from the azygos to spinal veins when injected at the level of the middle and upper esophagus.[6] Variceal band ligation is effective for controlling bleeding but site of banding is not clearly defined. The risk of bleeding or perforation seems higher because of the weakness of the proximal esophageal posterior wall and overall lack of serosa. The use of a Sengstaken-Blakemore tube can be lifesaving in case of uncontrolled bleeding.[6]

This case represents a rare but physiologically plausible cause of acute upper gastrointestinal bleeding. Though standard recommendations are currently unavailable to help guide physicians to manage acute bleeding associated with "downhill" varices, we suggest that awareness, prompt diagnosis, and management on a case by case basis using available endoscopic, radiological, and surgical interventions can be successful.

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Progressive familial intrahepatic cholestasis: clinico-molecular correlation in Indian children

Progressive familial intrahepatic cholestasis (PFIC)is an autosomal recessive disorder characterized by early onset cholestasis, pruritus, hepatomegaly and growth failure and can progress to liver failure before adolescence due to secondary cirrhosis.[1] PFIC accounts for 10-15% of cases of cholestasis in children and is the cause of 10-15% of pediatric liver transplants. PFIC I and II represent about two-third of the cases of PFIC, the remaining being PFIC III.[2] Although PFIC has been reported worldwide, only 11 cases have been described from India.[3-5] Here we present a case series of five PFIC patients who enrolled at our liver clinic and were diagnosed to be PFIC by molecular studies, and discuss their clinical phenotypes.

Case Series

We present the cases of five children who presented with jaundice in their infancy of which three had itching, one had clay colored stools and 4 had recurrent jaundice. Patient 4 and 5 were born of parents who were in a consanguineous marriage. Liver biopsies was done in 2 patients, which showed intrahepatic bile stasis. **(Table 1)**

Additionally, Patient 1 had early bilateral cataracts. Thyroid functions, GALT enzyme levels, echocardiography, urinary organic acids screen, urinary reducing substances and hepatobiliary immunodiacetic acid scan (HIDA) were normal. TORCH titres were also not suggestive of infection by these agents. Since child had resolution of liver functions and a genetic test had been sent, a liver biopsy was not done in the patient. Child was started on vitamin A, D, E, K and ursodeoxycholic acid and was doing well on follow up.

In addition to jaundice and itching, patient 2 had delayed milestones at presentation. She had achieved head holding at 9 months of age and at 1.5 years, the child could only babble and sit with support. Currently the child is 2 ½ years of age; she continues to have jaundice but no itching, has developed portal hypertension and has been counseled about liver transplant.

Patient 3 had jaundice in neonatal period and again at 7 months and 10 months. At presentation at the age of 1 year, the patient had failure to thrive with persistent jaundice. She also has itching and is on regular follow up.

Patient 4 had jaundice, hepatosplenomegaly and failure to thrive since neonatal period, and subsequent episodes of conjugated hyperbilirubinemia at 2months, 8 months, 14 months and 18 months of age with the latter episodes associated with pruritus. Initial serum alpha fetoprotein was 151544ng/ml which was subsequently monitored, with last serum alpha fetoprotein 194 ng/ml. Child has been counseled about eventual liver transplant and is on regular follow up.

Patient 5 presented at 2 years of age with signs of liver cell failure, large hepatomegaly, failure to thrive and atypical pneumonia. He did not have itching. He had a history of having been admitted at 5 months of age for conjugated hyperbilirubinemia. This child was lost to follow up.

Discussion

Progressive familial intrahepatic cholestasis (PFIC) refers to a heterogeneous group of autosomal recessive disorders of childhood that present with cholestasis of hepatocellular origin due to disrupted bile formation.[2] PFIC is characterized by early onset cholestasis, pruritus, poor growth, progressive liver cirrhosis, and an inexorable progression to liver cirrhosis in early childhood.[1] Though initially cholestasis is episodic interspersed with disease free intervals, eventually cholestasis becomes non-remitting and pruritus typically becomes severe, persistent and disabling.1In our case series, all the patients had onset of cholestasis before one year of life and failure to thrive, only 3 had pruritus and 4 had recurrent jaundice thus suggesting that not all patients with PFIC may have pruritus.

