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Improved neurologic prognosis for a patient with propionic acidemia who received early living donor liver transplantation

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ABSTRACT

Despite medical therapy, patients with propionic academia (PA) still display a tendency to develop epilepsy. Patients with neonatal-onset PA who have received early living donor liver transplantation (LDLT) are limited in number, and the effect on neurologic prognosis, including epilepsy, is not clear. We report a patient with PA whose EEG findings improved dramatically after undergoing LDLT at age 7 months. The patient's neurologic development and brain MRI findings were quite satisfactory at age 2 years and 3 months. LDLT is effective not only in preventing metabolic decompensation, but also in improving neurologic function to ensure better quality of life.

1. Introduction

Propionic acidemia (PA) is an autosomal recessive metabolic disorder with an incidence of 1:50000 in Japan [1]. It is caused by a deficiency in propionyl-CoA carboxylase (PCC) activity, leading to metabolic decompensation and mitochondrial dysfunction [2]. This occurs during the metabolism of amino acids, odd-numbered fatty acids, and intestinal bacteria. Many patients present with PA during the neonatal period. The mortality is quite high, with a survival rate of 41% despite intensive care [3]. Severe neurologic complications are frequent in survivors [4].

Recent advances in medical management have improved the prognosis of PA, but the long-term neurologic outcome is generally disappointing. In particular, EEG abnormalities and epileptic seizures are frequent findings, with long-term manifestations occurring at a rate of almost 100% [5]. The relationship between the development of metabolic failure and the occurrence of EEG abnormalities has not been well understood. Principal problems in management are unpredictable metabolic decompensation, elevated ammonia levels, and difficulties with dietary restriction. Liver transplantation (LT) has been proposed to minimize the risk of further metabolic decompensation and to improve the quality of life [6]. Recent case studies have reported that supplementing the hepatic enzyme (PCC) by LT leads to clinical improvement, including better feeding and increased neurologic development, with fewer episodes of metabolic acidosis and decreased incidence of cardiomyopathies [7–10]. However, experience with LT for PA is still limited. In addition, the effect of LT on neurologic prognosis, including the role of LT in preventing the development of epilepsy in patients with PA, is not clear and remains controversial.

We report a female patient with neonatal-onset PA who showed progressive EEG abnormalities in infancy, but dramatically improved without having any epileptic seizures after undergoing LT at age 7 months.

2. Case report

A girl was born at term with normal delivery. Her body weight was 3243 g. She developed severe hyperammonemia (3170 μg/dl) and metabolic acidosis (venous blood pH of 7.02, HCO_3^- 7.2, base excess −17) at age 3 days. Metabolic encephalopathy was suspected, as evidenced by apnea and seizure. The patient was successfully rescued by continuous hemodiafiltration to decrease the levels of ammonia and organic acids. Ammonia levels normalized within 18 h after onset. Biochemical diagnosis was promptly performed. Acylcarnitine analysis revealed elevation of propionyl-carnitine (C3) to 12.7 nmol/ml (normal 2±0.8); the C3/C2 (C2: acetyl-carnitine) ratio was 0.90 (normal<0.25). Urinary organic acid analysis gave typical findings compatible with propionic acidemia. Methylcitrate (100.2, normal<3.3), 3OH-propionate (210, normal<2.0)

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and propionyl glycine (14.9, normal<0.5) were increased greatly. The diagnosis of PA was finally confirmed by mutation analysis in the *PCCA* gene, which was compound heterozygous for 1196G>A and IVS18+1G>A. 1196G>A caused an R399Q amino acid substitution. This mutation also co-segregated with 1676G>T (W559L) on the same allele (maternal, in the present case), as reported by Yang et al. [11]. IVS18+1G>A caused skipping of exon 18. Homozygotes of each mutation were all symptomatic during the neonatal and infantile periods [11]. Propionyl-CoA carboxylase (PCC) activity in cultured fibroblasts was below 1% of control mean activity (5 pmol/min/mg protein; control value, 1345±286 pmol/min/mg protein; $n=10$). Patients with PCC activity levels below 5% of control levels had all shown neonatal onset in previous studies [12,13].

The patient recovered rapidly from metabolic failure through receiving a low protein diet using the special formula for PA and medication with L-carnitine and metronidazole. The post-newborn period was uneventful, and hyperammonemia and metabolic acidosis were well controlled. Her body weight and height were comparable to the control level. Head control was almost complete, but she remained slightly hypotonic in the lower limbs. Developmental quotient (DQ) at 3 months of age was 90. She experienced no seizures, but sometimes became inactive and lethargic. EEG showed a disturbance of background activity, as well as some epileptiform discharges at age 4 months (Fig. 1A). Diffuse irregular polyspike and spike-and-wave complexes from multifoci were clearly increased at 6 months, and further deteriorated to show hypsarrythmia and burst suppression (Fig. 1B). Administration of zonisamide was started for seizure prevention. Cerebrospinal fluid free carnitine, acethylcarnitine and propionylcarnitine were 32.9 nmol/ml (range 3.35±0.43), 9.7 nmol/ml (range 1.85±0.41), and 27.6 nmol/ml (range 0.04±0.005), respectively, which suggested the accumulation of organic acids in the central nervous system (CNS). She could not roll over, and was sometimes unresponsive to the voices of family members. DQ deteriorated to 77.

