We report this case to highlight a rare manifestation of a common disease. A high index of suspicion may help in timely diagnosis and avoid unnecessary investigations or surgical intervention.

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Benign Recurrent Intrahepatic Cholestasis - Unravelleing the Paradox

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive bile salt transport disorder, characterized by recurrent episodes of pruritus, cholestatic jaundice with normal or low gamma glutamyl transpeptidase (ggt). Bric and progressive familial intrahepatic cholestasis (PFIC) represent two extremes of a continuous spectrum of genetic intrahepatic cholestatic disorders. The exact prevalence of BRIC still remains unknown. BRIC can present at any age but usually before the second decade [1] with disturbing pruritus as the primary symptom. Very few case reports have been published in Indian literature [2,3]. We report the clinico-laboratory profile and follow up of seven patients with BRIC seen over a period 20 years (2000-2020).

Patient 1: A 16 year old adolescent boy, 1st born to 3^0 consanguineous parents, presented with 2 weeks history of severe pruritus associated with mild jaundice. His first cousin died of cholestatic liver disease at the age of 7 years. On examination, he was well nourished with icterus and scratch marks on his skin. There was no hepatosplenomegaly. Complete hemogram and renal profile were normal. His total serum bilirubin was 5.1 (direct:4.1) mg/dL, alamine aminotransferase (ALT) was 133U/L, aspartate aminotransferase (AST) was 143U/L, γ-glutamyl transferase-20 U/L, serum alkaline phosphatase-268 U/L, cholesterol -145 mg/dL and serum bile acids 491 µmol/L (0.5-10). Prothrombin time was normal. USG abdomen showed normal liver echogenecity and intrahepatic radicles were not dilated. Liver biopsy was deferred due to refusal of consent. In view of the strong positive family history of cholestatic liver disease, gene testing was done that showed a single heterozygous missense mutation [c.1244A>G] in exon 13 of *ATP8B1* gene confirming BRIC type 1. He was treated with rifampicin for 3 weeks, and at 5 months follow up, all his laboratory parameters were normal.

Patient 2: A 16-year-old boy presented with intense pruritus and jaundice for 20 days. There was history of two stereotypical episodes of pruritus associated with cholestatic jaundice in the last 1 year. During the icterus free intervals, he was normal. He was second born to second degree consanguineous parents, and his elder sister had been diagnosed as BRIC type 1. On examination, he was well nourished with deep icterus and scratch marks on his skin. There was no hepatosplenomegaly. Investigations revealed normal hemogram and renal profile. Total bilirubin was 31 (direct: 25.3) mg/dL. ALT, AST and total protein were normal. Serum bile acids were 350 µmol/L and GGT was 12 U/L. Magnetic resonance cholangiopancreatography (MRCP) showed mild hepatomegaly without intra or extra hepatic biliary dilatation. Liver biopsy showed marked canalicular cholestasis, mild lobular inflammation, with intact interlobular bile ducts and no fibrosis. He was treated with ursodexycholic acid (UDCA) and rifampicin, and at 4 weeks his jaundice had cleared. Genetic testing showed a homozygous missense mutation [c.922G>A] in exon 10 of *ATP8B1* gene confirming BRIC type 1. He is under follow up for the last three years, and is doing well without any worsening.

In the remaining five patients (3 girls) with BRIC diagnosed histologically, the median age at onset of symptoms was 11 (range: 8-18) years. The cholestatic episodes varied with an average of 1 to 3 per year and the reported asymptomatic periods were lasting for a maximum period of 3 years. There was history of consanguinity in 80%, of which second and third degree consanguinity was seen in 50% each. One child was adopted. Liver histology done in all five patients showed intrahepatic cholestasis with intact interlobular bileducts and no fibrosis. All were treated with UDCA, rifampicin and cholestyramine in varying combinations. Over these 20 years, 2 girls got married and both had pruritus during pregnancy. Another boy diagnosed with BRIC at 8 years was given complementary and alternative medicine for refractory pruritus at 17 years, that worsened his liver function following which, the jaundice deepened, bilirubin rose to 40 mg/dL and his INR reached 4. He underwent 3 cycles of plasmapheresis, but succumbed to the illness prior to liver transplant.

