Magnetic Resonance Spectroscopy in Adult-Onset Citrullinemia

Elevated Glutamine Levels in Comatose Patients

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**Background:** Adult-onset type II citrullinemia is an inborn error of urea cycle metabolism that can lead to hyperammonemic encephalopathy and coma. However, type II citrullinemia is rare outside Japan, and diagnosis and treatment can be delayed. Magnetic resonance spectroscopy may be a useful adjunct to magnetic resonance imaging, and has been applied to noninvasively study chemical metabolism in the human brain.

**Patients:** We describe 2 patients with type II citrullinemia who presented with episodic postprandial somnolence and coma. Diffusion-weighted magnetic resonance imaging showed bilaterally symmetrical signal abnormalities of the insular cortex and cingulate gyrus. On magnetic resonance spectroscopy, glutamine and glutamate levels were elevated, and choline and myoinositol levels were decreased. The diagnosis of citrullinemia was confirmed based on elevated plasma ammonia and citrulline levels.

**Conclusion:** Characteristic features found at the time of magnetic resonance imaging and magnetic resonance spectroscopy may be helpful for early diagnosis of type II citrullinemia in adult patients who present with hyperammonemic encephalopathy and coma.

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**TYPE II CITRULLINEMIA IS A rare inborn error of urea cycle metabolism caused by an autosomal recessive disorder of the citrin gene (SLC25A13) on chromosome 7q21.3.** Deficient argininosuccinate synthetase in the liver results in accumulation of citrulline and ammonia in the plasma, leading to hyperammonemic encephalopathy and (sometimes) coma and death. Unlike type I neonatal citrullinemia, patients with type II citrullinemia present in adulthood with lethargy, postprandial cognitive disturbance, confusion or coma, seizures, delusions, and hallucinations. However, because type II citrullinemia is rarely reported outside Japan, and patients may present with nonspecific neuropsychiatric symptoms, diagnosis and lifesaving treatment may be delayed.

In vivo magnetic resonance spectroscopy (MRS) can noninvasively examine chemical metabolism in the human brain, and may be used to complement magnetic resonance imaging (MRI) in various clinical situations, including neoplasia, infections, epilepsy, and metabolic disease. In patients with hyperammonemia from hepatic failure or urea cycle disorders, MRS has revealed increased glutamine, decreased myoinositol, and decreased choline levels. Although type II citrullinemia is a rare disease, this condition should be considered in patients with delirium, subacute encephalopathy, or coma; MRS can be helpful in making the diagnosis. We describe 2 patients with adult-onset type II citrullinemia with characteristic MRS findings of hyperammonemia.

**REPORT OF CASES**

**CASE 1**

A 25-year-old Chinese man suffered recurrent episodes of drowsiness, confusion, delirium, and coma. Initial MRI showed bilateral, nonenhancing abnormalities of the globus pallidus, insular cortex, and cingulate gyrus on T2-weighted and diffusion-weighted MR images. Findings from various laboratory investigations, including complete blood cell count, renal panel, thyroid function, toxicology, erythrocyte sedimentation rate, autoimmune screening, VDRL test, and human immunodeficiency virus (HIV) serology were negative. Liver panel showed...
transient mildly elevated serum transaminase levels but no viral hepatitis serologic findings.

The patient was unavailable for follow-up, but was admitted 2 years later with recurrent postprandial coma. Magnetic resonance spectroscopy (1.5-T multivoxel point-resolved spectroscopy; echo time, 35 milliseconds; relaxation time, 1500 milliseconds) showed visibly elevated glutamine and glutamate (Glx) and decreased myo-inositol and choline levels (Figure 1). His plasma ammonia (655 µg/dL [to convert to micromoles per liter, multiply by 0.714]; reference range, 13-46 µg/dL) and citrulline (553 µmol/L; reference range, 14-61 µmol/L) levels were elevated, and argininosuccinic acid was not detected in the plasma and urine. Plasma glutamine (6 mg/dL [to convert to micromoles per liter, multiply by 68.423], reference range, 4-10 mg/dL) level was not increased. The patient was diagnosed as having adult-onset type II citrullinemia, and was treated with oral sodium benzoate and arginine supplements and prescribed a low-protein diet. The patient responded well initially but was admitted to the hospital several times for exacerbations as a result of failure to follow the low-protein diet. Three years after diagnosis, he was again admitted with seizures but, despite aggressive treatment and hemodialysis, he developed complications and died of fulminant pneumonia 1 month after admission.

CASE 2

A 28-year-old Chinese man was admitted to the hospital in a coma after 3 months of lethargy, episodic postprandial somnolence, and confusion. Physical examination showed that he was drowsy but arousable. He was ataxic and weak (Medical Research Council grade 4) in all 4 limbs, with hyperreflexia, but absent Babinski sign. Mental state examination was limited by drowsiness. There was no sign of meningism. General examination findings were normal.

Results of complete blood cell count, urea and electrolyte measurements, liver function test, serum copper and ceruloplasmin levels, erythrocyte sedimentation rate, vasculitic screen, porphyria screen, thyroid function test and thyroid autoantibodies, and cerebrospinal fluid examination (including polymerase chain reaction for herpes simplex virus type 1) were unremarkable. Brain MRI showed bilaterally symmetrical areas of hyperintensity on T2-weighted and diffusion-weighted images in the insular cortex and cingulate gyrus (Figure 2A). Magnetic resonance spectroscopy (1.5-T single-voxel point-resolved spectroscopy; echo time, 35 milliseconds; relaxation time, 1500 milliseconds; 8 cm³ voxel over the insular cortex) was performed, and revealed prominently elevated Glx and lactate levels; N-acetylaspartate, myoinositol, and choline levels were decreased (Figure 2B). The diagnosis of adult-onset citrullinemia was considered on the basis of characteristic MRI and MRS findings, and confirmed with elevated levels of plasma ammonia (1147 µg/dL), plasma citrulline (6 mg/dL [to convert to micromoles per liter, multiply by 57.081]), and urine citrulline (129 mmol/mol; reference range, 0-4 mmol/mol). The plasma glutamine (4 mg/dL) level was not increased. Oral sodium benzoate treatment and he-

modialysis were started, but the patient developed status epilepticus and became comatose. Despite treatment, his condition deteriorated rapidly and he died 12 days after diagnosis.

