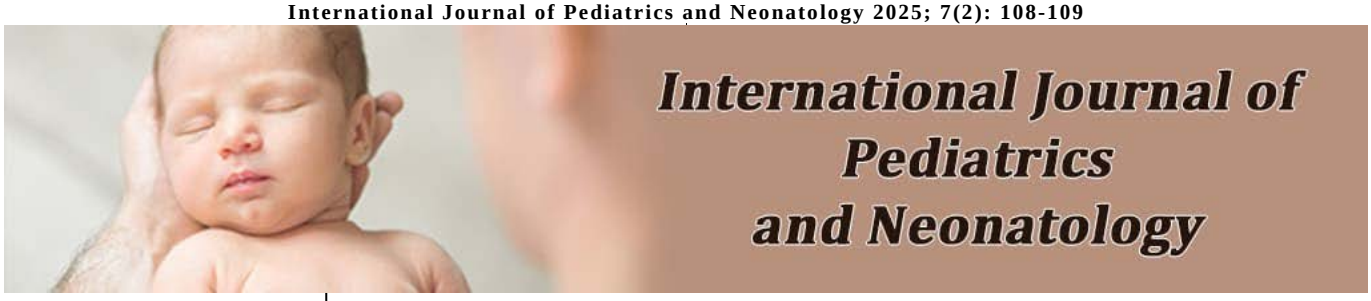

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Type 4 Progressive Familial Intrahepatic Cholestasis - A Rare Cause of Cholestasis in Children

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Abstract
Progressive familial intrahepatic cholestasis (PFIC) represents a heterogenous group of rare autosomal recessive liver disorders characterized by impaired bile secretion, leading to progressive cholestasis and potentially end-stage liver disease. PFIC type 4, caused by mutations in the *TJP2* gene, is a particularly uncommon subtype.

We describe the case of a previously healthy 5.5-month-old female infant who presented with a two-week history of progressive jaundice and poor weight gain. Physical examination revealed diffuse jaundice, hepatomegaly and growth failure. Laboratory findings showed elevated liver transaminases, significant cholestasis with markedly increased bile acids and normal gamma-glutamyl transferase (GGT) levels. Abdominal ultrasound demonstrated hepatosplenomegaly. Extensive investigations excluded infectious, metabolic and other genetic causes of cholestasis. Next-generation sequencing identified a pathogenic homozygous variant in the *TJP2* gene, confirming the diagnosis of PFIC type 4.

The patient was treated with ursodeoxycholic acid and supplementation of fat-soluble vitamins. Due to persistent and severe pruritus, rifampicin and antihistamines were added, with limited symptomatic improvement. After one year of follow-up, liver function has progressively improved, although refractory pruritus persists. The patient is currently awaiting treatment with odevixibat, an ileal bile acid transport inhibitor recently introduced as a targeted therapy for PFIC.

This case illustrates the diagnostic challenges of pediatric cholestasis and highlights the role of next-generation sequence in establishing an early, non-invasive genetic diagnosis, thereby avoiding unnecessary liver biopsy. Recognition of PFIC type 4 is essential, as affected patients remain at risk for progressive liver disease and hepatocellular carcinoma. Novel therapeutic approaches, including bile acid transport inhibitors, offer promising perspectives for symptom control and improved outcomes in these patients.

Keywords: Pediatric cholestasis, progressive familial intrahepatic cholestasis, PFIC type 4, *TJP2* gene

Introduction
Progressive familial intrahepatic cholestasis (PFIC) encompasses a heterogeneous group of disorders characterized by impaired production or secretion of bile acids or other bile components, generally associated with liver failure [1]. It is a rare disease, with an estimated prevalence ranging from 1 in 50 000 to 1 in 100 000 live births [2]. Several types of PFIC have been identified, classified according to the mutations found in genes encoding proteins involved in hepatocellular transport, with types 1, 2, and 3 being the most common [3].

