Short reports

Alpha-1-antitrypsin deficiency presenting as a bleeding diathesis in the newborn

P L HOPE, M A HALL, G H MILLWARD-SADLER, AND I C S NORMAND

Department of Child Health and Department of Histopathology, Southampton General Hospital

SUMMARY Three cases of \( \alpha \)-1-antitrypsin deficiency are reported. Each infant presented in the newborn period with a haemorrhagic diathesis which responded to vitamin K. Two of them subsequently developed cirrhosis, and Case 2 is one of the few reported cases of infantile cirrhosis associated with the heterozygous protease inhibitor (Pi) SZ phenotype. On the basis of these 3 patients we feel that the exclusion of \( \alpha \)-1-antitrypsin deficiency by Pi phenotyping should be considered in any baby presenting with a bleeding diathesis, especially in view of the genetic implications of the homozygous Pi ZZ phenotype.

The relationship of \( \alpha \)-1-antitrypsin (\( \alpha \)-1-AT) deficiency with liver disease in infancy has been well known since 1968.\(^1\) Hepatic dysfunction and subsequent cirrhosis have been reported most often in individuals designated phenotype Pi ZZ by acid starch gel electrophoresis, but there are also reports of liver disease associated with the heterozygous phenotype Pi SZ.\(^2 \)\(^3\) While the relationship of liver disease with \( \alpha \)-1-AT deficiency is therefore well known, reports and reviews concentrate almost exclusively on the presentation of liver damage as a neonatal hepatitis syndrome.

We report 3 cases of \( \alpha \)-1-AT deficiency; each first presented with a bleeding diathesis in the first month of life and responded to vitamin K. Although it was subsequently proved that they had conjugated hyperbilirubinaemia, their presentation was with haemorrhagic phenomena rather than with prolonged jaundice (Table).

Case reports

Case 1. This white boy was born at term by forceps delivery, did not receive vitamin K at birth, and was fully breast fed. At age 3 weeks he was admitted with a 3-day history of vomiting and jaundice. On examination he was mildly jaundiced, with a bleeding umbilical stump, and bruising over the sacrum. Haemoglobin (Hb) was 11.9 g/dl, platelet count normal, and clotting function so abnormal it was said to be impossible to estimate prothrombin index (PTI) or partial thromboplastin time (PTT). Vitamin K was given, the PTI 5 hours later was 1-6, and the next day 1-1. Liver function tests showed total bilirubin 100 \( \mu \text{mol/l} \) (5-8 mg/100 ml), direct bilirubin

<table>
<thead>
<tr>
<th>Table Details of the 3 infants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case 1</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Serum ( \alpha )-1-antitrypsin level (g/l)</td>
</tr>
<tr>
<td>Pi phenotype</td>
</tr>
<tr>
<td>Aspartate transaminase at presentation (IU/l)</td>
</tr>
<tr>
<td>Current aspartate transaminase (IU/l)</td>
</tr>
<tr>
<td>Total bilirubin at presentation (( \mu \text{mol/l} ))</td>
</tr>
<tr>
<td>Direct bilirubin at presentation (( \mu \text{mol/l} ))</td>
</tr>
<tr>
<td>Liver biopsy</td>
</tr>
<tr>
<td>Current clinical status</td>
</tr>
</tbody>
</table>

Conversion—SI to traditional units—\( \alpha \)-1-antitrypsin: 1 g/l = 100 mg/100 ml.
45 μmol/l (2.6 mg/100 ml), aspartate transaminase (AST) 69 IU/l, and alkaline phosphatase (AP) 1080 IU/l. Two days later he was still vomiting and was noted to have a bulging fontanelle. Cerebrospinal fluid obtained by spinal tap was normal and bilateral subdural taps were negative. His clinical state improved and he was discharged from hospital. During an intercurrent illness at age 5 weeks, liver function tests were still abnormal, and at 10 weeks the PTI was noted to be 1.8 and further vitamin K was given.

Since then he has remained asymptomatic, with no evidence of liver disease and no hepatomegaly. Liver function tests at age 13 months showed PTI and PTT normal, total bilirubin 2 μmol/l (0.1 mg/100 ml), AST 82 IU/l, AP 622 IU/l. Level of α1-AT was estimated at 0.7 g/l (70 mg/100 ml) with a phenotype Pi ZZ. Liver biopsy has not been performed, but family studies are under way.

Case 2. This white boy was born at term by normal delivery and did not receive vitamin K at birth. He had been breast fed since birth and was mildly jaundiced for the first week of life. At age 4 weeks he was admitted with a 1-day history of pallor, jaundice, and diarrhoea. An enlarging haematoma was noted in the axilla on admission. Initial results showed Hb 5.4 g/dl, platelets normal, PTI 19 times control, PTT 180 seconds (control 33.5), thrombin time 2 seconds longer than control, and factor VII assay 1%. Vitamin K was administered and he was transfused. The next day his Hb was 12 g/dl, PTI 1.0 and PTT within normal limits; the haematoma was resolving and other liver function tests showed total bilirubin 120 μmol/l (7.0 mg/100 ml), direct bilirubin 81 μmol/l (4.7 mg/100 ml), total protein 59 g/l, albumin 37 g/l, AST 167 IU/l. He was discharged 2 days later asymptomatic but still jaundiced with a total bilirubin level of 200 μmol/l (11.7 mg/100 ml). Thereafter he remained clinically very well; there were no further bleeding episodes, and the jaundice gradually resolved with a total bilirubin level of 27 μmol/l (1.6 mg/100 ml) 2 months later, and 8 μmol/l (0.47 mg/100 ml) 3 months later. PTI remained normal and PTT showed marginal increase only. AST rose steadily to a level of 519 IU/l at one year. AP was consistently >1500 IU/l and 5-nucleotidase (>62 IU/l) was consistently above our laboratory's range.

