Liver Transplantation in Children With Propionic Acidemia: Medium-Term Outcomes

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Liver transplantation (LT) for patients with propionic acidemia (PA) is an emerging therapeutic option. We present a retrospective review of patients with PA who underwent LT at a tertiary liver center between 1995 and 2015. A total of 14 children were identified (8 males) with median age at initial presentation of 3 days (range, 0-77 days). Pretransplant median protein restriction was 1 g/kg/day (range, 0.63-1.75 g/kg/day), 71% required supportive feeding, and 86% had developmental delay. Frequent metabolic decompensations (MDs) were the main indication for LT with a median age at transplantation of 2.4 years (range, 0.8-7.1 years). Only 1 graft was from a living donor, and 13 were from deceased donors (4 auxiliary). The 2-year patient survival was 86%, and overall study and graft survival was 79% and 69%, respectively. Three patients died after LT: at 43 days (biliary peritonitis), 225 days (acute-on-chronic rejection with multiorgan failure), and 13.5 years (posttransplant lymphoproliferative disease). Plasma glycine and propionylcarnitine remained elevated but reduced after transplant. Of 11 survivors, 5 had at least 1 episode of acute cellular rejection, 2 sustained a metabolic stroke (with full recovery), and 3 developed mild cardiomyopathy after LT. All have liberalized protein intake, and 9 had no further MDs: median episodes before transplant, 4 (range, 1-30); and median episodes after transplant, 0 (range, 0-5). All survivors made some developmental progress after LT, and none worsened at a median follow-up of 5.8 years (range, 2-23 years). LT in PA significantly reduces the frequency of MDs, can liberalize protein intake and improve quality of life, and should continue to be considered in selected cases.

Liver Transplantation 26 419–430 2020 AASLD.
Received May 7, 2019; accepted October 9, 2019.

Propionic acidemia (PA) is a rare autosomal-recessive inherited metabolic disorder with a worldwide incidence of 1 in 100,000-150,000.[1] It is caused by a deficiency of the biotin-dependent mitochondrial enzyme, propionyl-coenzyme A carboxylase (PCC), which is responsible for the conversion of propionyl–coenzyme A (CoA) to methylmalonyl-CoA and is expressed ubiquitously. PCC is formed of 2 subunits, PCCA and PCCB, which are encoded for by *PCCA* and *PCCB*, respectively. Propionyl-CoA is formed by the following processes: the catabolism of the branched-chain amino acids valine, methionine, isoleucine, and threonine; β-oxidation of odd-chain fatty acids; and production by intestinal flora and cholesterol metabolism. Deficiency of PCC leads to elevation in propionyl-CoA, 3-hydroxy-propionic acid, and methylcitrate, ultimately leading to mitochondrial toxicity and end organ effects. PA gives rise to a multisystem disease affecting the bone marrow, central and peripheral nervous systems, heart, pancreas, and skeletal system.[2] Classically, PA presents in the first few days of life with encephalopathy (ENC), metabolic acidosis, moderate hyperammonemia, often with basal ganglia

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; ARDS, acute respiratory distress syndrome; ASD, autistic spectrum disorder; BP, biliary peritonitis; BS, biliary sepsis; CMV, cytomegalovirus; CoA, coenzyme A; CR, chronic rejection; DCM, dilated cardiomyopathy; ENC, encephalopathy; FG, faltering growth; FM, fine motor; FS, fractional shortening; GFR, glomerular filtration rate; GIP, gastrointestinal perforation; GM, gross motor; HA, hyperammonemia; HAT, hepatic artery thrombosis; HF, heart failure; HYPO, hypoglycemia; IQ, intelligence quotient; JAU, jaundice; LCR, late cellular rejection; LLC, lobar lung collapse; LT, liver transplantation; LVEF, left ventricular ejection fraction; MD, metabolic decompensation; MOF, multiorgan failure; MS, metabolic stroke; NA, not available; NGT, nasogastric tube; PA, propionic acidemia; PCC, propionyl-coenzyme A carboxylase; PE, pleural effusion; PEG, percutaneous endoscopic gastrostomy; PEM, preemptive management; PF, poor feeding; PICU, pediatric intensive care unit; PTLD, posttransplant lymphoproliferative disease; RD, renal

injury, and, if left untreated, coma. Movement disorders and cognitive impairment are commonly described in patients who survive into childhood and adolescence.[3] PA is described according to the initial presentation as early-onset (within the first month of life) or late-onset (presenting after the first month); the prognosis and phenotype are favorable in the latter. Historic cohorts that included both early-onset and late-onset PA patients showed an overall mortality of 42%-65%, but when focusing on early-onset PA patients alone, mortality has been reported as high as 59%-100%.[3-5]

