BANGLADESH J CHILD HEALTH 2009; VOL 33 (2): 66-69

CASE REPORTS

Progressive Familial Intrahepatic Cholestasis - A Case Report

NAZMA BEGUM[1], ASM BAZLUL KARIM[2]

Introduction

Progressive familial intrahepatic cholestasis (PFIC) represents a group of disorders which usually begin in the first months of life and progress to cirrhosis before the end of second decade. The disease occurs due to a defect in bile acid transport leading to cholestasis and resultant hepatocelluler injury[1-3]. Recent molecular and genetic studies have identified genes responsible for three types of PFIC[4]. Significant pruritus, hepatomegaly and growth failure are the typical features of PFIC[5]. Initially described in Amish descendants of Jacob Byler, the condition was originally named Byler disease. Subsequently, numerous phenotypically similar non-Amish patients were reported, and the term Byler syndrome was used to describe these patients' condition. These terms now have been superseded by the term PFIC[6,7]. The pattern of appearance of the affected children within families is consistent with autosomal recessive inheritance[5]. Males and females are affected equally[8]. Exact frequency is unknown. Fewer than 200 patients have been reported in the medical literature[9]. Though cholestatic jaundice in infancy is not an uncommon diagnosis in Bangladesh, still we are not very much familial and acquainted to PFIC. Detailing the clinical characterstics will give better information to this syndrome and allow it to be diagnosed with greater frequency and accuracy as well as permitting a more focused investigation of its etiology and pathogenesis. Since no case of PFIC has been reported from Bangladesh, we report the case of progressive familial intrahepatic cholestasis (PFIC) who was admitted in Paediatric Gastroenterology and Nutrition department of Bangabandhu Sheikh Mujib Medical University (BSMMU).

Case Report

Noble, a 2 months and 15 days old male infant, 6th issue of his consanguineous parents admitted with the complaints of jaundice, dark urine and intermittent pale stool since one month of age. He had no history of delayed passage of meconium, constipation, feeding difficulties, vomiting, diarrhea, fever, convulsion or bleeding from any site. But the boy had sleeping disturbance and had history of frequent inconsolable crying. Noble's mother had a bad obstetrical history. She had previous history of four still birth babies. Noble was delivered at preterm by LUCS. His postnatal period was uneventful. He was on exclusive breastfeeding. On examination, Noble was well and alert, but moderately icteric. He was moderately wasted (Weight for length Z score -2.9) but not stunted (Length for age Z score -0.75). His OFC was 39 cm and upper segment lower segment ratio was 1.5:1. The size of anterior fontanelle was normal (2x2cm) and posterior fontanelle was almost closed. His vital signs were within normal limit. He had no facial dysmorphism and no associated apparent congenital anomalies. Bedside urine for reducing substance and albumin were absent. He had hepatomegaly (6 cm) which was firm, nontender and splenomegaly (4 cm) but no ascites. His opthalmoscopic examination was done to see any evidence of cataract, chorioretinitis, cherry red spot and posterior embryotoxon but was unremarkable. Other systemic examination revealed no abnormalities.

Laboratory investigations showed normal total and differential count with mild anaemia (Hb 9.9gm/dl) and normal ESR (05 mm in 1st hour). Fractionated bilirubin showed direct hyperbilirubinemia. Serum total bilirubin was 4.86mg/dl of which direct bilirubin was 4.7mg/dl. Evaluation of liver function showed gross impairment. Serum ALT was raised (441U/L), prothrombin time was prolonged (control 11.8 sec, patient 31.6 sec, INR 2.68), serum albumin was reduced (26g/L), serum alkaline phosphatase raised to 1268 U/L. Serum Gamma glutamyl transpeptidase (g-GT) level was normal (34 U/L). Serum Ferritin level was within upper limit of normal (503.8 microgram/L). Free T4 and TSH was normal, TORCH screening was nonreactive, urinanalysis and chest X-ray was also normal. Ultrasonogram of hepatobiliary system showed mild hepatosplenomegaly, well visualized gall bladder which contracted after feeding. Serum gamma glutamyl transpeptidase level rechecked from a different laboratory and was found normal again (28U/L).

1. Assistant Professor, Paediatrics, Student MD thesis Part (Paediatric Gastroenterology), Department of Paediatric Gastroenterology and Nutrition, BSSMU
2. Professor, Department of Paediatric Gastroenterology and Nutrition, BSSMU

Correspondence: Dr. Nazma Begum

Considering the history, clinical findings and investigation and by exclusion of other common differential diagnosis of neonatal cholestatic jaundice (infection, endocrine, metabolic, chromosomal, genetic, biliary atresia, choledocal cyst etc) Noble was diagnosed as a case of Progressive Familial Intrahepatic Cholestasis (PFIC). He was managed with supportive medical treatment by oral ursodeoxycholic acid (20 mg/kg/day), phenobarbitone (5mg/kg/day), injection vitamin K (0.2 mg/kglday for 3 days) and fresh frozen plasma (10 ml/kg). He was advised to continue oral ursodeoxycholic acid (20 mg/kg/day) along with Vitamin A (50,000unit), vitamin D (30,000unit) parenterally in every alternate month, vitamin K (1 mg/kg) parenterally and vitamin E (25 U/kg) orally in every fortnightly. Genetic counseling was also done to the parents. On subsequent follow up after one month his bilirubin was found 3.2mg/dl (direct 2.9mg/dl), Serum ALT 396U/L, prothrombin time was 16 sec (control 11.8 sec, INR 1.3).

