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# Fatal Encephalopathy Caused by a Urea Cycle Disorder

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Dear Editor,

We present a rare case of hyperammonemic encephalopathy caused by adult-onset urea cycle disorder (UCD), which is more common in males. UCD is a genetic enzyme disorder of the metabolic process that converts ammonia to urea, resulting in the accumulation of ammonia and other byproducts that are neurotoxic.[1,2] UCD rarely presents for the first time in adulthood and may be a life-threatening cause of metabolic encephalopathy. It can cause irreversible neurological deficits and has a high mortality rate of 11%.[1-3] Therefore, early diagnosis and prompt treatment of hyperammonemia are crucial to preventing or reducing its neurological sequelae.

A 32-year-old Vietnamese male was admitted with altered mentality. He had a progressive headache with nausea and vomiting, causing starvation for the previous 3 days. He had no previous history of underlying disease. After admission to the department of internal medicine, he was only treated for gastrointestinal symptoms. He went into a state of stupor [Glasgow Coma Scale (GCS) E2V2M2] with respiratory failure after 1 day, and so the patient was transferred to the neuro-intensive care unit.

Laboratory tests (including cerebrospinal fluid) were normal except for hyperammonemia (174 μmol/L; normal 12−66 μmol/L). Further evaluation revealed no evidence of gastrointestinal bleeding or liver disease. Brain magnetic resonance imaging revealed insular cortical high signal intensities at 2 days after admission (Fig. 1A and B). Electroencephalography demonstrated intermittent triphasic waves without ictal activity.

Lactulose enema was performed, but the ammonia level increased to 403 μmol/L. We applied sodium benzoate (600 mg/day) and initiated hemodialysis (HD). We suspected a non-hepatic hyperammonemia disorder and so started treatment with a dextrose solution (10%) and protein-free formula until the level of serum ammonia decreased to 80−100 μmol/L. However, the patient deteriorated to a comatose state (GCS E1VtM1) with global cerebral edema on hospital day 3 (Fig. 1C and D). HD could not be maintained due to the patient's unstable vital signs despite adjusting the HD settings. Thus, emergency continuous renal replacement therapy (CRRT) was performed to eliminate ammonia by administering inotropics continuously. We also considered increased intracranial pressure (IICP) treatment by cerebral edema due to hyperammonemia. However, the use of osmolar agents was restricted by hypernatremia (157 mEq/L) and a high osmolar gap (>60 mOsm/kg). With spontaneous hyperventilation due to brain edema, the patient's body temperature spontaneously decreased during CRRT, which can contribute to IICP control. Hyperammonemia resolved at 78 μmol/L on hospital day 6 (Fig. 1E), but the neurological deficit did not improve. The patient eventually died of pneumonia with sepsis after 1 month.

UCD was considered as the cause of non-cirrhotic hyperammonemia. Checking the plasma amino acid and urine organic acid levels revealed decreased plasma citrulline (9.5 nmol/mL; normal 12−55 nmol/mL) and elevated urinary orotic acid (169.8 mmol/mol Cr) with a uracil peak (4.1 mmol/mol Cr), which were suggestive of adult-onset ornithine transcarba-

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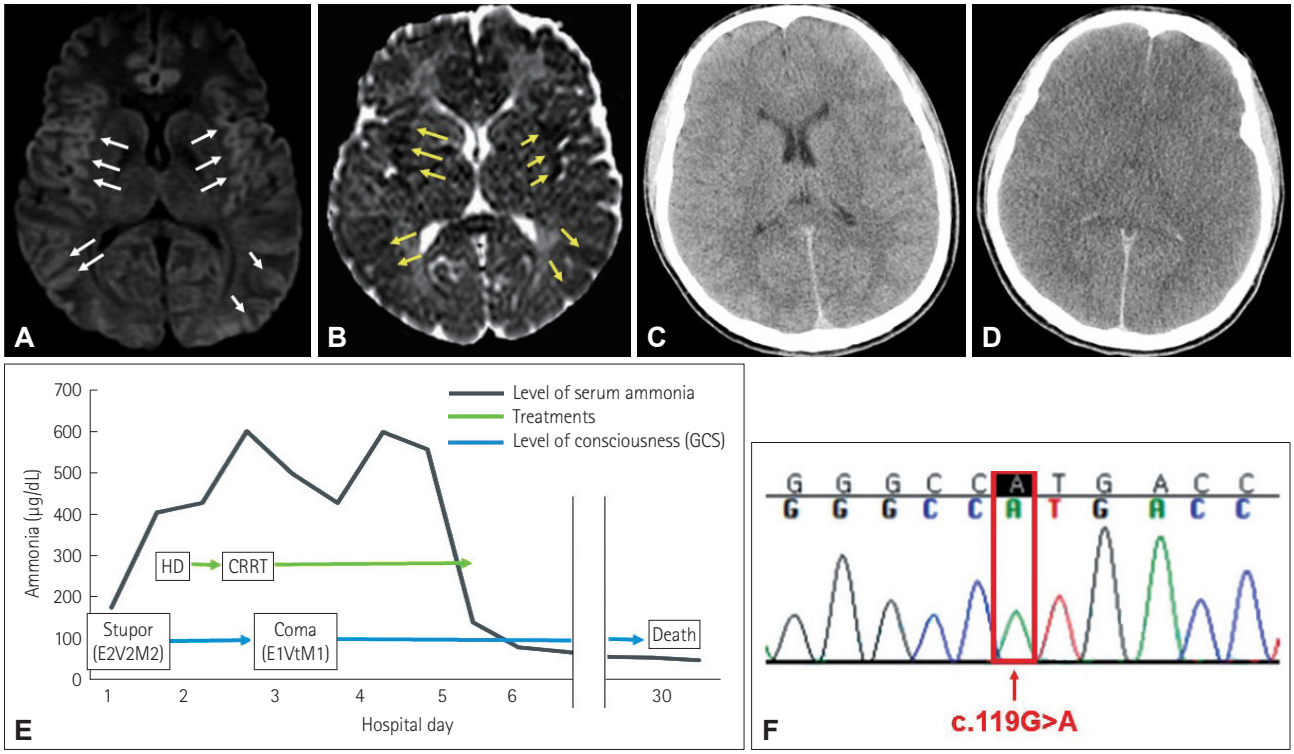