The mainstay of medical therapy is a supervised protein-restricted diet, carnitine supplementation, oral metronidazole to reduce gut flora production, avoidance of fasting, and sick day regimens. Despite optimal medical therapy, longterm outcomes remain poor. With this study, we aimed to reanalyze and extend our initial single-center experience of liver transplantation (LT) in PA.[6]

Patients and Methods

Patients were identified retrospectively from a transplant database at a single UK tertiary liver center. Data were collected through a review of electronic notes (from 1999) and written case notes. Demographic data were collected including age, ethnicity, consanguinity, positive family history, comorbidities, and features of initial presentation. Transplantation details were recorded, including duration on waiting list, age at LT, graft type, duration of intensive care and hospital stay, and short-term and longterm complications. Patient and allograft survival were analyzed using a Kaplan-Meier estimate. Ethical permission was not required as this was considered a retrospective anonymised review of clinical practice.

Plasma glycine and propionylcarnitine (C3) levels were collected before and after LT. Statistical analysis was undertaken using Microsoft Excel for analysis of biochemical changes (paired sample *t* test) and frequency of metabolic decompensations (MDs; Wilcoxon signed rank test). Because the data collection was retrospective and anonymized, ethical approval was not required according to local protocols.

Results

DEMOGRAPHICS

A total of 14 patients (8 males) were identified between 1995 and 2015 (1 previously described by Rela et al.[7] and a further 4 by Vara et al.[6]). Ethnicities included 6 British Pakistani, 3 White British, 2 British Indian, 1 White Irish, 1 British Afghanistani, and 1 Kuwaiti. There were 7 from consanguineous parents, and 6 had a previously affected relative. A total of 12 had early-onset presentations with ENC and hyperammonemia (HA). Of the remaining 2 patients, 1 had a prenatal diagnosis and was managed prospectively from birth and 1 presented at 11 weeks of life with ENC (Table 1).

TRANSPLANTATION DETAILS

Indications for LT were frequent MDs (10 patients), previous mortality in an affected sibling (2 patients), and elective (2 patients). The mean time on the waiting list was 10.9 months (range, 0.2-57.6 months). Median age at transplant was 2.4 years (range, 0.8-7.1 years). All patients were metabolically stable prior to LT.

From 2011 onward, the patients were managed with a local guideline advising minimal fasting and optimization of intravenous calories from dextrose (delivered at 8-10 mg/kg/minute) perioperatively and intravenous carnitine.

There were 9 patients who received deceased donor grafts (6 left lateral segments, 2 right lobes, and 1 whole liver), 4 had auxiliary grafts (3 right lobes and 1 left lateral segment), and 1 patient received a left lateral segment from a living related donor. The average stay in the pediatric intensive care unit (PICU) was 8 days (range, 2-30 days). The average length of stay in the hospital was 24 days (range, 13-41 days).

dysfunction; RT, renal transplantation; RV, right ventricular; S&L, speech and language; SD, standard deviation; SEZ, seizures; Soc, social communication; WD, wound dehiscence.

