Successful renal transplantation in primary hyperoxaluria

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Summary

A successful live related renal transplant in a 29-year-old male patient with Type I primary hyperoxaluria, who remains well 32 months postoperatively, is described. The plasma oxalate and exchangeable oxalate pool before transplantation were 160 μmol/l and 4429 μmol respectively. Since the transplant these have been greatly reduced although they remain elevated above the normal by a factor of 2. Pyridoxine therapy and the avoidance of oxalate-rich foods have been effective in maintaining these reduced levels and the 24-hr urinary oxalate excretion has also been maintained close to normal levels on this regime. After review of the previously reported transplants in patients with well documented primary hyperoxaluria and from the experience with this patient, the following guidelines for successful renal transplantation in primary hyperoxaluria are suggested: transplants should only be carried out in those who have shown a response to adequate pyridoxine therapy; frequent haemodialysis pre-operatively and during periods of oliguria postoperatively is necessary; oxalate-rich foods should be avoided and a high fluid intake should be maintained after transplantation. If these guidelines are followed there is no contra-indication to live related renal transplants in primary hyperoxaluric patients.

Introduction

Primary hyperoxaluria is a general term for at least 2 rare recessive genetic disorders of metabolism (Archer et al., 1957; Williams and Smith, 1968) characterized by increased endogenous synthesis of oxalic acid, recurrent nephrolithiasis, extra-renal oxalate deposits (oxalosis), progressive nephrocalcinosis and renal failure with eventual terminal uraemia.

In Type I primary hyperoxaluria, the patients lack the enzyme 2-oxoglutarate glyoxylate carboxigase, and the urinary excretion of glycollate and glyoxylate as well as oxalate are increased (Williams and Smith, 1968). In Type II primary hyperoxaluria, the metabolic lesion is a lack of D-glycerate dehydrogenase, the excretion of L-glycerate is increased but glycollate and glyoxylate excretion are normal (Williams and Smith, 1968). Only 4 patients with Type II primary hyperoxaluria are known.

The management of terminal renal failure in primary hyperoxaluric patients by dialysis and/or transplantation has been the subject of a number of reports over the past 10 years. Peritoneal dialysis does not seem sufficiently efficient to prevent ischaemic lesions, secondary to diffuse infiltration of arteries by oxalate crystals developing (Arbus and Snidman, 1974; Klauwers, Wolff and Cohn, 1969; Zarembski, Rosen and Hodgkinson, 1969). Results achieved with haemodialysis are better, but nevertheless numerous complications arise and the average duration of survival of patients with primary hyperoxaluria appears to be significantly shorter than for the other groups of patients treated with intermittent haemodialysis (Jacobs et al., 1975a; Boquist et al., 1973; Blackburn et al., 1975; Jacobs et al., 1975b; Toussaint et al., 1976). Most reports of the results of renal transplantation in these patients have suggested a very poor prognosis with only 2 transplanted kidneys functioning more than 2 years postoperatively in a total of 16 transplants in 13 patients with well documented primary hyperoxaluria. An additional successful transplant in a primary hyperoxaluric subject is reported with, for the first time, pre- and post-transplant studies of plasma oxalate and exchangeable oxalate pool, and the previously published reports of renal transplantation in this condition are reviewed.

Case report

The patient was born in Iran in 1947, the second of 6 children. Both parents were healthy, but the older sibling, also a male, had died with renal failure

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Case reports

There was out, carried 68th tion, azathioprine suppressives, after one failure (creatinine function continued, umol 7680 high-dose intravenous diuresis of was, umol/24 hr), which carried authors' care and, urinary clearance, was only 270 μmol/24 hr; the plasma oxalate and the exchangeable oxalate pool (both measured using a method described by the present authors (Constable et al., 1979) were 160 μmol/l and 4429 μmol respectively, these are the highest levels ever recorded at this hospital. After the transplant, the plasma oxalate and the exchangeable oxalate pool showed a very large reduction although they remain elevated beyond the normal range by a factor of 2, even allowing for the reduced creatinine clearance (personal observation); the urinary oxalate has been less than 1100 μmol since the operation and with improved communication, allowing better dietary instructions, resulting in the avoidance of oxalate-rich foods, a reduction almost to normal levels has recently been achieved; the creatinine clearance is now quite stable at about 60 ml/min.

