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Case Report

Brain MR Imaging in Acute Hyperammonemic Encephalopathy Arising from Late-Onset Ornithine Transcarbamylase Deficiency

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Summary: The brain MR imaging characteristics of three patients with acute hyperammonemic encephalopathy resulting from late-onset ornithine transcarbomylase deficiency are presented. MR images revealed injury to the cortex, especially the cingulate gyrus and insular cortex, with sparing of the perirolandic and occipital cortices. These findings presumably reflect the distribution of brain injury from hypoperfusion secondary to hyperammonemia. Knowledge of the MR findings may help expedite diagnosis and treatment and prevent chronic impairment.

Ornithine transcarbamylase deficiency (OTCD) is the most common inborn error of metabolism of the urea cycle, with an incidence of one case per 14,000 live births (1). OTCD is an X-linked disorder characterized by signs and symptoms of encephalopathy, which are induced by the accumulation of precursors of urea, principally ammonia and glutamine. The most severe clinical form of OTCD occurs in full-term infants who appear healthy for 24–48 hours and then exhibit signs of progressive lethargy, hypothermia, and apnea. Milder forms of OTCD also occur. In these milder forms, signs of encephalopathy (vomiting, abnormal mental status, ataxia, seizures, or developmental delay) may become evident at any age from infancy to adulthood. Late-onset OTCD commonly occurs in women who have a mutation at the *OTC* locus of one of their X chromosomes.

Recently, reports of late-onset OTCD described neuroimaging findings that resemble those of extensive ischemic strokes (2–6). We herein describe three patients with late-onset OTCD. MR images in these patients with acute hyperammonemic encephalopathy revealed a pattern of injury in the cortex, especially in the cingulate gyrus and the insular cortex. To our knowledge, this has not been reported previously.

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From the Neuroradiology Section, Department of Radiology (J.T., A.J.B.); Division of Medical Genetics (S.F.C., D.K., S.P.), Department of Pediatrics, University of California San Francisco; and Department of Medical Genetics, Kaiser Permanente (J.C.B.), Oakland, CA.

Address correspondence to Jun-ichi Takanashi, MD, Department of Pediatrics, Graduate School of Medicine, Chiba University, 1–8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan.

Case Report

The three subjects of this study were a 2.5-year-old boy, 7-year-old girl, and a 62-year-old man. Analysis of the *OTC* gene revealed a missense mutation in all three patients. Pertinent clinical data are given in the Table. Each patient underwent MR imaging by using the same 1.5-T superconducting magnet (GE Medical Systems, Milwaukee, WI). Brain spin-echo T1-weighted (TR/TE/NEX, 600/8/2) and T2-weighted (2500/80/1) images and spin-echo echo-planar diffusion-weighted images (TR, 7000, b = 800) were obtained in each patient. For all images, a 5-mm section thickness was used. (The clinical and genetic workup of patient 3 is also reported elsewhere [7] and is discussed only briefly in this report.)

MR Imaging Findings

Patient 1.— MR imaging was performed 7 days after the onset of symptoms. Spin-echo T1- and T2-weighted images demonstrated no parenchymal lesion. Diffusion-weighted images, however, revealed reduced diffusion in the posterior portion of the left insular cortex (Fig 1).

Patient 2.— MR imaging was performed 2 days after symptom onset. T2-weighted images of the brain demonstrated swelling and T2 prolongation. This was extensive within the cerebral cortex, most prominently in the insular cortex and cingulate gyrus, with sparing of the perirolandic and occipital cortices (Fig 2A and B). The deep gray matter structures, white matter, and cerebellum were normal. Diffusion-weighted imaging showed reduced diffusion in these lesions (Fig 2C). Follow-up MR imaging at 5 months showed diffuse cerebral atrophy.

Patient 3.— MR imaging was performed 10 days after symptom onset. T2-weighted images of the brain demonstrated swelling and T2 prolongation in the bilateral cingulate gyri and the right insular cortex (Fig 3A). Coronal fluid-attenuated inversion recovery images (TR/TE/TI, 10,002/140/2200) showed hyperintense lesions in the right cingulate gyrus and bilateral insulae and hyperintense foci in the left cerebral hemispheric white matter (Fig 3B). The apparent diffusion coefficient map revealed reduced diffusion in the bilateral cingulate gyri, in the entire right insular cortex, and in the most anterior aspect of the left insular cortex (Fig 3C).

