Teaching Point

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A young patient with end-stage renal disease, dyspnoea, weakness, peripheral neuropathy and an unsuspected underlying disease

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Case

In July 1998, a 37-year-old patient on chronic haemodialysis developed weakness, dyspnoea, pleural effusions, ankle oedema and peripheral paraesthesiae for the first time. In addition, physical examination demonstrated muscle atrophy, absence of deep tendon reflexes and an ataxic gait. The patient had received maintenance haemodialysis since 1997. He was dialysed three times a week for 4.5 h. The past medical history recorded oxalate stones and chronic pyelonephritis beginning at age 12. The right kidney had been removed in May 1998 because of frequent urinary tract infections. The family history was non-contributory. The results of his laboratory evaluation were in the expected range for patients on chronic haemodialysis, including blood count, electrolytes, liver and cardiac enzymes. In particular, an acute or chronic inflammation was excluded. Due to his weakness, together with dyspnoea on exertion, several cardiac evaluations had been performed. The chest X-ray, myocardial isotope scan (including an exercise scan) and echocardiogram showed evidence of heart failure, with a left ventricular ejection fraction (LVEF) of 25–30%. Coronary angiography failed to demonstrate coronary artery disease. In addition, the cardiology service found no evidence of endocarditis or myocarditis. Therefore, the dialysis prescription was intensified and the dry weight was decreased by 6 kg. We performed tests of the patient’s peripheral neuropathy. An EMG suggested ‘neurogenic damage’, but found no evidence of a primary neuropathy. An electrophysiological study of sensor and motor functions produced evidence of an atypical demyelinating neuropathy. A biopsy of the sural nerve was made in an attempt to specify the neurological diagnosis. It was reported to be compatible with uraemic peripheral neuropathy; the biopsy excluded inflammation, amyloid and crystal deposition. A rectal biopsy also excluded amyloidosis. The increase in the patient’s dialysis prescription improved his condition somewhat. His dyspnoea, oedema and pleural effusion disappeared temporarily. Because of the persistent peripheral neuropathy, his dialysis regime was intensified further to four dialysis sessions per week of 5 h duration each. This appeared to stabilize the patient’s condition over the next 3 years, during which the weakness and the polyneuropathy both continued to be slowly progressive. The patient was now able to walk 200 m slowly but without interruption. In July 2001, an echocardiogram demonstrated an ‘echo-rich’ appearance of the myocardium together with evidence of myocardial hypertrophy and diastolic dysfunction (Figure 1). There appeared to be disturbances of myocardial contractility that seemed to be regionally different. The LVEF was now clearly <30%. The rectal biopsy was repeated; again there was no evidence of amyloidosis. In 2002, the patient presented chest pain for the first time. An acute myocardial infarction was excluded by ECG and biochemical tests. The coronary angiography was repeated; it was unremarkable although the LVEF was now 25%.

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An endomyocardial biopsy was obtained. It showed myocardial deposition of oxalate by light and electron microscopy (Figure 2). The serum concentration of oxalate was measured immediately before and after dialysis (Table 1). A liver biopsy was performed to ascertain the diagnosis further and to differentiate between the subtypes of the primary hyperoxalurias (PHs). The liver biopsy provided evidence of a PH type 2 (Table 2).

### Table 1. The patient’s serum concentrations of oxalate before and after a haemodialysis session (acetate-free biofiltration; 4.0 h) in comparison with normal values

<table>
<thead>
<tr>
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<th>Patient</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum oxalate before haemodialysis session (µmol/l)</td>
<td>114</td>
<td>9–27</td>
</tr>
<tr>
<td>Serum oxalate after haemodialysis session (µmol/l)</td>
<td>35</td>
<td>9–27</td>
</tr>
<tr>
<td>Serum oxalate before next haemodialysis session (µmol/l)</td>
<td>93</td>
<td>9–27</td>
</tr>
</tbody>
</table>

