Brain MR Imaging in Neonatal Hyperammonemic Encephalopathy Resulting from Proximal Urea Cycle Disorders

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Summary: We present brain MR images in three patients with neonatal-onset hyperammonemic encephalopathy resulting from urea-cycle disorders (two sisters with deficiency of the carbamyl phosphate synthetase I reaction step and one boy with an ornithine transcarbamylase deficiency). MR imaging revealed almost identical findings of injury to the bilateral lentiform nuclei and the deep sulci of the insular and perirolandic regions; to our knowledge, this pattern has not been previously reported. We hypothesize that these lesions presumably reflect the distribution of brain injury due to hypoperfusion secondary to hyperammonemia and hyperglutaminemia in the neonatal period.

The urea cycle incorporates excess nitrogen into urea, a water-soluble waste product, preventing the accumulation of toxic nitrogenous metabolites in the body. Five well-documented urea cycle disorders have been described, each representing a defect in the catalytic efficacy of one of the enzymes of the cycle (1). Although brain MR imaging findings in late-onset types have been described (2–9), few reports describe the neuroimaging results in neonatal-onset cases (10, 11). We herein describe the clinical presentation and brain MR imaging findings in three patients with neonatal-onset urea-cycle disorders. The patients were two sisters with deficiency of the carbamyl phosphate synthetase (CPS) I reaction step and one boy with an ornithine transcarbamylase deficiency (OTCD). The images revealed almost identical findings in the bilateral lentiform nuclei and in the perirolandic and insular cortices.
was marked by late prenatal care and treatment for positive vaginal GBS culture. Like her older sister, this patient presented with lethargy, anorexia, and vomiting at the age of 2 days. She required intubation because of respiratory distress, and anticonvulsant therapy was started with the onset of clonic arm jerking. Her serum ammonia concentration increased to 978 μmol/L, with simultaneous urine orotate levels ranging from 1 to 2 μmol/mol Cr. Serum amino acid analysis revealed these levels: glutamine, 1710 μmol/L; citrulline, 0 μmol/L; arginine, 24 μmol/L; and ornithine, 48 μmol/L. Argininosuccinate was undetectable. Urine organic acid analysis revealed no specific abnormalities. The patient’s ammonia level normalized after 34 hours of hemodialysis and medical therapy. She showed gradual neurologic improvement. DNA analysis showed no mutation in the OTC gene. Hepatic CPS I enzyme activity was 20% the control value; this finding was consistent with the diagnosis of a deficiency of CPS I reaction step.

At the age of 2 weeks, T1-weighted images showed T1 shortening in the bilateral lentiform nuclei (globi pallidi more than the putamina) and insular cortex (arrowheads). Left intraventricular hemorrhage is recognized.

B. T2-weighted image (3000/120/1) shows low signal intensity in the left globus pallidus and high signal intensity in the corpora striata and white matter subjacent to the insular cortex (arrowhead).

C. Sagittal T1-weighted image shows T1 shortening in the deep sulci of the insular and perirolandic regions and a retrocerebellar subdural hematoma.

D. T1-weighted image obtained at the age of 7 months shows volume loss in the basal ganglia with T1 shortening in the putamina, reduced volume of cerebral white matter, and diffuse cortical atrophy. Myelination was recognized in the posterior limb of the internal capsule and in the optic radiation.

Case 3

This boy, 3 years old at this writing, was the first child born to healthy young nonconsanguineous parents. His mother’s pregnancy was uncomplicated, and delivery was by means cesarean section because of his breech presentation at term. The patient presented with lethargy, vomiting, and generalized tonic seizures at the age of 4 days. Elevated serum ammonia levels as high as 1420 μmol/L were found, with normal routine laboratory test results. The serum ammonia level normalized after 2 weeks of intermittent multiple rounds of hemodialysis plus medical therapy. DNA analysis revealed a missense mutation (Ser-90-Asn) in the OTC gene, confirming the diagnosis of OTCD.

