DOI: 10.7860/JCDR/2023/64846.18663

Case Report

Pathology Section

Cholestatic Liver Disease in Late Childhood: A Report of Two Rare Cases

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ABSTRACT

Cholestatic liver disease in late childhood has a comprehensive list of aetiologies, requiring a multidimensional approach. Among these, the genetic aetiology can range from having a self-limiting course to being associated with morbidity and mortality, requiring liver transplantation. Progressive Familial Intrahepatic Cholestasis (PFIC) and Benign Recurrent Intrahepatic Cholestasis (BRIC) are two rare inherited autosomal recessive cholestatic disorders. Both are related to mutations in the bile formation transport system and typically manifest in infancy or early childhood. Among the PFIC types, The PFIC type 3 rapidly progresses to end-stage liver disease, while BRIC follows a benign course with intermittent asymptomatic periods. Here, authors describe two (17-year-old male, 19-year-old male) such unusual inherited autosomal recessive cholestatic disorders in late childhood: PFIC (type 3) and BRIC, which have distinct clinical presentations and liver function derangements.

Keywords: Benign recurrent intrahepatic cholestasis, Progressive familial intrahepatic cholestasis type 3

CASE REPORT

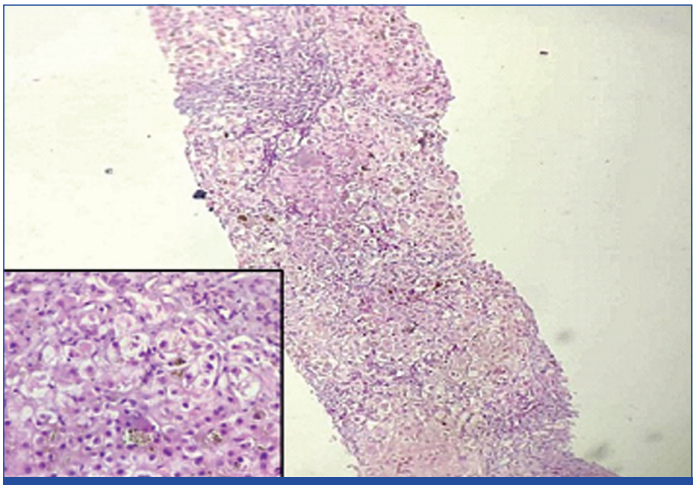
Case 1

A 17-year-old male presented with itching of seven months' duration, which was insidious in onset, gradually progressive, and accompanied by jaundice for the past four months. During the physical examination, the patient's spleen was palpable, measuring 3 cm. Biochemical investigations revealed deranged Liver Function Tests (LFT) with a significant increase in bilirubin and hepatic enzymes, as well as low levels of protein, as shown in [Table/Fig-1].

Parameters	Result	Normal value
Total bilirubin	12.8 mg%	Upto 1 mg%
Direct bilirubin	8 mg%	Upto 0.3 mg%
SGOT	245 U/L	5-40 U/L
SGPT	172 U/L	5-40 U/L
Serum alkaline phosphatase	261 U/L	44-144 U/L
Serum gamma GT	111 U/L	5-40 U/L
Total protein	5.4 gm%	6-7.5 gm%
Albumin	2.8 gm%	3-4.5 gm%

[Table/Fig-1]: Baseline values of investigations.
SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, GT: Glutamyl transpeptidase

Radiological investigations, including Magnetic Resonance Cholangiopancreatography (MRCP) and ultrasound of the abdomen, were unremarkable, ruling out obstructive biliary pathology as the cause. Oesophagogastroduodenoscopy also did not reveal any abnormalities. Histopathological examination {Haematoxylin and Eosin (H&E)} of a core liver biopsy showed normal architecture of the liver parenchyma, which was distorted by the presence of incomplete regenerative nodules indicating stage 2-3 fibrosis. The hepatocytes exhibited marked ballooning degeneration, pseudoacinar transformation, significant intrahepatic and canalicular cholestasis, cholate changes, and moderate portal tract inflammation and lobular inflammation [Table/Fig-2]. The hepatitis activity index was calculated as 6/18 (Modified Ishak score: portal inflammation 3/4, lobular inflammation 3/4, interface activity 0/4, necrosis 0/6). Based on these characteristic histopathological findings and correlation with the LFT, a diagnosis of cholestatic liver disease with biliary pathology was established. Since the MRCP findings were normal, ruling out obstructive biliary pathology, PFIC type 3 was suspected, and further genetic studies were recommended. Genetic testing using targeted exome gene sequencing method revealed a homozygous missense variation in exon 14 of the ABCB4 gene (chr7:g.87069036T>C; Depth: 252x), confirming PFIC type 3. However, there was no known family history of similar cholestatic liver disease in the patient. The patient was managed conservatively in line with cholestatic liver disease treatment and was counselled for liver transplantation. Unfortunately, the patient succumbed to complications following end-stage liver disease.



