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A 6-year-old boy with hyperammonaemia: partial N-acetylglutamate synthase deficiency or portosystemic encephalopathy?

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Abstract We describe a 6-year-old boy admitted with lethargy and somnolence. Laboratory tests showed hyperammonaemia (arterial level 186 μmol/l) and slightly elevated prothrombin time. The patient was treated with sodium benzoate, lactulose and a protein-restricted diet. This resulted in an insufficient decrease in blood ammonia levels. Metabolic investigations were unrevealing apart from a slightly elevated urinary glutamine concentration. Liver tissue showed steatosis and mildly decreased activity of N-acetylglutamate synthase suggesting partial deficiency. Treatment with N-carbamyl glutamate did not affect serum ammonia levels. Colour Doppler sonography and MR angiography demonstrated a patent ductus venosus. After surgical ligation of the ductus venosus, serum ammonia levels returned to normal and mental and motor performance improved markedly.

Conclusion In late onset hyperammonaemia, partial N-acetylglutamate synthase deficiency and portocaval shunt should be ruled out.

Key words Atretic encephalocele · Hyperammonaemia · Partial N-acetylglutamate synthase deficiency · Patent ductus venosus (Arantii) · Portosystemic encephalopathy

Abbreviations *CPS* carbamoyl phosphate synthase · *MRA* magnetic resonance angiography · *NAGS* N-acetylglutamate synthase · *PDV* patent ductus venosus · *PSE* portosystemic encephalopathy · *PSVS* portosystemic venous shunt

Introduction

Hyperammonaemia related to inborn errors of metabolism should be distinguished from that related to liver diseases and other causes. Hyperammonaemia has been associated with disorders of organic acid metabolism, urea metabolism, carbohydrate metabolism, mitochondrial fatty acid oxidation and familial lysinuric

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protein intolerance [11, 20]. In addition, hyperammonaemia can be caused by hepatocellular insufficiency or abnormal shunting of portal blood from the intestine directly into the systemic circulation. The first description of a patient with portal-systemic fistula and encephalopathy (PSE) was published by Raskin et al. in 1964 [18]. Congenital intrahepatic portosystemic venous shunts (PSVS) are rare and may remain asymptomatic until a later age [9, 13–16, 21, 22]. We present a 6-year-old patient with symptomatic hyperammonaemia in whom the differentiation between an inborn error of metabolism and the underlying cause was difficult.

Case report

A 6-year-old boy was admitted because of increasing irritability and lethargy. A distinct change in mental status and impairment in word finding were noted. The medical history included an operation for a mid-parietal atretic encephalocele. Psychomotor development was mildly delayed. Neurological examination on admission showed somnolence, roving eye movements, sluggish pupillary reflexes and bilateral pyramidal tract signs with ankle clonus. Laboratory investigations revealed hyperammonaemia (arterial ammonia 186 μmol/l, normal < 50 μmol/l), and normal urea, lactate, bile acids and albumin levels. The liver enzymes and specified liver functions were normal except for a slightly elevated prothrombin time of 1.40 INR (normal < 1.20 INR). Analysis of plasma amino acids showed no abnormalities; citrulline and glutamine concentrations were normal. The urinary amino acid concentrations were normal; only glutamine was slightly elevated (190 mmol/mol creatinine, reference range 23–134 mmol/mol creatinine). There were no abnormalities in the urinary organic acid profile. The orotic acid concentration was normal. MRI of the brain (Fig. 1A) showed symmetrical high signal intensity in the globus pallidus and putamen on T1-weighted images, consistent with hyperammonaemia [23] but otherwise no abnormalities.

Plasma ammonia levels improved insufficiently after institution of a protein-free diet with high caloric intake, i.v. sodium benzoate and oral lactulose. A liver biopsy showed moderate to severe fatty degeneration without signs of fibrosis or inflammation. Enzyme assay in liver tissue revealed mildly decreased N-acetyl glutamate synthase (NAGS) activity (68 pmol/min per mg protein, normal > 144 pmol/min per mg protein) and normal carbamoyl phosphate synthase (CPS) activity. N-carbamylglutamate (100 mg/kg per day) had no effect on plasma ammonia levels. Further investigations were focused on the vascular anatomy of the liver. Colour Doppler sonography and magnetic resonance angiography (MRA) (Fig. 1B) demonstrated a portosystemic shunt due to patent ductus venosus (PDV). The intrahepatic branches of the portal vein were normally developed.

Surgical treatment was performed via a right subcostal laparotomy and the PDV was transected. Ammonia levels decreased directly after surgery and remained normal during follow-up despite discontinuation of sodium benzoate, lactulose and re-introduction of a normal diet. The psychomotor performance improved markedly.

