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The Nephropathy of Type I Tyrosinemia after Liver Transplantation

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ABSTRACT

Type I tyrosinemia (HTI) is an autosomally recessively inherited disease caused by deficiency of fumarylacetoacetate hydrolase. The disease manifests with liver failure, renal tubular defects, and neurologic crises. Currently orthotopic liver transplantation (OLT) enables patients to survive. However, renal fumarylacetoacetate hydrolase deficiency is not corrected by OLT, and the long-term prognosis of the nephropathy is not known. We investigated tyrosine metabolism, GFR, renal tubular function, and histopathology before and 18–36 mo after OLT in eight patients with HTI. Progressive renal dysfunction was not documented despite continuing, although diminished, urinary succinylacetone excretion in all patients. The mean GFR was 82 mL/min/1.73 m^2 before and 102 mL at 18 mo and 93 mL at 36 mo after OLT. All patients showed tubular dysfunction before OLT. At 18 mo, glucosuria occurred in one, amino aciduria and phosphaturia in three, and hypercalciuria in six patients. Only hypercalciuria was seen at 36 mo. Renal biopsies showed mild nonspecific changes caused either by minimal progression of the renal disease or by mild cyclosporine nephrotoxicity. In conclusion, patients with HTI had normal GFR, but showed signs of tubular dysfunction 18–36 mo after OLT. Renal function and histopathology should be monitored after OLT for HTI. (***Pediatr Res* 37: 640–645, 1995**)

Abbreviations

CsA, cyclosporine A
FAH, fumarylacetoacetate hydrolase
HTI, hereditary tyrosinemia type I
OLT, orthotopic liver transplantation
SA, succinylacetone
SAA, succinylacetoacetate
TmP/GFR, maximal fractional tubular phosphate reabsorption

Type I tyrosinemia is an autosomally recessively inherited disease caused by FAH deficiency (1). FAH catalyzes the last step of tyrosine metabolism, and the deficiency leads to the accumulation of maleyl- and fumarylacetoacetate and to the appearance of SA and SAA. Increased urinary excretion of SA and SAA occurs only in tyrosinemia and is diagnostic for the disease. The gene coding for FAH has been assigned to chromosome 15q23-q25 (2). Seven separate disease-inducing mutations of the gene have been described (3–6).

Clinically type I tyrosinemia can be divided into two forms. The acute form of the disease is characterized by signs of severe liver failure—ascites, bleeding tendency, and hypoglycemia—from the first months of life, and previously the patients died in early infancy. The chronic form is milder, and liver function less abnormal. However, the risk of hepatocellular carcinoma is increased, and carcinoma has been estimated to develop in at least 37% of patients surviving beyond 2 y of age (7). Currently the standard therapy in both forms of the disease is OLT which cures the liver disease and corrects most of the metabolic abnormalities (1). Recently a pharmacologic therapy based on *p*-OH-phenylpyruvate dioxygenase inhibition has been suggested as an alternative to OLT (8).

Renal tubular dysfunction is a constant finding in type I tyrosinemia (1). Renal proximal tubular defects with glucosuria, amino aciduria, tubular acidosis, and hypophosphatemic rickets may be present. In the chronic form tubular dysfunction may be the leading symptom. In a series of 19 patients evaluated for OLT, 12 also had poor glomerular function and two received both liver and kidney allografts (9). At another center four of five patients developed nephrolithiasis before OLT (10). Renal histopathologic findings at OLT or at autopsy are proximal tubular dilatation and vacuolation, simplification of the tubular epithelial cells, glomerulosclerosis, and interstitial fibrosis (11).

The effect of OLT on renal function is not clear. Urinary succinylacetone excretion continues in the majority of patients (12, 13). This is probably due to local production of SA in

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tubular cells as the enzyme defect persists in the kidneys. Thus, renal function may deteriorate further after OLT. In short-term studies, some degree of dysfunction persists in most patients, although complete resolution of the tubular abnormalities has been reported in three patients (13, 14). Long-term glomerular and tubular function after OLT has been investigated in only two patients (14). In these patients both glomerular and proximal tubular function were normal after 3 y. However, one of the patients did not excrete measurable amounts of SA after OLT, and the other excreted it only during infections. They may therefore have had a more favorable prognosis than patients with continuous SA excretion after OLT.