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DOI 10.1002/lt.25679

TABLE 1. Patient Characteristics

	Patient 1*	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6*	Patient 7	Patient 8	Patient 9*	Patient 10	Patient 11	Patient 12	Patient 13*	Patient 14
Sex	Female	Male	Female	Female	Male	Male	Male	Male	Female	Female	Male	Male	Male	Female
Ethnicity	White British	Kuwaiti	British Indian	White British	British Pakistani	British Pakistani	White Irish	British Pakistani	British Pakistani	British Indian	White British	British Pakistani	British Pakistani	British Afghanistani
Consanguineous	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Previously affected relative	No	Yes	Yes	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes
Age at presentation, days	21	Antenatal diagnosis	3	5	3	28	2	3	5	5	77	3	<30	3
Clinical presentation	FG, PF, HA, ENC, SEZ	PEM	PF, ENC	ENC, HA	PF, HA, ENC	ENC, SEZ, HA	ENC	ENC	JAU, HYPO, ENC	PF, ENC	PF, ENC	HA	ENC	ENC
Additional diagnoses	Cyclical vomiting syndrome	None	Hearing impairment, epilepsy	Cerebellar ataxia	Hearing impairment	Autism	None	Prolonged QT syndrome	None	Dystonia	None	None	Wolf-Parkinson White	Autism
Age at LT, years	1.8	1.1	0.8	7.1	1.1	7.0	5.0	6.6	5.9	2.7	1.3	1.1	3.7	2.0
Year of LT	1995	1999	2001	2008	2008	2011	2012	2013	2013	2013	2013	2014	2015	2015
Indication for transplant	Frequent decompensation	Family history	Family history	Frequent decompensation	Elective	Frequent decompensation	Frequent decompensation	Frequent decompensation	Frequent decompensation	Frequent decompensation	Frequent decompensation	Frequent decompensation	Frequent decompensation	Elective
Days on the waiting list	50	233	5	593	11	214	574	340	273	183	91	153	1736	189
Living related or deceased donor	Deceased donor	Living related	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor	Deceased donor
Graft type	Auxiliary right lobe	Left lateral segment	Left lobe	Left lateral segment	Left lateral segment	Auxiliary right lobe	Left lateral segment	Left lobe	Auxiliary left lateral segment	Left lateral segment	Left lateral segment	Whole liver	Auxiliary right lobe	Left lateral segment
PICU admission length, days	4	7	2	2	3	3	2	30	10	8	8	4	25	2
Total hospital admission length, days	22	36	15	13	21	26	17	33	28	29	30	13	41	16
Complications	PE	ACR (×4), PTLD	PE, MS	CMV mismatch, ACR (×3)	ACR, CMV Viraemia (×2), HAT, second LT	ACR, CMV Viraemia (×2), LCR	PTLD, LCR, GIP	PE, LLC, GIP, BP, WD, CMV Viraemia, MOF	LLC, ACR (×3), CMV Viraemia	PE, ACR (×2), CMV Viraemia, Cholangiopathy, Second LT	PE, Extravasation injury	MS	PE, LLC, Tacrolimus toxicity, ACR (×2)	-
Follow-up duration, years	22.3	13.5	16.3	9.2	9.4	6.3	5.8	0.1	3.6	0.6	3.7	3.4	2.0	2.2
Age at last follow-up, years	24	Died aged 14	17	17	10	14	11	Died aged 6	10	Died aged 3	6	4	10	4

*Patient who received an APOLT graft.

Patient 1 was commenced on azathioprine, cyclosporin, and prednisolone for immunosuppression, whereas all other patients received tacrolimus and prednisolone after LT. Subsequently, 7 patients required additional mycophenolate mofetil for renal-sparing treatment, and 1 was converted from tacrolimus to sirolimus due to chronic rejection (CR). Renal function was normal in all patients before LT, as measured with ^{51}Cr–ethylene diamine tetraacetic acid (glomerular filtration rate [GFR], in mL/minute/1.73 m^2) or cystatin C [<1 mg/L]; Table 2).

ACUTE COMPLICATIONS

There were 6 patients who developed pleural effusion (PE), and 3 had single-lobe lung collapse in PICU. Two patients required chest drain insertion for the PEs, whereas the others were managed conservatively. One patient died 43 days after LT of biliary peritonitis (BP), wound dehiscence (WD), and multiorgan failure (MOF).

VASCULAR AND BILIARY COMPLICATIONS

Biliary leak was diagnosed in 2 patients; both were managed conservatively. One other patient developed hepatic artery thrombosis (HAT) within the first week after LT and subsequent ischemic cholangiopathy. He was successfully retransplanted 101 days after the first LT.

IMMUNE-RELATED COMPLICATIONS

Acute cellular rejection (ACR) occurred in 7 patients, and all were treated with high-dose intravenous steroids. Late cellular rejection (LCR) occurred in 2 patients. One patient developed CR and was retransplanted 6.7 months after the first LT; however, this patient died of MOF 16 days later. Cytomegalovirus (CMV) mismatch or acquired infection occurred in 6, and all were treated with intravenous ganciclovir.

BIOCHEMICAL FINDINGS

Ten patients had at least 1 plasma glycine level recorded before and after LT. Mean plasma glycine levels were calculated separately for each patient (Table 2). Calculated individual mean levels reduced from an overall cohort mean of 797 μmol/L (standard deviation [SD] ± 736 μmol/L) before LT to 399 μmol/L (SD ± 85 μmol/L) after LT. This reduction in the overall cohort mean of 398 μmol/L did not reach statistical significance using paired sample t test (t [9] = 1.68; $P = 0.06$), and mean glycine levels remained above the normal reference range (81-303 μmol/L) after LT.

There were 11 patients who had at least 1 plasma or blood spot C3 level recorded before and after LT. Mean C3 levels were calculated separately for each patient. Calculated individual means were reduced from an overall cohort mean of 47.0 μmol/L (SD ± 22.5 μmol/L) before LT to 28.0 μmol/L (SD ± 16.9 μmol/L) after LT. This reduction in the overall cohort mean of 19.0 μmol/L reached a statistical significance using a paired sample t test (t [10] = 3.18; $P = 0.005$), but mean C3 levels also remained above the normal reference range (0.4-2.7 μmol/L) after LT (Table 2).

