Chronic Cholestatic Liver Disease With Associated Tubulointerstitial Nephropathy in Early Childhood

ABSTRACT. We report the clinical and morphological features of an unusual hepatorenal disorder in 2 patients. The main clinical features were early onset of cholestatic liver disease and progressive tubulointerstitial nephritis, leading to renal death in early childhood. Renal histology showed interstitial fibrosis, tubular atrophy and dilatation, glomerular cysts in the cortex and periglomerular fibrosis; liver histology was characterized by portal fibrosis and bile duct abnormalities. Evaluating the 12 patients published in the literature, the long-term prognosis of the liver function appears bad, suggesting the possibility of a combined liver and kidney transplantation. Pediatrics 1997;100(3). URL: http://www.pediatrics.org/cgi/content/full/100/3/e10; cholestasis, tubulointerstitial nephritis, end-stage renal disease, liver and kidney transplantation, childhood.

ABBREVIATIONS. AR-PKD, autosomal recessive polycystic kidney disease; NPH, nephronophthisis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; ESRF, end-stage renal failure.

The association between congenital hepatic and renal disease is intriguing and sometimes poses a difficult interpretation for the physician. Autosomal recessive polycystic kidney disease (AR-PKD) and nephronophthisis (NPH) are the renal problems known to be associated with liver disease.1,2 There are instead situations in which the clinical picture poses numerous nosologic problems, and even the pathologic features are lacking the typical elements for a specific diagnosis. Furthermore, as kidney transplantation is necessary for these patients, the physician also has to face the long-term prognosis of the liver function, especially if a precise knowledge of the underlying disease is lacking. We describe 2 children with an unusual hepatorenal disease and early end-stage renal insufficiency. We also review the data of 12 children from the literature3–9 with an associated early renal death and progressive tubulointerstitial nephritis, leading to renal death in early childhood. Renal histology showed interstitial fibrosis, tubular atrophy and dilatation, glomerular cysts in the cortex and periglomerular fibrosis; liver histology was characterized by portal fibrosis and bile duct abnormalities. Evaluating the 12 patients published in the literature, the long-term prognosis of the liver function appears bad, suggesting the possibility of a combined liver and kidney transplantation.

Case 1

The patient is the product of a full-term, uncomplicated pregnancy and delivery. He is the second child of unrelated, healthy parents; there is no family history of renal or liver disease. His weight has always been below the third centile. At the age of 19 months, blood biochemistry was performed because of the mother’s positivity for hepatitis B surface antigen, and it showed a mild anemia and increased values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) (Table 1); plasma urea and creatinine concentrations were 30 and 0.6 mg/dL (10.7 mmol/L and 53 μmol/L), respectively. At the age of 2.5 years, he was referred to our hospital because of the biochemical features of advanced renal failure, with severe edema and circulatory overload, marked anemia, hypertension, oligoanuria, and metabolic acidosis. The patient had been apparently well and active until 2 weeks earlier, when he experienced a flu-like symptomatology and a few days before admission his breathing became labored. Laboratory studies, performed on the day of admission, confirmed severe renal failure and showed moderate hepatocytolysis (AST and ALT were twice the normal values), and cholestasis (high plasma values of GGT and alkaline phosphatase (ALP), mild hypercholesterolemia without hyperbilirubinemia), [Table 1]. Coagulative tests have always been normal. Serologic markers for hepatitis viruses (A, B, and C) were negative. Normal values of α1-antitrypsin were referred to our hospital at the age of 5.5 years, severe itching developed and was associated with an increased concentration of serum total bile acids. Cholestyramine treatment was not beneficial, whereas ursodesoschisic acid markedly reduced the symptomatology. A hepatobiliary scintigraphy (with TC-99M Disida) was performed and confirmed mild intrahepatic cholestasis. This examination showed a worsening of cholestasis 3 years later. The patient is now 6 years old and is maintained by chronic peritoneal dialysis. He has hepatomegaly (5 cm below right costal margin) without clinical signs of portal hypertension. Liver tests are reported in Table 1.

