3β-Hydroxy-Δ⁵-C₂₇-steroid Dehydrogenase Deficiency; Effect of Chenodeoxycholic Acid Therapy on Liver Histology

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Summary: The second step in the pathway for synthesis of bile acids from cholesterol is catalysed by the enzyme 3β-hydroxy-Δ⁵-C₂₇-steroid dehydrogenase. Deficiency of this enzyme has been reported to produce cholestatic liver disease with progressive cirrhosis. Treatment with chenodeoxycholic acid led to clinical and biochemical improvement in one patient. We report a further child with this disorder who presented with prolonged neonatal jaundice followed by symptoms of malabsorption of fat-soluble vitamins. Bile acid replacement therapy resulted in clinical and biochemical improvement; it was also possible to demonstrate improvement in the histological appearance of the liver biopsy 4 months after commencing treatment.

The primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in the liver principally as shown in Figure 1 (Björkhem, 1985). The first step is catalysed by the enzyme cholesterol 7α-hydroxylase. This reaction is the rate-limiting step and is inhibited by the end-products, cholic and chenodeoxycholic acids. The next step in the pathway, converting 7α-hydroxycholesterol to 7α-hydroxy-4-cholesten-3-one, is catalysed by 3β-hydroxy-Δ⁵-C₂₇-steroid dehydrogenase. However, in a patient who lacks this enzyme, 7α-hydroxycholesterol can undergo side-chain oxidation to produce 3β,7α-dihydroxy-5-cholenoic acid and, after 12α-hydroxylation, 3β,7α,12α-trihydroxy-5-cholenoic acid (Clayton et al., 1987; Buchman et al., 1990; Ichimiya et al., 1990, 1991).

The unsaturated bile acids are excreted in large amounts in the urine as sulphates. It seems likely that they are inefficiently secreted into the bile and therefore do not promote bile salt-dependent bile flow. Affected individuals certainly have evidence of cholestasis as well as fat and fat-soluble vitamin malabsorption. Chronic cholestasis is associated with progressive liver damage which may be fatal (Clayton et al., 1987).
Bile Acid Treatment of Bile Acid Biosynthetic Defect

Figure 1 Outline of the pathway for the synthesis of cholic and chenodeoxycholic acids from cholesterol, indicating how C24 bile acids with a 3β-hydroxy-Δ5 structure are produced by a lack of the enzyme 3β-hydroxy-Δ5-C27-steroid dehydrogenase

Only one patient with 3β-hydroxy-Δ5-C27-steroid dehydrogenase deficiency has been reported in detail (Clayton et al., 1987; Buchman et al., 1990; Ichimiya et al., 1990, 1991). Clinical and biochemical improvement were documented following treatment with chenodeoxycholic acid; information on the effect of the treatment on the liver biopsy appearance was not obtained.

This report gives details of a further case. Again there was a good clinical and biochemical response to treatment, but unlike the previous case we have been able to demonstrate an improvement in the histological appearance of the liver.

CASE HISTORY

The patient, F.F., was the third child of Lebanese parents who were first cousins. He was born at term following an uneventful pregnancy and delivery. He weighed 3.65 kg at birth and was delivered in good condition. He was breast-fed from birth and developed jaundice at 3 days; however, his stools were pigmented and his urine not obviously dark. Total bilirubin on day 3 was 160 μmol/L and on day 10 was 180 μmol/L.

F.F. was still jaundiced at 2 months with a total bilirubin of 75 μmol/L and a conjugated bilirubin of 50 μmol/L; however, the transaminases were not strikingly elevated at 53 IU/L for both the aspartate aminotransferase (AST) and alanine aminotransferase (ALT). At this stage the alkaline phosphatase was high at 1230 IU/L (reference range 250–1000) and the calcium was low (1.79 mmol/L) with phosphate