

Benign recurrent intrahepatic cholestasis: report of two local cases

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Abstract

Benign Recurrent Intrahepatic Cholestasis (BRIC) is a rare disorder characterized by recurrent episodes of cholestasis without permanent liver damage. Familial and sporadic cases have been reported and both autosomal recessive and autosomal dominant inheritance described. We report two children with BRIC without any previous family history.

Introduction

Cholestatic syndromes are inborn or acquired disorders of bile formation and transport.¹ Benign intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC) are two inherited cholestatic syndromes characterized at molecular level in recent years. Clinical differentiation of the two syndromes may be difficult but is essential as patients with PFIC will progress to liver cirrhosis and require liver transplantation later on in life while the natural history of patients with BRIC is benign. Only recently was it recognized that BRIC, which was previously believed to be a milder form of PFIC¹, might be caused by more than one gene mutation. Both syndromes are rare and characterized by recurrent episodes of intense pruritus, hyperbilirubinaemia and steatorrhoea. Attacks last from several weeks to months and resolve spontaneously. Between attacks patients remain well for months to years.² Biochemical analysis

reveals elevation of alkaline phosphatase levels and markedly raised serum bilirubin. Gamma glutamyl transferase (GGT) concentrations are normal or slightly elevated with levels returning to normal after the attack subsides.

Treatment is usually symptomatic and limited to relief of pruritus. The use of specific drugs such as ursodeoxycholic acid and cholestyramine is questionable. The long-term prognosis for BRIC patients is good and both our patients are thriving and otherwise well.

Case 1

VA is the first child of healthy unrelated parents. She presented at the age of one year two months with increasing jaundice, dark urine and pruritus. She continued to have recurrent episodes of jaundice and pruritus with variable intervals between episodes, approximately every year and lasting about three weeks. Between episodes the child was completely asymptomatic. In total she had around seven episodes of jaundice and was hospitalised only once at presentation. There is no history of liver disease in the family.

On examination during episodes the child was icteric without pallor. She had obvious scratch marks and mild hepatomegaly. Otherwise the examination was completely normal. Liver function tests carried out during these episodes showed conjugated hyperbilirubinaemia with bilirubin level ranging from 185-358 $\mu\text{mol/l}$ (direct bilirubin fraction in the range of 130-181 $\mu\text{mol/l}$) with a high alkaline phosphatase level (range 466-768 IU/l). Other liver enzymes including alanine transaminase, aspartate transaminase and gamma glutamyl transferases were within normal limits. Serum protein, albumin and prothrombin time were always normal and serum caeruloplasmin was also within normal limits. Treatment has always been limited to symptomatic relief of pruritus only, and spontaneous improvement has usually occurred within 3 weeks, with complete normalisation of serum bilirubin and alkaline phosphatase concentrations. The child is thriving well and being followed up at our outpatient's clinic. DNA analysis has been requested to identify further and results are pending.

Case 2

MB was born at term following a normal pregnancy and delivery. He had no history of any significant childhood illnesses. He is the only child of healthy unrelated parents with no family history of liver disease.

Key words

Benign recurrent intrahepatic cholestasis

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He first presented at the age of 10 months with mild jaundice and pruritus. His second episode of jaundice was at 18 months of age with severe pruritus, pale stools and dark urine. These exacerbations of jaundice recurred approximately every year since then, lasting about one to one and a half months.

During episodes the child appeared jaundiced and had multiple scratch marks but was otherwise normal. Blood investigations performed at that time showed a conjugated hyperbilirubinaemia with a bilirubin level of 138 μ mol/l (direct fraction of 76 μ mol/l) and an alkaline phosphatase level of 1387IU/l. These investigations normalized when the symptoms resolved. Alpha-1-antitrypsin, serum haptoglobin level, caeruloplasmin level and other liver function tests were all normal. An ultrasound of the liver was also normal.

A liver biopsy was performed at 18 months of age and showed mild portal changes and almost no inflammation. Pure cholestasis was seen with distinct bile lakes and these features together with the clinical picture were consistent with BRIC.

To date MB remains well and has exacerbations of jaundice, steatorrhoea and pruritus almost yearly.

Discussion

Summerskill and Walshe first described benign recurrent intrahepatic cholestasis in 1959^{3,4} as recurrent episodes of jaundice and pruritus. It is now recognized as BRIC, is a syndrome due to a mutation in ATP8B1, an aminophospholipid transporter, while BRIC2 is caused by a mutation in ABCB11. There are at least three forms of BRIC all with a similar phenotype. BRIC types 1 and 2 are inherited as autosomal recessive and are related to mutations on chromosomes 18 and 2 respectively. BRIC type 3 is transmitted as an autosomal dominant disease and is not linked to mutations on chromosomes 18 or 2.⁵ The hallmark of the disease is cholestasis. Patients present with recurrent bouts of jaundice and cholestasis lasting from two to twenty four weeks. Typically the disease manifests early in life but later presentations have been reported.⁶ Pruritus is a prominent symptom in BRIC patients and usually occurs early on during exacerbations sometimes before the appearance of jaundice.

Biochemical findings consist of elevated total and direct bilirubin, raised alkaline phosphatase levels and elevated bile salts but normal gamma glutamyl transferase levels.

Elevation of alanine aminotransferase (AST) and aspartate aminotransferase levels (ALT) levels may occur but this is usually mild to moderate and levels return to normal following resolution of the exacerbation.⁶ Ultrasonographic examination of the liver, gallbladder and bile ducts is normal and cholangiography does not reveal any abnormalities. Histological findings on liver biopsy reveal accumulation of bile plugs in the bile canaliculi.⁷ Often the diagnosis in BRIC patients is made very late and patients are subjected to invasive investigations. Elevation in gamma glutamyl transferase levels or rising levels of ALT and AST should suggest an alternative diagnosis of progressive familial intrahepatic cholestasis (PFIC).

Treatment of the condition is purely symptomatic and aimed mainly at the relief of pruritus. Reports of the benefits of cholestyramime and ursodeoxycholic acid are conflicting⁶ and the use of rifampicin has been recently shown to shorten the duration of cholestasis.⁸ Both our patients were prescribed ursodeoxycholic acid for the latest exacerbation and both reported an improvement in pruritus and duration of exacerbation.

They have been followed up for three and eight years respectively and continue to have intermittent attacks of cholestasis.

References

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