Case 2

The patient is the product of a full-term uncomplicated pregnancy. He has no family history of renal or liver disease. The child had been apparently well until the age of 4.5 years, when polyuria, polydipsia, and ingavrescent pallor developed. He was first hospitalized in another hospital where laboratory data were consistent with severe renal failure and cholestatic liver disease (high plasma values of GGT and ALP and moderate increase of serum total bile acids and cholesterol), with hepatocytolysis (Table 1). After 1 month of conservative treatment, he was started on chronic peritoneal dialysis. When age of 5.5 years, he was referred to our hospital at the age of 5.5 years, he was in poor general condition, had severe and diffuse itching, and hypertension was not controlled by the usual treatment. Liver tests are reported in Table 1. Blood tests of coagulation, ammoniemia, ceruloplasmin, cupremia, and α1-antitrypsin were within normal ranges. Serologic markers for hepatitis viruses were negative. Ultrasound showed two kidneys at the inferior limit of normal range, with loss of corticomedullary differentiation and diffuse hyperechogenic structure; the liver had a normal size, morphology, and echo structure. Needle biopsy of kidney, represented only by cortical tissue,
showed tubular atrophy, severe interstitial fibrosis, mild inflammatory infiltrate, thrombosis of some arterioles, cystic aspect of some glomeruli, and sclerojalinization of others. Liver biopsy showed moderate portal fibrosis and paucity of interlobular bile ducts (ratio of ducts to portal areas 0.6).

At the age of 7 years he underwent renal transplantation, which failed a few months later because of serious cyclosporine toxicity, probably caused by the presence of cholestasis. Our patient showed cyclosporine levels in the low range for the drug measured by a monoclonal antibody-based radioimmunoassay (range 73 to 198 ng/mL) and very high for the polyclonal antibody-based radioimmunoassay (range 901 to 2400 ng/mL), with a ratio of nonspecific-to-specific cyclosporine levels ranging from 9 to more than 20 (normal value around 2.0). The dosage of the drug was around 13 to 14 mg/kg/day. Furthermore, a fine needle aspiration biopsy, performed 16 days after transplantation, showed changes secondary to cyclosporine A toxicity together with rejection.

We have since lost the child to follow-up.

DISCUSSION

The 2 patients reported in this article have clinical and pathologic features that do not conform to the childhood nephropathies known to be associated with hepatic involvement: AR-PKD and NPH with congenital hepatic fibrosis. More recently a tubulo-interstitial nephritis has been described associated with arteriohepatic dysplasia (Alagille syndrome).7 In fact our children showed: 1) early onset of tubulo-interstitial nephritis, leading to renal death within the first years of life; 2) renal histology characterized by tubular atrophy and dilatation, interstitial and periglomerular fibrosis, and even by glomerular cysts in the cortex; 3) clinical and laboratory signs of