The patient was referred for living donor liver transplantation (LDLT); the indication for LDLT was considered carefully through genetic counseling. The patient's pre-liver transplantation characteristics are listed in Table 1; most of the results were quite satisfactory. With parental concurrence, elective LT was thought to be a good option. LDLT (donated by the patient's father, a heterozygous carrier of IVS18+1G>A) was successfully performed at the National Center for Child Health and Development in Tokyo when the patient was 7 months old. She developed intestinal perforation on postoperative day 7, and experienced cytomegalovirus infection on day 48. Both events were well managed and her course has been uneventful since achieving normal graft function. After liver transplantation, the EEG dramatically improved to show only sporadic paroxysms. At 9 months of age, only small spikes in the frontal lobe were observed, and the burst suppression pattern had completely disappeared (Fig. 2A). At age 2 years and 3 months, the EEG showed normal background activity without epileptic discharge (Fig. 2B).

Table 1
Summary of the pre-LT evaluation.

Age at presentation	3 days
Consanguinity	*N*
UCG[a]	Normal
ALT (U/L)	13–24 (normal 8–42)
Total Bilirubin (mg/dl)	0.15–0.73 (normal 0.3–1.2)
γGT (U/L)	15–27 (normal 10–47)
Ammonia (μg/dl)	53–92 (normal 18–75)
Protein restriction	2 g/kg/day
Nutrition	Bottle feeding
Metabolic attack	None after the onset
Indication for LT	Elective

[a] Ultrasound cardiography.

When the patient was 5 months of age, a magnetic resonance imaging (MRI) scan had revealed cortical atrophy, caused by neonatal metabolic failure and continuing exposure to propionate. After LT, when the patient was 10 months of age, dramatic improvement was observed in the brain mass, both in the grey and white matter. A recent MRI scan (at age 2 years and 3 months) showed myelination to be age-appropriate, and signal abnormalities in the basal ganglia were not observed (Fig. 3). She was able to walk around by herself and play with various toys. DQ had improved to 100.

Although there was no apparent change in the elevated C3 level after LT, the C3/C2 ratio decreased to less than 1 (Fig. 4). This suggests that propionyl-CoA produced by extrahepatic tissues was more efficiently converted to acetyl-CoA in the transplanted liver. Urinary organic acid analysis also revealed a prominent decrease in propionate-related metabolites (methylcitrate 4.0–8.0, 3OH-propionate<2.0).

3. Discussion

Epileptic seizures and related EEG abnormalities have been described as major neurologic complications of inborn errors of metabolism [14]. Neuronal cells are very susceptible to the accumulation of toxic metabolites or deficiency in the energy supply in the central nervous system, which induces a burst suppression pattern in the EEG of an infant having progression of the disease. In reverse, such electrophysiological findings raise the suspicion of metabolic disorder

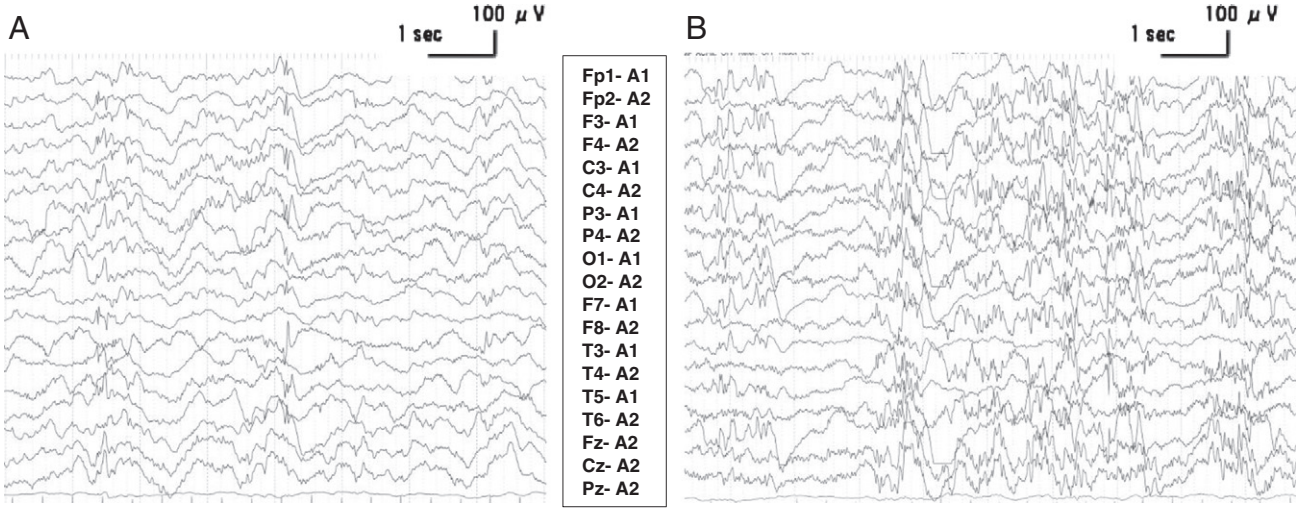

Fig. 1. EEG investigations before liver transplantation: (A) age 4 months; (B) age 6 months.