Discussion

Progressive familial intrahepatic cholestasis (PFIC) is characterized by early onset of persistent cholestasis, neonatal hepatitis, progressive biliary cirrhosis and hepatic failure in the first or second decade[10]. Significant pruritus, hepatomegaly and failure to thrive are typical features of this disease[5]. In some children, the initial symptom is loose, foul--smelling, pale, greasy stool, usually present from birth[10]. Pruritus is disproportionately severe for the degree of hyperbilirublinemia[11]. Prolonged malabsorption of fat-soluble vitamins may lead to easy bruising or bleeding (caused by vitamin K deficiency), rickets (caused by vitamin D deficiency) and neurologic abnormalities (resulting from vitamin E deficiency)[10]. The average age at onset is 3 months, although some patients do not develop apparent cholestasis until later, even as late as adolescence[12]. Consanguinity is a major risk factor[8]. The reported case presented at the age of one month with the features of cholcstasis (jaundice, dark urine, pale stool), hepatomegaly and growth retardation. In our studied case pruritus was not a complaint. But it should be considered that the onset of pruritus is difficult to pinpoint because detection depends upon an infant's ability to scratch in a coordinated manner. Irritability and sleep disturbance may be the initial manifestation of pruritus in some infants which were also present in our studied case[13].

Recent molecular and genetic studies have allowed the identification of genes responsible for three types of PFIC[4]. The first type, called PFIC type-l (previously called Byler syndrome) is caused by mutations in the FIC 1 gene which encodes a P-type ATPase responsible for aminophospholipid transport. Children with PFIC type l are small for their age, and in addition to cholestasis and pruritus they often have diarrhea and pancreatitis[14]. The second type, called PFIC type 2 (recently named BSEP deficiency) is caused by mutation in the BSEP gene which encodes the ATP-dependent canalicular bile salt export pump (BSEP) of human liver. Mutation in this protein is responsible for the decreased biliary bile salt secretion, leading to accumulation of bile salts inside the hepatocyte and ongoing severe hepatocellular damage. Extrahepatic manifestations are uncommon in PFIC type 2[14] . The third type of PFIC, called PFIC3 is caused by genetic defect in the MDR3 gene involved in biliary phospholipid (phosphatidylcholine) excretion[15].

The diagnosis of PFIC 1 and PFIC2 is primarily based on clinical and laboratory findings[16]. Low-to-normal serum γ-GT (an enzyme located in the epithelial lining of biliary tree and canaliculi) activity despite conjugated hyperbilirubinemia is the hallmark of PFIC1 and PFIC2, as γ-GT activity is elevated in most types of cholestasis[16]. PFIC type 3 can be distinguished from the other types by a high serum γ-GT activity[16]. In the studied case normal level of γ-GT was found on two separate occasions in presence of direct hyperbilirubinemia. However we could not differentiate between PFIC1 and PFIC2. As the studied case is only two and half month old, it will be too premature to comment on extra hepatic manifestations which can clinically differentiate PFIC1 from PFIC2. Benign recurrent intrahepatic cholestasis (BRIC) and Intrahepatic cholestasis of pregnancy (ICP) are two milder form of low γ-GT familial intrahepatic cholestasis[17].

BRIC is characterized by episodes of jaundice, pruritus and normal liver function[17]. Episodes may last from weeks to months. Symptom-free intervals may last from months to years[17]. In the reported case persistent nature of cholestatic jaundice, impaired liver function and normal γ-GT render us to consider the case as PFIC rather than BRIC. In intrahepatic cholestasis of pregnancy (ICP) affected women generally do not experience symptoms between pregnancies but ICP confers an increased risk of fetal

complications and high incidence of fetal loss. In our reported case the mother had history of four stillborn babies which can be possibly explained by ICP.

No imaging study helps in the diagnosis of PFIC[2]. Liver biopsy at initial presentation manifests as giant cell formation and ballooned hepatocyte which is indistinguishable to idiopathic neonatal giant cell hepatitis[18]. Liver histology of PFIC on light microscopy shares the common features with other forms of intrahepatic cholestasis and also can not differentiate different types of PFIC. Coarse appearance of canalicular bile on electron microscopy is characteristics of type 2 PFIC. As liver biopsy is not necessary for the diagnosis of PFIC and also due to coagulopathy we postponed liver biopsy in our case[18]. Prenatal diagnosis for pregnancies at risk for intrahepatic cholestasis caused by PFIC is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 week gestation or chorionic villus sampling (CVS) at approximately 10-12 weeks gestation[5].