A renal biopsy (Fig. 1) carried out 9 months post-transplant, shows some rejection changes and just a few intratubular birefringent calcium oxalate crystals. A plain X-ray of the abdomen at 20 months postoperatively (Fig. 2) shows the patient's 2 original kidneys in situ with bilateral nephrocalcinosis and nephrolithiasis but no suggestion of nephrocalcinosis or calculi in the transplanted kidney.

In the 29 months since the transplant, the patient has remained well with no evidence of extra-renal oxalate deposits in the retina, cardiac conducting system or peripheral arteries.

Discussion

Since the transplant, pyridoxine therapy has been of importance to this patient in maintaining his urinary oxalate, plasma oxalate and exchangeable oxalate pool at levels which avoid the severe renal, vascular, ocular and cardio-conductive lesions associated with primary hyperoxaluria. Pre-transplant maintenance haemodialysis and pre-transplant pyridoxine therapy may also have reduced the oxalate load on the allograft but it proved capable of excreting 7680 μmol of oxalate in the first 24 hr postoperatively with only minimal intrarenal calcium.

Table 1. Results of 24-hr urinary oxalate, plasma oxalate, exchangeable oxalate pool and creatinine clearance during the first 21 months after renal transplantation

<table>
<thead>
<tr>
<th>Time in relation to transplant</th>
<th>24-hr urinary oxalate (μmol) (normal &lt; 550)</th>
<th>Plasma oxalate (μmol/l) (normal &lt; 1.55)</th>
<th>Exchangeable oxalate pool (μmol) (normal &lt; 40)</th>
<th>Creatinine clearance ml/min</th>
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<tr>
<td>One week pre- 24 hr post-</td>
<td>270</td>
<td>160.0</td>
<td>4429</td>
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<tr>
<td>One month post-</td>
<td>7680</td>
<td>8.4</td>
<td>266</td>
<td>50</td>
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<td>2 months post-</td>
<td>1000</td>
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<td>1020</td>
<td>11.1</td>
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</tr>
<tr>
<td>21 months + one week post-</td>
<td>630</td>
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</tbody>
</table>
Case reports

Oxalate crystal deposition, no doubt the diuresis of 36 litres in this time maintained a sufficiently dilute urine to avoid renal damage.

Fig. 1. Transplanted kidney biopsy at 9 months. Note birefringent crystals of calcium oxalate within the distal tubule photographed under partially polarized light; no evidence of nephrocalcinosis. Glomerulus shows coarsening of its architecture and an irregular increase in mesangial matrix, narrowing of the capillary lumina and some hypercellularity. These changes are consistent with a rejection process (HE, partially crossed polaroids ×357).

Many drugs have been tested in an effort to reduce endogenous oxalate formation in primary hyperoxaluric patients, only pyridoxine has been shown to be consistently effective in a large proportion. In initial animal studies, pyridoxine deficiency was found to cause hyperoxaluria and oxalate nephrocalcinosis (Gershoff et al., 1959a). Subsequent experimental pyridoxine deficiency in human subjects increased oxalate excretion and studies have shown that pyridoxine reduces urinary oxalate in mentally subnormal children (Gershoff, Mayer and Kulczycki, 1959b) and normal adults (McLaurin et al., 1961). A definitive reduction of the urinary oxalic acid in patients with primary hyperoxaluria given large doses of pyridoxine was shown by Smith and Williams (1967) and Gibbs and Watts (1970). In addition to the transplant recipient, this has also been the experience in this hospital with 4 of 6 other Type I primary hyperoxaluric patients treated and studied.