### Discussion

The PHs are rare inherited diseases characterized by endogenous oxalate overproduction. Two forms of PH are distinguished. PH-1 is caused by a deficiency of hepatic alanine:glyoxylate aminotransferase (AGT) [1]. The incidence of the PH-1 is 1:120 000 live births. In contrast, patients with PH-2 have deficiencies of both glyoxylate reductase (GR) and hydroxypyruvate reductase (HPR) [2]. PH-2 is a very rare autosomal recessive disorder. The ratio of primary PH-1 to PH-2 is estimated to be 20:1. GR prevents the cytosolic accumulation of glyoxylate. In the state of GR deficiency, glyoxylate is metabolized by lactate dehydrogenase to oxalate. HPR deficiency causes an accumulation of hydroxypyruvate which is degraded by lactate dehydrogenase to L-glycerate [3]. PH-2 is characterized by increased urinary excretion of both L-glycerate and oxalate.

The median age at onset of initial clinical symptoms is 5 years. PH is a systemic disease involving many tissues and organs. Oxalate, as a poorly soluble substance, is excreted mainly by the kidneys. PH patients suffer from symptoms of the urinary tract in >80% of all cases: calcium oxalate stones, recurrent urinary tract infections, haematuria and loin pain. Hyperoxaluria leads to formation of calcium oxalate stones, nephrocalcinosis, following renal insufficiency and end-stage renal disease (ESRD). In PH-1, ESRD usually develops at the age of 15 years. The progressive decline in glomerular filtration rate is associated with a significant increase of plasma oxalate levels, which in turn lead to formation of calcium oxalate deposits in different tissues and organs. Bone is the major compartment of the oxalate pool. Oxalate deposition results in an increased bone resorption and a decreased bone formation rate. The bone X-ray resembles that of hyperparathyreoidism. Deposition of calcium oxalate in the heart frequently results in decreasing LVEF and life-threatening arrhythmias. The oxalate deposition in nerves is associated with peripheral neuropathy and mononeuropathy multiplex. Skin involvement includes ulcerating subcutaneous calcium oxalate deposition and livedo reticularis. Eye involvement can cause retinal deposits. Obliteration of retinal arteries may result in a loss of vision.

PH can be diagnosed by measurement of increased urinary excretion of glycolate (PH-1) and oxalate.
together with elevated plasma oxalate levels (PH-1 and PH-2). An increase in urinary excretion of l-glycerate in PH-2 is frequently observed, but is not necessarily present. It is therefore particularly difficult to diagnose PH in cases presenting with ESRD for the first time or in PH-2 patients without increased excretion of l-glycerate. The gold standard in the diagnosis of PH-1 and PH-2 is liver biopsy. It serves to prove deficiencies of AGT, GR and HPR, respectively. Therefore, liver biopsy is recommended for confirming the diagnosis and distinguishing the subtypes [4,5].

The principal aim of therapy is a significant reduction of oxalate plasma levels. Yamauchi et al. [6] demonstrated in ESRD patients with PH-1 that even a major prolongation of the time of haemodialysis (6 × 8 h per week) or the additional institution of peritoneal dialysis was unable to prevent formation of deposits in tissues and organs. It was noted in those studies, however, that dialysis was effective in lowering the concentration of oxalate in plasma temporarily, as in our patient. Similar studies are not available for PH-2. However, since oxalate plasma levels are similar to those observed in PH-1, it is possible that dialysis is not more advantageous in PH-2 than it is in PH-1. Unfortunately, kidney transplantation in ESRD patients with PH is associated with poor graft survival rates (3-year graft survival for cadaveric donors 17%) [7]. Therefore, the treatment of choice in patients with PH-1 and ESRD is combined kidney and liver transplantation. In this way, it is possible to correct the enzymatic deficiency responsible for PH-2 and is presented in hepatocytes and leukocytes as well, although the hepatic deficiency appears to be the dominant one [5]. Controlled studies for the therapy of PH-2 are lacking. Since the prognosis of the disease is poor, a similar approach to that in PH-1 (i.e. combined kidney and liver transplantation) should be considered.

Teaching point

Since weakness, peripheral neuropathy and fluid overload are not uncommon in haemodialysis patients, it is probable that the nephrologists treating this patient missed his peculiarities for some time. In particular, they overlooked his past history of kidney stones and the important fact that the stones were made up of oxalate.

Conflict of interest statement. None declared.

References