

# Recurrent Altered Mental State Associated with Nonhepatic Hyperammonemia Presented in an Elderly Female Patient: Probable Late-Onset Urea Cycle Disorder

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## Case Report

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Altered mentality associated with hyperammonemia is usually diagnosed in patients with liver disease. Nonhepatic hyperammonemia may be present in critically ill patients or may be caused by high protein diets or certain drugs. Urea cycle disorders (UCDs) rarely present with altered mentality with hyperammonemia in adult patients. An 82-year-old female visited our hospital with complaints of abnormal behavior and confusion. Routine blood tests revealed elevated serum ammonia. Her mentality and serum ammonia level normalized after lactulose enema and she was discharged thereafter. However, she was later re-admitted because of recurrent altered mentality. Amino acid analysis revealed that serum levels of ornithine and glutamine increased significantly, whereas the levels of alanine and glutamic acid increased slightly, and the levels of arginine, lysine, and citrulline were normal, which were probably caused by reduced activity of the mitochondrial ornithine carrier-1. Although our patient was not diagnosed genetically, this case illustrates the under-recognized fact that UCD can occur in a senile age. Clinical suspicion of UCDs in patients with hyperammonemia is critical for early diagnosis and to prevent the significant neurologic sequelae. (2021;11:96-99)

**Key words:** Hyperammonemia, Amino acids, Urea

## Introduction

Hyperammonemia, which is usually caused by liver diseases, is often accompanied by altered mentation, stigmata of chronic liver disease, and abnormalities in the liver function test results. Nonhepatic hyperammonemia may be caused by clinical situations, such as high protein supplementation, total parenteral nutrition, chemotherapy, gastric bypass surgery, organ transplantation, status epilepticus, and administration of valproic acid.<sup>1</sup> Recently, the cases of adult-onset urea cycle disorders (UCDs) have been rarely reported. Severe forms of this disorder present with severe encephalopathy in infancy, but milder forms may become evident in later stages.<sup>2,3</sup> Here, we report the case of an elderly patient who showed recurrent altered mentation with nonhepatic hyperammonemia and discuss the possible diagnosis and clinical significance of this case.