COMMENT

We describe characteristic MRS findings of elevated Glx levels in 2 patients with hyperammonemia caused by type II citrullinemia. Failure of the liver to metabolize and detoxify the body’s nitrogenous waste results in accumulation of ammonia; this can lead to central nervous system damage and a fatal outcome unless effective treatment is instituted. Examples of conditions that can cause hy-
perammonemia include acute and chronic liver failure and inherited urea cycle defects.

Although most fatal inborn errors of metabolism occur early in the neonatal period, the late-onset disorders of urea metabolism are usually less severe, presenting with intermittent episodes of hyperammonemic encephalopathy. These adult-onset enzyme disorders of urea metabolism include ornithine transcarbamylase deficiency (OTCD), carbamylphosphate synthetase deficiency, argininosuccinate synthetase deficiency (citrullinemia), and argininosuccinate lyase deficiency.

Elevation in serum ammonia results in cerebral accumulation of glutamine, predominantly in the astrocytes leading to cerebral edema and encephalopathy. Increased cerebral glutamine levels can be detected on MRS as Glx, a mixture of glutamine and glutamate. Previous MRS studies in adult patients with hyperammonemic hepatic encephalopathy and OTCD showed mild but quantifiable increased glutamine levels, even in brains that appeared normal on MRI. Case reports of MRS studies in neonatal/infantile type 1 citrullinemia and OTCD also showed elevated Glx levels, decreased myoinositol, and decreased choline levels. In our patients, prominently elevated Glx levels were detected on MRS. However, although the spectral pattern is similar to that seen in early-onset urea metabolism disorders, as far as we are aware, this has not been reported in adult patients.

In our patients, the anatomical lesion distribution on MRI is consistent with those seen in previous reports of adult patients with hyperammonemia. Abnormal MRI findings involving the cingulate gyrus and the insular cortex bilaterally and symmetrically have been described in patients with citrullinemia, OTCD, acute hepatic encephalopathy, and valproic acid–induced hyperammonemic encephalopathy. These findings, although reversible, may result in cortical atrophy if not successfully treated, and may progress to involve the basal ganglia and the depths of the cortical sulci. Diffusion-weighted images on MRI have been reported in only a few hyperammonemic patients, showing corresponding reduced apparent diffusion coefficient in the affected areas, consistent with cytotoxic damage. The characteristic regional variation in MRI lesions may represent areas of selective vulnerability, perhaps as a result of hypoperfusion secondary to hyperammonemia. Further investigations in larger numbers of patients using diffusion-weighted MRI and MRS may be useful to determine if this lesion distribution pattern might be useful for differential diagnosis and if it might provide clues to the physiological mechanism of hyperammonemic brain damage.

In patient 1, the significance of the MRS findings was not appreciated, but in patient 2, the typical spectral pattern was recognized and contributed to the correct diagnosis.

The combination of characteristic lesion distribution on MRI and the distinctive MRS peak of Glx may be helpful for the diagnosis of acute hyperammonemia encephalopathy in comatose adult patients with disorder of urea cycle metabolism. However, although the combination of characteristic MRI and MRS may suggest adult-onset OTCD and citrullinemia in the absence of liver disease, these 2 conditions appear to be indistinguishable on neuroimaging without detailed plasma amino acid analysis. Adult-onset citrullinemia is rarely reported outside Japan, and confirmatory blood and urine tests are not routinely performed, especially in adult neurology services, which may be less accustomed to inborn errors of metabolism compared with pediatric neurology services. Hence, diagnosis and life-saving treatment of citrullinemia may be delayed. Ammonia-lowering strategies, including a low-protein diet, arginine supplementation, sodium benzoate, lactulose, nonabsorbed antimicrobial agents, and branched chain amino acid infusion, may be supplemented with hemodialysis to rapidly reduce the blood ammonia level in severe cases. However, unless treated with liver transplantation, which has shown en...

![Figure 2](https://example.com/image.png)

**Figure 2.** Patient 2. A, Diffusion-weighted magnetic resonance (MR) image shows a bilaterally symmetrical high signal in the insular cortex (arrow) and cingulate gyrus (arrowhead). B, MR spectrum showing prominent elevation of glutamine plus glutamate (Glx) level. N-acetylaspartate (NAA) (at 2.0 ppm), choline (Cho) and myo-inositol (Mi) levels are decreased. Lactate (Lac) (at 1.4 ppm) level is also elevated. Cr indicates creatine.
couraging therapeutic results, patients with adult-onset citrullinemia usually follow a rapidly deteriorating clinical course and die of severe brain edema within a few years.

Type II citrullinemia should be considered in the differential diagnosis of adults who present with encephalopathy and episodic postprandial somnolence or coma, especially when serum ammonia levels are elevated in the absence of liver disease. On MRI and MRS, these patients show typical distribution of brain lesions and characteristic abnormalities of elevated levels of Glx from accumulation of serum ammonia. Recognition of these distinctive findings may be helpful for early diagnosis and treatment.

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