### TABLE 1. Summary of Laboratory Data

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Age (Years)</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>3.5</th>
<th>4</th>
<th>4.5</th>
<th>5</th>
<th>5.5</th>
<th>6</th>
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</thead>
<tbody>
<tr>
<td>AST</td>
<td>(10–55 U/L)</td>
<td>77</td>
<td>129</td>
<td>94</td>
<td>101</td>
<td>116</td>
<td>137</td>
<td>143</td>
<td>102</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>ALT</td>
<td>(5–55 U/L)</td>
<td>156</td>
<td>215</td>
<td>80</td>
<td>258</td>
<td>100</td>
<td>289</td>
<td>266</td>
<td>195</td>
<td>138</td>
<td>148</td>
</tr>
<tr>
<td>Serum bilirubin total</td>
<td>(0.1–1 mg/dL)</td>
<td>0.4</td>
<td>0.8</td>
<td>1</td>
<td>1.5</td>
<td>1.4</td>
<td>1.3</td>
<td>1.1</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>(1.7–17 mmol/L)</td>
<td>7.3</td>
<td>15</td>
<td>17</td>
<td>26.9</td>
<td>24.4</td>
<td>22.8</td>
<td>20</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>(40–141 U/L)</td>
<td>464</td>
<td>495</td>
<td>234</td>
<td>213</td>
<td>502</td>
<td>522</td>
<td>552</td>
<td>357</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>(30–65 U/L)</td>
<td>388</td>
<td>571</td>
<td>600</td>
<td>790</td>
<td>975</td>
<td>641</td>
<td>607</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bile acids</td>
<td>(0–3.5 umol/L)</td>
<td>14.6</td>
<td>100</td>
<td>50</td>
<td>20</td>
<td>26</td>
<td></td>
<td></td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Case 2</th>
<th>Age (Years)</th>
<th>5.5</th>
<th>6</th>
<th>6.5</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>(10–55 U/L)</td>
<td>175</td>
<td>295</td>
<td>294</td>
<td>149</td>
</tr>
<tr>
<td>ALT</td>
<td>(5–55 U/L)</td>
<td>186</td>
<td>530</td>
<td>351</td>
<td>179</td>
</tr>
<tr>
<td>Serum bilirubin total</td>
<td>(0.1–1 mg/dL)</td>
<td>0.8</td>
<td>0.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>(1.7–17 mmol/L)</td>
<td>14</td>
<td>14</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>(40–141 U/L)</td>
<td>300</td>
<td>335</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>(30–65 U/L)</td>
<td>1215</td>
<td>1133</td>
<td>498</td>
<td></td>
</tr>
<tr>
<td>Serum bile acids</td>
<td>(0–3.5 umol/L)</td>
<td>606</td>
<td>1070</td>
<td>662</td>
<td>261</td>
</tr>
</tbody>
</table>

Normal values are in brackets.

Fig 1. Renal biopsy of case 1. Mild diffuse inflammatory infiltrate; cystically dilated proximal tubules, three glomerular cysts, some glomeruli almost completely fibrotic, mild diffuse interstitial fibrosis. (Masson trichrome × 120.)
cholestasis; and 4) hepatic histology characterized by portal fibrosis with bile duct proliferation in 1 patient and paucity in the other.

We ruled out the diagnosis of AR-PKD and of NPH, because AR-PKD manifests with renal enlargement, whereas our patients’ kidneys were both small, without the typical collecting duct ectasia, and because in the NPH complex the first symptoms occur between 3 and 7 years of age and end-stage renal failure (ESRF) is usually reached during the second decade of life. The hepatic involvement of these nephropathies is typically represented by congenital hepatic fibrosis, clinically characterized by minimal disturbances of the liver function without cholestasis.

Alagille syndrome was excluded in the patient with bile duct paucity, because of the absence of the typical clinical features.

We have reviewed 12 children (Table 2) from the literature with a renal histologic pattern characterized by chronic tubulointerstitial lesions and cortical

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Age of Onset</th>
<th>Age of ESRF</th>
<th>AST, ALT* U/L</th>
<th>GGT* U/L</th>
<th>Clinical Features</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popovic ’93</td>
<td>4</td>
<td>0–2 years</td>
<td>2–9 years</td>
<td>1284</td>
<td>Itching, jaundice, hepatomegaly</td>
<td>Two died during hemodialysis, 1 received combined RT and LT, 1 RT and worsening of liver disease</td>
</tr>
<tr>
<td>Hernot ’90</td>
<td>1 birth</td>
<td>10 months</td>
<td>AST:176 ALT:289</td>
<td>1054</td>
<td>Jaundice, hepatomegaly</td>
<td>Died at the age of 10 months</td>
</tr>
<tr>
<td>Gagnadoux ’89</td>
<td>1 1 month</td>
<td>11–12 months</td>
<td>Increased</td>
<td>Jaundice, hepatomegaly, splenomegaly</td>
<td>Died at the age of 1 year (portal hypertension with gastrointestinal bleeding)</td>
<td></td>
</tr>
<tr>
<td>Harris ’86</td>
<td>2 4–12 months</td>
<td>14 months</td>
<td>AST:156 ALT:112</td>
<td>Itching</td>
<td>Both received RT and 1 developed portal hypertension</td>
<td></td>
</tr>
<tr>
<td>Hyams ’83</td>
<td>1 2 weeks</td>
<td>10 months</td>
<td>AST:162 ALT:112</td>
<td>Itching</td>
<td>Died at 10 months for renal failure</td>
<td></td>
</tr>
<tr>
<td>Proesman ’79</td>
<td>2 1 month</td>
<td>Increased</td>
<td>Jaundice, hepatomegaly, splenomegaly</td>
<td>Died at 10 months for renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolia ’87</td>
<td>1 birth</td>
<td>25 days</td>
<td>AST:43 ALT:24</td>
<td>Jaundice</td>
<td>Died at the age of two months</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>2 years</td>
<td>2 years</td>
<td>AST:143 ALT:289</td>
<td>975</td>
<td>Itching, hepatomegaly</td>
<td>Received RT, lost because of severe nephrotoxicity</td>
</tr>
<tr>
<td>Case 2</td>
<td>4.5 years</td>
<td>5 years</td>
<td>AST:295 ALT:530</td>
<td>1070</td>
<td>Itching, hepatomegaly</td>
<td></td>
</tr>
</tbody>
</table>