At the age of 2 weeks, T1-weighted images showed T1 shortening in the bilateral lentiform nuclei (the globi pallidi more than the putamina) and the deep sulci of insular and perirolandic regions. T2-weighted images demonstrated high signal intensity in the caudate head, medial putamina, and white matter subjacent to the insular and perirolandic cortices, as well as heterogeneous high and low signal intensity in the globi pallidi. These findings were almost identical to those of the previous two cases. This patient underwent cadaveric liver transplantation at the age of 7 months. After transplantation, he had been asymptomatic, but he had moderate neurodevelopmental delays.

Discussion

Urea-cycle disorders are important causes of neonatal metabolic encephalopathy. Affected patients are healthy at birth, but they later manifest signs and symptoms of encephalopathy related to the accumulation of urea-cycle metabolites, including ammonia and glutamine. Full-term neonates, with no obstetric risk factors, appear healthy for 24–48 hours and then exhibit progressive lethargy, hypothermia, and apnea.
accompanied by high blood ammonium levels. Patients with milder cases can present with encephalopathy (e.g., vomiting, abnormal mental status, ataxia, seizures, or developmental delay) at any age from infancy to adulthood.

The pathophysiologic mechanism of central nervous system injury in urea-cycle disorders is not completely understood. One theory invokes the intracerebral accumulation of glutamine as the major cause of the encephalopathy (1). The presence of high levels of ammonia results in the conversion of large amounts of glutamate to glutamine by glutamine synthetase; this occurs mainly in astrocytes. The accumulation of large quantities of glutamine is thought to cause changes in intracellular osmolality and result in subsequent astrocyte swelling, brain edema, intracranial hypertension, and cerebral hypoperfusion. In support of this theory, some have demonstrated that the cerebral edema associated with hyperammonemia can be prevented by impeding glutamine accumulation in the brain, suggesting that hyperammonemia is necessary but not sufficient to produce cerebral edema (1). This theory is consistent with the confirmation of high glutamine concentrations in patients with hyperammonemic encephalopathy with proton MR spectroscopy results (3, 12) and with the presence of extraordinarily high cerebrospinal concentrations of glutamine in OTCD patients with hyperammonemic encephalopathy.

The MR images in our three cases revealed almost identical findings in the bilateral lentiform nuclei and in the perirolandic and insular cortices; to our knowledge, these occurred in a pattern not previously reported. Previous reports in the literature (2–9) represent mostly late-onset urea-cycle disorders. Although the findings in these reports are varied, we were able to divide them into four common patterns: type 1, diffuse severe cerebral edema followed by diffuse atrophy (10, 11); type 2, extensive infarct-like lesions (diffuse severe cerebral edema followed by lesions characterized by the absence of thalamic injury (characteristic in profound hypotension in neonates) and by normal neurologic status within the first few days of life. Asphyxiated neonates typically have abnormal findings from the time of delivery, with seizures starting in the first 24 hours after birth.

A prolonged hyperammonemic coma is associated with impairment of intellectual function and substantial parenchymal injury in patients who survive neonatal hyperammonemic encephalopathy (17). Thus, early diagnosis and treatment may prevent chronic impairment. Despite therapy with all treatment options (except for liver transplantation), twin patients with neonatal-onset deficiency of the CPS I reaction step had subsequent neurologic deterioration (associated with a type 1 lesion) after subsequent episodes of hyperammonemic encephalopathy (10). Accordingly, we would suggest that early liver transplantation should be considered in patients with neonatal-
onset urea-cycle disorders. Knowledge of the MR findings may help to expedite the diagnosis and treatment.

**Conclusion**

We herein described the brain MR imaging findings in three patients with neonatal-onset urea cycle disorders: two sisters with a deficiency of the CPS I reaction step and one boy with OTCD. The MR images revealed almost identical findings in the bilateral lentiform nuclei and in the perirolandic and insular cortices, a pattern that has not been reported previously, at least to our knowledge. We speculate that the MR imaging results in our cases reflect injury to those regions most susceptible to hypoperfusion in the neonate under hyperammonemic conditions. Knowledge of the MR findings may help to expedite the diagnosis and treatment of neonatal-onset urea-cycle disorders. We also reviewed and discussed the previous neuroradiologic findings in urea-cycle deficits divided them into four common patterns.

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**References**