Previously patients with acute type I tyrosinemia died in early infancy, and their renal prognosis was irrelevant. Current treatment with OLT has enabled these patients to survive, and the prognosis of the disease in extrahepatic organs has a major impact on their well-being. To elucidate the prognosis of the renal lesion, we have investigated renal function and histopathology 18–36 mo after OLT in eight patients with type I tyrosinemia. The pretransplant period was analyzed using retrospective data from patient records; posttransplantation data were obtained by prospective investigation.

METHODS

Patients. The patients were enlisted in the study after obtaining informed consent from the parents. The study protocol was approved by the ethical board of our institution. The diagnosis of tyrosinemia was based on the typical clinical picture, high urinary excretion of SA and SAA and absence of immunoreactive FAH in fibroblasts (15). All patients showed consanguinity at a distance of nine to 14 generations (patient 8 not investigated), and have the same disease-inducing single amino acid mutation in their FAH gene (6) (Tanquay, RM, personal communication). Neither immunoreactive FAH nor enzymatic activity was found in their liver. The patients' mean age at diagnosis was 0.4 y (range 0.1–0.6) (Table 1). After diagnosis all patients were placed on a phenylalanine- and tyrosine-restricted diet, and plasma concentrations of tyrosine and methionine were monitored until liver transplantation, which was performed at a mean age of 1.5 y (range 0.4–2.7).

Patients 1, 2, and 4–8 are currently well with a mean follow-up of 3.2 y after transplantation (range 2.3–4.3 y). Major complications have been vanishing bile duct syndrome occurring within the first 6 mo in patients 2 and 3. Both patients required retransplantation (24 and 22 mo after OLT, respectively). Patient 2 is currently well 12 mo after retransplantation. Patient 3 died of septic infection 1 mo after retransplantation.

Immunosuppression after OLT. CsA (5 mg/kg p.o.) was given preoperatively. Methylprednisolone (100 mg i.v.) and azathioprine (1.4 mg/kg i.v. in two doses) were given intraoperatively. Postoperative immunosuppression included methyl-

Table 1. *Parameters of liver function and tyrosine metabolism in eight patients with type I tyrosinemia before and after OLT*

Parameter*	Patient 1	2	3	4	5	6	7	8
On diagnosis								
Age (y)	0.5	0.4	0.1	0.3	0.6	0.1	0.6	0.5
Presenting symptoms	Glucosuria	Ascites	Tyrosinemia in brother	Ascites	Diarrhea	Ascites rickets	Rickets	Failure to thrive
P-TT-SPA (%)	19	8	30	11	10	8	16	6
S-AFP (U/L)	212 700	349 010	199 000	76 200	142 600	201 700	188 900	303 000
P-tyrosine (μmol/L)	278	542	370	185	383	770	314	659
U-SA + SAA (mmol/mol creatinine)	87	248	376	197	580	199	+†	778
At OLT‡								
Age (y)	2.3	1.8	2.7	1.4	0.9	0.4	1.1	1.1
P-TT-SPA (%)	78	20	59	49	33	20	24	33
S-AFP (U/L)	14 533	39 404	769	13 008	71 690	255 300	188 900	91 973
P-tyrosine (μmol/L)	95	80	53	34	106	93	75	32
U-SA + SAA (mmol/mol creatinine)	44	56	283	199	143	158	+†	302
18 months after OLT								
P-TT-SPA (%)	71	88§	16§	61	91	77	68	67
S-AFP (U/L)	5	10	149	2	19	10	5	7
P-tyrosine (μmol/L)	28	81	76	38	ND‖	66	36	58
U-SA + SAA (mmol/mol creatinine)	1.7	7.2	3.2	12.4	8.8	4.3	5.8	11.3
36 months after OLT¶								
P-TT-SPA (%)	72	54	—**	94	94	65	63	83
S-AFP (U/L)	10	10		2	12	4	6	8
P-tyrosine (μmol/L)	32	ND		ND	ND	ND	41	40
U-SA + SAA (mmol/mol creatinine)	5.4	12.5		6.7	7.4	5.4	11.0	6.2

