Progressive intrahepatic cholestasis type 2 and citrin deficiency with a novel mutation: a case report

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BACKGROUND

Citrin deficicency is a rare metabolic disorder which can lead to three clinical phenotypes. It can present as neonatal intrahepatic cholestasis which often resolves within the first year of infancy, it can also manifest as failure to thrive and dyslipidemia in older children and in adults as recurrent hyperammoniemia and neuropsychiatric symptoms in citrullinemia type 2 [1]. More than 60 mutations were described in the literature.
Herein, the authors describe a rare case of association between intrahepatic progressive familial cholestasis type 2 (PFIC2) and citrin deficiency with a novel mutation.

CASE PRESENTATION

A one-month-old male infant was referred to our department to explore a prolonged jaundice. He was born at term, with a body weight of 4200 g and body length of 52 cm. He was the seven child of healthy consanguineous parents. He had a history of two cousins who were died respectively at the age of seven months and two year secondary to unexplored liver dysfunction.
Since the age of three days, the parents had noticed jaundice and intermittent discoloration of his stool, which were initially neglected. At admission, his weight was 5400 g, his length was 54 cm. He had a generalized jaundice, he hadn't dysmorphic features or abnormal cardiac sound. In addition, no abdominal distention was observed, and no liver or spleen was palpable under the bilateral subcostal margin. He had light yellow-coloured stools. Liver function revealed alkaline phosphatase (ALP) 433U/L (reference range: 20- 250 U/L), alanine aminotransferase (ALT) 322U/L (reference range: 10 – 45 U/L), aspartate aminotransferase (AST) 176 U/L (reference range: 10 – 40 U/L), serum bilirubin 179,5 mmol/l (1,6- 15 mmol/l), conjugated bilirubin 102,6 mmol/l (0,2- 5,3mmol/l). He had normal level of gamma-glutamyltransferase (GGT): 23 U/l (10- 55U/l). Prothrombin time was 100%. Serum primary bile acid concentration was high (125, 8 µmol/l) suggesting the diagnosis of progressive familial intrahepatic cholestasis (PFIC) type 1 or 2. Alpha foeto-protein was normal (5,34 UI/l). Ammoniemia was 158µmol/l (16-60 µmol/l). Abdominal ultrasound was normal. Molecular studies (next-generation DNA sequencing NGS) revealed a mutation of BSEP gene (ABCB11) leading to premature stop codon (p.Tyr354). It showed also a pathogenic homozygous mutation in SLC25A13 gene encoding citrin. This identified mutation (NM 001160210:c.2011 del (p.Ala671LeufsTer 30) hasn't been described yet in the literature. The infant began to receive medical treatment (ursodeoxycholic acid), ADEK vitamins, medium chain triglycerides enriched formula and then he was discharged . The follow up was one year. No neurological impairments were observed and his growth is normal.

DISCUSSION

1- Here, we report a rare association between PFIC type 2 and citrin deficiency which were genetically identified. PFIC type 2 is an autosomal inherited disorder which is due to a bile salt export pump deficiency or BSEP which is encoded by ABCB11 [2].

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PFIC, generally present in the first few months of life, and manifest jaundice, high serum bile acids and transaminases, normal serum gGT levels, fat-soluble vitamin deficiency, and, in due course, pruritus [3]
BSEP deficiency typically progresses to end-stage liver disease within a few years. Many patients have actually been transplanted due to severe pruritus before they reach end-stage disease. Patients with PFIC2 were more likely than patients with PFIC1 or PFIC3 to experience progression to severe liver disease or hepatocarcinoma and to require liver transplantation. Progression to hepatocarcinoma appeared to be a common and early outcome in patients with PFIC2 [4].

2- Citrin deficiency is an autosomal recessive metabolic disease caused by mutations in the SLC25A13. Three main phenotypes are recognized, including neonatal intrahepatic cholestasis during infancy caused by citrin deficiency, which is generally not severe and symptoms often resolve by the age of one year, although liver transplantation has been required in rare instances, failure to thrive and dyslipidemia in older children, and recurrent hyperammoniemia with neuropsychiatric symptoms in adults [1].
In our case, cholestasis was secondary to BSEP deficiency; however, our patient must be followed periodically to detect neuropsychiatric abnormalities and needs a monitoring of ammoniemia. A liver transplantation was programed.
The protein encoded by SLC25A13, named citrin, contains four EF-hand Ca(2+) binding motifs in the N-terminal domain. This catalyzes the calcium-dependent exchange of cytoplasmic glutamate with mitochondrial aspartate across the inner membrane of mitochondria. Over 60 different mutations in the human SLC25A13 gene have been functionally characterized [5]
In our knowledge, the mutation identified in our case is a novel mutation, that hasn't been reported in the literature; in fact, it wasn't included in the list of mutations in a recent review of the literature, in which, authors retrieved 24 studies comprising 79 cases of citrin deficiency [6].

CONCLUSION

This paper report the first case of association between PFIC type 2 and citrin deficiency, the diagnosis was made thanks to genetics. Moreover, it reports a novel mutation in SCC25A13 gene which hasn't been reported yet in the literature.

Abreviations

No conflict of interest

An informed consent for biochemical, metabolic and genetic evaluation of the proband was obtained from the parents

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