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Short Communication

A surviving 24-month-old patient with neonatal-onset carnitine palmitoyltransferase II deficiency

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ABSTRACT

The early-onset form of carnitine palmitoyltransferase (CPT) II deficiency has severe outcomes; patients typically die during the newborn period. We report a case of neonatal-onset CPT II deficiency with prolonged survival, exceeding 24 months. The patient was successfully treated by continuous hemodialysis (CHD), which enabled her to overcome repeated crises. We suggest that early intensive treatment, including CHD, is a key for prolonged survival in patients with neonatal-onset CPT II deficiency.

1. Introduction

Carnitine palmitoyltransferase (CPT) II deficiency is an autosomal recessive disorder of fatty acid metabolism. It has three distinct phenotypes: a mild adult-onset myopathic form, a severe infantile form, and a lethal neonatal form. Patients with the early-onset form commonly show severe outcomes and die early. In this report, we describe a favorable outcome in a patient with neonatal CPT II deficiency, who has survived for over 24 months.

2. Case

The patient was a 2646-g female infant who was born at 38 weeks of gestation by normal vaginal delivery to a healthy mother. Apgar scores were 9 and 9 at 1 and 5 min, respectively. Her parents were unrelated and her elder sister (3 years old) was healthy. Her family history showed no sudden death or symptoms suggestive of metabolic disorders. At 1 day of age, she was hospitalized owing to difficulty sucking and presented with hypoglycemia (between 20 and 30 mg/dL). She developed drowsiness on day 3 and had hyperammonemia (NH_3 438 μg/dL) on day 5. She was transported to our hospital on day 6. Physical examination showed a respiratory rate of 40 breaths/min, pulse rate of 170 beats/min, and blood pressure of 70/34 mm Hg. She had no apparent physical anomalies. Abdominal examination showed hepatomegaly. Neurologic examination showed decreased activity and responsiveness (Glasgow Coma Scale: E2V1M4 = 7) and a lack of sucking reflex. Laboratory data showed hyperammonemia (NH_3 407 μg/dL) and elevated aspartate aminotransferase (472 IU/L), lactate dehydrogenase (1774 IU/L), and creatine kinase (4591 IU/L). Venous blood gas analysis showed respiratory compensation for metabolic acidosis. Blood ketones were not measured. Chest and abdomen radiograph showed auxocardia; the cardiothoracic ratio was 58%. Echocardiography showed hypertrophy of the cardiac muscle and a reduced left ventricular ejection fraction (Fig. 1). Abdominal ultrasound showed hypertrophy of the gallbladder wall and echoencephalography showed no brain edema. She was treated by continuous hemodialysis (CHD) in the intensive care unit. CHD was effective, as evidenced by decreased ammonia, improved metabolic acidosis, and consciousness. Tandem mass spectrometry-based screening of her dried blood specimen drawn at 6 days of age revealed an increase in long-chain acylcarnitines; C16 40.25 nmol/mL (cutoff > 3.0), C18:1 14.75 nmol/mL, (C16 + C18:1)/C2 9.14 nmol/mL (cutoff > 0.62), strongly suggesting a CPT II deficiency. Accordingly, she was treated with carnitine, sodium phenylbutyrate, and medium-chain triglyceride

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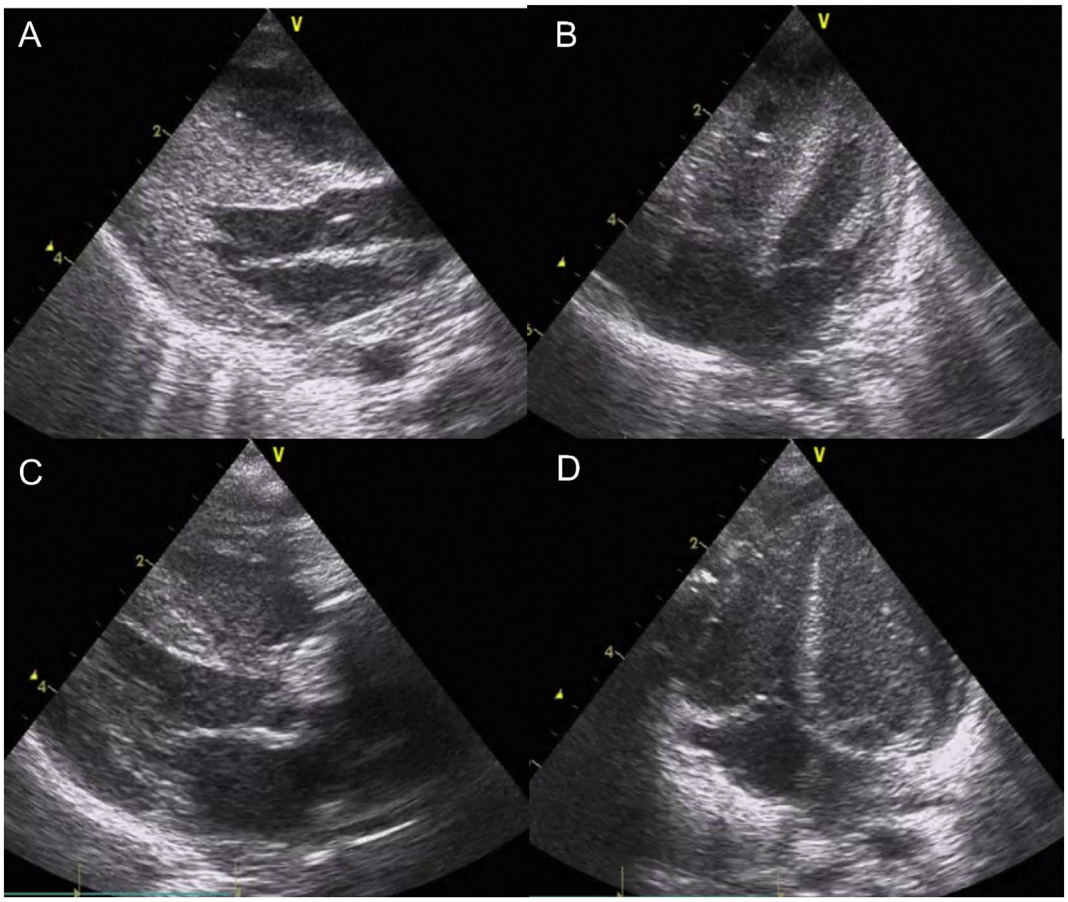