Standard therapies for pruritus associated with cholestasis, including choleretic agents such as phenobarbital and ursodeoxycholic acid (UDCA), cholestyramine, rifampin, antihistamines, carbamazepine, UV-B light therapy, and plasmapheresis, have been relatively ineffective in controlling the pruritus associated with PFIC[11]. Surgical therapy (partial external biliary diversion) that diverts bile salts from the enterohepatic recirculation arrests the progression of disease and relieves pruritus in most patients with low γ-GT PFIC[19]. Liver transplantation is indicated in patients with decompensate cirrhosis or with a failed diversion with debilitating pruritus. Survival rates after transplantation are excellent. Liver transplantation is the only effective treatment of high γ-GT PFIC[20].

PFIC results in end stage liver disease (ESLD) if not diagnosed before the development of cirrhosis. Early diagnosis and biliary diversion may prevent significant morbidity and mortality from ESLD.

Conclusion

Progressive familial intrahepatic cholestasis (PFIC) is a relentlessly progressive cholestatic liver disease of childhood. The diagnosis can be suspected in a cholestatic infant in whom priritus is prominent and in whom laboratory evaluation reveals normal to low level of γ-GT in presence of direct hyperbilirubinemia. Other known disorders resulting in intrahepatic cholestasis should be specifically excluded. It is expected that the better characterization of this syndrome will result in increased recognition of PFIC by the physicians, increased understanding of its pathogenesis and development of alternative therapies.

References

1. Jacqemin E. Progressive familial intrahepatic cholestasis. Genetic basis and treatment. Clin Liver Dis 2004; 4: 753-63.
2. Whitington PF, Freese DK, Alonso EM, Schwarzenberg SJ, Sharp HL. Clinical and to biochemical findings in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr 1994; 18: 134-41.
3. Whitington PF. Chronic cholestasis in infancy. Pediatr Clin North Am 1996; 43: 1-26.
4. Jacquemin E, Hadchouel M. Genetic basis of progressive familial intrahepatic cholestasis. J Hepatol 1999; 31: 377-79.
5. Chen ST, Chen HL, Ning YS, Yu-Jung L, Hsuan YN, Hong YI, et al. Prenatal Diagnosis of Progressive Familial Intrahepatic Cholestasis Type 2. J Gastroenterol Hepatol 2008; 23: 90-93.
6. Linarelli LG, Williams CN, Phillips MJ. Byler's disease: fatal intrahepatic cholestasis. J Pacdiatr 1972; 81: 484-92.
7. Clayton RJ, Iber FL, Ruebner BH, Me Kusick VA. Fatal familiar intrahepatic cholestasis in Amish kindred. J Paediatr 1965; 67: 1025-28.
8. Jansen PLM, Sturm E. Genetic cholestasis, causes and consequences for hepatobiliary transport. Liver International 2003; 23: 315-22.
9. Karan M. Progressive familial intrahepatic cholestasis. http://e medicine. medscape. com /view article/932794.
10. Whitington PF, Freese DK, Alonso EM, Schwarzenberg SJ, Sharp HL. Clinical and biochemical findings in Progressive Familial Intrahepatic Cholestasis. J Pediatr Gastroenterol Nutr 1994; 18: 134-41.
11. Jacquemin E, Hermans D, Myara A, Habes D, Debray D, Hadchoul M, et al. Ursodeoxycholic acid therapy in pediatric patients with progressive Familial Intrahepatic Cholestasis. Hepatology 1997; 25: 519-23.

12. Jacquemin E. Progressive familial intrahepatic cholestasis. J Gastroenterol Hepatol 1999; 14: 594-99.

13. Whitington PF, Whitington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. Gastroenterology 1988; 95: 130-36.

14. Bull LN, Van Eijk MJT, Pawlikowska L. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. Nat Genet 1998; 18: 219-24.

15. De Vree JML, Jacquemin E, Sturm E. Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. Proc Natl Acad Sci USA 1998; 95: 282-87.

16. Maggiorc G, Bernard O, Hadchouel M, Lemonnier A, Allagille D. Diagnostic value of serum Gamma glutamy transpeptidase activity in liver disease in children. J Pediatr Gastroenterol Nutr 1991; 12: 21-26.

17. De Pagter AG, Berge Henegouwen GP, Bokkel Huinink JA, Brandit K H. Familial benign recurrent intrahapatic cholestasis. Interrelation with intrahapatic cholestasis of pregnancy and oral contraceptives. Gastroenterology 1976; 71: 202-07.

18. Alonoso EM, Snover DC, Montag A, Frees DK, Whitington PF. Histologic pathology of liver in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr 1994; 18: 128-33.

19. Ekinci S, Karnak I, Gurakan F, Yuce A, Emin M, Tanyl C et al. Partial external bilary diversion for the treatment of intractable pruritus in children with progressive intratepatic cholestasis : report of two cases. Surg Today 2008; 38: 726-30.

20. Soubrane O, Gauther F, Devictor D, Bernard O, Valayer J, Houssin D, et al. Orthotopic liver transplantation for Byler disease. Transplantation 1999; 50: 804-06.