PATIENT AND ALLOGRAFT SURVIVAL

Of 14 patients, 3 died after LT, as described previously. The remaining 11 had a median follow-up of 5.8 years (range, 2-22.3 years; Table 1). Median age at last follow-up was 10.5 years (range, 4-24 years). The 2-year patient survival was 86%, and the overall study survival was 79%. There were 4 liver grafts that failed within the first year after LT, with 2 patients undergoing retransplantation, giving a 2-year allograft survival of 75% (Fig. 1). Overall study graft survival was 69%.

ONCOLOGY COMPLICATIONS

Posttransplant lymphoproliferative disease (PTLD) occurred in 2 patients. One patient developed a colonic perforation secondary to adhesions 4 months after LT, and PTLD was suspected but not proven. He recovered well following surgical intervention and remained on minimal immunosuppression. The other patient developed cervical lymphadenopathy 4 years after LT and was diagnosed with non-Hodgkin B cell lymphoma. Treatment with surgical excision and chemotherapy induced remission, but a relapse 9 years later resulted in death from respiratory failure 13.5 years after LT.

CARDIAC COMPLICATIONS

Pre-LT echocardiography was normal in all patients as part of the pretransplant assessment. One patient

TABLE 2. Comparison of Pre- and Post-LT Characteristics

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Decompensations before LT		8	1	1	17	1	30	4	30	8	2	8	4	1	3
Decompensations after LT		0	0	1	0	2	0	0	1	0	5	0	3	0	0
Protein restriction before LT, g/kg/day		1	1.75	1.2	1.2	1.7	0.9	0.63	1	1.22	1	0.95	1	1.07	1.05
Protein restriction after LT, g/kg/day		Self-restriction (vegetarian)	NA	Self-restriction (vegetarian)	Normal diet	1.6	2.7	1.12	NA	No formal restriction	2.21	Self-restriction	2.1	No formal restriction	1.5
Medications before LT		2	5	2	8	3	5	6	6	5	4	7	8	3	4
Medications 0-2 years after LT		3	6	4	7	5	3	8	NA	7	10	4	5	7	6
Medications 2+ years after LT		2	9	5	4	3	3	8	NA	4	NA	3	2	6	5
Feeding before LT		Oral	NGT	Oral	PEG	Oral	PEG	PEG	PEG	NGT	PEG	NGT	PEG	PEG	Oral
Feeding 0-2 years after LT		Oral	Oral	Oral	PEG	Oral	PEG	PEG	NA	NGT	PEG	Oral	PEG	Oral	Oral
Feeding 2+ years LT		Oral	Oral	Oral	Oral	Oral	PEG	PEG	NA	NGT	NA	Oral	Oral	Oral	Oral
Development before LT	GM	Mild	Mild	Normal	Moderate	Mild	Moderate	Mild	Moderate	Moderate	Mild	Moderate	Normal	Normal	Mild
	FM	Mild	Mild	Normal	Moderate	Normal	Moderate	Normal	Moderate	Moderate	Mild	Moderate	Normal	Normal	Moderate
	S&L	Mild	Mild	Normal	Moderate	Normal	Severe	Mild	Moderate	Moderate	Mild	Moderate	Normal	Mild	Mild
	Soc	Mild	Mild	Normal	Moderate	Normal	Severe	Normal	Moderate	Moderate	Normal	Moderate	Normal	Normal	Moderate
Post-LT development in infancy	GM	Mild	Mild	Moderate	NA	Mild	NA	NA	NA	NA	NA	Mild	Normal	NA	NA
	FM	Mild	Mild	Moderate		Mild						Mild	Normal		
	S&L	Mild	Mild	Moderate		Mild						Mild	Mild		
	Soc	Mild	Mild	Moderate		Mild						Moderate	Normal		
Post-LT development in childhood	GM	Normal	Mild	Mild learning difficulties	NA	Normal	Normal	NA	NA	Normal	NA	Normal	Normal	Normal	Normal
	FM	Mild	Normal			Normal	Moderate			NA		Normal	Normal	Normal	Moderate
	S&L	Mild	Mild			Mild	Moderate			Moderate		Normal	Mild	Mild	Moderate
	Soc	Mild	Normal			Mild	Autism			NA		Normal	Normal	Normal	Autism
Post-LT development in adolescence	GM	Mild learning difficulties	NA	Moderate learning difficulties	Moderate learning difficulties	NA	Moderate learning difficulties and autism	NA	NA	NA	NA	NA	NA	NA	NA
	FM														
	S&L														
	Soc														
Pre-LT schooling		NA	NA	NA	Mainstream with support	NA	Special needs	Special needs	Special Needs	Special needs	NA	NA	NA	Mainstream with support	NA
Post-LT schooling		Mainstream school with support	NA	Mainstream school with support	Mainstream school with support	Mainstream school with support	Special needs	Special needs	NA	Special needs	NA	Mainstream school	Mainstream with support	Mainstream with support	NA
Pre-LT echocardiogram		Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