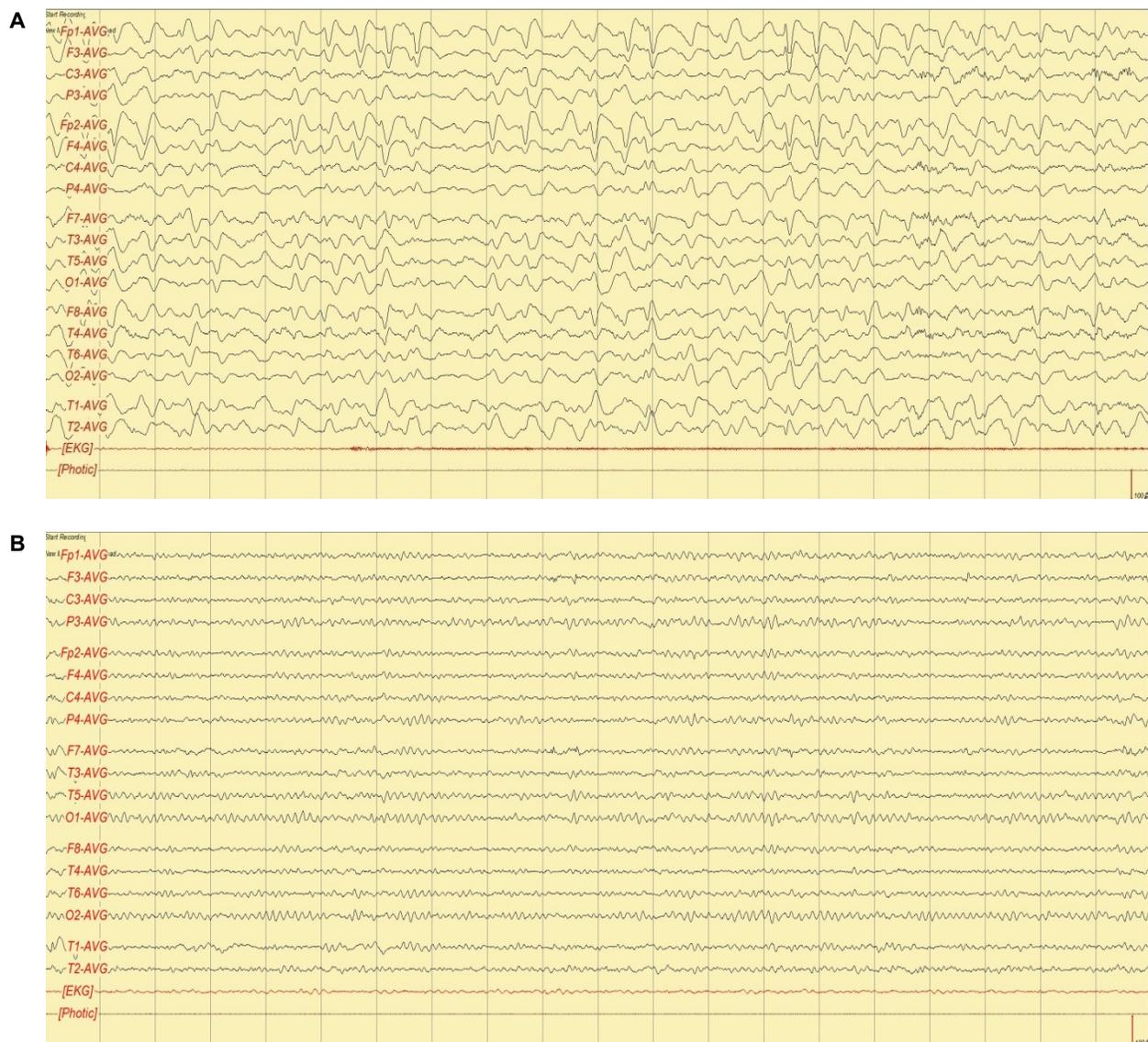
## Case Report

An 82-year-old-female patient was brought to our hospital with complaints of insidious development of abnormal behavior and altered consciousness. She regularly used medication for hypertension (losartan 50 mg/day), and denied using any other medication. Her family members stated that she had been obstinate and quarrelsome for 2 months before admission. Three days before admission, i.e., the day of Korean Thanksgiving, she did not speak spontaneously and responded in a few words only when her family members talked to her. On the day of admission, she went to a restroom in an undressed state in the morning. Since then, she became speechless and somnolent and could not walk unassisted.

On arrival in our hospital, she was drowsy and responded slowly to external stimuli. Her vital signs were stable. Focal neurological deficit was not evident on physical examination. Initial laboratory tests revealed that her blood cell counts, erythrocyte sedimentation rate,

C-reactive protein, total and direct bilirubin, liver enzymes, and gamma-glutamyl transpeptidase were all within normal limits. The serum level of ammonia was high (107 mcg/dL; normal value, 10-80 mcg/dL). Initial electroencephalography (EEG) showed generalized triphasic activity (Fig. 1A). After admission, she was treated with lactulose enema. On the second day of admission, she became alert and her serum ammonia level decreased to 75 mcg/dL. The triphasic activity disappeared on follow-up EEG (Fig. 1B) that was performed 20 hours after initial EEG. She returned to premonitory state and was discharged after 5 days of admission.

A month after discharge, she was re-admitted to our hospital with complaints of aggravated mentation. She progressed to a drowsy and confused state during the week before second admission. Negative myoclonus in bilateral upper extremities was observed on examination. Serum ammonia level was measured to be 200 mcg/dL. Magnetic resonance imaging revealed no abnormality. Abdominal computed tomography scan revealed evidence of neither liver cirrhosis nor abnormalities in the bile duct system. Generalized triphasic activity was observed again on EEG. Lactulose enema was performed again, and her mental state improved gradually. Subsequently, we performed additional tests; protein electrophoresis revealed no ab-



**Figure 1.** (A) Initial electroencephalography (EEG) of our patient. Intermittent bifrontal-dominant generalized triphasic waves are observed. (B) Follow-up EEG that was performed 20 hours after initial EEG. The triphasic waves disappear after treatment with lactulose enema.

**Table 1.** Results of serum amino acid analysis

Aminoacid	Value ( $\mu\text{mol/L}$ )	Normal value ( $\mu\text{mol/L}$ )
Glutamic acid	77	7-65
Glutamine	944	360-740
Glycine	232	158-302
Alanine	541	185-537
Citrulline	47	16-62
Alpha-amino-butyric acid	16	15-41
Methionine	22	16-37
Isoleucine	47	32-87
Leucine	82	61-183
Tyrosine	78	43-88
Phenylalanine	64	39-76
Ornithine	167	19-81
Lysine	158	108-233
Arginine	47	44-130

normality and the result of amino acid analysis is summarized in Table 1. The serum level of ornithine, glutamic acid, and glutamine were 167  $\mu\text{mol/L}$  (normal value, 19-81  $\mu\text{mol/L}$ ), 77  $\mu\text{mol/L}$  (normal value, 7-65  $\mu\text{mol/L}$ ), and 944  $\mu\text{mol/L}$  (normal value, 360-740  $\mu\text{mol/L}$ ), respectively. Her family members refused gene sequencing test and liver biopsy because of her advanced age.

She had been treated with continuous oral lactulose three times a day and suggested to follow a low protein diet since the second admission. She has been healthy for more than 3 years after discharge. Follow-up serum ammonia levels were normal. No recurrence was observed during the follow-up period.

## Discussion

Acute encephalopathy with nonhepatic hyperammonemia may develop in critically ill patients or patients using certain drugs.<sup>1</sup> However, our patient did not show any severe metabolic disturbances, malignancies, or relevant drug-use history; therefore, further diagnostic work-up including amino acid analysis had to be conducted. Hyperammonemia in adults may initially present with psychiatric symptoms.<sup>2,3</sup> Our patient had become obstinate and quarrelsome before significant alteration of her mental state occurred, which was probably the initial manifestation of hyperammonemic encephalopathy. On Korean Thanksgiving Day, families reunite and usually eat a lot of protein-rich food, which may have triggered excessive ammonia production, thereby inducing altered mentation.

UCDs are a group of inborn errors of metabolism with an estimated incidence rate of <1:8,000 births.<sup>4</sup> Urea cycle is involved in ammonia disposal; ornithine carrier-1 (ORC1) transports ornithine, lysine, and arginine from the cytosol to the mitochondrial matrix where citrulline synthesis occurs by carbamoyl phosphate synthetase and ornithine transcarbamylase.<sup>4</sup> Probably, the amino acid profile of our patient is a result of reduced activity of the mitochondrial ORC1.<sup>5</sup> DNA sequencing is helpful for confirming the diagnosis of UCDs. However, our patient could be diagnosed with adult-onset UCD by typical clinical features and amino acid profiles. Although the diagnosis could not be confirmed by genetics, this case illustrates the under-recognized fact that UCD can occur in a senile age. Our patient is the oldest among those in the case reported so far. Regardless of age, clinical suspicion of UCDs in patients with hyperammonemia is critical for early diagnosis and prevention of significant neurological sequelae.

## Conflict of Interest

The authors declare that they have no conflicts of interest.

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