* P-TT-SPA = prothrombin complex (normal, 70–130%), AFP = α-fetoprotein (normal 0–10), U = urinary. Normal plasma tyrosine <97 μmol/L in patients aged less than 0.3 y, <121 μmol/L in older children.

† "High urinary excretion."

‡ Values are given as mean of measurements performed during the last 2 mo preceding OLT.

§ Patient has vanishing bile duct syndrome.

‖ ND = not done.

¶ Patient 2 investigated 6 months after retransplantation due to vanishing bile duct syndrome (=30 mo after the first OLT).

** Patient died between 18 and 36 mo.

prednisolone, 3 mg/kg/d p.o., which was tapered down to 0.25 mg/kg at 1 mo and to 0.37 mg/kg every other day after 6 mo; azathioprine, 2 mg/kg/d p.o., which was reduced to 1 mg/kg/d after 2 wk and increased to 1.4 mg/kg at 6 mo when the methylprednisolone dose was reduced; CsA, given as a continuous i.v. infusion for the first 2 wk, aiming at a trough blood concentration of 500 μg/L (specific monoclonal radioimmunoassay, Sandimmun Kit, Sandoz, Basel, Switzerland). After 2 wk the patients were switched to peroral CsA three times daily, aiming at a trough blood concentration of 300–500 μg/L. The dose was slowly reduced to attain a concentration between 100 and 200 μg/L after 1 y.

Graft function and tyrosine metabolism. Total blood count, prothrombin complex, and concentrations of serum or plasma alanine and aspartate aminotransferases, γ-glutamyl transferase, coagulation factors F V and F VII, albumin, prealbumin, and total and conjugated bilirubin were determined before and at regular intervals after OLT.

Plasma tyrosine, serum α-fetoprotein, urinary δ-aminolevulinate, and urinary SA and SAA concentrations were monitored. Urinary SA and SAA were determined as trimethylsilyl derivatives by gas chromatography-mass spectrometry using the selective ion recording technique. The derivatives were formed by treating urine samples with hydroxylamine followed by lyophilization and trimethylsilylation (16). Sensitivity of the assay in routine use for both compounds was of the order of 0.5 mmol/mol creatinine. Using this assay SA or SAA could not be detected either in healthy persons or in obligate carriers of the disease.

Glomerular and tubular function. GFR was measured by ^{51}Cr-EDTA clearance (17). Tubular function was investigated by measuring serum concentrations and 24-h urinary excretions of amino acids, glucose, calcium, phosphate, and creatinine. Urinary calcium/creatinine ratio and fractional tubular phosphate reabsorption rate (TmP/GFR) were calculated. Capillary blood astrup analysis was obtained. Analyzes were performed 18 and 36 mo after transplantation. In addition, ^{51}Cr-EDTA clearance was done before OLT.

Urinary glucose excretion <2 g/24 h, urinary calcium/creatinine ratio <0.22 mg/mg (=0.63 mmol/mmol) and urinary α-amino nitrogen excretion ≤0.20 mmol/kg body weight/24 h (≤0.30 in patients under 1 y of age) were considered normal (18). Phosphaturia was defined as TmP/GFR more than 2 SD below age-corrected mean (19).

