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CASE REPORT

A suspected case of Progressive Familial Intra-hepatic Cholestasis in a Six-Year-Old Nigerian Child

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Summary

Progressive Familial Intra-hepatic Cholestasis (PFIC) is a group of heterogeneous, autosomal recessive disorders characterized by cholestasis, jaundice and mutilating pruritus, mostly in infancy. The incidence of PFIC ranges from 1:50,000 to 1:100,000. There are three subtypes; Types 1 and 2 typically present in the neonatal period and early infancy while Type 3 can present in early infancy, childhood or adolescence.

This report is about a 6-year old Nigerian girl who presented with jaundice and severe pruritus of one-month duration and abdominal pain of a week duration. The symptoms were preceded by ingestion of Atropine meant for ocular examination two days earlier. She was well-nourished, deeply icteric, had generalized healing scratch marks and hepatomegaly. The laboratory findings included conjugated hyperbilirubinaemia, moderately elevated liver transaminases and Gamma-Glutamyltransferase enzymes. She was managed for PFIC3 using oral ursodeoxycholic acid with complete resolution of the disease.

Keywords: *Childhood, Conjugated hyperbilirubinaemia, Progressive Familial Intra-hepatic Cholestasis, Pruritus, Ursodeoxycholic acid.*

Introduction

Cholestatic Liver Disease in children constitutes a diagnostic and therapeutic challenge. Progressive Familial Intra-hepatic Cholestasis (PFIC) refers to a clinically distinct group of autosomal recessive hereditary liver diseases. There are three subtypes of the disorder with different mutations in hepatocellular transport system genes responsible for bile formation. PFIC constitutes about 10 - 15% of paediatric cholestatic diseases. [1] PFIC1 and PFIC2 are rare diseases with incidence rates ranging between 1:50,000 and 1:100,000 births. [1] The number of cases reported from the two subtypes is less than 200, while PFIC3, which

is a rarer disease, has less than 20 reported cases. [2] This report is about a six-year-old girl who was empirically managed for Progressive Intra-hepatic Cholestasis Type 3 with a good outcome.

Case Description

This apparently healthy six-year-old girl was referred to the Paediatric Gastroenterology and Hepatology Clinic of the University of Benin Teaching Hospital, Benin City, Edo State, Nigeria, with complaints of jaundice, generalized itching of the body of a month's duration and right upper abdominal pain of a week's duration. The symptoms were

preceded by ingestion of oral Atropine for 2 days for an ocular procedure. The appearance of jaundice was associated with severe pruritus, which was generalized and distressing, often interfering with her sleep. Her urine was deep yellow, but stool pigmentation was normal. There was no fever, malaise or vomiting. There was no previous history of jaundice or contact with anyone with jaundice.

About three weeks into the illness, she developed dull abdominal pain at the right upper part of the abdomen. The pain typically occurred following ingestion of a fatty meal, not radiating, usually transient and subsides spontaneously. She is not on any medications (apart from the Atropine) and had no known history of allergy. She is the youngest of three children in a non-consanguineous monogamous marriage.

At the onset of symptoms, she was taken to the referring hospital where she received antiemetic drugs, intravenous fluids, antibiotic (Amoxicillin/Clavulanic acid) and cholestyramine. These offered some temporary relief with the itching. However, she was referred to the Teaching Hospital for evaluation and further management when the symptoms worsened.

Essential findings on physical examination included deep icterus with a greenish hue, healing scratch marks on the skin, hepatomegaly of about 6cm below the right costal margin with positive Murphy's sign. A provisional clinical diagnosis of cholestasis with cholecystitis was made. Initial laboratory findings included elevated liver enzymes and deranged clotting profile. [Alkaline Phosphatase (ALP) of 132 IU/L; Alanine Transaminase (ALT) of 51 IU/L; Aspartate Transaminase (AST) of 79 IU/L; Total Serum Bilirubin 24.3mg/dl and Conjugated Serum Bilirubin 11.0mg/dl; Prothrombin Time of 20 seconds; International Normalized Ratio (INR) of 1.76 and Partial Thromboplastin Time with

Kaolin (PTTK) in excess of 1 minute]. Urine analysis was positive for bilirubin (++) , pH was 5.0, and specific gravity was 1.015; other parameters were normal. The Random Blood Glucose, Serum Electrolytes, Urea and Creatinine were within the normal range. The haemoglobin genotype was AA while Hepatitis B surface Antigen (HBsAg) and Hepatitis C Virus (HCV) were negative.

