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Long-term survival of a patient with acute neonatal-onset metabolic encephalopathy with carbamoyl phosphate synthetase 1 deficiency

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Abstract. – OBJECTIVE: Long-term survival of patients with neonatal-onset carbamoyl-phosphate synthetase 1 deficiency (CPS1D), an autosomal recessive disorder characterized by repeated, life-threatening hyperammonemia, is rare. We describe the diagnosis and clinical management of a teenager with neonatal-onset CPS1D who did not undergo therapeutic liver transplantation.

CASE REPORT: Following emergent neonatal therapy, the patient was diagnosed with CPS1D based on clinical, radiological, biochemical and genetic analyses. Her clinical course, neurobehavioral development and therapeutic interventions are presented and discussed.

RESULTS: Born from nonconsanguineous parents, the proband underwent phototherapy for neonatal jaundice, associated with acute encephalopathy, apnea and cerebral edema. Based on blood and urinary biochemical abnormalities, neonatal-onset CPS1D was diagnosed. Her hyperammonemia was corrected by hemodialysis, followed by sodium benzoate, L-arginine, levocarnitine and protein-free diet therapy. Because of a relapse and persistent neurobehavioral regression by age 1, a planned liver transplantation was cancelled. At age 10, sodium phenylbutyrate was substituted as ammonia scavenger. Genetic testing revealed compound heterozygote c.2359C>T (R787X) and c.236+6T>C variants of CPS1, confirming her diagnosis. Despite severe neurological sequelae, the patient is 16 and in stable condition.

CONCLUSIONS: Our case suggests that early hemodialysis and pharmacologic interventions for acute neonatal hyperammonemia can improve the prognosis of patients with neonatal-onset CPS1D.

Key Words:
Carbamoyl phosphate synthase 1 deficiency, Neonatal, Hemodialysis.

Introduction

Carbamoyl phosphate synthase is an important enzyme involved in the synthesis of carbamoyl phosphate from ammonia in the urea cycle. Carbamoyl phosphate synthase 1 deficiency (CPS1D) is a rare autosomal recessive disorder with an inborn error of metabolism[1]. The onset of CPS1D includes the early neonatal type (develops during the first few days after birth) and late type (occurs in adulthood)[2]. The initial symptoms of neonatal-onset CPS1D include respiratory and consciousness disorders and convulsions within a few days after birth[3]. CPS1D commonly progresses with acute metabolic encephalopathy associated with acute severe hyperammonemia resulting in early postnatal death[1,4]. In this letter, we report on the long-term survival of a patient despite neonatal-onset CPS1D and severe neurological sequelae.

Case Report

The patient was born spontaneously during the 38th week of pregnancy from nonconsanguineous parents and has a healthy brother. She had been drinking milk since she was born. On the third to the fourth day after birth, the patient ran a fever of 38 degrees. On the fifth day, the patient underwent phototherapy for neonatal jaundice, after which she was referred to our neonatal intensive care unit (NICU) due to repeated vomiting and consciousness disorder. After admission to the NICU, the patient experienced frequent apnea and partial seizures. Brain computed tomography showed occipital-dominant mild cerebral edema and subarachnoid and subdural hemorrhages. Therefore, we adminis-

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tered the patient artificial respiration. The blood gas tests revealed a pH, bicarbonate levels, Base Excess and anion gap of 7.277, 16.6 mmol/L, −9.7 mmol/L, and 24.7 mEq/L, respectively. Moreover, blood tests revealed that aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels had increased to 99 U/L, 22 U/L, and 906 U/L, respectively. The blood glucose level was normal, and the urinary ketone test was negative. The blood ammonia level was abnormally high at 3197 μg/dL, and blood amino acid analysis showed a decrease in citrulline to 6.3 μmmol/L. Urinary organic acid analysis showed no excretion of orotic acid. Therefore, the patient was biochemically diagnosed with neonatal-onset CPS1D.

On day six, the patient was transferred to another medical center and treated with hemodialysis for hyperammonemia due to acute metabolic encephalopathy. After 30 h of dialysis, her blood ammonia levels improved to 131 μg/dL. The patient was started on sodium benzoate (320 mg/kg/day), arginine (400 mg/kg/day), and levocarnitine (40 mg/kg/day), and her ammonia levels were controlled. At one month, the patient was diagnosed through ultrasonography with encephalomalacia and ventricular enlargement. After the diagnosis, the patient's blood ammonia levels frequently increased; therefore, she started on a special protein-free milk. At the age of ten months, she began to sit with support. The patient frequently laughed, and her motor developed as expected. We, therefore, planned for a living-donor liver transplantation from her parents. After the transplantation had been planned, the patient relapsed into hyperammonemia due to a viral infection and was treated in the ICU. By the age of one year, her movement abilities and intelligence had regressed, she was unable to eat orally and had to be tube fed, and she showed persistent neurological sequelae. Therefore, we canceled her liver transplantation surgery and continued physical therapy rehabilitation. The patient's hepatic enzyme activity was not measured.