The pathogenesis of PFIC is due to defects in ATP-binding cassette (ABC) transporters like ATP8B1, ABCB11 and ABCB4 which cause PFIC I, PFIC II and PFIC III respectively. These ATP-binding cassette (ABC) transporters facilitate the secretion of bile salts, cholesterol and phosphatidylcholine across the canalicular membrane of hepatocytes into bile.[2]

PFIC I is caused by mutations in the ATP8B1 gene on chromosome 18q21. The clinical spectrum ranges from severe FIC1 deficiency or Byler's disease, named after the Amish descendants of Joseph Byler in which PFIC was first described, to milder phenotypes such as benign recurrent intrahepatic cholestasis type 1 (BRIC1), Greenland familial cholestasis and intrahepatic cholestasis of pregnancy (ICP1).[2] PFIC I is characterized by neonatal onset cholestasis, severe pruritus, normal serum gamma-glutamyltransferase (GGT) activity and cholesterol level, absence or very low levels of primary bile acids in bile with high serum bile acids, and absence of ductular proliferation on liver biopsy. It leads to death due to liver failure, mostly before adolescence.[1] FIC1 is expressed in several epithelial tissues and, surprisingly, more strongly in the small intestine than in the liver.This accounts for the extrahepatic features associated with

Table 1: Clinical and laboratory parameters of each patient.

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
Age of presentation	42 days		1.5 years		1 yr		2 months		2 yrs	
Gender	Male		Female		Female		Male		Male	
Jaundice	Since Day 3 of life		Since 6 months of life		Since day 45 of life		Since 15-20 day of life		Since 5 months	
of age										
Itching	No		Yes (initially)		Yes		Yes		No	
Clay stools	No		No		Yes		No		No	
Birth History	Neonatal sepsis		Normal		Normal		Normal		Normal	
Birth weight	2.4kg		Not known		2.2 kgs		2.75 kgs		2.5kgs	
Weight at presentation	2.65kg		7.9kgs		7.2kgs		3.8kgs		7.9 kgs	
Clinical hepatomegaly	No		Yes		Yes		Yes		Yes	
Splenomegaly	No		Yes		No		No		No	
Follow up										
Failure to thrive	Yes		Yes		Yes		Yes		Yes	
Recurrent jaundice	No		Yes		Yes,1.5,7, 10 and 12 months		Yes 2,8,14 and 18 months		Yes 5 months and 2 years	
Investigations										
USG abdomen and doppler	Hepatomegaly with coarse echotexture		Hepatomegaly with coarse echotexture and patent paraumblical vein with collaterals		Hepatomegaly with coarse echotexture		Hepatomegaly with normal echotexture		Hepatomegaly with coarse echotexture	
Hemoglobin (gm/dl)	11.8		6.2		7.7		8.3		5.0	
WBC (cells/cumm)	13300		8500		16700		10400		14500	
Platelets (cells/ cumm)	4,85,000		159000		315000		211000		605000	
	At presen-tation	Last follow up	At presen-tation	Last follow up	At presen-tation	Last follow up	At presen-tation	Last follow up	At presen-tation	Last follow up
Bilirubin (Dir) in mg/dl	11.3 (2.9)	0.4 (0.2)	0.8 (0.5)	0.7 (0.3)	6.0 (2.8)	2.9 (2.3)	3.9	6.3 (3.5)	2.5 (1.3)	-
SGOT (IU/L)	90	63	95	118	450	267	175	49	424	-
SGPT (IU/L)	166	39	68	68	500	121	78	103	204	-
Total protein (gm/dl)	5.8	7.4	5	5.8	5.3	6.6	4.9	7	6.3	-
Albumin (gm/dl)	3.1	4.6	2.9	3.1	3.0		2.9	3.4	2.8	-
PT (Sec)	16 (11.6)	12.6 (10.0)	18.0 (14.0)	11 (10.9)	13.7 (13.3)		28 (12.1)	14.9 (12.0)	23.2 (11.0)	-
PTT (sec)	36.8 (21.2)	33.8 (31.8)	65.2	31.2 (26.1)	38.1 (30.3)		72.4 (23.4)	28.1 (22.3)	42 (28.2)	-
GGTP (IU/L)	107	20	38	45	24	23	32	33		-
Alkaline phosphatase (IU/L)	1004	286	375	329	1227	448	721	161		-
Liver biopsy	Not done		Intrahepatic cholestasis with cirrhosis. Electron microscopy: hepatocytic and canalicular cholestasis with wispy, amorphous biliary material		Paucity of bile ducts with intrahepatic bile stasis		Not done as parents not willing		Not done as parents not willing	
Genetic mutation	Heterozygous sequence variant c.524C>T p.(Thr175Met) in ABCB4 gene and c.2498G>A p.(Arg833Gln) in ATP8B1 genes		Homozygous sequence variant c.1858_1860del AAG p.(Lys620del) of ABCB 4 gene.		Pathogenic missense mutation c.1409G>A p.(Arg470Gln) in the ABCB11 gene		Pathogenic homozygous splice site mutationc.1084-2A>G in ABCB11 gene		Pathogenic splice site mutation c.1230+1G>T in ABCB4 gene	

PFIC1 such as diarrhea, pancreatitis, persistent short stature, deafness and pneumonia. The higher occurrence of extrahepatic disease in PFIC I helps differentiate it from PFIC II.[1] In our study, patient 1 had heterozygous sequence variants in ABCB4 and ATP8B1 genes with initially high GGTP which subsequently normalised. He had conjugated hyperbilirubinemia since day 3 of life with bilateral cataracts but is subsequently doing well on follow up. Since neither variant of the gene has previously been reported in literature, it was not possible to predict the significance of these findings in this patient.