Renal histopathology. A surgical renal biopsy was performed on four patients at the time of transplantation. Protocol renal core needle biopsies were performed in seven patients 18 mo and in five patients 36 mo after transplantation regardless of renal function. The biopsies were obtained under ultrasound guidance using an automated punch device (Biopty-Cut, Radiplast, Bromma, Sweden). A needle with an outside diameter of 1.2 mm was used to obtain biopsies sized 0.9 × 20 mm. The specimens were fixed in 4% formaldehyde, embedded in paraffin, and cut into serial 4-μm thin sections. The sections were stained with hematoxylin-eosin, periodic-acid Schiff, Herowich, Masson's trichrome (or acid fuchsin orange G-trichrome), and methenamine silver periodic-acid Schiff methods for light microscopy. All biopsies were coded and blindly examined by two investigators (J.L. and L.K.). Biopsies with a minimum of five glomeruli were considered representative and accepted for analysis. The histologic findings in the renal interstitium, glomeruli, vessels, and tubuli were semiquantitatively scored using a method previously described (20). The method was modified so that changes were scored from − to +++, with increasing severity (− = none, + = mild, ++ = moderate, +++ = severe). The changes were classified as focal (less than two out of four visual fields) or diffuse.

RESULTS

Liver function and metabolic status. On diagnosis all patients presented with signs of severe liver failure, elevated plasma tyrosine, and serum α-fetoprotein concentrations, as well as high urinary SA, SAA, and δ-aminolevulinate excretion (Table 1). During conservative therapy the laboratory findings improved but remained abnormal. After OLT liver function was nearly normal in all patients except the two with vanishing bile duct syndrome. All patients continued to excrete SA in their urine after transplantation but the rate of excretion had decreased on an average to 5% of the pretransplant levels (mean urinary SA + SAA 169 mmol/mol creatinine before OLT, 6.8 and 8.1 mmol/mol creatinine at 18 and at 36 mo after OLT, respectively).

Renal function. The mean GFR before OLT was 82 mL/min/1.73 m^2. Six of the eight patients had a GFR less than 90 mL/min/1.73 m^2 (Table 2). After OLT the mean GFR increased and was 102 mL/min/1.73 m^2 18 and 93 mL/min/1.73 m^2 36 mo after transplantation. Clear metabolic acidosis (pH < 7.33 and serum HCO_3 < 20 mmol/L) was not seen after transplantation.

All patients except patient 3 showed evidence of either glucosuria or aminoaciduria before transplantation (no data of urinary amino acid excretion available of patient 3) (Table 2). All patients were hypophosphatemic and four had rickets. Eighteen months after OLT all patients except patient 2 showed evidence of either phosphaturia or hypercalciuria. In addition, aminoaciduria was present in three patients and glucosuria in one patient. At 36 mo only hypercalciuria was present in four patients.

Histopathology. The most common histopathologic findings 18 and 36 mo after transplantation are presented in Table 3. In most biopsies the observed changes were mild (Fig. 1).

Glomerular changes were mainly limited to the mesangium. The capillary basement membranes were normal in all biopsies except one taken at 36 mo (patient 6), which showed mild glomerulosclerosis (25% of glomeruli sclerosed). At transplantation the most common glomerular finding was mild to moderate mesangial cell proliferation. In addition, mild mesangial matrix increase was seen in one biopsy. At 18 mo the glomerular changes persisted but in two of the five biopsies taken at 36 mo all glomeruli appeared normal (Fig. 2).

The most common tubular findings were dilatation, epithelial swelling, epithelial vacuolation, and epithelial atrophy. Tubular dilatation was constantly present in most biopsies. Epithelial swelling and vacuolation were most prominent at transplantation and tended to diminish during follow-up. Tu-

Table 2. *Renal glomerular and tubular function in eight patients with type I tyrosinemia before and after OLT*