TABLE 2. *Continued*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Post-LT echocardiogram	Normal	Cardiomyopathy	LVEF 60% Normal RV function DCM	Normal	Mild LV dysfunction with FS 36%	Normal	NA	Normal	Mild subaortic stenosis No DCM	NA	Normal	Normal	Mildly reduced LV systolic function	Normal
Pre-LT GFR, mL/minute corrected	57	77	122	76	81	Not recorded	Not recorded	95	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	54
Pre-LT cystatin C, mg/L	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	0.89	Not recorded	0.78	0.84	0.96	0.98	0.87	0.68	1.09
Post-LT cystatin C, mg/L	1.14	Not recorded	0.88	1.00	0.88	1.26	0.79	Not recorded	1.50	Not recorded	0.95	0.95	1.26	1.18
Pre-LT mean propionylcarnitine, µmol/L	Not recorded	52.0	Not recorded	36.2	47.2	42.8	Not recorded	102.7	61.1	26.0	25.8	26.1	60.4	37.2
Post-LT mean propionylcarnitine, µmol/L	22.5	5.9	38.6	23.5	11.1	19.0	25.9	49.2	51.2	40.7	25.5	12.6	50.5	18.6
Pre-LT mean glycine, µmol/L	Not recorded	Not recorded	Not recorded	669	385	445	629	2830	Not recorded	440	873	330	816	555
Post-LT mean glycine, µmol/L	559	Not recorded	221	304	339	428	573	391	550	489	345	326	349	452

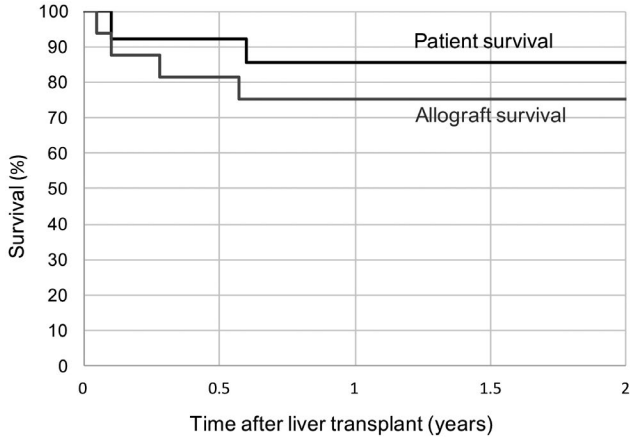

FIG. 1. Patient and graft survival at 2 years.

who died 13.5 years after LT had evidence of cardiomyopathy in the period prior to death, though further information is not available. Of the 11 survivors, 10 have had formal cardiology assessment after LT: 7 are normal at last follow-up and 3 have developed changes. There are 2 with mild left ventricular dysfunction (requiring lisinopril and, in addition, bisoprolol in patient 3 for mild dilated cardiomyopathy [DCM]), and 1 has mildly reduced left ventricular systolic dysfunction, which is under close monitoring with no medical intervention required at last follow-up.

NEUROVASCULAR COMPLICATIONS

Metabolic stroke (MS) occurred in 2 patients after LT: 1 presented with acute-onset seizures (SEZ) with a right-sided hemiparesis 12 months after LT. She subsequently required lamotrigine for epilepsy. The other patient had a viral illness with an atypical febrile convulsion 1 month after LT. There were new magnetic resonance imaging findings of basal ganglia stroke (diffuse increased T_2 signal in the putamen bilaterally). Both patients were not formally protein-restricted after LT, and neither showed evidence of biochemical disturbance during the episodes. Both have made a full neurological recovery.

METABOLIC DECOMPENSATIONS

The median number of recorded MDs before LT was 4 (range, 1-30), but it decreased to 0 (range, 0-5) after LT, which reached statistical significance using the

Wilcoxon signed rank test ($z = 2.68$; $P = 0.003$). Eight children had no further MDs after LT.

DIET AND MEDICATIONS

Median protein restriction before LT was 1 g/kg/day (range, 0.63-1.75 g/kg/day). All surviving patients increased their protein intake with no formal restrictions after LT. Of these, 3 are now adults with 2 choosing a vegetarian diet and 1 taking a normal diet with high-protein foods. The median protein intake has been estimated in 5 patients at 1.5 g/kg/day (range, 1.12-2.7 g/kg/day). The dietetic data are not available for 3 patients; however, according to clinic visit notes, 2 have a normal diet with no formal restrictions, and 1 self-selects a lower-protein diet. Supportive feeding was required in 10 patients before LT and reduced to 5 patients within the first 2 years after LT. After 2 years after LT, only 3 patients require supportive feeding.

