorebeek N *et al*. Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy. Acta Gastroenterol Belg 2004; 67: 313-9.
10. van Mil SW, Klomp LW, Bull LN, Houwen RH. FIC1 disease: a spectrum of intrahepatic cholestatic disorders. Semin Liver Dis 2001; 21: 535-44.
11. Strautnieks SS, Kagalwalla AF, Tanner MS *et al*. Identification of a locus for progressive familial intrahepatic cholestasis PFIC2 on chromosome 2q24. Am J hum Genet 1997; 61: 630-3.
12. Jacquemin E, de Vree JML, Cresteil D *et al*. The wide spectrum of multidrug resistance 3 deficiency: from neonatal cholestasis to cirrhosis of adulthood. Gastroenterology 2001; 120: 1448-58.