

CASE REPORT

Diagnosis of Urea Cycle Disorders in Adulthood: Late-Onset Carbamyl Phosphate Synthetase 1 Deficiency

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CASE PRESENTATION

A 44-year-old man presented to hospital with sudden onset of nausea, vomiting, confusion, reduced level of consciousness, and seizures. He was acutely ill for three days, yet continued to experience episodic attacks of similar presentation over the following two years. Magnetic resonance imaging of the brain demonstrated mild to moderate cortical atrophy with numerous small, non-specific foci of increased signal within the subcortical white matter and, to a lesser extent, the periventricular white matter. The patient's medical history was otherwise unremarkable. However, he mentioned that he had been experiencing increasingly frequent episodes of unprovoked dizziness since his mid-30s. A review of his nutritional history revealed that he avoided high-protein foods (meat, fish, eggs) in favor of fruits and vegetables. Because he responded well to phenytoin, he was thought to have some form of epileptic encephalopathy. The exact cause of the patient's recurrent symptoms remained elusive until the birth of his grandson.

The patient's grandson presented on the second day of life with dehydration, hyperbilirubinemia, respiratory alkalosis, encephalopathy, and an ammonia level of 789 $\mu\text{mol/L}$. The boy was diagnosed with carbamyl phosphate synthetase 1 deficiency (CPS1D) on gene sequencing with a transversion mutation (G>C) at position 3558 on one allele and a transition mutation (T>C) at position 4101 on the other allele. He responded promptly to treatment with hemodialysis, sodium phenylbutyrate, and L-arginine. At three years of age, however, he died of brain herniation following a presentation of pneumonia, raised intracranial pressure, and ammonia level of 200 $\mu\text{mol/L}$. Molecular studies of the patient revealed that he shared exactly the same mutations as his grandson. Treatment with sodium benzoate began, along with genetic counselling. The patient was referred to a nutritionist for proper dietary management of CPS1D.

The patient and his grandson originated from a mountain village in Mount Lebanon. Clans of minority religions

(mostly Christian and Druze) survived in the isolation and protection of the mountain with high rates of inter-marriage. Although the patient and his wife once resided in the same mountain village, they did not believe that inter-marriage had occurred between their two families in preceding generations. However, the patient's daughter, who was the mother of the affected grandson, married her second cousin (Figure 1). The patient had a sister who died unexplainably at eight months of age. He also had two sisters and a brother who were alive and well. His parents were consanguineous (second cousins) and his father was the only surviving son of 20 children. The other 19 children died in the 8 to 15 year range from unknown causes. The patient had five children, including two daughters and three sons, who were asymptomatic.

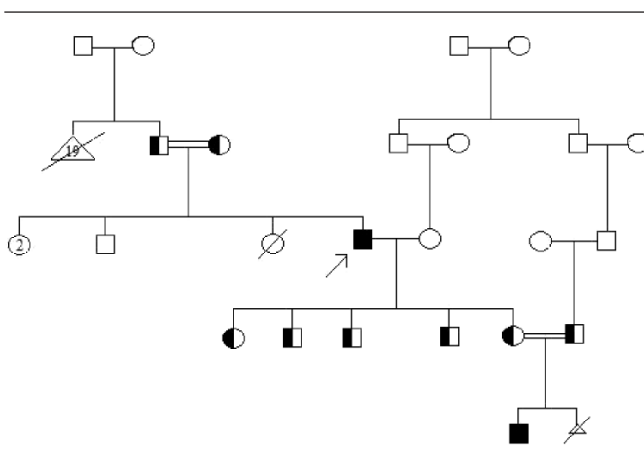


Figure 1. Patient's pedigree

UREA CYCLE DISORDERS

In humans, the urea cycle is critical for the maintenance of nitrogen balance. Surplus nitrogen takes the form of ammonia, which is generated as a waste product of protein

metabolism. Without excretion, ammonia accumulates in the arterial blood and crosses the blood-brain barrier. Encephalopathy may result through multiple mechanisms, including glutamine-induced cerebral edema, impaired cerebral oxidative metabolism, and neurotransmitter abnormalities.¹ To prevent neurotoxicity, the urea cycle converts ammonia to urea, a form of nitrogen that is easily excreted in urine. The urea cycle is mediated by five enzymes in hepatocytes (Figure 2): carbamyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase. Deficiencies in each enzyme are referred to collectively as the urea cycle disorders.

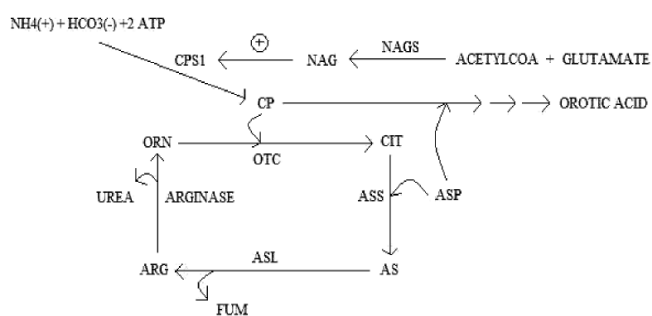


Figure 1. Urea cycle. ARG, arginine; AS, argininosuccinate; ASL, argininosuccinate lyase; ASP, aspartate; ASS, argininosuccinate synthetase; ATP, adenosine triphosphate; CIT, citrulline; CP, carbamyl phosphate; CPS1, carbamyl phosphate synthetase 1; FUM, fumarate; HCO_3^- , bicarbonate; NAG, N-acetylglutamate; NAGS, N-acetylglutamate synthetase; NH_4^+ , ammonium; ORN, ornithine; OTC, ornithine transcarbamylase.