Discussion

Elevated plasma ammonia levels in association with only mild or no other evidence of liver dysfunction is primarily suggestive of an inherited metabolic disorder. Hyperammonaemia is the leading sign in inborn errors of the urea cycle. A partial defect in the urea cycle can explain a delayed onset of neurological signs. Precipitating events such as infection, accidental injury, ingestion of large amounts of protein and other forms of stress can usually be found in "late-onset" cases [11].

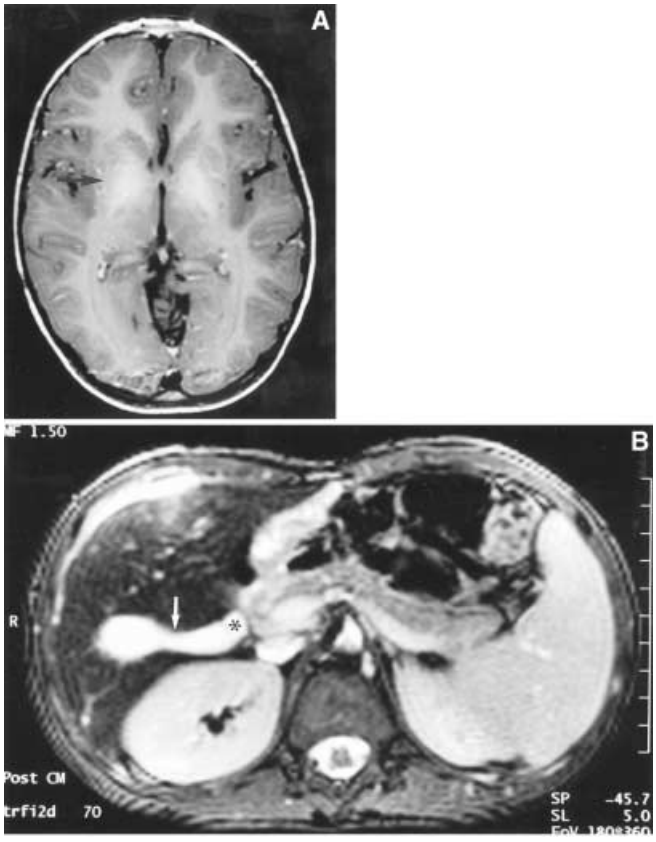

Fig. 1 **A** MRI of the brain. The T1-weighted image shows symmetrical high signal intensity in the globus pallidus and putamen (*arrow*). **B** MRA of the liver. Axial GRE pulse sequence TR (4.8 ms)-TE (2.3 ms)-FA, shows the inferior vena cava (*asterisk*) and the patent ductus venosus (*arrow*)

The initial metabolic work-up of hyperammonaemia includes plasma and urinary amino acid analysis, urinary organic acid profile and assessment of urinary orotic acid concentration [20]. Partial NAGS or CPS deficiency requires a liver biopsy to establish the diagnosis. Patients with partial NAGS deficiency may present with their first symptoms at a later age [3, 17]. A negative response of plasma ammonia levels to carbamylglutamate (100 mg/kg per day) makes a partial NAGS deficiency unlikely [6]. The decreased NAGS activity in our patient was possibly caused by structural or functional changes of the enzyme related to the hepatic steatosis.

The exclusion of an inborn error of the urea cycle prompted further investigations leading to the discovery of the portosystemic shunt. Several congenital anomalies of the portal venous system have been described, among which a PDV in paediatric patients is very unusual [1, 4, 7–9, 13–15, 21–23]. The ductus venosus is an embryonic vascular structure between the umbilical vein and the inferior vena cava, bypassing the liver. Complete closure occurs in almost all neonates during the first weeks of

life leaving the ligamentum venosum behind [1–3, 10]. If the ductus does not close, substances that are normally metabolised in the liver are shunted directly into the systemic circulation, mainly resulting in hyperammonaemia.

Neurological symptoms in PSE usually have their onset in adulthood and may consist of recurrent bouts of encephalopathy or asterixis [19]. The reason for the usually late onset of neurological symptoms remains unclear. One of the explanations is that the brain becomes more sensitive to toxic materials with increasing age. It has been demonstrated that the shunt ratio ($>60\%$) is another important factor in determining the age of onset of encephalopathy [21, 22].

In patients with hyperammonaemia, colour Doppler sonography and MRA are suitable noninvasive methods for studying PSVS in the hepatic region [4, 5, 7, 8, 10, 16]. The managment of patients with PSE with PDV is generally dietary and supportive. There are few case reports of transvenous coil embolisation in children with PDV [7]. When conservative measures are unsuccessful, surgical closure of the ductus venosus can attempted once the integrity of the intrahepatic vascular system has been established [16]. The aetiology of PDV is unknown. The contribution of a genetic factor was proposed by Uchino et al. [8, 22]. They described three brothers with the same type of PDV and clinical presentation. Most paediatric patients with PDV had congenital heart defects, abnormalities of the hepatobiliairy system, or other congenital disorders [5, 18]. The coincidence of atretic encephalocele and PDV in our patient is another example of two rare congenital disorders [12].

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