[Table/Fig-2]: Photomicrograph showing cirrhotic liver architecture. Hepatocytes show marked intrahepatic and canalicular cholestasis, feathery degeneration, inflammation and pseudoacinar change (inset) (H&E, 100x and 400x).

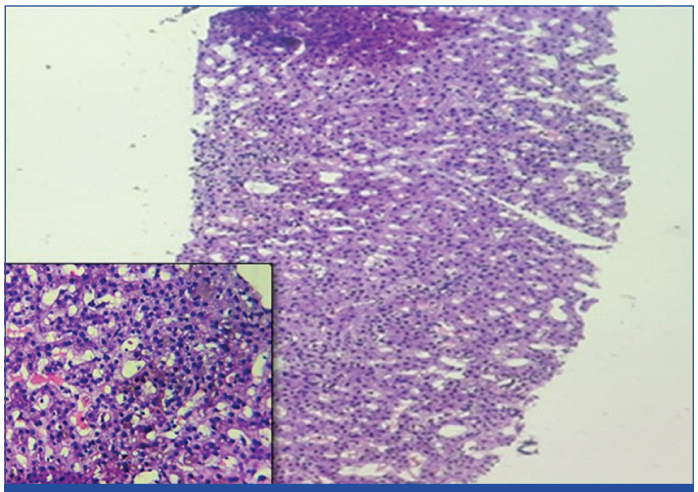
Case 2

A 19-year-old male presented with clinical features of jaundice lasting for one month, accompanied by itching all over the body and vomiting for the past two days. Upon clinical examination, the patient's spleen was palpable at 2.4 cm. The patient also had a past history of recurrent episodes of jaundice with associated itching, alternating with symptom-free periods. Biochemical investigations revealed abnormal liver function tests, showing a significant increase in conjugated bilirubin and alkaline phosphatase levels, as shown in [Table/Fig-3]. Radiological studies did not reveal any abnormalities, ruling out obstructive biliary pathologies such as primary biliary cirrhosis or primary sclerosing cholangitis.

Parameters	Results	Normal value
Total bilirubin	29.3 mg%	Upto 1 mg%
Direct bilirubin	20.5 mg%	Upto 0.3 mg%
SGOT	30 U/L	5-40 U/L
SGPT	18 U/L	5-40 U/L
Serum alkaline phosphatase	539 U/L	44-144 U/L
Serum gamma GT	15 U/L	5-40 U/L
Total protein	6.5 gm%	6-7.5 gm%
Albumin	3.4 gm%	3-4.5 gm%

[Table/Fig-3]: Baseline values of investigations.
SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, GT: Glutamyl transpeptidase

Histopathological examination of a liver biopsy core revealed preserved architecture. Hepatocytes exhibited bland intrahepatic cholestasis, along with congested and dilated sinusoids. There was no evidence of inflammation in the lobules or portal areas, and no steatosis was observed. Fibrosis was absent, as indicated in [Table/Fig-4]. Based on these characteristic histopathological features, along with the patient's past clinical history of episodic symptoms and intermittent disease-free periods, laboratory findings, and normal radiological results, a final diagnosis of BRIC was made. The patient is currently doing well with conservative management during follow-up.



[Table/Fig-4]: Photomicrograph shows maintained normal liver architecture. Bland intrahepatic cholestasis without cholate changes, inflammation and fibrosis (H&E 100x and 400x).