A reduction of the dietary oxalate has not previously been considered to be important in the management of primary hyperoxaluric patients. However, with these patients, whose urinary oxalate can often be reduced to approximately 1000 μmol/24 hr with pyridoxine therapy, a further reduction to normal levels can be achieved by avoiding the oxalate-rich foods. More strict dietary monitoring following the discovery he was eating large quantities of oxalate-rich nuts, resulted in a reduction of 24-hr urinary oxalate from 1020 μmol to 630 μmol in the transplant recipient 21 months after transplantation (Table 1).

A 1975 report from the American College of Surgeons/National Institute of Health Renal Transplant Registry (ACS/NIH), concluded that ‘oxalosis is a form of chronic renal failure that is unsuitable for treatment by renal transplantation’ (Wilson, 1975). A number of other authors reporting their own cases and reviewing some others in the literature, have suggested that cadaveric renal transplantation should be approached with great caution and that live related donor transplants should be avoided because of the possible susceptibility of heterozygous kidneys with the oxalosis trait (Mahony et al., 1972; Saxon et al., 1974; Halverstadt and Wenzl, 1974; Jacobs et al., 1975a).

As Leumann, Wegmann and Lorgiader (1978) have said, a review of the literature on renal transplantation in primary hyperoxaluria is made difficult...

Fig. 2. Plain X-ray of abdomen 20 months after renal transplant. There is extensive nephrocalcinosis in the original kidneys but no evidence of calcium oxalate nephrolithiasis or nephrocalcinosis in the transplanted kidney.
by the fact that primary hyperoxaluria has not always been sufficiently documented and the presence of oxalosis alone has been accepted as sufficient for diagnosis. In addition, 2 of the reported transplant series are difficult to analyse because the criteria for diagnosis of primary hyperoxaluria in some cases are suspect and some cases are obviously common to both series (Jacobs et al., 1975b; Wilson, 1975). Therefore only 16 transplants in 13 patients with well-documented primary hyperoxaluria can be reviewed.

Some details of these cases are summarized in Table 2. Of the first 8 transplants in 5 patients in Table 2, no pyridoxine therapy was given in 7 (Zarembski et al., 1969; Deodhar et al., 1969; Mahony et al., 1972; Koch et al., 1972) and, in one case, an inadequate dose of 100 mg daily was given (Solomons, Goodman and Riley, 1967). Saxon et al.'s patient (1974) was given pyridoxine 400 mg daily and, on reviewing the report, it seems doubtful that the failure of the graft, which never functioned satisfactorily, could have been due to the scattered intratubular calcium oxalate crystals seen on renal biopsy 17 days and 49 days postoperatively, when haemodialysis had already been re instituted because of renal failure on the 11th postoperative day. The 4-year-old patient of Halverstadt et al., treated with 150 mg of pyridoxine daily, had minimal calcium oxalate deposition on serial percutaneous renal biopsies during the first 15 months of follow-up, but at the time of post-mortem, 23 months after transplantation, extensive deposits had accumulated. The authors say that it is unclear whether these deposits resulted from the basic disease or occurred as the terminal effect in the rejected fibrotic kidney (Halverstadt and Wenzl, 1974).

Jacobsen and Mosbaek's patient was maintained on peritoneal dialysis for several months before transplantation, the graft never functioned satisfactorily and after 2 weeks of oliguria, during which only two haemodialyses were given, a creatinine clearance of 7 ml/min with a urinary excretion of 1875 ml/24 hr, was achieved. Pyridoxine in a dosage of only 100 mg daily was given (Jacobsen and Mosbaek, 1974). This kidney would appear to have been unable to cope with the massive oxalic acid load which must have accumulated during the several months of maintenance peritoneal dialysis before transplantation and the 2 weeks' oliguria after the transplant, also pyridoxine 100 mg daily, would not be sufficient to reduce endogenous oxalic acid production.