CPS1 deficiency (CPS1D; OMIM 237300; EC 6.3.4.16) is an autosomal recessive disorder that is caused by partial or complete inactivity of CPS1, the mitochondrial-matrix enzyme that catalyzes the first committed step of the urea cycle. CPS1 channels ammonia into the urea cycle by using N-acetylglutamate (NAG) as an allosteric activator to catalyze the conversion of bicarbonate, ATP, and ammonia to carbamyl phosphate.² Thus, CPS1D is characterized by acute episodes of hyperammonemic encephalopathy. Based on the age of onset, two phenotypes of CPS1D are recognized: neonatal-onset and late-onset. Most cases of CPS1D are of neonatal-onset. Hyperammonemia typically manifests after the commencement of feeding with nonspecific clinical features, namely vomiting, hypothermia, somnolence, lethargy, apnea, seizures, or coma. Neonatal-onset CPS1D is associated with high mortality despite intensive treatment because the plasma ammonia level at initial presentation is often high enough to cause irreversible brain damage.³ Some patients with CPS1D may remain healthy for months to years beyond the neonatal period until symptoms of the

enzyme deficiency are triggered. Such cases of late-onset CPS1D are infrequent in the medical literature.

DIAGNOSIS

CPS1D is an inborn error of metabolism that occurs with an estimated incidence of 1 in 62,000 in the United States and 1 in 800,000 in Japan.^{4,5} Reported incidences of CPS1D are likely underestimated, however, because they do not account for neonates that die within the first few days of life from undiagnosed CPS1D. Because affected neonates present initially with nonspecific signs of distress, the diagnosis of CPS1D may be delayed, with detrimental effect, as more common causes of distress are investigated first. The neonatal presentation of CPS1D is commonly misinterpreted as sepsis.⁶ The index of suspicion for a urea cycle disorder should be raised by laboratory findings of respiratory alkalosis and elevated ammonia level. Definitive diagnosis can sometimes be made by urine or plasma amino acid quantitation. CPS1D, in particular, exhibits an elevated blood level of glutamine and trace or undetectable levels of citrulline and arginine. CPS1D is distinguished from deficiencies in OTC, ASS, ASL, or arginase by a normal urinary level of orotic acid, which is produced through an alternative pathway of carbamyl phosphate metabolism.⁷ Because CPS1D is indistinguishable from N-acetylglutamate synthetase (NAGS) deficiency on the basis of these blood and urine tests, definitive diagnosis of CPS1D requires demonstration of reduced CPS1 enzymatic activity (< 20% of controls) by liver biopsy or molecular studies to identify pathogenic mutations in the CPS1 gene, which consists of 38 exons⁸ mapped to chromosome 2q35.⁹ Neonatal-onset CPS1D is associated with virtually absent CPS1 activity (< 5% of controls) and several types of mutations in the CPS1 gene, including missense, nonsense, insertion, and deletion mutations.^{8,10-17} Although homozygous mutations are expected, both the patient and his grandson are compound heterozygous for two splice site mutations in the CPS1 gene (c.3558 + 1G>C and c.4101 + 2T>C). Although they have identical mutations, the temporal variation in the onset of their symptoms may be explained in part by an imbalance in CPS1 allelic expression between them.¹⁸ Newborn screening is not routine given the low prevalence of CPS1D mutations and the current lack of reliable biochemical screens.

Individuals with milder CPS1D (approaching 20% activity of controls) may remain asymptomatic for months to years beyond the neonatal period before the enzyme deficiency manifests. Correct diagnosis of a urea cycle disorder in adult patients is challenging because the clinical presentation is not only nonspecific, but also episodic with alternating periods of health and illness. Adults usually present with intermittent metabolic attacks of nausea, vomiting, headache, gait ataxia, and mental status changes (disorientation, depression, lethargy, visual hallucinations, seizures) that may progress to coma.¹⁹⁻²² However, clinicians frequently assign diagnoses

that do not fully explain the clinical picture, including cyclic vomiting syndrome, drug ingestion, encephalitis, basilar migraine, schizophrenia, and seizure disorders.²³ Although these attacks may be spontaneous, known triggers include high or overly-restricted protein intake, rapid weight loss, internal bleeding, viral infection, postpartum stress, corticosteroids, cyclophosphamide, and valproic acid.²⁴ Children with CPS1D may present with learning difficulties in the form of delayed language acquisition, mild-to-moderate mental retardation, or behavioural troubles consistent with attention-deficit disorder.²⁵⁻²⁷ Late-onset urea cycle disorders may be suspected on histories of secondary school failure or childhood enrolment in special education classes. Early experience of nausea and vomiting with high protein intake may prompt children to self-select a vegetarian diet to alleviate symptoms. Pedigree analysis to identify relatives with known disease or unexplained morbidity or mortality is diagnostically useful.

MANAGEMENT

Hyperammonemia constitutes a medical emergency. Initially, intravenous 10% dextrose should be given as caloric supplementation to reverse any catabolic state that may have triggered the decompensation. To lower the elevated plasma ammonia level, dialysis or hemofiltration^{28,29} should be started immediately along with administration of intravenous arginine, sodium benzoate, and sodium phenylacetate.³⁰ Sodium benzoate and sodium phenylacetate are nitrogen-scavengers that conjugate with glycine and glutamine, respectively, to produce excretable forms of nitrogen. Chronic management of CPS1D requires these nitrogen-scavenging medications in conjunction with individualized restrictions in dietary protein. Protein consumption should be high enough to meet cellular requirements for physiological functioning while low enough to prevent hyperammonemia. L-citrulline supplementation and seizure-control medications may be useful as adjunct therapy. Consultation with a metabolic physician should be sought in the care of any patient with CPS1D. †

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