PART VIII
DIALYSIS—MISCELLANEOUS
Chairman: Dr M G McGeown
Terminal Renal Failure due to Oxalosis in 14 Patients

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Summary
The present status of regular dialysis and renal transplantation in patients with end-stage renal disease secondary to primary hyperoxaluria is reported. Clinical studies include one personal case with an 18-month period of follow-up and data concerning thirteen patients treated in 10 centres in Europe which have been collected through a cooperative survey carried out with the assistance of the Registry of the EDTA. On January 1st, 1974, mean survival of patients with oxalosis treated by RDT was 30.4 months (range 6 to 102 months). Five cadaveric renal transplants have been performed in four patients; two patients are surviving with grafts functioning for 18 and 45 months. Dialysis and/or transplantation should be performed in patients with oxalosis early enough to prevent ischaemic, cardiac and neuromuscular complications which occur at the end-stage of the disease. Evidence for blood coagulation disorders, particularly chronic consumption coagulopathy, should be investigated for with adequate laboratory methods and long-term heparin therapy instituted if necessary. No convincing reports concerning the efficiency of the various drugs which have been tried out to reduce the biosynthesis of oxalic acid in patients with oxalosis have been issued to this date.

Introduction
Several attempts to treat patients with terminal renal failure secondary to primary hyperoxaluria by regular dialysis or renal transplantation have been reported since 1969 (Deodhar et al, 1969; Zarembsky et al, 1969). By 1972, 17 adult patients and three children under the age of 15 had been treated in Europe by these techniques. Results of a cooperative survey involving 14 patients from 10 centres in Europe and details of one personal case are presented in order to outline the present status of regular dialysis treatment (RDT) and renal transplantation in patients with oxalosis.
Mrs GEN, age 24, was admitted on May 21st, 1973 because of oliguric acute renal failure of progressive onset. Three months before admission her renal function was normal. The diagnosis of primary hyperoxaluria was based on recurrent oxalate nephro-lithiasis beginning at the age of four associated with hyperoxaluria and diffuse infiltration of tissue and organs with calcium oxalate crystals. Prolonged oliguria required treatment with peritoneal dialysis for 33 days and subsequent haemodialysis.

Since the beginning of renal failure various complications occurred. Complete right-bundle branch block associated with cardiac arrhythmias were present for 24 hr and subsequently disappeared. Distal ischaemia of the four limbs developed during peritoneal dialysis. Following treatment with heparin and urokinase, ischaemic lesions of the upper limbs subsided. An arterio-venous shunt and later a saphenous vein graft were performed without further complications. Gangrene resulted in amputation of both forefeet.

Severe neuro-muscular complications occurred by the fourth month of RDT in spite of intensive dialysis. Considerable muscular atrophy was present with tendon contractures in both hands. Massive infiltration of muscle and nerve fibres by oxalate crystals was noted on neuromuscular biopsy. The patient was confined to bed. All these manifestations subsided in part by the eighth month of treatment, with reduction of the weekly dialysis schedule; institution of heparin therapy and slight improvement of the nutritional status.

In February 1974 blood coagulation disorders revealed by prolonged bleeding of puncture sites after dialysis were related to a chronic consumption coagulopathy (Raby, 1974). After heparin administration, first with a permanent infusion technique (3 mg/hr), subsequently with twice-daily subcutaneous injections, clinical troubles disappeared quickly while correction of major biological disturbances was delayed (Figure 1).

Febrile abdominal pain attacks occurred in June 1974. No accurate explanation for these symptoms is available, but they disappeared with small doses of prednisone (15–10 mg/day).

Throughout the RDT period, determinations of blood oxalic acid levels were performed before and after dialysis using gas chromatography (Desgrez et al, 1975).

Pre-dialysis oxalate levels in our patient were 1809 μg/100 ml (mean of 19 determinations) while the post-dialysis levels were at 477 μg (mean of 17 determinations) – (Figure 2), the normal range being between 100 and 300 μg/100 ml with this technique.

In October 1974, after 17 months of RDT, the overall clinical status of the patient was poor but slowly improving. Stabilisation of neuromuscular damage had been obtained, and blood coagulation disorders had disappeared. In spite of the transfusion of 39 units of blood, no serum lymphocytotoxic antibodies were detected. Immune ‘non response’ is considered to be favourable to cadaveric renal transplantation.
Figure 1. Influence of heparin-treatment on biological signs of chronic consumption coagulopathy in patient GEN.

RESULTS

The prominent clinical features which have been recorded in this series of 14 patients (8 female, 6 male) treated by RDT or renal transplantation are the following.