**Fig. 1.** Clinical course with radiologic findings and genetic diagnosis. A and B: Brain magnetic resonance imaging. Diffusion-weighted image (A) shows bilateral extensive high signal intensities in the insular cortex and temporoparietal lobes with cortical edema (white arrows). Apparent diffusion coefficient map (B) shows bilateral extensive low signal intensities in the same legion with cortical edema (yellow arrows). C and D: Brain CT. Brain CT (D) shows a blurred gray–white junction and ventricular and sulcal effacement, indicating brain edema compared with the initial brain CT (C). E: Timeline of serum ammonia levels and the level of consciousness. The measured ammonia level (black line) and the level of consciousness (blue line, GCS classification) were related to treatment (green line, conventional HD and CRRT). F: Genetic diagnosis of ornithine transcarbamylase deficiency. The 119th base guanine of the ornithine transcarbamylase gene had mutated to adenine. A hemizygous mutation from the 40th amino acid arginine to histidine was identified. CRRT: continuous renal replacement therapy, CT: computed tomography, GCS: Glasgow Coma Scale, HD: hemodialysis.

mylase deficiency (OTCD). Genetic testing (Fig. 1F) identified a hemizygous variant in the OTC gene: c.119G>A (p.Arg40His).

OTCD accounts for approximately 55% of cases of UCD, and is an X-chromosome-linked disorder with an incidence of 1/40,000 to 1/80,000 births.[1,2] While males are severely affected during the neonatal period, females present with various enzymatic activities and clinical courses.[1] Hyperammonemia due to OTCD presents with various neurological symptoms such as nausea, irritability, neuropsychiatric changes, coma, or even death.[4] Asymptomatic OTCD patients may develop symptoms due to hyperammonemia if triggered by physiological stress or catabolism.[2] In this rare case of adult-onset OTCD in male, catabolism by starvation was thought to have caused hyperammonemia.

The symptoms of hyperammonemia mimic other diseases such as drug intoxication, cerebrovascular stroke, and central nervous system infection, resulting in misdiagnosis and consequent worsening of symptoms. In astrocytes, ammonia and glutamate metabolize to glutamine. The main hypothesis is that glutamine causes water inflow and swelling of astrocytes, leading to brain edema. Other hypotheses are that glutamine enters the astrocytic mitochondria and causes cell death, or that glutamine can interrupt neurotransmission.[4]

There are imaging findings typical to hyperammonemic encephalopathy. Symmetrical extensive cortical signal abnormalities are detected in the insula, cingulate gyrus, and thalami, as in our case, and often accompany cytotoxic edema with spared perirolandic and occipital areas.[4] These imaging findings can be shown in hypoxic-ischemic encephalopathy, limbic encephalitis, hypertensive, metabolic, and Creutzfeldt-Jakob encephalopathy.[4] However, in the setting of acute ammonia elevation, hyperammonemic encephalopathy should be considered first.

Treatment includes lowering serum ammonia levels and reducing the production of byproducts. The rapid initiation of treatment is important since the neurological outcome depends on the duration and severity of hyperammonemia.[2] Protein intake must be stopped until the serum ammonia level is decreased to 80–100 μmol/L. Moreover, high-calorie fluid should be administered intravenously as soon as possible.[5] Ammonia-scavenging agents and HD help improve hy-

perammonemia and are associated with an increased survival probability. Recent guidelines recommend starting HD rapidly, especially if the serum ammonia exceeds 200 μmol/L despite an unconfirmed diagnosis.[2] In addition, prompt and early treatment of hyperammonemia is crucial to prevent fatal complications such as cerebral edema, brain herniation, and brain death.

Our case suggests that OTCD can appear as altered mentality in adult males and that delayed lowering of ammonia can cause irreversible neurological deficits. Serum ammonia levels should be measured in patients with unexplained loss of consciousness. UCD must be suspected in a patient with hyperammonemia to avoid misdiagnosis. High suspicion is required to diagnose UCD, in which prompt and aggressive management can prevent a potentially irreversible condition.

## Author Contributions

Conceptualization: Soo-Hyun Park, Nam-Hee Kim. Data curation: Soo-Hyun Park, Seok-Jin Choi. Formal analysis: Soo-Hyun Park, Nam-Hee Kim. Investigation: Soo-Hyun Park, Jung Hwan Lee. Methodology: Soo-Hyun Park, Jung Hwan Lee, Seok-Jin Choi. Software: Hee Sup Kim, Nam-Hee Kim. Validation: Hee Sup Kim, Nam-Hee Kim. Writing—original draft: Soo-Hyun Park. Writing—review & editing: Soo-Hyun Park, Nam-Hee Kim.

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## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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