RT, renal transplantation; LT, liver transplantation; GGT, gammaglutamyltransferase; ESRF, end-stage renal failure.

* Highest recorded value.
microcysts, with rapid progression to ESRF, and associated marked hepatic damage and cholestasis. Liver histology was represented by bile duct proliferation and portal fibrosis in all the cases, apart from the 2 patients described by Hyams and Tolia in which paucity of bile ducts was present. For these 12 patients, especially for the cases with onset in the first 2 years of life, it has been suggested that a NPH-like nephropathy associated with an unusual form of liver disease could represent a new syndrome. Our 2 patients are very similar, from the clinical and histologic point of view, to the 4 described by Popovic et al, in whom the liver disease was progressive.

In the other 9 patients described, the age of onset of the disease and of ESRF is earlier (first year of life) than in our patients but the overall prognosis was poor as for the 4 children above.

It seems, therefore, that the 12 patients reported by the literature have a poor overall prognosis and the liver function contributes to a relevant part of it. It is tempting to speculate that, at some stage, these patients with cholestasis and portal fibrosis will also need a liver transplant.

Furthermore, 1 of our patients who underwent kidney transplantation, lost his graft after 2 months and we believe that a relevant part was played by cyclosporine toxicity. In fact, the liver is the major site of the metabolism of this drug, through several cytochrome P450 isoenzymes, and also the primary excretion site via biliary secretion and fecal elimination (more than 90% of the drug is excreted in the bile, whereas less than 6% is excreted in the urine). As cyclosporine A-associated nephrotoxicity has also been related to an increase in circulating metabolites, resulting from severely disturbed cyclosporine excretion, with parent drug level within the normal range, this pattern has to be anticipated in those patients with severe liver dysfunction (poor absorption and excretion of the drug secondary to the cholestasis).

The clinical pattern of the liver disease in our patients and in the ones described by Popovic could be similar to Byler disease. In effect, this disease comprises a heterogeneous group of conditions, characterized by progressive intrahepatic cholestasis. Although serum GGT levels are usually normal in Byler disease, a minority of older children demonstrate elevated levels. To date, liver transplantation is the only successful treatment for this rare disease.

Very recently mitochondrial respiratory enzyme activity impairment has been shown to be responsible for a case of tubulointerstitial nephritis associated with hepatic involvement (hepatomegaly with cytolyis, anicteric cholestasis, and severe pruritus; a liver biopsy revealed interportal fibrosis and noninflammatory bile duct proliferation). The suspicion of mitochondrial cytopathies was considered only in our first patient, but the lactate/pyruvate ratio was normal, although the clinical picture is very similar to the child described by Berard et al. This child had a combined liver and kidney transplantation and the renal and hepatic functions tests are described as normal 20 months after transplantation.

We conclude that the 2 patients described in this report have both a tubulointerstitial nephropathy similar to NPH and a liver disease with intrahepatic cholestasis. The clinical distinguishing features of the 2 children reported in this study are: early onset of renal impairment, particularly in the first case, with necessity of dialytic treatment at the age of 2 years, and the presence of marked cholestasis. The natural history of this pathologic entity in unknown. After restoration of renal function with renal transplantation, the long-term survival of these patients may depend on the progression of the liver disease and, therefore, combined liver and kidney transplantation could be considered for these children.

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