All patients were on carnitine supplementation and metronidazole before LT, 10 patients required sodium benzoate in addition, and 4 were given carglumic acid. Medications after LT are as described previously. The median number of medications before transplant was 5 (range, 2-8) and increased to 6 (range, 3-10) within the first 2 years after LT. Following 2 years after LT, the median number of medications reduced to 4 (range, 2-9). After LT, 4 patients remain on carnitine supplementation.

SCHOOLING AND DEVELOPMENT

Six patients were of school age immediately before LT: 4 required special educational needs schooling, and 2 are in the mainstream education with additional support. Of 11 patients who have reached school age after LT, 3 continue to require special education, and 8 are in mainstream schools (6 of whom require extra support).

All patients had a developmental delay in at least 1 domain during infancy (0-2 years), childhood (>2 - <13 years), or adolescence (13+ years). Formal developmental assessments (in patients under 5 years) were undertaken with the Griffiths Mental Developmental Scale and the Wechsler Scale for Children III (UK version) in 6 patients. In the remaining patients, developmental information from metabolic and hepatology clinicians was descriptive. Of the patients, 10 had a global delay (defined as a delay in at least 2 domains), and 2, both aged <1 year, were assessed as having normal development before LT. Of 10 patients with childhood development recorded, 9 had speech and language delay. Mild-to-moderate learning difficulties were seen in 5 patients including 2 with a formal diagnosis of autism (Table 2).

Discussion

Our series of 14 patients with PA treated with LT is the largest to date from a single center. In addition, we now present a medium-term follow-up and supporting observations from our original series,[6] which strengthen the argument for an early LT consideration for children with PA.

Since 1992, 49 patients (56 grafts) with PA and LT have been reported (Table 3).[6-29] The median age at transplant was 3 years with a median follow-up of 2.5 years (range, 0.01-21 years). Preexisting cardiomyopathy was reversed in all 10 reported patie nts.[11,17,18,22,23,26] The most common reported complication was HAT occurring in 25% of the grafts. An estimate of the 1-year patient and allograft survival based on these patients is 74% and 65%, respectively, which is similar to the estimates previously reported by Barshes et al.[8] We demonstrate improved patient and allograft survival compared with the estimated 1-year survival reported by Barshes et al.[8]

The multicenter study by Charbit-Henrion et al.[22] reported poorer outcomes; 12 patients with PA transplanted in the United Kingdom and France had an overall survival of 42% compared with 79% in our series. Of our patients, 11 underwent transplantation within the last decade, whereas only 2 transplants were performed within this period in their series. It is possible that this difference can partly be attributed to improved surgical techniques, intensive care practices, and immunosuppression regimes. It is also possible that there is a center and age difference in the outcomes. When our series is combined with previous reports (overall median age at LT of 3.5 years and median follow-up of 3.4 years), the estimated 1-year patient and allograft survival is 75% and 66%, respectively. The estimated 5-year patient and allograft survival is 59% and 49%, respectively. Sass et al.[30] reported a survival of 66% in 42 PA patients who were not transplanted with a median age of 0.58 years at death. This may suggest that those who are transplanted have already survived the most vulnerable period and are amenable to LT.

Some studies have raised a possibility that LT for PA could be associated with a higher rate of HAT, with an incidence of 35% in 1 series.[22] In our series, HAT occurred in 6% (1 graft), which is similar to the