The death of the patient reported by Toussaint et al. (1976) 6-5 months after transplant was caused by miliary tuberculosis, the graft was still functioning at the time of death, but at post-mortem there was extensive intra-renal calcification and stone formation. The very high urinary oxalate excretion (e.g. 1440 mg/24 hr on the 150th postoperative day) suggests that pyridoxine was either completely ineffective or that 250 mg daily was an inadequate dose to reduce endogenous oxalic acid formation.

The 2 transplants reported by Chailley et al. (1978) were both in children. No details of therapy were given, one kidney failed after 5 months and extensive intra-renal calcium oxalate deposition was found at post-mortem, the other kidney was still functioning 8 months after transplantation but with a moderate degree of intra-renal calcium oxalate deposition.

Personal communication in 1978 with E. B. Leumann and A. G. Dietheim revealed that the 2 successful transplants described by Morgan et al. (1974) and Leumann et al. (1978) were both still functioning almost 7 years and 5 years after transplantation respectively. The patient of the latter had been treated with pyridoxine 300 mg daily from the time of transplantation and that of the former with pyridoxine one g daily for 5 months postoperatively; in addition, substances such as methylene blue, magnesium hydroxide and orthophosphate were used at various times in both patients in an effort to increase calcium oxalate solubility and prevent crystallization and deposition. Both kidneys on biopsy have shown some intratubular calcium oxalate deposition, more extensive in Leumann's case. Another problem seen in Leumann's case was a rapid progression in bone age without linear growth. In the case reported by Morgan et al., the patient has passed several calcium oxalate calculi and surgery has been necessary on one occasion to remove renal calculi, this is despite a 50% reduction in urinary oxalic acid excretion achieved by pyridoxine therapy.

The following guidelines should be followed in the management of renal transplantation in primary hyperoxaluric patients. The transplants should be carried out only in patients who have shown a response to an adequate dose of pyridoxine as evidenced by a reduction in urinary oxalate excretion and/or a reduction in plasma oxalate or exchangeable oxalate pool. Care must be taken in the assessment of the efficacy of pyridoxine that an adequate dose of the drug is given (at least 600 mg daily) and that therapy is maintained for an adequate length of time, at least 2 weeks, to allow depletion of the exchangeable oxalate pool before the reduction in the endogenous formation of oxalate can be fully judged. In addition, as previous authors have suggested, frequent haemodialysis pre-operatively and during periods of oliguria associated with acute tubular necrosis or rejection postoperatively, should reduce the eventual oxalate load on the kidney and thus avoid heavy intratubular calcium oxalate
<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Age of recipient (years)</th>
<th>No. of transplants</th>
<th>Donor</th>
<th>Transplant survival</th>
<th>Pyridoxine dosage mg/day</th>
<th>Pathology of allograft Specimen type</th>
<th>Time post-transplant</th>
<th>Degree of Ca oxalate crystal deposition</th>
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<td>5*</td>
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</table>

* Months, † days.
crystal deposition. It would also seem wise to instruct patients to maintain a high fluid intake and avoid oxalate-rich foods. Living related donor kidneys may be preferable for transplantation as the degree of tubular necrosis is likely to be less than in cadaveric kidneys and there is no evidence that the heterozygous kidneys are more susceptible to oxalosis than normal. On the other hand, this does not seem to be too important as the 2 other successful renal transplants in primary hyperoxaluric patients have been carried out from cadaveric donors.

The ACS/NIH report (Wilson, 1975) and the authors quoted earlier, take an unjustifiably gloomy view of renal transplantation as a treatment for terminal uraemia in patients with primary hyperoxaluria. Review of the literature and experience with the patient now reported suggests that it should be considered in patients with this condition and, provided the guidelines outlined are followed, it may indeed be a successful form of treatment.

References


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