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Case report

Acute severe encephalopathy related to human herpesvirus-6 infection in a patient with carnitine palmitoyltransferase 2 deficiency carrying thermolabile variants

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Abstract

We describe a male infant with carnitine palmitoyltransferase 2 (CPT2) deficiency who presented with acute encephalopathy related to human herpesvirus-6 (HHV-6) infection. He was hospitalized for pylexia and status epilepticus, diagnosed with acute encephalopathy, and treated with intensive supportive care including mechanical ventilation, support for hypothermia, and control of the intracranial pressure, that caused severe neurological sequelae. HHV-6 was detected in his cerebrospinal fluid, indicating HHV-6 related encephalopathy. In the acute phase, acylcarnitine analysis of blood suggested a defect of long chain fatty acid β-oxidation, and CPT2 deficiency was genetically confirmed. In addition, other gene alterations that have been previously reported as "thermolabile variants" were found. Some patients with the infantile form of CPT2 deficiency present with acute encephalopathy, but others do not develop encephalopathy. The correlation between phenotype and genotype has not been clarified. Our case may contribute to the elucidation of the genetic factor involved in acute encephalopathy in CPT2 deficiency.

Keywords: Acute encephalopathy; CPT2 deficiency; HHV-6; Thermolabile variants

1. Introduction

Carnitine palmitoyltransferase 2 (CPT2) catalyzes the formation of acyl-CoA from acylcarnitine and CoA. Mutations of the *CPT2* gene, which is located on chromosome 1q32, cause CPT2 deficiency [1,2]. In patients with defects in CPT2 activity, nonketotic hypoglycemia and muscular symptoms can be provoked by starvation or infection. CPT2-deficient patients present with different age-dependent clinical phenotypes: an adult myopathic form (MIM#255110), a lethal neonatal form (MIM#600649), or a severe infantile form (MIM#600649) [3,4]. The adult form is characterized by muscle pain and stiffness triggered by exercise, fasting, extremes in temperature, or anesthesia. The neonatal form is characterized by nonketotic hypoglycemia, cardiomyopathy, and congenital anomalies; the infantile form has predominantly liver, heart, and skeletal-muscle symptoms. In this report, we describe a patient with CPT2 deficiency presenting with acute severe encephalopathy related to human herpesvirus-6 (HHV-6) infection. The patient was categorized as having the severe infantile form, which often has a fatal course or severe sequelae. Mutation analysis revealed that the patient

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had disease-causing mutations plus thermolabile variants. This is the first clearly established case of acute severe encephalopathy in a patient with genetically confirmed CPT2 deficiency carrying thermolabile variants, that might affect the clinical phenotype.

2. Case report

Our patient was the first child of nonconsanguineous parents. No family history of neurological or metabolic disorders was reported. The mother's pregnancy and delivery were uncomplicated, and the expanded newborn screening showed no positive results. The early developmental milestones were not obviously delayed, and no specific symptoms associated with congenital metabolic disorders had been documented. At the age of 7 months, this male infant was urgently hospitalized for generalized tonic–clonic seizures following prodromal illness consisting of high fever and vomiting for several hours. Although generalized convulsions persisted on arrival, his seizures ceased following intravenous administration of midazolam. On admission, an intracranial computed tomography scan demonstrated diffuse brain edema. The laboratory data exhibited nonketotic hypoglycemia (plasma glucose, 23 mg/dL; total ketone bodies, 126.78 μmol/L; 3-hydroxybutyric acid, 79.75 μmol/L) with hyperammonemia (451 μg/dL), indicating a metabolic-disorder-based encephalopathy. Although no seizures were seen after intravenous administration of midazolam on the first day after admission, prolonged generalized convulsions occurred again on the second day of illness. His seizures could not be controlled by intravenous administration of phenytoin, phenobarbital, and secobarbital sodium; thus, he was referred to our hospital to treat intractable seizures and evaluate underlying disease.

On admission to our hospital, laboratory findings showed elevated leaking enzymes (AST, 317 IU/L; ALT, 73 IU/L; LDH, 1319 IU/L; CK, 19,990 IU/L) and mild hyperammonemia (54 μmol/L) without hypoglycemia or ketosis (plasma glucose, 111 mg/dL; total ketone bodies, 126.7 μmol/L). Cardiac dysfunction was not shown by ultrasonic cardiogram or electric cardiogram, and hepatomegaly was not noted. Brain MRI was performed on the second day of illness. Diffusion-weighted imaging (DWI) and fluid-attenuated

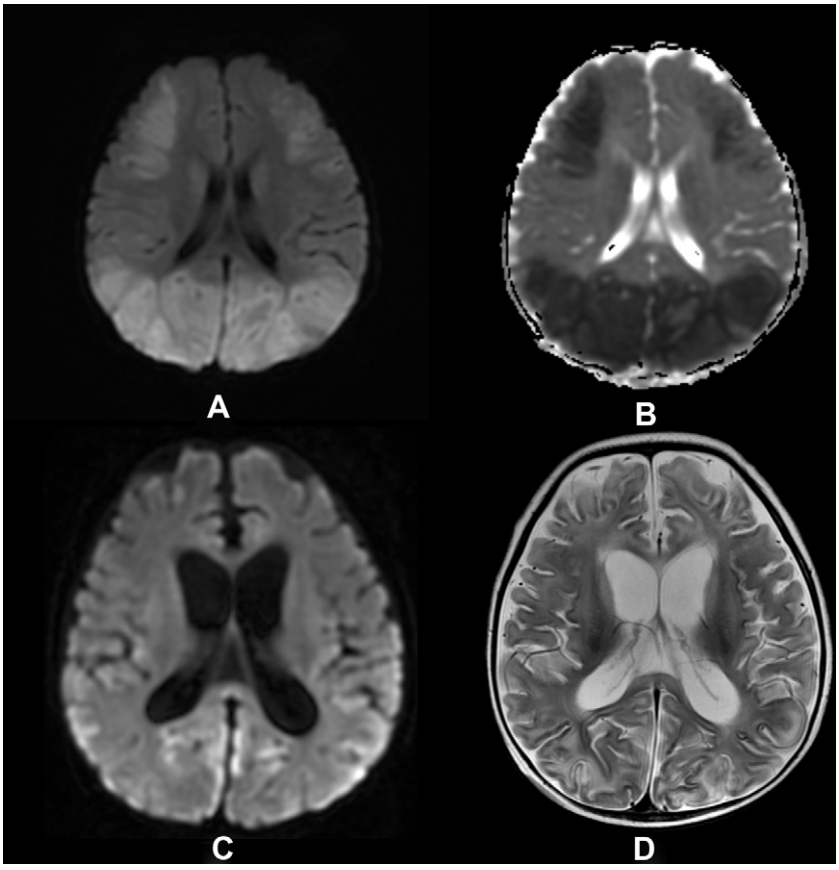

Fig. 1. (A) Axial DWI at the second day of illness. There are abnormal high intensity areas in the bilateral caudate, frontal lobes, predominantly occipital lobes. (B) Axial ADC maps on the second day of illness. The corresponding lesion (bilateral caudate, frontal lobes, predominantly occipital lobes) had decreased ADC values. (C) Axial DWI on the 22nd day of illness. The abnormal high intensity areas largely disappeared. (D) Axial FLAIR on the 22nd day of illness. Prominent ventricles are evident, and diffuse brain atrophy is evident.