A typical episode of BRIC usually starts with pruritus which increases in intensity and impairs the quality of life followed by jaundice as seen in our series [4]. The symptoms may persist from 2 weeks to 18 months before spontaneous resolution and asymptomatic period may vary from 1 month - 33 years [3]. Low GGT, a hallmark biochemical finding in this metabolic disorder in spite of clinical and biochemical stasis excludes all the intra- and extra- hepatic causes of cholestasis except bile acid synthesis defect (BASD). However, in BASD, itching is not common and low GGT occurs with normal level of bile acids. The characteristic changes seen in liver biopsy in BRIC are the intracanalicular cholestasis with lobular inflammation without fibrosis, which was seen in all the 6 patients, thus satisfying the diagnostic criteria [5]. PFIC1 and BRIC 1 share the same genotype but have different phenotypes, the former being universally progressive. *ATP8B1* gene is a translocator present on canalicular membrane of hepatocytes and mutation leads to membrane instability and decreased function of bile salt export pump thereby resulting in cholestasis. Missense mutations are most common in BRIC type 1 [6] (seen in patient 1 and 2) and can either be homozygous (patient 2) or compound heterozygous mutations (patient 1). However, Lee, et al. [7] have reported a similar phenomenon of heterozygous frame shift mutation only on one allele of *ATP8B1* gene. Cholestyramine, UDCA and rifampicin have been used in various combinations for the treatment of pruritus and in our experience, neither cholestyramine nor UDCA worked well while rifampicin alone gave a sustained relief in one patient. Rifampicin, though considered as hepatotoxic, works well in BRIC by activating transcription of CYP3A4, thereby stimulating hydroxylation of bile salts and excretion at the basolateral membrane, thereby relieving pruritus [8]. Endo-scopic nasobiliary drainage [9], biliary diversion procedures [10], plasmapheresis and liver transplant have been suggested for refractory pruritus.

This case series highlights the paradoxical perceptions in diagnosis and management of BRIC, namely low GGT in spite of cholestasis and use of rifampicin-a hepatotoxic drug, inspite of underlying liver disease.

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Diabetes Mellitus Due to Wolfram Syndrome Type 1 (DIDMOAD)

Wolfram syndrome (WFS) type 1 is a monogenic disorder with autosomal recessive inheritance caused by mutations in *WFS1*, a gene (location 4p16.1) associated with endoplasmic reticulum function in neuronal and endocrine cells [1]. WFS is also known as DIDMOAD syndrome and is characterised by Diabetes insidipus (DI), Diabetes mellitus (DM), Optic atrophy (OA), and Deafness (D). Here, we report 5 unrelated Indian children presenting to us over the last 2 years with a referral diagnosis of type 1 diabetes mellitus (T1DM), subsequently diagnosed to have DIDMOAD syndrome. We also highlight atypical presentations and early pointers to the disease.

A 9-year-old girl was diagnosed to have T1DM 2 years back and was on insulin therapy. She presented with decreased visual acuity and polyuria (urine output 4 L/day) that persisted despite good glycemic control. On evaluation, urine osmolality was 158 mosmol/L and serum osmolality was 302 mosmol /L. Urine osmolality increased to 280 mOsm/L with intravenous vasopressin suggestive of central DI. Magnetic resonance imaging (MRI) brain revealed an absent pituitary bright spot. Detailed evaluation revealed hydroureteronephrosis, neurogenic bladder, bilateral optic atrophy and bilateral moderate sensorineural hearing loss. Direct sequencing of *WFS1* gene by Sanger method, revealed a novel homozygous variant frame shift mutation c.2486_2489dupTGGA (p.Glu830Asp*111) in exon 8. She was managed with oral desmopressin tablets, clean intermittent urinary catherization and continued on insulin therapy.