Inborn Errors of Bile Acid Metabolism

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Summary: Cholesterol is converted to cholic acid and chenodeoxycholic acid by a series of reactions involving modifications to the steroid nucleus and oxidation of the side chain. These reactions can be affected by a number of inborn errors of metabolism. When this happens unusual bile acids or bile alcohols are synthesized; these can be identified using gas chromatography–mass spectrometry and fast atom bombardment mass spectrometry techniques. Two defects affecting the modifications to the steroid nucleus have been described; both present with cholestatic liver disease of neonatal onset. The better characterized of the two – 3β-hydroxy-A5-C27-steroid dehydrogenase deficiency – leads to excretion of 3β-7α-dihydroxy-5-cholenoic acid and 3β,7α,12α-trihydroxy-5-cholenoic acid in the urine. The liver disease improves dramatically on treatment with chenodeoxycholic acid. Deficient activity of 3-oxo-A4-steroid 5α-reductase is thought to be the cause of familial liver disease in some infants who excrete 7α-hydroxy-3-oxo-4-cholenoic acid and 7α,12α-dihydroxy-3-oxo-4-cholenoic acid in the urine. However, diagnosis of this disorder is problematical; a similar pattern of metabolite excretion can occur as a result of liver damage caused by viruses or inborn errors of pathways unrelated to bile acid synthesis. Defective side chain oxidation in patients with cerebrotendinous xanthomatosis (CTX) leads to synthesis of bile alcohols such as 5β-cholestane-3α,7α,12α,25-tetrol and 5β-cholestane-3α,7α,12α,23,25-pentol. Patients with CTX do not have cholestatic liver disease. Their major problems (neurological disease, atherosclerosis and xanthomata) are caused by accumulation of cholestanol and cholesterol in the tissues. Bile acid precursors are probably diverted into synthesis of cholestanol. Chenodeoxycholic acid suppresses the production of abnormal metabolites from cholesterol (by inhibition of cholesterol 7α-hydroxylase) and leads to improvement in the neurological disease. Defective side chain oxidation also occurs in peroxisomal disorders but this time it leads to accumulation of C27 bile acids such as 3α,7α,12α-trihydroxy-5β-cholestanolic acid (trihydroxycoprostanic acid, THCA). This compound is readily detected in the bile and plasma of patients with defects of peroxisome biogenesis. In patients with defects of a single peroxisomal β-oxidation enzyme (the 3-hydroxyacyl-CoA component of the bifunctional protein or the thiolase), the major C27 bile acid in bile may be 3α,7α,12α,24-tetrahydroxy-5β-cholestanolic acid (varanic acid). In addition to the above inborn errors, others which are less well characterized undoubtedly exist, as do defects of bile acid transport across membranes.
The primary bile acids (the taurine and glycine conjugates of chenodeoxycholic acid and cholic acid) are synthesized from cholesterol in the liver. The synthetic pathway is regulated by feedback inhibition; bile acids passing through the liver in the enterohepatic circulation inhibit the first step in the synthetic pathway, cholesterol 7α-hydroxylase. An inborn error affecting bile acid synthesis may have effects attributable to bile acid deficiency or to accumulation of intermediates and the metabolites of these intermediates.

Two of the effects of bile acid deficiency are readily predictable. The major component of bile secretion is bile-acid dependent – it is driven by the active transport of bile acids from the hepatocytes into the canaliculi. Thus inborn errors affecting the synthesis of bile acids may produce cholestasis, reduced bile flow. The role of bile acids in the intestinal lumen is to facilitate the digestion and absorption of fats and fat-soluble vitamins. Thus reduced luminal bile acid concentrations are associated with steatorrhoea and symptoms of fat-soluble vitamin malabsorption. Where cholestasis and malabsorption are due to bile acid deficiency these problems should be correctable by therapeutic administration of cholic and/or chenodeoxycholic acid.

The fact that intermediates in bile acid synthesis accumulate is also not surprising – not only is their usual route of metabolism blocked but their production is accelerated by loss of the bile acid feedback on cholesterol 7α-hydroxylase. In cerebrotendinous xanthomatosis the metabolites which accumulate can be converted to cholestanol, and cholestanol accumulation plays an important role in the pathogenesis of neurological damage and xanthomata (Björkhem, 1985). Treatment is directed at suppressing the activity of cholesterol 7α-hydroxylase, using a bile acid known to inhibit the enzyme, chenodeoxycholic acid.

Some of the disorders which affect bile acid synthesis also affect other pathways (e.g. disorders of peroxisome biogenesis where many peroxisomal pathways are interrupted). In such cases the neurological and hepatic disease may be attributable to something other than interruption of the bile acid synthesis pathway. None the less, bile acid analyses can be a useful means of diagnosis.

**DIAGNOSIS OF INBORN ERRORS OF BILE ACID METABOLISM**

There are three groups of patients in whom we have diagnosed inborn errors affecting bile acid synthesis:

(i) infants and children with unexplained cholestatic liver disease (especially if familial, present from the neonatal period and associated with steatorrhoea and fat-soluble vitamin malabsorption);

(ii) infants and children with (predominantly) neurological problems suggestive of a peroxisomal disorder – motor delay and hypotonia, ocular abnormalities (particularly a reduced electroretinogram and pigmentary retinopathy), seizures, dysmorphic features, failure to thrive, sensorineural deafness, hepatomegaly;

(iii) patients suspected of having cerebrotendinous xanthomatosis. In adults the combination of tendon xanthomata, low intelligence, progressive spasticity and ataxia