Function*	Patient 1	2	3	4	5	6	7	8
Before OLT								
GFR (ml/min/1.73 m^2)	72	90	76	89	46†	60	86‡	137
Aminoaciduria	+	+	ND§	−	+	+	+	+
Glucosuria	+	−	−	+	−	−	+	+
Hypophosphatemia/rickets	+/+	+/+	±	±	+/+	±	+/+	±
18 mo after OLT								
GFR (ml/min/1.73 m^2)	90	71‡	87	136	110	71	109	145
Aminoaciduria	−	−	−	+	−	−	+‖	+
Glucosuria (g/L)	−	−	−	−	−	−	+(12)	−
Phosphaturia (TmP/GFR, mmol/L)	+(0.84)	−(1.30)	+(0.61)	−(1.39)	−(1.35)	+(0.92)	−(1.07)	−(1.31)
Hypercalciuria (U-Ca/Crea)	¶+(0.70)	−(0.11)	+(1.04)	+(1.15)	+(0.92)	−(0.31)	+(1.38)	+(1.82)
36 mo after OLT**								
GFR (ml/min/1.73 m^2)	95	103	—††	—‡‡	89	79	92	98
Aminoaciduria	−	−			−	−	−	−
Glucosuria	−	−			−	−	−	−
Phosphaturia (TmP/GFR, mmol/L)	−(1.13)	−(0.95)		−(1.66)	−(1.40)	−(0.96)	−(1.01)	−(1.20)
Hypercalciuria (U-Ca/Crea)	+(0.71)	−(0.53)		+(1.44)	+(1.15)	−(0.02)	−(0.27)	+(0.75)

* GFR (^{51}Cr-EDTA-clearance), U-Ca/Crea given as mmol/mmol (normal <0.63). U = urinary.

† Creatinine clearance.

‡ GFR estimated according to the formula of Schwartz et al. (21).

§ ND = not done.

‖ Twelve months after transplantation.

¶ Twenty-four months after transplantation.

** Patient 2 investigated 6 mo after retransplantation due to vanishing bile duct syndrome (=30 mo after the first OLT).

†† Patient died between 18 and 36 mo.

‡‡ ^{51}Cr-EDTA-clearance failed due to technical difficulties.

bular atrophy was not seen at transplantation but was present in some of the follow-up biopsies. Mild microcalcification was present in one biopsy at transplantation and in one at 36 mo.

The most prominent finding in the renal interstitium was mild focal fibrosis which was seen in 18-mo biopsies of patients 1, 3, 6, and 7. It was accompanied by a small focal infiltration of lymphocytes in the biopsy of patient 6. Diffuse fibrosis was not seen.

Vascular changes were rare. Mild arteriolar endothelial proliferation was seen in 18 mo biopsies of patients 1 and 3. Mild intimal proliferation was present in the surgical biopsy of patient 2. Arteriolar hyalinosis was not seen.

DISCUSSION

In the present study, renal glomerular and tubular function improved during the first 3 y after OLT in patients with type I tyrosinemia despite total lack of immunoreactive FAH and persistent, although markedly decreased, urinary SA and SAA excretion implying a severe form of the disease.

Current treatment with OLT enables patients with type I tyrosinemia to survive and normalizes the hepatic tyrosine metabolism (1). However, the prognosis of the disease in extrahepatic organs remains unknown. FAH deficiency persists in the kidneys, and most patients excrete SA and SAA in their urine after OLT (12, 13). The reported reduction of the pre-OLT glomerular function and the persistence of abnormal renal tyrosine metabolism raise the possibility of progressive renal failure especially when the potentially nephrotoxic CsA is used for immunosuppression.

The Finnish tyrosinemia patients presumably represent a homogenous group distinct from other patients with type I tyrosinemia. All patients investigated are consanguinous and have the same unique mutation in their FAH-gene (6). This mutation leads to a severe form of the disease in which no immunoreactive FAH is found. Renal involvement is evidenced by persistent urinary SA and SAA excretion after OLT reflecting abnormal tyrosine metabolism in the tubular epithelial cells.