The diagnosis of oxalosis was made at the mean age of 20 years (range 3 to 58 years). Terminal renal failure occurred in five patients, recurrent oxalate renal lithiasis in five, association of renal stones and renal failure in two, and nephrocalcinosis in two others. Criteria for the diagnosis have been: histopathology in five patients, hyperoxaluria in six patients, diffuse manifestations of the disease in three others. A story of familial recurrent renal lithiasis or renal failure was found in five patients. The mean duration between detection of oxalosis and the beginning of renal failure (i.e. blood urea nitrogen > 50 mg/100 ml) was 6.3 years in six patients, not recorded in two. Simultaneous evidence of oxalosis and terminal renal failure occurred in six patients. The mean duration between detection of renal failure and the beginning of RDT was 10 months in eight patients and was unknown in the other six. The average age of patients at beginning of
Figure 2. Blood oxalic-acid rates in patient GEN with oxalosis during the first 14 months of regular dialysis treatment.

RDT was 24.7 years.

The average weekly duration of dialysis was 21.5 hr: six patients were dialysed thrice weekly, eight patients twice weekly. All types of dialysers were used. Residual diuresis was nil in six patients, bilateral nephrectomy having been performed in three, and less than 200 ml/day in the eight others. Blood oxalic acid determinations were performed in four patients.

On January 1st, 1974, the mean survival of the 14 patients treated with RDT was 30.4 months (range 6 to 102 months). Two have died, one after 35 months of treatment because of heart failure, the other after 102 months because of cachexia. The following complications have been reported: cardiac in seven patients, with auriculo-ventricular blocks in four; ischaemic in five patients, amputation being necessary in two (one leg, two forefeet); neuromuscular in three patients; severe hyperparathyroidism in five. Extensive calcium oxalate crystal deposits in various parts of the body occurred in five patients. These complications occurred in spite of phosphate binding agents which were given to 13 patients; pyridoxin was given to two patients and succinimide to one.

Cadaveric renal transplantation has been performed in four patients; one patient has been transplanted twice. Transplantation was done after a mean period of RDT of 24 months. Of the four transplanted patients' two are alive with a functioning kidney 18 and 45 months after transplantation. One returned to the dialysis program 28 days after transplantation, pathological examination
of the graft showed recurrence of oxalosis. Another graft was removed four months after transplantation because of recurrence of the disease. A second transplant was performed later, but the patient committed suicide 19 months after her second transplantation. At time of death, the function of the transplanted kidney was good.

DISCUSSION

Already published data (Boquist et al, 1973) and the results collected in the present survey indicate that dialysis and/or transplantation may be considered as effective methods of treatment in patients with terminal renal failure due to oxalosis. Nevertheless, frequent complications, mainly in relation to calcium-oxalate crystal precipitation in various tissues and organs, do occur and account for the high failure rate.

Distal ischaemia of the limbs with gangrene is frequently reported (Klauwers et al, 1969; Koch et al, 1972) and occurred in five of the 14 patients in this series. Amputation may be necessary and had to be performed in the four limbs in one case (Arbus and Snidermans, 1974). Ischaemic lesions are secondary to diffuse infiltration of most arteries by oxalate crystals (Arbus and Snidermans, 1974; Boquist et al 1973; Walls et al, 1969). In our case evidence of chronic consumption coagulopathy was established. It is suggested that careful investigations of the blood coagulation system should be performed in such patients and heparin therapy prescribed, if justified.

Cardiac complications in association with deposits of oxalate crystals in the myocardium and in the conductive tissue are frequently present (Coltart & Hudson, 1971; Deodhar et al, 1969; Koch et al, 1972; Walls et al, 1969). Cardiac-arrhythmias may be transitory or prolonged and severe. The implantation of a pace-maker may be necessary (Coltart & Hudson, 1971; Deodhar et al, 1969). Cardiac enlargement may develop even if cardiac failure or hypertension are absent (Walls et al, 1969).

Neuro-muscular complications occurred in only three patients in this series. They may be of great severity as in our personal case and in several patients reported (Boquist et al 1973; Walls et al, 1969) and may lead to confinement to bed, because of a predominantly motor polynuropathy with considerable muscular atrophy. Neurologic lesions are due to the deposition of calcium-oxalate crystals in the vasa vasorum and the nerve fibres, as has been shown in our own case and in others (Arbus and Snidermans, 1974). Distinction from uraemic neuropathy may be difficult. In our patient the neuro-muscular status worsened in spite of an intensive dialysis technique which consisted of three dialyses per week, each of 7 hr, with a Gambro—Lundia Nova dialyser, the weight of the patient being 37 kg. Relative improvement was noticed as dialysis hours were reduced.
The success of dialysis treatment in patients with oxalosis does not depend solely on an adequate control of the uraemic state, but also on achieving a satisfactory balance between the biosynthesis and dialysis of oxalic acid. Peritoneal dialysis which has been used for several patients for up to three months does not seem efficient enough and has been unable to prevent ischaemic lesions of the limbs from developing in several patients (Arbus and Snidermans, 1974; Klauwers et al, 1969; Zarembski et al, 1969). Low values have been found for oxalic acid clearance by the peritoneum: 6 ml/min with one litre per hour cycles (Zarembski et al, 1969), but better performances with peritoneal dialysis can be expected by using large volumes of dialysis fluids according to recent techniques (Tenckhoff et al, 1973).

