Can Genetic Testing Guide the Therapy of Cholestatic Pruritus? A Case of Benign Recurrent Intrahepatic Cholestasis Type 2 With Severe Nasobiliary Drainage-Refractory Itch

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Benign recurrent intrahepatic cholestasis (BRIC) is a peculiar familial disease caused by mutations of the genes encoding hepatocanalicular flippase for phosphatidylserine (ATP8B1; BRIC type 1) or the bile salt export pump (ABCB11; BRIC type 2). Here, we report on a patient with nasobiliary drainage-refractory BRIC type 2 who improved under plasma separation and anion absorption therapy. We also suggest that nasobiliary drainage might be an ineffective approach in carriers of severe loss-of-function mutations of the bile salt export pump ABCB11. (*Hepatology Communications* 2018;2:152-154)

Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is a peculiar familial disease caused by mutations of the genes encoding hepatocanalicular flippase for phosphatidylserine (ATP8B1; type 1) or the bile salt export pump (ABCB11; type 2). It is characterized by episodes of jaundice accompanied by severe cholestatic itch but no signs of chronic liver disease in the symptom-free intervals. To date, no evidence-based treatment strategy has been established, but ursodeoxycholic acid and rifampicin might be helpful and nasobiliary drainage (NBD) and extracorporeal blood purification represent rescue therapies for refractory pruritus.[1,2] Here, we report on a patient with NBD-refractory BRIC type 2 who improved under plasma separation and anion absorption therapy. We also introduce the concept that NBD might be an ineffective approach in carriers of severe loss-of-function mutations of the bile salt export pump ABCB11.

Case Presentation

A 23-year-old male Caucasian patient was referred to our department with jaundice and a prolonged episode of refractory pruritus due to BRIC type 2. Genotyping demonstrated that he was a heterozygous carrier of the *ABCB11* mutations c.3491delT and c.3826C>T, corresponding to p.V164GfsX7 and p.R1276H, respectively. It was his fourth BRIC episode; it had lasted 5 weeks at the time of referral and was most likely triggered by a viral infection. During this period, he underwent therapies with ursodeoxycholic acid, rifampicin, and NBD, without itch improvement. At admission, the patient suffered from

Abbreviations: BRIC, benign recurrent intrahepatic cholestasis; NBD, nasobiliary drainage.

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severe pruritus with an intensity of 7/10 on a numeric rating scale. His serum bilirubin concentration was 27.6 mg/dL, alkaline phosphatase activity was 342 U/L (standard value <129 U/L), but gamma-glutamyltransferase was normal, which is typical for BRIC type 2. A liver biopsy showed severe pronounced canalicular cholestasis with partly ballooned but otherwise normal hepatocytes without inflammatory infiltrates.

Given the refractory pruritus, we performed extracorporeal blood purification with plasma separation and anion adsorption (Plasorba BR-350; Diamed, Cologne, Germany). This resulted in rapid improvement of the pruritus. The numeric rating dropped to 4/10 by the evening after the first intervention. In total, we performed nine procedures resulting in almost total relief of pruritus (1/10), and serum bilirubin concentrations decreased to 9.6 mg/dL. In parallel, total serum bile salt concentrations fell from 101 μmol/L to 20 μmol/L, with an initial drop of 15% after the first blood purification (Fig. 1). In particular, cholic acid decreased by 84% and chenodeoxycholic acid by 68%. In addition, we measured serum levels of lysophospholipase D, also known as autotaxin, which is regarded to be a key regulator of cholestatic pruritus.[3] Here, we observed a reduction of autotaxin from 1,606 ng/mL at baseline to 998 ng/mL at the end of treatment (Fig. 1). Overall, during the 4-month course of extracorporeal therapy, pruritus almost vanished and bilirubin concentrations dropped below 2.0 mg/dL. Currently, the patient remains symptom free, and blood tests do not indicate any signs of cholestasis.

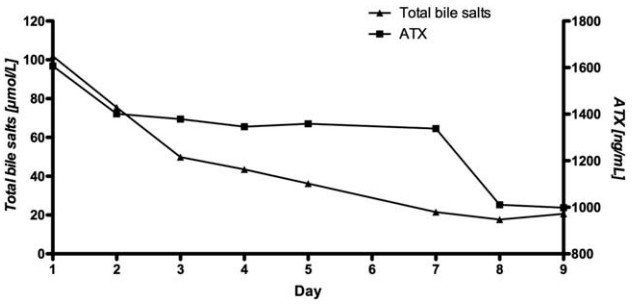

FIG. 1. Time course of TBS and ATX concentrations during blood purification. During 9 days of therapy (plasma separation and anion adsorption), TBS decreased by 80.2% and ATX by 37.9% of baseline. In parallel, itch intensity was strongly improved from 7/10 to 1/10 on the numeric rating scale. Blood samples were drawn after blood purification. ATX concentrations were measured as described by Kremer et al.,[3] and serum TBS were determined by isotope dilution (gas chromatography–mass selective detection). Abbreviations: ATX, autotaxin; TBS, total serum bile salts.

Discussion

Therapy of cholestatic pruritus is troublesome; hence, invasive techniques have been applied to relieve pruritus in cases of severe cholestatic itch. Bile flow is mainly driven by bile salt secretion; however, the dysfunction of the hepatocanalicular bile salt export pump in the setting of BRIC type 2 may lead to a complete cessation of bile salt-dependent bile flow. This might also explain why NBD did not lower or improve pruritus in our patient. Thus, in contrast to other cholestatic conditions for which NBD was shown to be successful in attenuating refractory cholestatic itch,[2] this approach might fail in particular in the subgroup of BRIC patients with severe dysfunction of ABCB11.[4,5] Consistent with our data, a case series demonstrated that pruritus in patients with *ABCB11* mutations is less likely to respond completely to partial external biliary diversion compared to carriers of *ATP8B1* variants.[6] Hence, for patients with BRIC type 2, we recommend extracorporeal blood

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purification but not NBD as treatment of choice for refractory itch. Analyses of additional patients with the rare BRIC type 2 are, however, needed to validate this hypothesis.

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