Abdominal ultrasonographic scan (USS) revealed a small capacity gall bladder containing biliary sludge without signs of calculi, mass or inflammation (Figure 1). Other findings were essentially normal. Magnetic Resonance Imaging (MRI) of the abdomen showed a normal gall bladder and intra-hepatic and extra-hepatic bile ducts. There was no evidence of Chronic Liver Disease, cholelithiasis or cholecystitis. The child was commenced on Ciprofloxacin 250mg b.d.s, oral cholestyramine 2g t.d.s and oral Vitamins A, D, E and K.

In the second week of follow-up care, abdominal pain had subsided, but jaundice got worse with associated pruritus despite compliance with therapy. A repeat Liver Function Test (LFT) showed an increase in the conjugated bilirubin (16.0mg/dl) while the liver enzymes were slightly reduced (ALP of 122 IU/L; AST of 52 IU/L; ALT of 20 IU/L and Total Serum Bilirubin of 22.3mg/dl). The Gamma Glutamyl Transferase (GGT) was 97 U/L (4 - 30U/L), with a normal prothrombin time (12.0sec) and INR while PTTK remained in excess of 1 minute. A diagnosis of PFIC3 was entertained, and she was commenced on Ursodeoxycholic acid (UCDA) (250mg b.d.s) while Vitamins A, D, E and K were continued. On further review two weeks later, pruritus had reduced markedly, and jaundice had cleared significantly. A review at one month after the commencement of UCDA, the symptoms had subsided with normal liver function test results (ALP of 78 IU/L; AST of 12 IU/L; ALT of 8 IU/L and

Total Serum Bilirubin of 2.3mg/dl, and Conjugated Serum Bilirubin of 0.6mg/dl).

Consent: The parents of the child consented to the documentation of the case in the literature following assurance of confidentiality.

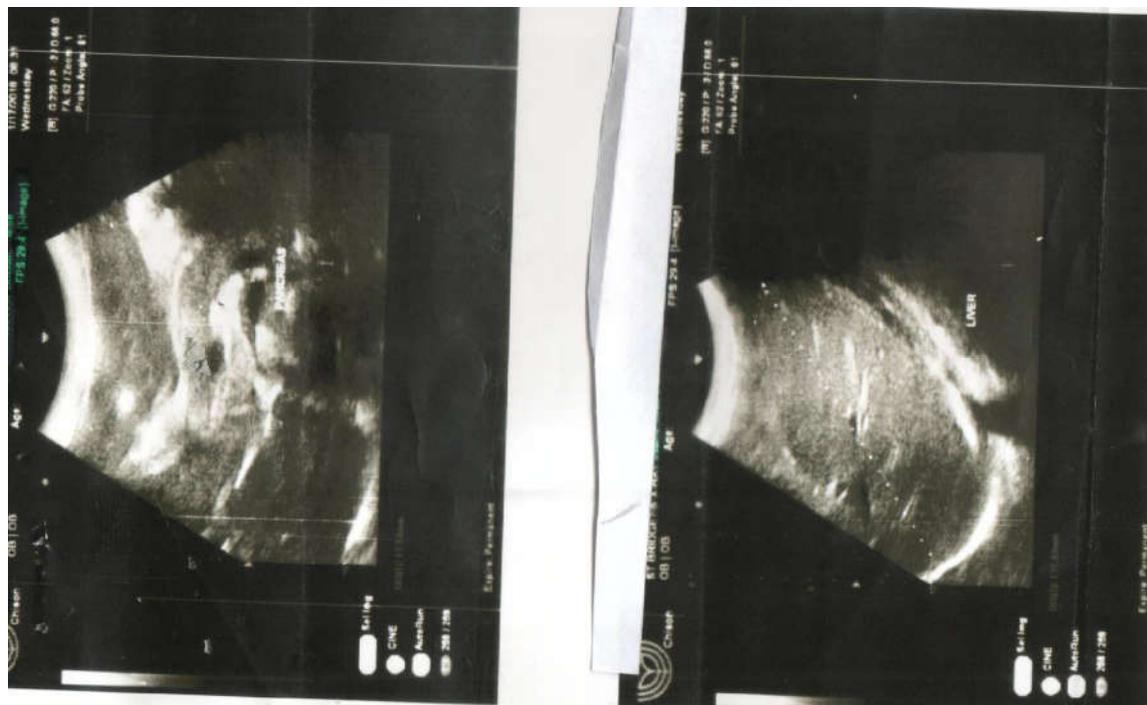


Figure 1: Abdominal Ultrasonograph showing a small capacity gall bladder containing biliary sludge without signs of calculi, mass or inflammation.

