Chronic Cholestatic Liver Disease With Associated Tubulointerstitial Nephritis 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.

ABBREVIATIONS. AR-PKD, autosomal recessive polycystic kidney disease; NPH, nephronophthisis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; ESRT, 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. 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 literature with an associated early renal death and cholestatic liver disease and discuss the role of a combined liver and kidney transplant in these patients.

CASE REPORTS

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. The child had been apparently well until the age of 4.5 years, when polyuria, polydipsia, and ingravescent pallor developed. He was first hospitalized 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. After 1 month of conservative treatment, he was started on chronic peritoneal dialysis. When he was 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 ursodesoxsicholic 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 ingravescent 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), with hepatocytolysis (Table 1). After 1 month of conservative treatment, he was started on chronic peritoneal dialysis. When 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 of the kidneys at the inferior limit of normal range, with loss of corticomедullary differentiation and diffuse hypeerechogenic 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 $5 \times 0.6$).

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. (Masson trichrome $\times 120$.)

### 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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<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>143</td>
<td>102</td>
<td>79</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>
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<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>
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<tr>
<td>Serum cholesterol</td>
<td>($\leq$200 mg/dL)</td>
<td>280</td>
<td>450</td>
<td>385</td>
<td>550</td>
<td>515</td>
<td>505</td>
<td>410</td>
<td>490</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>(40–141 U/L)</td>
<td>464</td>
<td>495</td>
<td>234</td>
<td>213</td>
<td>502</td>
<td>522</td>
<td>552</td>
<td>357</td>
<td>250</td>
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<tr>
<td>GGT</td>
<td>(30–65 U/L)</td>
<td>388</td>
<td>571</td>
<td>600</td>
<td>790</td>
<td>975</td>
<td>641</td>
<td>607</td>
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<tr>
<td>Serum bile acids</td>
<td>(0–3.5 umol/L)</td>
<td>14.6</td>
<td>100</td>
<td>50</td>
<td>20</td>
<td>26</td>
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<table>
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<th>Case 2</th>
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<th>6.5</th>
<th>7</th>
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<tbody>
<tr>
<td>AST</td>
<td>(10–55 U/L)</td>
<td>175</td>
<td>295</td>
<td>294</td>
<td>149</td>
</tr>
<tr>
<td>ALT</td>
<td>(5–55 U/L)</td>
<td>186</td>
<td>530</td>
<td>351</td>
<td>179</td>
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<tr>
<td>Serum bilirubin total</td>
<td>(0.1–1 mg/dL)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>($\leq$200 mg/dL)</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>19</td>
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<tr>
<td>ALP</td>
<td>(40–141 U/L)</td>
<td>5</td>
<td>6</td>
<td>6.7</td>
<td>5</td>
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<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 $\times 120$.)
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,\textsuperscript{1,2} whereas our patients' kidneys were both small, without the typical collecting duct ectasia,\textsuperscript{1,2} 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.\textsuperscript{2,10,11}

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,\textsuperscript{3–9} with a renal histologic pattern characterized by chronic tubulointerstitial lesions and cortical

<table>
<thead>
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<th>TABLE 2. Clinical and Laboratory Data on Patients From the Literature and on Our Two Patients</th>
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<tbody>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Popovic ’93</td>
</tr>
<tr>
<td>Hernot ’90</td>
</tr>
<tr>
<td>Gagnadoux ’89</td>
</tr>
<tr>
<td>Harris ’86</td>
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<td>Hyams ’83</td>
</tr>
<tr>
<td>Proesman ’79</td>
</tr>
<tr>
<td>Tolia ’87</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Case 1</td>
</tr>
<tr>
<td>Case 2</td>
</tr>
</tbody>
</table>

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

* Highest recorded value.
GGT levels are usually normal in Byler disease, a mi-
progressive intrahepatic cholestasis. Although serum
heterogeneous group of conditions, characterized by
Byler disease. In effect, this disease comprises a
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 pa-
tients with cholestasis and portal fibrosis will also
need a liver transplant.

Furthermore, 1 of our patients who underwent kid-
ney transplantation, lost his graft after 2 months and
we believe that a relevant part was played by cyclospo-
rine 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 se-
verely disturbed cyclosporine excretion, with parent
drug level within the normal range, this pattern has to
be anticipated in those patients with severe liver dys-
function (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 mi-
nority 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, an-
icteric cholestasis, and severe pruritus; a liver biopsy
revealed interportal fibrosis and noninflammatory bile
duct proliferation). The suspicion of mitochondrial cy-
topathies 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 func-
tions 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 transplanta-
tion, 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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