PFIC type 4 is a less frequent type, caused by mutations in the *tight junction protein 2* (TJP2) gene. This leads to reduced integrity of the canalicular membrane, resulting in bile acid reflux into hepatocytes and subsequent hepatocellular injury [4]. Laboratory findings typically include elevated total and direct bilirubin and hepatocellular injury markers, with normal or low gamma-glutamyl transferase (GGT) levels [1, 4]. Diagnosis is currently confirmed through genetic testing, such as next-generation sequencing (NGS) or whole-genome sequencing (WGS) [4]. We report the case of a 5-month-old infant presenting with generalized jaundice, ultimately diagnosed with PFIC type 4.

Case Report
A 5.5-month-old Caucasian female infant, previously healthy, with no significant perinatal history and unremarkable family history, particularly consanguinity, presented to the emergency department with progressive generalized jaundice over the past two weeks and

poor weight gain since 3 months of age (weight tracking below the 3rd percentile). There was no history of fever, dark urine, pale stools, pruritus, vomiting, recent infections or relevant epidemiological exposures.

On physical examination, weight was 5400 g (-2.18 Standard Deviation Score), with evident jaundice of the skin and sclerae. The liver was rigid, palpable approximately 2 cm below the costal margin.

Initial laboratory tests showed mild normocytic normochromic anemia, elevated hepatocellular enzymes (aspartate aminotransferase (AST) 242 U/l, alanine amino transfersase (ALT) 159 U/l) and cholestasis (total bilirubin 9.41 mg/dl, conjugated bilirubin 7.07 mg/dl), with markedly elevated serum bile acids (241 mmol/l), and normal GGT (56 U/l). Coagulation profile was normal. Abdominal ultrasound revealed hepatosplenomegaly without other significant findings.

The patient was admitted to the Pediatrics Department for further evaluation. Infectious causes were ruled out - negative serologies for hepatotropic viruses and toxoplasmosis, negative blood and urine cultures, negative respiratory virus panel, and negative stool enterovirus PCR. Metabolic disorders were excluded (normal metabolic screening, negative urinary reducing sugars chromatography), as were certain genetic conditions (absence of S and Z mutations in the *α1-antitrypsin* gene, and no *CFTR* mutations). An NGS panel for cholestasis was performed and, after six weeks, revealed a pathogenic variant in presumed homozygosity in the *TJP2* gene, consistent with PFIC type 4.

Treatment with ursodeoxycholic acid was initiated upon admission. Due to low serum levels of vitamins A, D, and E and newly developed coagulation abnormalities (INR 1.34), supplementation with fat-soluble vitamins was started. During follow-up, the patient developed severe pruritus, poorly responsive to treatment with rifampin and cetirizine.

At present, after twelve months of follow-up and ongoing treatment with ursodeoxycholic acid (30 mg/kg/day), hydroxyzine, rifampicin and fat-soluble vitamins, liver enzyme levels and bilirubin concentrations - which had remained elevated for several months - have recently begun to decrease. Hepatic function has normalized however, hepatomegaly persists on abdominal palpation and pruritus remains refractory. The patient is currently awaiting authorization to begin treatment with odevixibat for pruritus control.

Discussion

Cholestasis is defined as impaired bile flow, which may result from defects in bile production, transport, or physical obstruction[5]. Given this broad definition, the differential diagnosis of pediatric cholestasis is extensive and can be challenging - especially in the context of potentially treatable causes that may prevent progression to irreversible liver damage. The increasing use of NGS facilitates earlier and less invasive diagnosis, often obviating the need for liver biopsy, which is particularly advantageous in pediatric care. Despite earlier diagnosis, pruritus remains a debilitating and frequently refractory symptom in PFIC, with limited effective treatment options to date. Regarding symptomatic management, agents such as antihistamines, rifampicin and cholestyramine are some available options, yet their effectiveness is also generally modest. Surgical intervention with biliary diversion may be considered as an alternative in patients with persistent pruritus despite pharmacological therapy, however, there is considerable interpatient variability in therapeutic response [6]. The emergence of ileal bile acid transport (IBAT) inhibitor, a non-surgical pharmacological option to interrupt the enterohepatic circulation in patients with PFIC, brings new hope in the treatment of these patients [6, 7].

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