Discussion

Progressive Familial Intra-hepatic Cholestasis is a rare group of inherited autosomal recessive disorders with no gender bias, which is more prevalent in cultures where consanguineous marriages are practised. A defect in bile secretion from hepatocytes to canalicular cells is responsible for the three subtypes of PFIC. PFIC1, also known as Byler's disease, results from a mutation in the ATPase Phospholipid Transporting 8B1 gene (ATP8B1), which is located on human chromosome 18. This gene encodes a phospholipid transporting transmembrane P-type ATPase known as FIC1. It is localized on the apical membrane of epithelial cells, including the canalicular membrane of hepatocytes. ATP8B1 is involved in

maintaining an asymmetric distribution of phospholipid across the canalicular membrane bilayer of hepatocytes. It plays a protective role against high bile salt concentrations in the canalicular lumen. PFIC1 presents typically in the neonatal period with recurrent episodes of intra-hepatic cholestasis, intractable pruritus, diarrhoea and failure to thrive in the first several months of life. This condition progresses to cirrhosis and liver failure in the first decade of life. [3]

PFIC2 is caused by mutations in the ATP binding cassette subfamily B member 11 gene (ABCB11) which is located on chromosome 2q24. This gene encodes canalicular bile salt export protein (BSEP). BSEP is the main transporter of bile acids from hepatocytes to the canalicular lumen. Its deficiency can lead to impaired secretion of bile salt, accumulation

of bile salts and subsequent hepatocellular injury, apoptosis or necrosis. Pruritus is more severe in PFIC2 compared to PFIC1, and the former often presents with jaundice in the neonatal period. There is a considerable risk of hepatobiliary malignancy, hepatocellular carcinoma or cholangiocarcinoma in affected patients.

PFIC-3 is caused by mutations in the ATP binding cassette subfamily B member 4 genes (ABCB4). This gene encodes the multidrug resistance protein-3 gene (MDR3). It is located on chromosome 7q21 and is involved in the transportation of phospholipids into the biliary epithelia and bile canaliculi. Defects of ABCB4 lead to impaired excretion of phosphatidylcholine, which leads to cholangitis and cell death resulting from the continuous exposure to hydrophobic bile salts, whose detergent action is no longer countered by phospholipids. There are varied types of mutations, and those with missense mutation have less severe phenotype, with later onset of disease, slower progression and better response to treatment. Heterozygous mutations can lead to intrahepatic cholestasis of pregnancy, cholesterol gall stone formation, drug-induced cholestasis and adult biliary cirrhosis. [4]

A combination of clinical and laboratory parameters helps in the diagnosis of PFIC, but genetic testing is required for a definitive diagnosis. [5] Jaundice, pruritus, hepatomegaly, pale stools, failure to thrive, diarrhoea and splenomegaly were the symptoms reported in a systematic review of studies on PFIC. [6] Pruritus was reported to be severe in 76 - 80% of cases and was described as the most burdensome symptom in some studies. The index child presented with jaundice, severe pruritus and abdominal pain. Abdominal pain is not a common presentation in PFIC and could have resulted from the biliary sludge (reported in the abdominal USS) which can be accompanied by cholecystitis and cholelithiasis. A systematic review of PFIC

reported the occurrence of symptoms within the first three months of life in PFIC1 and PFIC2 while PFIC3 typically presents after 2 to 3 years, [6] thus making PFIC3 the most likely type in our patient.

Conjugated hyperbilirubinaemia (conjugated serum bilirubin greater than 2mg/dL), as observed in this patient, is a feature of PFIC and other causes of cholestasis. Typically, alkaline phosphatase is elevated in the three subtypes of PFIC while ALT and AST are marginally increased in PFIC1 but significantly elevated in Types 2 and 3. Studies with a marginal increase in ALT and AST have occasionally been reported in Type 3. [7] Gamma Glutamyltransferase (GGT) is usually elevated in PFIC3 while it is normal in PFIC1 and PFIC2. The child in this report had more than a three-fold increase in GGT, which conforms more with PFIC3. The ALT, ALP and AST were marginally increased. Other relevant biochemical tests in the diagnosis of PFIC include serum bile acids, which is elevated in all types of PFIC; alpha-fetoprotein which is normal in PFIC3 but elevated in Types 1 and 2; biliary phospholipid which is normal in Types 1 and 2 but low in PFIC3. However, the investigations mentioned above were not carried out in this patient.

Histomorphological findings of biopsied liver tissue can give useful information in the diagnosis of PFIC. Types 1 and 2 are associated with canalicular cholestasis with more prominent fibrosis and giant cell hepatitis in Type 2. There is a proliferation of bile ducts with fibrosis. The abnormal BSEP in PFIC2 and the MDR3 in Type 3 can be stained for determination of the subtype. Immunohistochemistry of liver tissue will show the presence of antibodies to BSEP in Type 2 and against MDR3 in Type 3. Unfortunately, liver biopsy for histology and immunohistochemistry was not done for the index patient. Genetic testing has of recent been used to confirm the diagnosis of PFIC in a vast number of cases. Deletion/duplication analysis, sequence

analysis of the coding region and targeted variant analysis can be performed. [2] Genetic testing could not be done for the index patient.