Glomerular function was good in our patients, in fact better than previously reported in pediatric liver transplant recipients on CsA (22, 23). GFR even increased, although not significantly, during the follow-up overriding a possible CsA related decrease. This suggests that liver disease was the main determinant of the pre-OLT glomerular dysfunction. The lack of CsA nephrotoxicity may in part be due to CsA administration in three doses/day instead of the traditional two doses/day resulting in more constant trough blood levels and lower and less toxic peak concentrations (24). A switch from two to three daily doses has been reported to improve GFR by 18–134% (25). Significantly, in one patient a pre-OLT GFR of 46 mL/min/1.73 m^2 showed substantial improvement to 110 mL/min/1.73 m^2 by 18 mo. In view of our results a policy of performing a combined liver and renal transplantation in patients with GFR <40 mL/min/1.73 m^2 adopted by one center (9) should not be categorically followed.

Renal tubular function, especially the handling of glucose and amino acids, also improved. However, some signs of dysfunction were present late after transplantation. At 18 mo, glucosuria, aminoaciduria, phosphaturia, and hypercalciuria were observed, and at 36 mo hypercalciuria was still present in four patients. SA has been shown to impair sugar, amino acid, and phosphate uptake by rat renal proximal tubular brush

Table 3. *The most common histopathologic light microscopy findings in kidneys of seven children with type I tyrosinemia who received liver transplants*

Findings	Patient 1	2	3	4	6	7	8
At transplantation (OLT)*							
Glomerulosclerosis	ND†	−	−	−	ND	ND	−
Mesangial cell proliferation		+	+	++			−
Mesangial matrix increase		−	−	+			−
Proximal tubular dilatation		−	+	+			+
Tubular atrophy		−	−	−			−
Tubular vacuolation		+	+	+			+
Tubular epithelial swelling		++	+	+			−
Microcalcification		+	−	−			−
18 mo after OLT‡							
Glomerulosclerosis	−	−	−	−	−	−	−
Mesangial cell proliferation	+	+	+	−	+	+	+
Mesangial matrix increase	−	−	−	−	−	+	−
Proximal tubular dilatation	+	−	+	−	+	+	−
Tubular atrophy	+	−	+	−	−	−	−
Tubular vacuolation	−	−	−	−	+	−	−
Tubular epithelial swelling	−	−	−	−	−	−	−
Microcalcification	−	−	−	−	−	−	−
36 mo after OLT‡							
Glomerulosclerosis	−	NA§	—‖	−	+	−	−
Mesangial cell proliferation	−			+	−	−	+
Mesangial matrix increase	−			−	+	−	+
Proximal tubular dilatation	+			−	+	+	−
Tubular atrophy	+			−	+	−	−
Tubular vacuolation	+			−	−	−	−
Tubular epithelial swelling	+			−	−	−	−
Microcalcification	−			−	−	+	−

Findings are semiquantitatively scored from + to +++ with increasing severity.
* Surgical biopsy.
† ND = not done.
‡ Core needle biopsy.
§ NA = not applicable.
‖ Patient died between 18 and 36 mo.

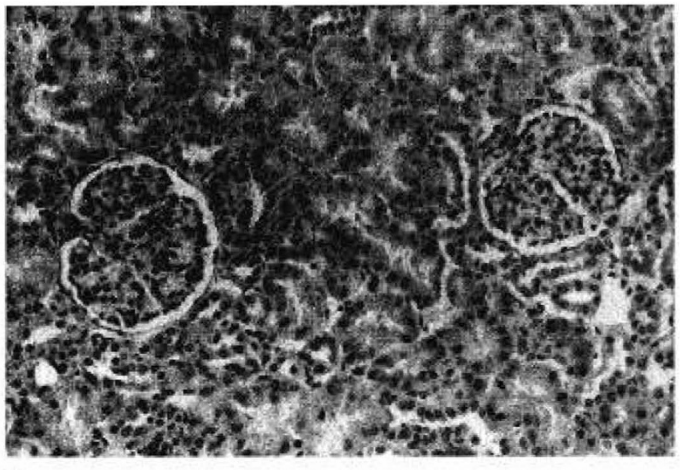

Figure 1. Mild tubular dilatation and mesangial cell proliferation in a surgical renal biopsy taken at liver transplantation of patient 3 (Masson's trichrome staining, original magnification ×200).

