REVERSAL BY LIVER TRANSPLANTATION OF THE COMPLICATIONS OF PRIMARY HYPEROXALURIA AS WELL AS THE METABOLIC DEFECT

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LIVER transplantation reverses a number of inborn errors of metabolism that result from the genetically determined absence of an enzyme.[1] The earliest enzyme-deficiency disorders to be treated by liver transplantation were those that caused the anatomical destruction of the host liver. The replacement of a grossly normal liver to correct a defect that had caused the destruction of another organ was first performed to treat homozygous familial hypercholesterolemia.[2] Although homozygous familial hypercholesterolemia is not the result of an enzyme defect, this experience undoubtedly encouraged others to attempt to correct primary hyperoxaluria in the same way.[3-5]

Three patients with primary hyperoxaluria are known to have undergone combined hepatic and renal transplantation.[3-5] Their experience established that the metabolic defect could be partially[4] or totally[5] corrected in this way. We report on a patient whose case differs from theirs: not only were the metabolic defects corrected and deposits of oxalate in the renal allograft resorbed, but the kidney and liver transplantations were performed sequentially rather than simultaneously.

METHODS

The urinary oxalate concentration was determined by Smith-Kline Bioscience Laboratories, Shreveport, Louisiana, with the use of a procedure that measured the oxidation products resulting from the catalytic activity of oxalate oxidase on oxalate. An aliquot of urine was extracted with an oxalate absorbent. The oxalate was eluted with alkali, and the eluate was exposed to excess oxalate oxidase in the presence of oxygen. The oxalate was oxidized to form hydrogen peroxide. The hydrogen peroxide was mixed with benzothiozolinone hydrazone and 3-(dimethylamino)benzoic acid in the presence of excess peroxidase to yield indamine dye and water. The concentration of the dye was measured by absorption spectrophotometry at 500 nm and compared with that in standard samples processed in an identical fashion. The values in healthy men ranged from 78 to 489 μmol per day.[6] The coefficient of variation of the method was 7.1 percent.

The blood oxalate concentration was measured by Galbraith Laboratories, Knoxville, Tennessee. The specimens were deproteinated by ultrafiltration, and the protein-free eluate was diluted 1:20 with distilled water. The diluted sample was injected into an ion chromatograph (Dionex, model 2000i/Sp), and the oxalate was eluted with 0.00075 M sodium bicarbonate and 0.002 M sodium carbonate at a flow rate of 2 ml per minute. The elution pattern of the oxalate was recorded with a recording integrator (Hewlett–Packard, model 3390A). The area of the sample was compared with that of a standard sample of oxalate processed in an identical fashion. The oxalate concentration of our sample was then calculated by dividing its area by the area of the standard sample times the concentration of the standard sample times the dilution factor.[7] The normal values were less than 67 μmol per liter. The coefficient of variation was 13.6 percent.

Creatinine-clearance values were adjusted for body-surface area (milliliters per second × 1.73 m^2). The results were analyzed by linear regression with use of the Bioquant computer program (R&M Biometrics, Nashville). P values of less than 0.05 were considered to indicate significance.

CASE REPORT

A 38-year-old man with end-stage renal disease attributed to recurrent nephrolithiasis, nephrocalcinosis, and chronic pyelonephritis was referred to us for bilateral nephrectomy in preparation for a cadaveric renal transplantation. Calcium oxalate stones had formed in the patient from the age of five, but he had never had a metabolic evaluation. A brother had a similar history of recurrent nephrolithiasis, and a cousin had received a kidney transplant for renal failure of uncertain cause. The patient had been undergoing hemodialysis for two months, and he had severe hypertension, recurrent urinary tract infection, and one episode of third-degree atrioventricular block attributed to hyperkalemia (serum potassium level, >6.5 mmol per liter).

His kidneys were removed on January 23, 1987, through bilateral posterior incisions. Within hours after recovery from anesthesia both his feet and ankles were cold, with areas of cyanosis. At no time did the patient have hypotension or any decrease in hematocrit. Within 24 hours both legs were cyanotic and cold to midthigh, both hands became involved, and exquisite pain and tenderness developed in all muscle groups. The suspected diagnosis of oxalosis with a livedo reticularis crisis was confirmed by skin biopsy, which revealed oxalate crystals; the analysis of the renal stones, which contained calcium oxalate; and by measurement of blood oxalate, which was 166 μmol per liter. A description of the livedo reticularis crisis has been published.[8] During this period a heart block developed that necessitated a pacemaker.

The patient's condition improved somewhat with frequent hemodialysis and vasodilator and oxygen therapy. Patchy eschars developed on his lower legs and ultimately sloughed, but skin grafts were not required. His right foot and left forefoot became gangrenous. Appropriate amputations were performed, and the wounds were left open, but they failed to heal despite repeated attempts at secondary closure. His right nephrectomy incision also failed to heal. Although never infected, it also failed to close despite repeated attempts. A biopsy specimen of muscle from this wound contained oxalate crystals, as did muscle from the amputation specimens on histologic examination.

Because of his open wounds, protein loss, and catabolic state, the patient was thought to be near death. We decided on an urgent kidney transplantation in the hope that a decrease in the total-body oxalate concentration would save his life.

On February 4, 1987, pyridoxine therapy (200 mg three times daily) was initiated and continued until the patient's liver transplantation, without apparent benefit. A kidney obtained locally on February 24, 1987, was implanted within three hours. Immunosuppressive treatment consisted of cyclosporine, azathioprine, and prednisone. The kidney was a complete HLA mismatch, but no rejection occurred. During the next month the patient recovered rapidly. His creatinine-clearance rate reached 1.27 ml per second. He gained weight, his amputation sites were successfully closed, and the wound in his back began to heal.

During the 250 days after renal transplantation, large amounts of oxalate were excreted by the renal allograft and the patient's blood oxalate level declined to normal within a month (Fig. 1). Throughout this period he was following a low-oxalate diet. At the same

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Reprinted from the *New England Journal of Medicine*
321:1100-1103 (October 19), 1989