Short Report

Elevation of gamma-glutamyl transferase in adult: Should we think about progressive familial intrahepatic cholestasis?

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ABSTRACT

Background: There are three types of progressive familial intrahepatic cholestasis (PFIC). Type 3 is characterized by elevated gamma-glutamyl transferase (γ -GT) and it can be diagnosed in adolescence/adulthood. The genetic defect of PFIC 3 appears to explain the pathogenesis of intrahepatic cholestasis of pregnancy (ICP).

Aims: Draw attention to this rare disease, especially in adulthood, and clarify the association between ICP and PFIC 3.

Results: We describe a series of cases from a Portuguese northern family with two brothers presenting chronic cholestasis since adolescence. Brother 1: since 15-years-old with pruritus and elevated γ -GT $\sim 6\times$. Brother 2: pre-term, due to severe maternal pruritus and jaundice, since 13-years-old with pruritus, jaundice and $\sim 8\times$ γ -GT elevation. Common causes of cholestasis were excluded and liver histologies were nonspecific. Research for mutation on ABCB4 gene showed mutations in both alleles.

Conclusion: Disease and mechanisms that determine cholestasis are complex and their understanding may provide new therapeutics.

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1. Introduction

Liver has a central role in metabolism and the accumulation of endogenous or exogenous compounds in liver has a toxic effect. Whereby bile formation is essential for the elimination of these compounds [1]. Cholestasis can result from a defect in bile formation at the bile ducts or from impairment on its secretion [2].

Progressive familial intrahepatic cholestasis (PFIC) refers to heterogeneous group of autosomal recessive liver disorders, with childhood predominance, which causes cholestasis of hepatocellular origin [3]. Throughout the years, genetic and molecular studies allowed the identification of three types of PFIC and their associated genes, related to hepatocellular transport-system involved in bile formation. The exact incidence of PFIC is unknown, but it is

estimated to be around 1/50,000 to 1/100,000 births [3]. Type 1 and type 2 represent two thirds of cases of PFIC and PFIC 3 the remaining third [3]. In expert paediatric hepatology units, PFIC is responsible for 10–15% of cholestasis and 10–15% of liver transplantation indication in this group [4].

Despite cholestasis is a clinical sign common to all forms of PFIC, there are phenotypical differences between them. PFIC 1 and 2 seem to be more comparable, with recurrent or permanent jaundice, respectively, usually in the first months of life and normal values of serum gamma-glutamyl transferase (γ -GT) [5]. PFIC 3 usually manifests in the first year of life, but can also develop later such as adolescence or adulthood [6]. Generally PFIC 3 patients complain of recurrent pruritus and/or jaundice with chronic high levels of serum γ -GT, typically 10 times the upper limit [6]. Authors suggest that in PFIC 3 patients the family history may reveal intrahepatic cholestasis of pregnancy (ICP) in their mothers [7]. Liver histology in an initial stage shows portal fibrosis and ductular proliferation with mixed inflammatory infiltrate, progressing to an extensive portal fibrosis and biliary cirrhosis [6].

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Fig. 1. Family genogram.

Graphic 1. Evolution of serum gamma-glutamyltransferase.

Graphic 2. Evolution of serum total bilirubin.

The genetic defect of ABCB4 gene, located in the short arm of chromosome 7, is responsible for PFIC 3 [8]. This gene encodes the class III multidrug resistance protein (MDR3), a phospholipid translocator expressed in the canalicular membrane of hepatocytes, responsible for the excretion of biliary phospholipids. In the absence of biliary phospholipids, bile salts are not inactivated, leading to biliary epithelium injury [6]. The latest reviews point to more than 45 mutations, 1/3 being caused by STOP codons leading to an unstable transporter. The remaining 2/3 results from a *missense* mutation thereby the transporter can preserve some of its function [6].

2. Clinical cases

We describe the cases of two brothers from non-consanguineous parents, admitted at our outpatient clinic with complaints of cholestasis since adolescence.

2.1. Brother 1

The oldest, term birth, with maternal history of jaundice and pruritus in the last month of pregnancy. Since 15 years old with complaints of fluctuating episodes of pruritus, jaundice and chronic

elevation of γ -GT (up to 6 times the normal). On admission at our clinic, there were no clinical signs of chronic hepatic disease and the blood tests revealed: total bilirubin 0.4 mg/dL, AST 45 UI/L, ALT 78 UI/L, γ -GT 630 UI/L and alkaline phosphatase (AP) 130 UI/L.