Results achieved with haemodialysis are far better and long-term survivals are reported in this series and in several patients in the literature (Boquist et al, 1973; Walls et al, 1969). Dialysance of oxalic acid through the cuprophane membrane appears to be fairly high. In our experience, it has been found to be 80 ml/min with the Gambro—Lundia Nova 13.5 μ dialyser (Desgrez and Jacobs, unpublished data).

Nevertheless, numerous complications occur and the average duration of survival in patients with oxalosis appears to be significantly shorter than for the other patients treated with RDT. It is suggested that an improvement of those results may be obtained through earlier institution of RDT for example in patients with a creatinine clearance of about 10 ml/min, in order to prevent cardiac and ischaemic complications which do frequently occur at the end-stage of the disease. Such an approach requires early diagnosis. The dialysis schedules should be determined according to the oxalic-acid levels in the blood. This was not achieved in our patient (Figure 2).

Recurrence of oxalosis lesions are constantly reported on transplanted kidneys (Saxon et al, 1974), often very early after transplantation, the deposition of oxalate crystals in the graft being accelerated by episodes of renal failure of ischaemic or immunologic origin (Klauwers et al, 1969; Saxon et al, 1974). Pathological damage is not necessarily associated with early complete functional loss (Mahony et al, 1972). Renal transplantation should be performed early, and because of the high failure rate of renal transplantation, living donors should not be considered for recipients with oxalosis, even if evidence of enzymatic activity in α-ketoglutarate glyoxylate carboligase in renal cells is present on renal biopsy studies performed in the prospective donor (Saxon et al, 1974). Such an attitude for patients with oxalosis is similar to that adopted by us and by many other groups as regards the indications for renal transplantation and RDT (Legrain et al, 1974).

Many drugs have been tried in order to reduce the biosynthesis of oxalic acid in patients treated by RDT or renal transplantation including calcium carbimid, pyridoxin, and disulfiram. At present no definite proof of their efficiency has been given (Koch et al, 1972; Saxon et al, 1974; Solomon et al, 1967; Williams
and Smith, 1968). On the other hand, the data reported in the present survey and in the literature demonstrate the importance of several other features of medical treatment complementary to RDT: severe secondary hyperparathyroidism is present in most of the patients, and has to be successfully controlled with high doses of phosphate binding agents or parathyroidectomy. Careful investigations for blood coagulation disorders should be performed and if evidence of chronic consumption coagulopathy arises, low-dose long-term heparin therapy should be instituted with adequate laboratory control (Raby et al, 1974).

References

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Discussion

A AVIRAM Did you find any difference in removal of oxalic acid between different dialysers?

JACOBS This is the result of a cooperative survey, and I have no results on the dialysance in different centres.

B LINDQUIST (Sweden) We have had two patients. The first one we haemodialysed for two years. He suffered intensely and it was not justifiable to go on haemodialysing him. We have tried taurine by mouth, do you have any experience of taurine?

JACOBS I am afraid we have no experience of this compound.

R DE ROSKVIL (Holland) We have also two home dialysis patients with oxalosis, and we found high levels of acid phosphatase in both patients. Our normal values are from four to eleven units, and in this patient we found eighty to ninety units. Have you had the same experience, and can you explain this?

JACOBS We did not screen for acid phosphatases. We will try to get the information from our colleagues.

S COHEN (London) I wonder if I could ask you two things briefly. Firstly, in your patients transplanted with good renal function, is there any evidence of progression of generalised vascular lesions, and secondly, of the patients maintained on long-term dialysis, how many have been rehabilitated sufficiently to go back to work?

JACOBS First we have no biopsy material, and second I have no information about rehabilitation.

R JONTAFSOHN (Freiberg) We have dialysed three patients who have oxalosis. Two died and one is very well, so I think there must be different degrees of oxalosis.

JACOBS I absolutely agree with you. The different ages of patients with severe disease suggests considerable variability of its manifestations during the patient’s life.