Fig. 1. Echocardiography.A,B: Onset. Echocardiography showed hypertrophy of the cardiac muscle, especially in the apex, and the left ventricular ejection fraction was reduced (65%).C,D: After treatment. Hypertrophy of the cardiac muscle and cardiac function were improved.

milk. The interval between feeding was adjusted to < 3 h to avoid hypoglycemia. Hyperammonemia, cardiac function, and the gallbladder wall improved (Fig. 1).

We confirmed the diagnosis of CPT II deficiency by an enzymatic assay and genetic testing. CPT II activity in lymphocytes was as low as 6.6% of the average of normal controls (8.4 pmol/min/10^5 cells; control: 126.3 ± 39.8 pmol/min/10^5 cells (n = 22)). At *CPT2*, the homozygous genotype c.451C > T (p.R151W) was identified. The parents were heterozygous carriers of the same variant.

At the age of 5 months, she presented with hyperammonemia without hypoglycemia. At the age of 12 months, she had liver and renal dysfunction, metabolic acidosis, and hyperammonemia transiently during enterogastritis. Similar episodes occurred at the ages of 21 and 24 months. She recovered from these crises by intensive treatment, including CHD. At present, she walks independently and can say several words. We conclude that she has nearly normal development.

3. Discussion

The neonatal form of CPT II deficiency is particularly severe. Hissink-Muller et al. reviewed 21 cases of neonatal CPT II deficiency [1] and found that all patients died before 6 months, typically before diagnosis [2,3,4]. A patient who survived for 6 months was diagnosed during the fetal period and was provided treatment immediately after birth [1]. We also reviewed past studies of neonatal-onset CPT II deficiency, and found that there is no report of survival for over 18.5 months in a patient with neonatal-onset CPT II deficiency [5]. The importance of early diagnosis by newborn screening has been established [6]. These past reports suggest that early treatment can prolong survival in patients with neonatal CPT II deficiency. The factors determining the survival period for patients with neonatal-onset CPT II deficiency may include multi-organ involvement, levels of residual enzyme activity, gene mutation site, and complicated congenital anomalies. Our patient, who survived for longer than 24 months, supports the importance of early diagnosis and therapy, especially CHD.

Thuillier et al. observed associations between clinical presentations and genotype and enzyme activity [7]. Specifically, CPT II enzyme activity levels in infantile-onset patients with homozygous *CPT2* mutations were < 10%. In our case, CPT II activity was 6.6% of the average level observed in normal controls. These findings suggest that lower levels of residual CPT II activity are associated with greater severity of CPT II deficiency. Patients homozygous for the c.451C > T (p.R151W) variant have not been reported previously. We previously observed a compound heterozygous patient with the c.451C > T mutation and another known variant who died suddenly during early childhood (unpublished data). Additionally, a patient homozygous for p.R151Q (c.452G > A) was classified as having the neonatal form [7]. Based on these findings, we inferred that individuals with the homozygous variant are at a high risk of the neonatal form of the disease.

The following treatments are considered effective for CPT II deficiency: (i) avoidance of known triggers, (ii) a high-carbohydrate and low-fat diet to provide fuel for glycolysis and supplementation of medium chain triglycerides, and (iii) infusions of glucose to prevent catabolism when dietary treatments are difficult. The patient in this case study survived with intensive care, including CHD. In neonates, CHD allows for more efficient ammonium removal compared with peritoneal dialysis (PD). However, the optimal dialysis modality is not known. PD is easy to initiate and manage, facilitating early treatment. Accordingly, PD is a potential therapeutic option for the future [8,9]. It is possible that CHD is effective for the recovery of metabolic decom-

pensation related to metabolic acidosis and hyperammonemia. No report to date has indicated that CHD prolongs the survival of patients with CPT II deficiency. We suggest that CHD treatment as early as possible after primary manifestations could be an effective therapy.

Our findings strongly suggest that early therapeutic intervention, including CHD, is effective for improving survival during acute attacks. In addition, the prognosis of CPT II deficiency might be related to the functions of multiple organs.

4. Conclusion

We observed the longest survival reported to date for a patient with neonatal-onset CPT II deficiency. We suggest early intensive treatment, including CHD. In the future, it is necessary to accumulate additional cases and follow-up data.

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