At age 1 year he was noted to have a firmly enlarged liver palpable 4 cm below the costal margin, with a palpable spleen; he was admitted for investigation and liver biopsy. Level of α1-AT was low at 1.0 g/l (100 mg/100 ml). Ultrasound and radionucleotide scans confirmed hepatomegaly, and no oesophageal varices could be seen on barium meal. Needle biopsy of the liver showed extensive fibrosis linking portal tracts and isolating parenchymal nodules, with peripheral hepatocytes containing diastase resistant periodic acid-Schiff (PAS) positive globules. Appearances were typical of cirrhosis secondary to α1-AT deficiency and the presence of α1-AT in the globules was confirmed by immunoperoxidase staining. The patient's phenotype subsequently proved to be Pi SZ, his father and elder sister have the same phenotype with no clinical evidence of liver disease and his mother is Pi MZ. Since biopsy he has remained clinically asymptomatic.

Case 3. This white boy was born at term by normal vaginal delivery; he did not receive vitamin K at birth and was breast fed. At age 9 days he was admitted elsewhere with blood oozing from the umbilicus. PTT was less than 1% and there was rapid clinical response to vitamin K. Jaundice developed at 6 weeks when investigations showed total bilirubin level 112 μmol/l (6.5 mg/100 ml) and the direct bilirubin level 66 μmol/l (3.9 mg/100 ml). Breast feeding was stopped and the jaundice slowly subsided. When he presented at age 5½ months with an inguinal hernia, he was noted to have a distended abdomen with ascites, prominent abdominal wall veins, and a hard palpable liver 2 cm below the costal margin. Total bilirubin level was 24 μmol/l (1.4 mg/100 ml), direct bilirubin 10 μmol/l (0.58 mg/100 ml), AST 253 IU/l, AP 1188 IU/l, total protein 47 g/l, albumin 29 g/l, and PTI 1.3. Level of α1-AT was 1.0 g/l with a phenotype Pi ZZ. Radionucleotide scan showed patchy uptake consistent with cirrhosis and portal hypertension, and oesophagoscopy revealed oesophageal varices. Needle biopsy of the liver showed established cirrhosis with broad bands of fibrosis separating small parenchymal nodules. Hepatocytes containing diastase resistant, PAS-positive globules typical of α1-AT deficiency were seen, and the presence of α1-AT in the globules was confirmed by immunoperoxidase staining.

Discussion

Our patients were all breast fed and none had received vitamin K at birth. Because of their presentation with bleeding disorders they were all initially diagnosed as having haemorrhagic disease of the newborn. However their presentation at 3 weeks, 4 weeks, and 9 days respectively was later than one would expect for classical haemorrhagic disease of the newborn. They all had conjugated hyperbilirubinaemia in the first few months of life associated with raised transaminases consistent with
neonatal hepatitis, and a clotting disorder due to lack of vitamin K dependent factors should always be considered in such circumstances. Although early reports of \( \alpha \)-1-AT and liver disease mentioned umbilical bleeding as part of the presenting symptomatology,\(^4\) more recent reviews have not stressed this mode of presentation. Greater awareness of these early features may lead to earlier diagnosis and Pi phenotyping should always be considered in cases of haemorrhagic disease in early life, especially if associated with raised hepatic enzymes.

The Pi ZZ phenotype has an incidence of 1 in 3500,\(^5\) and is associated with a 7% incidence of clinical liver disease in childhood,\(^6\) and a 39% risk of developing obstructive airways disease before age 40 years.\(^6\) The report of Case 2 is one of the few to have been published of histologically proved cirrhosis associated with the Pi SZ phenotype.\(^7\)

The clinical progression of liver disease varies greatly and our cases clearly show this. All 3 had neonatal hepatitis of comparable severity at presentation, yet Case 1 had only marginally raised transaminases at age 13 months and Case 3 had developed cirrhosis, portal hypertension, and oesophageal varices by age 6 months. With such variability of clinical expression it is difficult to give parents a reliable prognosis or constructive genetic counselling.

References


Correspondence to Dr P L Hope, University College Hospital Medical School, Department of Paediatrics, The Rayne Institute, 5 University Street, London WC1E 6JF.

Received 11 August 1981

Early biochemical findings in familial hypophosphataemic, hyperphosphaturic rickets and response to treatment

MARTIN W MONCRIEFF

Department of Paediatrics, John Radcliffe Hospital, Oxford

SUMMARY Regular biochemical measurements were made in 4 babies, each of whom had one parent with familial hypophosphataemic, hyperphosphaturic rickets. Hypophosphataemia developed by 2 months and levels of alkaline phosphatase had increased by 3 months in all four. Decreased tubular reabsorption of phosphate and x-ray changes of rickets did not develop until 6 months in 3 of the babies. In the fourth these abnormalities developed at 9 days and 3 months. The babies were treated with oral phosphate and small doses of 1-x-hydroxycholecalciferol. The rickets healed readily in 3 babies and their linear growth is within the normal range. Healing took much longer in the remaining child and his linear growth is below the 3rd centile. Hypercalcaemia has not been a problem of treatment.

Familial hypophosphataemic, hyperphosphaturic rickets (FHHR) is diagnosed generally in the second year of life, or later, by which time growth is considerably retarded.\(^1\) Diagnosis and treatment in the first months of life may prevent this, but the criteria for early diagnosis are not well defined, and few babies have been fully studied early in life.\(^2\)–\(^4\)

The development of the biochemical and radiological features of rickets from the neonatal period onwards in 4 children with FHHR and their response to treatment are described.

Materials and methods

Four children (2 boys and 2 girls) were born into families in which one parent was known to have FHHR, the mother in 3 cases and the father of one of the girls. All were referred because of the family