ORIGINAL ARTICLE

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

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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. It was originally described as 'Byler disease' in Amish descendants of Jacob Byler. Affected children had pruritus, steatorrhoea, poor growth and inexorable progression to cirrhosis. A prominent finding of PFIC, which has since been described in children of non-Amish origin, is a low or normal serum gamma-glutamyl transferase (γGT), which is discordant with the severe cholestasis. To date, PFIC have mostly been reported in the Caucasians children. 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. A positive family history was a necessary additional diagnostic criterion if the γGT was raised. 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 Whittington et al: 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 patients 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.
### Table I: Clinical and laboratory features of 5 infants with progressive familial intrahepatic cholestasis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at liver biopsy (days)</th>
<th>Stools</th>
<th>Size of liver (cm)</th>
<th>Pruritus</th>
<th>Growth*</th>
<th>TB (µmol/L)</th>
<th>γ-GT (IU/L)</th>
<th>ALT (IU/L)</th>
<th>ALP (IU/L)</th>
<th>Total chol (IU/L)</th>
<th>PTR</th>
<th>aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>Giant cell hepatitis, marked cholestasis</td>
<td>UDCA, lipid-soluble vitamins, anti-histamine, rifampicin</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>3-17</td>
<td>15-85</td>
<td>30-65</td>
<td>&lt;400</td>
<td>3.6-5.2</td>
<td>1-1.2</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>Mild stasis, mild hepatitis</td>
<td>UDCA, lipid-soluble vitamins, anti-histamine, rifampicin</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>3-17</td>
<td>15-85</td>
<td>30-65</td>
<td>&lt;400</td>
<td>3.6-5.2</td>
<td>1-1.2</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Giant cell hepatitis, marked cholestasis</td>
<td>UDCA, lipid-soluble vitamins, anti-histamine, rifampicin</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>3-17</td>
<td>15-85</td>
<td>30-65</td>
<td>&lt;400</td>
<td>3.6-5.2</td>
<td>1-1.2</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>Giant cell hepatitis, cirrhotic nodules</td>
<td>UDCA, lipid-soluble vitamins, anti-histamine</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>3-17</td>
<td>15-85</td>
<td>30-65</td>
<td>&lt;400</td>
<td>3.6-5.2</td>
<td>1-1.2</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>Marked giant cell hepatitis, early cirrhosis</td>
<td>UDCA, lipid-soluble vitamins, anti-histamine</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>UDCA, lipid-soluble vitamins</td>
<td>3-17</td>
<td>15-85</td>
<td>30-65</td>
<td>&lt;400</td>
<td>3.6-5.2</td>
<td>1-1.2</td>
<td>ND</td>
</tr>
</tbody>
</table>

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

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

* Patient no. 3 succumbed to sepsis one week after receiving a living-related liver transplant performed at age of 22 months.

**Table notes:**
- TB - total bilirubin
- γ-GT - gamma glutamyl transpeptidase
- ALT - alanine transaminase
- ALP - alkaline phosphatase
- PTR - prothrombin ratio
- aPTT - activated partial thromboplastin time
- ND - not done

**Table definitions:**
- Wt: weight, Ht: height
- Size of liver was parameter obtained upon first admission. The size of liver was measured in cm below the right costal margin.
- 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.
- Growth recorded were the parameters obtained at the latest follow-up (age in months).
Four of the five patients had 99mTc-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 haematemesis at two years of age, but upper gastrointestinal endoscopy showed no oesophageal varices. The serum albumin level and coagulation were normal at gastrointestinal endoscopy showed no oesophageal varices.

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 PFIC1. 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 study2. 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 favourable3. 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 criteria4. Mutations in three canalicular membrane proteins have been identified that result in cholestasis and progress to chronic liver disease5. PFIC are disorders caused by mutations in the genes coding for familiar 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 months6. The gene ATP8B1, has been found to code for the protein FIC17. 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 liver8. MDR3 is clinically similar to FIC1 and BSEP, but with an elevated γGT level9. The gene causing MDR3 is ABCB4, which is located on chromosome 7q21, codes for MDR3, an ABC transporter protein10.

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