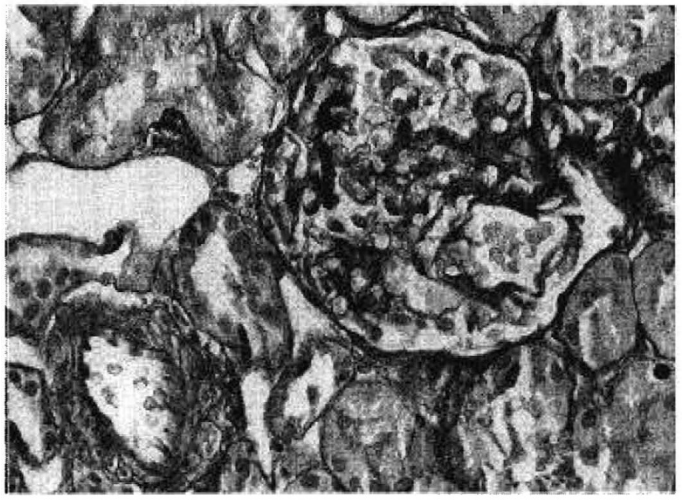

Figure 2. A normal glomerulus and an arteriole, mild tubular atrophy in a core needle biopsy of patient 3 taken 18 mo after liver transplantation (acid fuchsin orange-G staining, original magnification ×400).

border vesicles *in vitro* (26, 27) and cause glucosuria, aminoaciduria, and proteinuria when administered to adult rats (28). The etiology of hypercalciuria is not clear as it has not been previously reported in these patients. However, it is also likely to be caused by impaired proximal tubular reabsorption. The persistence of hypercalciuria is important considering the reports of renal stones and nephrocalcinosis in patients with type I tyrosinemia already at an age less than 3 y (10). In our patients hypercalciuria has been mild and therapeutic intervention has not yet been considered necessary. In general, the improvement of tubular function despite continuing renal SA

production supports the notion that abnormal hepatic FAH activity causes most of the renal abnormalities in type I tyrosinemia.

Clear histopathologic evidence of progression of the renal disease was not seen. In the surgical biopsies taken at transplantation, tubular dilatation and vacuolation and epithelial cell swelling were common corresponding to previous descriptions of renal histopathology in tyrosinemia (11). In our patients glomerulosclerosis or interstitial fibrosis were not seen at this time, but mild mesangial cell proliferation and mesangial matrix increase were present. In most patients glomerular changes decreased in severity during follow-up in accordance with their good glomerular function. However, the mild glomerulosclerosis in one patient at 36 mo may indicate progression of tyrosinemia. Progression of the tubular findings was not seen in the follow-up biopsies. On the other hand, mild tubular epithelial atrophy and focal interstitial fibrosis were only seen in the follow-up biopsies. These findings may be caused by progression of the tyrosinemia-related renal lesion. However, the findings are nonspecific and may also be due to mild CsA nephrotoxicity (29). They are probably clinically unimportant at the present stage.

In conclusion, convincing functional or histopathologic evidence of progression of the renal lesion was not seen during the first 18–36 mo after OLT. Lack of hepatic FAH activity is therefore likely to be the main determinant of the renal lesion seen at OLT and abnormal renal enzymatic activity plays a lesser role. However, signs of tubular dysfunction, especially hypercalciuria, and mild nonspecific histopathologic changes were persistently present after OLT. Although renal function was good in our patients, given the previous reports of poor glomerular function and nephrocalcinosis in patients with type I tyrosinemia, we feel that investigation of renal function, both GFR and tubular parameters, and histopathology should be part of the routine follow-up after liver transplantation for type I tyrosinemia. Renal handling of calcium should receive special attention.

Type I tyrosinemia presumably represents a disease in which separate genetic mutations lead to different prognosis. The differences between our results and those of some previous reports are probably partially due to genetic factors. The tendency of established disease-entities to split into multiple subgroups places new demands on the clinician.

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