PFIC II is characterized by cholestasis due to reduced bile secretion and decreased bile flow as a result of ABCB11 gene mutation. This gene encodes the ATP-dependent canalicular bile salt export pump (BSEP), which is the major exporter of primary bile acids against extreme concentration gradients at the hepatocyte canalicular membrane. Mutations lead to intrahepatocytic accumulation of bile salts causing severe hepatocellular damage.3 A less severe form of cholestatic liver disease due to ABCB11 mutation is BRIC 2.2 Clinical features are jaundice, intractable pruritus and vitamin deficiency. Patients have high serum but very low biliary bile salts, elevated serum alanine aminotransferase (ALT) activity but low or normal serum GGT activity and occasionally elevated serum cholesterol. Histological examination reveals giant cell hepatitis, bile duct proliferation and portal fibrosis with amorphous or filamentous bile seen on electron microscopy. Increased tendency to develop gallstones and risk of developing hepatocellular carcinoma or cholangiocarcinoma is seen in these patients.[2] Several authors recommend monitoring with serum alpha fetoprotein dosage every 6 months and liver ultrasonography annually in PFIC2 patients from the first year of life for hepatocellular carcinoma.[2] In our study, patient 3 and patient 4 had features of PFIC II with early onset jaundice, severe pruritus, failure to thrive, recurrent jaundice and normal GGTP. Genetic analysis was suggestive of PFIC II in both children and both children are being monitored with serial alpha fetoprotein and ultrasonography.

The third type of PFIC, called PFIC III, is caused by a genetic defect in the ABCB4 gene (also designated MDR3) located on chromosome 7. ABCB4 gene is responsible for transport of phospholipids across the canalicular membrane which in turn protects the canalicular membrane from solubilization by bile salts by forming micelles with bile salts.[2] Cholestasis is likely to be related to the absence of biliary phospholipids and injury to bile canaliculi and biliary epithelium. Also contributory is the small bile duct obstruction due to continuous exposure to hydrophobic bile salts, the detergent effects of which are no longer countered by phospholipids. This leads to cholangitis and increased lithogenicity of bile with crystallization of cholesterol.[2] PFIC3 patients present with cholestatic jaundice later in infancy or in young adulthood, and only rarely in the neonatal period,as seen with other types of PFIC.[2] Disease is characterized by modestly elevated levels of serum primary bile acids, normal concentration of biliary primary bile acids, mild and inconstant pruritus and high GGT serum activity. Histologic characteristics are patent intra and extrahepatic bile ducts with ductular proliferation and inflammatory infiltrate.[1] Patient 2 and 5 in our study had features of PFIC III with late onset jaundice at 6 and 5 months respectively, recurrent jaundice, failure to thrive and high GGTP which was documented in patient 2. Patient 2 also had initial itching which was uncharacteristic of PFIC III,however on eventual follow ups, itching was absent.Gene mutation study of patient 2 revealed a novel homozygous sequence variant in ABCB11 gene which has not previously been reported in the literature. Patient 5 had clinical features of PFIC III and a confirmatory gene analysis , but was lost to follow up.

Treatment for PFIC is both medical and surgical. Alleviation of pruritus associated with cholestasis is by choleretic agents such as phenobarbital, ursodeoxycholic acid (UDCA), cholestyramine, rifampin, antihistamines and carbamazepine. Medium-chain triglycerides should be incorporated in diet as they are absorbed relatively independent of bile flow.[6] External biliary diversion including cutaneous cholecystostomy, cholecysto-jejuno-cutaneostomy, cholecysto-appendico-cutaneostomy, and the internal diversion approach of ileal exclusion is successful in reducing pruritus in patients affected with low GGT PFIC.[6] Early institution of biliary drainage can delay progression of this disease to end stage liver failureand need for liver transplantation.[6] An endoscopic

biliary diversion, nasobiliary drainage, is also effective in aborting a cholestatic episode in BRIC patients. When all of these treatments fail, the only option is liver transplantation. However caution must be exercised in PFIC1 patients as the extrahepatic symptoms persist or even worsen (e.g., diarrhea) after the liver transplant.[2]

In our case series, both patients with severe pruritus were well controlled on choleretic drugs till last follow up. Two patients were counseled about need for liver transplant in view of worsening hepatic functions.

Conclusion

PFIC should be suspected in every child with a history of neonatal cholestasis, intermittent jaundice and pruritus so that appropriate therapy may be provided early in the disease course. Identification of the pathogenic mutation may allow pre-implantation genetic diagnosis (PGD) and reduce the incidence of the disease within families.

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