2.2. Brother 2

The youngest, preterm birth at 28 weeks due to severe maternal pruritus and jaundice. Since 13 years old with complains of fluctuating episodes of pruritus, jaundice and chronic elevation of γ -GT (up to 8 times the normal). On admission there were no clinical signs of chronic hepatic disease and the blood test revealed: total bilirubin 1.6 mg/dL, AST 51 UI/L, ALT 155 UI/L, γ -GT 840 UI/L and AP 205 UI/L.

Revising their family history, up to 2 previous generations (Fig. 1), besides their mother there is no evidence of liver disease or cholestasis. Moreover, the region from which they originate is not known to have a higher incidence of liver disease. Both brothers' liver ultrasonography showed a normal size and shape liver, with no bile duct dilatations or gallstones. Drugs, viral hepatitis, Wilson disease, haemochromatosis, alpha-1-antitrypsin deficiency, autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis were excluded. Brother 1 liver biopsy revealed ductular proliferation and portal fibrosis, without porta-portal bridges. Brother 2 liver biopsy showed portal polymorphic inflammatory infiltrate, portal fibrosis with septum and rare porta-portal bridges. Therapy with ursodeoxycholic acid (UDCA) was initiated, two years after first observation, with improving of the complaints and a slightly decrease of the values of γ -GT and bilirubin in both cases (Graphics 1 and 2). Occasionally, there was exacerbation of cholestasis in the context of infectious disorders and there was also an erratic compliance of UDCA by brother 2. In both brothers there was evolution to liver cirrhosis. Brother 2 progressed to decompensated liver cirrhosis.

We decided to search for mutation in ABCB4 gene. In both brothers and in their parents a complete sequencing of ABCB4 gene was performed using the sequence NM.000443.3. Polymorphisms were not reported, both brothers had two mutated alleles in heterozygosity: c.959C>T and c.2682+1G>A, allowing the diagnosis of PFIC 3 in both brothers. The genetic study of their parents showed the presence of a heterozygous mutation in ABCB4 gene: c.2682+1G>A in their mother and c.959C>T in their father (*trans* mutation).

3. Discussion

Over the past years, there has been an increasing knowledge about the different forms of PFIC [4], theretofore poorly characterized. This alerted the medical community to this group of diseases, that should be suspected in all patients with cholestasis of unknown origin after exclusion of common causes, such as biliary atresia, Alagille syndrome, alpha-1-antitrypsin deficiency and sclerosing cholangitis [3]. Descriptions of PFIC 3 cases even in young adulthood [6] led the authors, after excluding the most frequent causes of cholestasis, to proceed to genetic study of PFIC 3 in these patients.

Studies show that chronic administration of UDCA can improve liver enzymes levels in nearly half of the patients [7]. Thereby, therapy with UDCA should be considered an initial approach to all types of PFIC, especially those with PFIC3 with *missense* mutations, who have less severe disease [6]. Despite equal mutations, the phenotype and disease progression on both brothers were distinct. Apart from a precarious compliance of UDCA in brother 2 we lack other reasons why there is this discrepant evolution. Such fact can strengthen previous studies showing that chronic administration of UDCA can improve liver function on those patients [7]. In case of disease progression, liver transplantation is the only alternative, leading to disease cure [7]. Based on that, brother 2 is currently waiting for a liver transplantation.

ICP is a transient form of cholestasis, characterized by pruritus and jaundice that usually appears in the 3rd trimester of pregnancy [9]. Although its complex aetiology, possibly involving genetic, endocrine and environmental factors, studies point to a relation between genetic defects in MDR3 and ICP [7–9]. It is our belief that the complaints developed by the mother during pregnancy are compatible with ICP and her genetic study revealed her heterozygous carrier state of ABCB4 gene mutation, corroborating previously published studies that advocate the association between MDR3 defects and ICP [9].

The mechanisms leading to cholestasis are complex. Understanding the mechanisms of bile regulation and transport represents a powerful tool for the development of novel therapeutic approaches to cholestatic liver diseases. MDR3 deficiency should be looked for in young adults with unexplained biliary cirrhosis. Identification of MDR3 mutations in affected patients and within families is essential for prenatal diagnosis. The description of these two cases aims to alert for this rare pathology in adulthood and to the association between PFIC 3 and ICP.

Conflict of interest

None declared.

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