TABLE 3. Literature Review of LT for PA

Reference	New Cases	Onset of PA	Age at Transplant (years)	Donor (Living or Deceased)	Preexisting Cardiomyopathy	Complications	Follow-up Time (years)	Graft Survival	Patient Survival
Murphy et al.[9] (1992)	1	Early	1.9	Deceased	Unknown	HF	0.01	0/1	Died
Schlenzig et al.[10] (1995)	2	Early	7	Deceased	No	ACR, CMV, CR, HAT, PTLD	1.3	0/1	Died
		Early	9	Deceased	Yes, resolved*	ACR, CMV	13.5*	1/1	Alive
Rela et al.[7] (1997)	1	Early	1.8	Deceased (auxiliary)	No	RD†	15†	1/1	Alive
Yorifuji et al.[12] (2000)	1	Early	2	Living	No	MD	5‡	1/1	Alive
Kayler et al.[15] (2002)	1	Early	3	Deceased	No		0.3	0/1	Died
Yorifuji et al.[13] (2004)	2	Early	1.2	Living	No		1.8	1/1	Alive
		Early	5	Living	No		2.5	1/1	Alive
Barshes et al.[8] (2006)	2	Early	1.3	Deceased	No		3.7	1/1	Alive
		Early	2	Deceased	No	HAT	0.5	1/2	Alive
Sato et al.[16] (2009)	1	Late	2	Living	Yes, resolved§		3.4§	1/1	Alive
Romano et al.[11] (2010)	1	Late	6	Deceased	Yes, resolved		0.3	1/1	Alive
Ameloot et al.[18] (2011)	1	Late	16	Deceased	Yes, resolved		1‖	1/1	Alive
Vara et al.[6] (2011)	4	Early	1.1	Living	No	ACR, PTLD	11.4	1/1	Alive
		Early	0.8	Deceased	No	MS	7.3	1/1	Alive
		Early	7	Deceased	No	ACR	4.9	1/1	Alive
		Early	1.1	Deceased	No	ACR, HAT	2.2	1/2	Alive
Kasahara et al.[17] (2012)	2	Early	0.6	Living	No	CMV, GIP	0.8	1/1	Alive
		Early	2	Living	No	CMV	1.4	1/1	Alive
Nagao et al.[20] (2013)	1	Early	0.6	Living	No		1.7	1/1	Alive
Ryu et al.[21] (2013)	1	Early	1.8	Living	No	HAT	0.01	0/1	Died
Charbit-Henrion et al.[22] (2015)	12	Early	2.2	Deceased	No	Primary nonfunction, HF	0.02	0/2	Died
		Early	7.1	Deceased	Yes, resolved	PTLD, HAT	0.69	0/1	Died
		Early	9	Deceased	No	RD, RT	21	1/1	Alive
		Early	1.2	Deceased	No		21	1/1	Alive
		Early	1.1	Deceased	No	Primary nonfunction	0.01	0/1	Died
		Early	2.4	Deceased	No	HAT ×2, BS	17	1/3	Alive
		Early	1.1	Deceased	No	Primary nonfunction	0.01	0/1	Died
		Early	1.7	Deceased	No	HAT ×2	0.04	0/2	Died
		Early	3.9	Deceased	No	HF	0.08	0/1	Died
		Early	6.7	Deceased	Yes, resolved	ARDS ×2, HAT, PTLD	8	1/2	Alive
		Early	6.5	Deceased	No	HF	0.03	0/1	Died
		Early	8.3	Deceased	Yes, resolved	ARDS, RD	1	1/1	Alive

TABLE 3. *Continued*

Reference	New Cases	Onset of PA	Age at Transplant (years)	Donor (Living or Deceased)	Preexisting Cardiomyopathy	Complications	Follow-up Time (years)	Graft Survival	Patient Survival
Arrizza et al.[23] (2015)	1	Late	22	Deceased	Yes, resolved		10	1/1	Alive
Rajakumar et al.[24] (2016)	2	Early	3	Living (auxiliary)	No		0.04	1/1	Alive
		Late	4	Living (auxiliary)	No	HAT	0.27	1/1	Alive
Honda et al.[25] (2016)	1	Early	4	Living	No	AMR, IPB	0.13	0/1	Died
Silva et al.[26] (2017)	2	Early	12	Deceased	Yes, resolved		4	1/1	Alive
		Late	5	Deceased	Yes, resolved		5	1/1	Alive
Moguilevitch and Delphin[27] (2018)	1	Early	4	Deceased (domino)	No		2	1/1	Alive
Critelli et al.[28] (2018)	3	Early	8.7	Deceased	No	HAT, CMV	2.5	1/1	Alive
		Early	11.8	Deceased (domino)	No	ACR	2.1	1/1	Alive
		Early	1.2	Deceased	No	GIP, ACR	1.7	1/1	Alive
Quintero et al.[29] (2018)	6	Late	7.5	Living	No	HAT	4	1/1	Alive
		Late	5.4	Deceased	No		3.4	1/1	Alive
		Early	4.9	Deceased	No		1.7	1/1	Alive
		Early	2.9	Living	No		1.3	1/1	Alive
		Early	1.3	Deceased	No		0.9	1/1	Alive
		Late	5.9	Live	No	HAT	0.5	1/1	Alive

*Follow-up publication by Romano et al.[11]
†Follow-up publication by Vara et al.[6]
‡Follow-up publication by Morioka et al.[14]
§Follow-up publication by Kasahara et al.[17]
||Follow-up publication by Vermeer et al.[19]

overall reported rate of 7.8% in 400 pediatric LTs from our center.[31] When our data are combined with the previously published 49 PA cases, the rate of HAT is 22%. Therefore, we could not confirm an increased susceptibility for thrombotic events in our PA patients. In addition, the biliary complication rate in our cohort was 14.3%, which is comparable to a rate of 16.7% in children transplanted for other indications.[32] The overall retransplantation rate in children is reported as 13.3%, and in our cohort, it was 14.3%.[33] Therefore, we have not shown a particular increase in posttransplant complications in our cohort when compared with LT for other indications.