The management of PFIC consists of medical and surgical interventions. A cholagogue such as ursodeoxycholic acid (UDCA) at a dose of 20 – 30mg/kg is the first line therapy for this condition. The rationale underlying this therapy is that enrichment of bile with this hydrophilic bile acid reduces cytotoxic injury to hepatocytes and bile ducts. About a third of those with PFIC3, especially those with missense mutation, [8] who were treated with UDCA responded well to the drug. The excellent response of the index child to UDCA heightened our suspicion of PFIC3, which was further supported by the history of ingestion of Atropine prior to the onset of jaundice and severe pruritus. The MDR3 defect in PFIC3 has been associated with drug-induced cholestasis and cholesterol gallstone disease. [9] Atropine has been reported to cause biliary stasis by inhibiting gallbladder contractility [10], which can trigger cholestasis in individuals with a genetic predisposition, in this case, PFIC 3. Other medications which can be used in the treatment of PFIC include cholestyramine and rifampicin, but this child did not respond to cholestyramine.

Surgical procedures such as partial external biliary diversion, partial internal biliary diversion and ileal by-pass have been successfully used in the management of PFIC1 and PFIC2. [11] These procedures inhibit the toxicity of bile salt by interrupting their enterohepatic circulation. Their effects are marked when performed early in the course of the disease. Liver transplantation is performed for patients with severe disease that has not responded to the above medical and surgical management.

Conclusion

Progressive Familial Intra-hepatic Cholestasis is rarely reported as a cause of jaundice in Sub-Saharan Africa. It is even less likely to be considered as a cause of jaundice outside infancy. PFIC3 should be suspected in an older child presenting with jaundice and severe pruritus. Relevant investigations and treatment with UDCA should be instituted early.

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References

1. Gaur K, Sakhuja P. Progressive familial Intra-hepatic cholestasis: A comprehensive review of a challenging liver disease. *Indian J Pathol Microbiol* 2017; 60(1): 2-7.
2. Gunaydin M, Bozkurter Cil AT. Progressive familial Intra-hepatic cholestasis: diagnosis, management, and treatment. *Hepat Med* 2018; 10: 95-104. Available at <https://doi.org/10.2147/HMER.S137209>. Accessed on 30 July 2018.
3. Amer S, Hajira A. Comprehensive Review of Progressive Familial Intra-hepatic Cholestasis (PFIC): Genetic Disorders of Hepatocanalicular Transporters. *Gastroenterol Res* 2014; 7(2): 39-43. doi: [10.14740/gr609e. Accessed on 04 August 2018.
4. Lucena JF, Herrero JI, Quiroga J, Sangro B, Garcia-Foncillas J, Zabalegui N, Sola J, *et al.* A multidrug resistance 3 gene mutation causing cholelithiasis, cholestasis of pregnancy, and adulthood biliary cirrhosis. *Gastroenterology* 2003; 124(4): 1037-1042. doi: 10.1053/gast.2003.50144 Accessed on 04 August 2018.

5. Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ. Systematic review of progressive familial Intra-hepatic cholestasis. *Clin Res Hepatol Gastroenterol* 2019; 43(1): 20-36.
6. Ramraj R, Finegold MJ, Karpen SJ. Progressive familial Intra-hepatic cholestasis type-3 overlapping presentation with Wilson disease. *Clin Pediatr (Phila)* 2012; 51(7): 689-691.
7. Jacquemin E, De Vree JM, Cresteil D, Sokal EM, Sturm E, Dumont M, *et al.* The wide spectrum of multidrug resistance 3 deficiency: From neonatal cholestasis to cirrhosis of adulthood. *Gastroenterology* 2001; 120: 1448-1458.
8. Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial Intra-hepatic cholestasis. *Orphanet J Rare Dis* 2009; 4: 1. Available at <https://doi.org/10.1186/1750-1172-4-1> Accessed on 10 September 2018.
9. Reshetnyak VI. Concept of the pathogenesis and treatment of cholelithiasis. *World J Hepatol* 2012; 4(2): 18-34.
10. Kurbegov AC, Setchell KD, Haas JE, Mierau GW, Narkewicz M, Bancroft JD, *et al.* Biliary diversion for progressive familial Intra-hepatic cholestasis: Improved liver morphology and bile acid profile. *Gastroenterology* 2003; 125: 1227-1234.



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