DISCUSSION

The authors hereby describe PFIC type 3 and BRIC, cholestatic diseases with a genetic aetiology that belong to the spectrum of mutations involving bile canalicular transport proteins ATP8B1, ABCB11, and ABCB4. PFIC is a progressive form of BRIC. PFIC represents a heterogeneous group of autosomal recessive disorders that mainly affect children of different age groups. The exact prevalence of these disorders is unknown, and the estimated incidence varies between 1 in 50,000 and 1 in 100,000 births. Among these cases, PFIC 3 represents only one-third of the total [1]. A literature search revealed cases of PFIC reported as a few case reports and case series in the Indian population. The largest series reported 25 cases and 13 cases by Agarwal S et al., and Mehta S et al., respectively, highlighting the rarity of these cases. This rarity might be due to a low index of suspicion on histopathology, with the possibility of a lack of a multidimensional approach involving various diagnostic facilities such as genetic testing and immunostaining [1,2].

The PFIC type 3 arises from a mutation in the Adinosine Triphosphate (ATP)-binding cassette subfamily B member 4 (ABCB4) gene, causing a deficiency of the MDR3 protein. This mutation leads to impaired biliary phospholipid secretion, which is essential for inactivating detergent bile salts. Consequently, it results in injury to the biliary epithelium and canaliculi, eventually causing cholestasis, cholangitis, and biliary cirrhosis. PFIC 3 typically presents in late childhood or early adolescence [3].

Among the 25 cases of PFIC analysed by Agarwal et al., they identified only three cases of PFIC 3 in children aged 9-12 years, indicating a prevalence of 34% in older children. All patients exhibited elevated Gamma-glutamyl Transferase (GGT) levels, two experienced significant pruritus with cholestasis, and the third presented with uncontrolled portal hypertension and upper gastrointestinal bleeding. These findings are consistent with the similar observations made in our case of PFIC type 3. Histological features also showed similarities, displaying characteristics of cholestatic liver disease with biliary pathology. Agarwal et al., performed immunostaining to identify PFIC, while Mehta et al., confirmed all PFIC cases through exome sequencing genetic testing, as we did in the present case [1,2]. Due to the lack of robust Indian literature, clinical trials are underway to establish an Indian registry of PFIC [4].

The BRIC is a rare benign autosomal recessive cholestatic liver disorder caused by mutations in ATP8B1 and ABCB11. It typically manifests in the first two decades of life with a male predominance and exhibits symptom-free intervals lasting from months to years. The estimated incidence varies between 1 in 50,000 and 1 in 100,000 births. The diagnosis is made by excluding other cholestatic liver diseases and correlating clinical features, radiology, laboratory, and histopathology findings, based on the diagnostic criteria proposed by Luketic and Shiffman. Literature search reveals single case reports or case series of 3-4 cases from India, as described by Kumar P et al., Gupta S et al., and Jha A et al., These cases occurred in individuals aged 23-25 years and presented with clinical features of episodic cholestasis, elevated conjugated bilirubin levels, and normal to mildly elevated liver enzymes, similar to the present case [5-7]. In BRIC, a normal serum GGT level, normal serum globulins, and specific histopathological findings consistent with the classical clinical presentation help identify this rare disorder, thus eliminating the need for expensive genetic testing, although milder forms of mutations within the PFIC spectrum may be present. This differentiation is crucial in distinguishing BRIC from other causes of episodic cholestasis, such as autoimmune hepatitis or primary biliary cirrhosis.

CONCLUSION(S)

Cholestatic liver disorders that present in late childhood and have a genetic aetiology are rare, requiring a multidisciplinary approach. Diagnosis often involves expensive diagnostic modalities for confirmation, such as specific protein immunostaining or genetic testing. The course of these disorders can vary, ranging from self-limiting conditions like BRIC to progressive forms such as PFIC type 3, which may necessitate liver transplantation. It is crucial for pathologists to be aware of these rare disorders and to suspect them based on characteristic histopathological features, in conjunction with clinical, laboratory, and radiological findings, in order to facilitate timely management.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 21, 2023
- Manual Googling: Jul 13, 2023
- iThenticate Software: Aug 11, 2023 (6%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Apr 18, 2023**
Date of Peer Review: **Jun 04, 2023**
Date of Acceptance: **Aug 14, 2023**
Date of Publishing: **Nov 01, 2023**