During her childhood, the patient experienced repeated vomiting and was diagnosed with gastroesophageal reflux disease. She required duodenal tube feeding and treatment with intravenous hyperalimentation. At the age of nine years, she underwent gastric fistula surgery for the gastroesophageal reflex. Cephalic computed tomography revealed dilation of both lateral ventricles and cerebral atrophy (Figure 1). At the age of ten years, the patient began therapy with 450 mg/kg/day of sodium phenylbutyrate, resulting in more stable blood ammonia levels. At the age of 12 years, she experienced repeated aspiration pneumonia. At the age of 13 years, she underwent tracheotomy and laryngotracheal isolation surgery. For her chronic respiratory failure, the patient employed a small home mechanical ventilator. At approximately 14 years of age, the patient experienced her menarche. Numerous complications such as partial epilepsy, hypothyroidism, diabetes mellitus, ulcerative colitis, proximal tubular acidosis, osteoporosis, bone fractures, and urinary tract infections because of rectal vaginal fistula were observed during this time.

Once the patient reached 16 years of age, we obtained informed consent from her parents and analyzed the amino acid changes at the *CPS1* gene on chromosome 2 through genetic testing. We analyzed the CPS1 gene using targeted next-generation sequencing employing the hybrid capture method on one of the

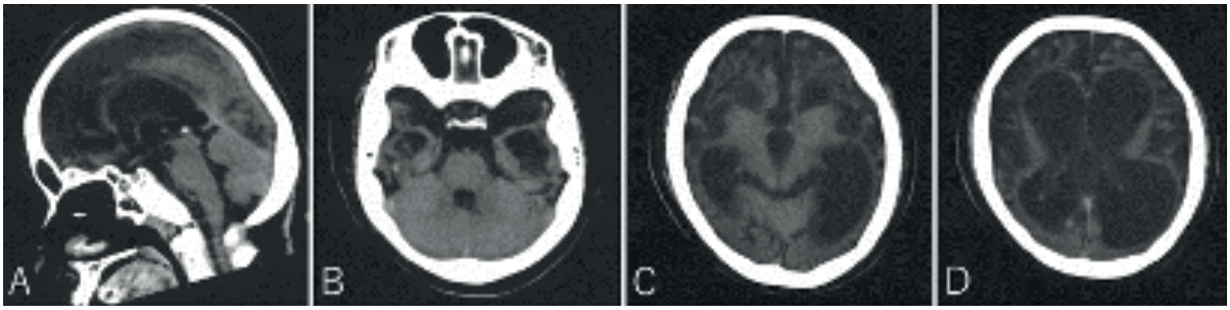

Figure 1. At 9 years of age, the patient's brain CT revealed severe cerebellar cortex atrophy compared with the preserved cerebellum. Leukoencephalopathy and ventricular enlargement can also be observed

patient's blood samples, resulting in the confirmation of 2 mutations: c.236 + 6T > C and c.2359C > T, exon 19, p.Arg787X. Despite her severe intellectual motor development disorder, the patient's physical condition was stable, and she is currently recovering at home with her family.

Discussion

CPS1D is a rare congenital inborn error of metabolism, and its incidence rate has been reported to range from 1 in 300,000 to 800,000[5,6]. Many cases of CPS1D develop within a few days after birth as neonatal onset and tend to result in death due to acute hyperammonemia and metabolic encephalopathy. There are numerous reports of genes involved in patients with CPS1D; however, there have been few reported cases of long-term survival. Kurokawa et al[2] reported 24 Japanese cases of CPS1D, including 19 neonatal patients. Thirteen of whom died within 60 days and nine of whom died within 2 weeks after birth. Only one patient underwent liver transplantation, and mental retardation was not noted. Considering the prognosis of neonatal CPS1D is usually fatal, our detailed clinical report of long-term survival without liver transplantation is invaluable.

Conclusions

Our case suggests that hemodialysis and the appropriate administration of sodium phenylbutyrate, sodium benzoate, arginine, and levocarnitine for acute neonatal hyperammonemia can improve the prognosis of patients with neonatal-onset CPS1D.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

J.I, Y.A, Shinya Yoshihara and Y.T treated and collected data of the patient in general ward. G.I, A.N and O.A were the treated patient in intensive care unit. G.I and Y.T analyzed patient's genetic samples. O.A and Shigemi Yoshihara supervised the findings of this work. G.I wrote this paper and all authors approved the final manuscript.

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