All of our patients who were previously restricted in their dietary protein intake could liberalize the diet after LT. Although no formal restrictions were in place for all patients, the majority choose to self-restrict high-protein foods. Safe protein intake is ensured with regular dietetic follow-up in the clinical setting, and in some cases, protein supplementation has been required for short periods in view of insufficient intake orally. Supplementary feeding methods with nasogastric or gastrostomy tubes were reduced by two-thirds following transplant, considerably adding to an improved quality of life. The proportion of children requiring supportive feeding after LT is almost half of that reported in a nontransplanted PA group.[2] All patients were advised to continue the carbohydrate emergency regimen during illness or fasting after LT.

Our study further endorses previous observations of reducing or even preventing MDs after LT with a potential benefit of improvement in neurocognitive development. Grünert et al. reported a rate of 75% of PA patients with cognitive impairment with a negative correlation between the number of MDs and intelligence quotient (IQ).[2,34] This implies that IQ could be improved in those with fewer MDs, but we could not formally elicit this from our study due to the lack of formal post-LT assessments.

The majority of our patients had global developmental delay with the speech and gross motor (GM) areas particularly affected. The majority of patients showed a progress in their overall development after LT. Special needs schooling was required in a third of our transplant survivors, but all children were noted to require extra support even in the mainstream education setting. We also note that 2 of our patients were diagnosed with autistic spectrum disorder (ASD) after LT. Within the last few years, ASD has been reported more frequently in patients with PA, and some authors now propose early routine screening.[35,36] Regular neurocognitive assessments before and after LT compared with nontransplanted patients would be an important area for further study.

Cardiomyopathy is a well-known complication of PA. Grünert et al.[2] reported an occurrence in 9% of 55 patients, whereas Romano et al.[11] reported hypokinetic DCM in 23% of nontransplanted children with PA. Reversal of cardiomyopathy in PA after LT was previously reported in all 10 patients with preexisting cardiomyopathy and, therefore, has been suggested as a bona fide indication for transplant.[11,18] Severe cardiomyopathy should not absolutely contraindicate LT in PA as recently demonstrated in children where extracorporeal membrane oxygenation or a left ventricular assist device has successfully been used as a bridge to LT in severe cardiac insufficiency.[18,19] None of our patients had evidence of cardiomyopathy before LT, but 27% of the survivors developed mild cardiomyopathy after LT. This observation is surprising and may reflect the natural history of PA, as the metabolic defect is not fully corrected in the myocardium.

LT in PA does not completely correct the underlying defect due to extrahepatic expression of the enzyme deficiency. Out of 14 patients, 4 received auxiliary grafts, and all are alive at last follow-up. There was no obvious discernible difference in their clinical outcomes. Auxiliary LT is a technically challenging procedure performed by few centers worldwide, but it has been shown to be effective in inherited metabolic diseases. The clinical success of this procedure demonstrates that a sufficient amount of enzymes is replaced and provides similar benefits to a whole liver replacement. The advantage is that if gene therapy becomes available in the future, these children could still be potential candidates.[37]

The use of living related donor grafts, ie, from heterozygote obligate carriers, for this autosomal-recessive condition was not common in our series. It was performed in only 1 patient who was not entitled to the cadaveric organ but who achieved adequate biochemical and clinical response in the short term. The patient unfortunately developed PTLD with the central nervous system involvement and died of relapse at the age of 13.5 years. Previous reports, predominantly from Japan, suggested that it is safe to use living related donors and that the patients show sufficient metabolic correction in the medium term.[38] However, our view

is that the use of an unrelated LT donor is preferential in patients with PA.

In conclusion, our series demonstrates good survival rates and satisfactory clinical outcomes in children with PA managed with LT. We demonstrate improved quality of life with liberalization of dietary protein and a reduction in episodes of MD in the majority. We would advocate ongoing specialist dietetic involvement after LT to ensure a safe and optimal protein intake, and oral feeding should continue to be encouraged. We would recommend regular cardiac surveillance and neurocognitive assessment in all patients after LT in view of the ongoing risk of decompensation. Selected patients with PA are potentially good candidates for early LT and are subject to careful consideration by the multidisciplinary team.

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