Discussion

We report on three patients with late-onset OTCD, all with similar MR imaging findings in the insula and cingulate gyri. Although the degrees of cortical involvement were different, the pattern of involvement was identical, suggesting that the pattern may be char-

Clinical data in patients with late-onset OTCD

Patient No./ Age (y)/Sex	*OTC* Mutation	Clinical Manifestations	Therapy	Outcome	Day of MR Imaging	NH_3 Level at MR Imaging	Maximum NH_3 Level
1/2.5/M	Arg40His	Obtunded, vomiting, ataxia	Medication	Improved, hospitalized 10 d	Day 7	165	235
2/7/F	Deletion involving exons 9 and 10	Lethargy, ataxia, seizure	Medication	Improved, hospitalized 7 d	Day 2	195	293
3/62/M	Pro225Thr	Vomiting, coma, seizure	Medication, hemodialysis	Died after 5 d	Day 10	183	2050

FIG 1. MR image in patient 1 obtained 7 days after the onset of symptoms. Spin-echo echo-planar diffusion-weighted image (TR, 7000, b = 800) reveals reduced diffusion in posterior portion of the left insular cortex (*arrow*). Standard spin-echo and fluid-attenuated inversion recovery images were normal.

acteristic for this metabolic disorder. Previous reports of MR imaging in patients with late-onset OTCD described the MR imaging results from later in the course of the disease. These results showed extensive (sometimes hemispheric) infarctlike abnormalities involving both the cortex and white matter (2–5) or presumed ischemic lesions in the cerebral intervascular boundary zones (4, 6). It may be that our patients' conditions will evolve to have similar imaging appearances. Intriguingly, similar reversible areas of T2 prolongation in the cingulate gyrus and insular cortex have been reported in some patients with hyperammonemia due to other causes, such as citrullinemia (8, 9), and in those with valproic acid-induced hyperammonemic encephalopathy (10). In addition, MR imaging in a patient with acute hepatic encephalopathy reveals widespread cortical signal intensity change, with sparing the perirolandic and occipital cortices (11), similar to the MR findings in our patient 2. DWI revealed prominent and reduced diffusion in the cingulate gyrus and insular cortex (11). Despite different causes of hyperammonemia, the patterns of damage to the cingulate gyrus and insular cortex were nearly identical. Therefore, it seems reasonable to speculate that this pattern may principally reflect acute injury due to hyperammonemia rather than that the underlying disorder itself.

The pathophysiologic mechanism of central nervous system injury in hyperammonemic encephalopathy is not completely understood. One theory states that intracerebral accumulation of glutamine is the major cause of the encephalopathy (1). The presence

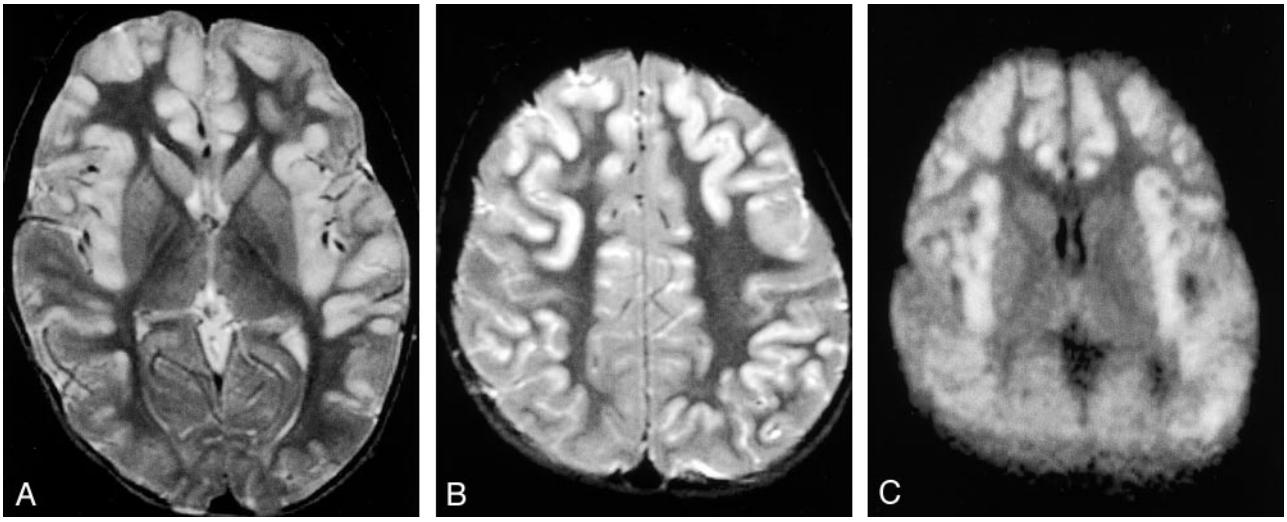

FIG 2. MR images in patient 2 obtained 2 days after the onset of symptoms.
A and *B*, Spin-echo images (2500/80/1) at the level of the basal ganglia (*A*) and centrum semiovale (*B*) demonstrate extensive swelling and T2 prolongation in the cerebral cortex, especially in the insular cortex and cingulate gyrus. The perirolandic and occipital cortices are spared. The deep gray matter, white matter, and cerebellum are normal.
C, Diffusion-weighted image (TR, 7000, b = 800) shows reduced diffusion in the cerebral cortex, especially in the cingulate gyrus and insular cortex.

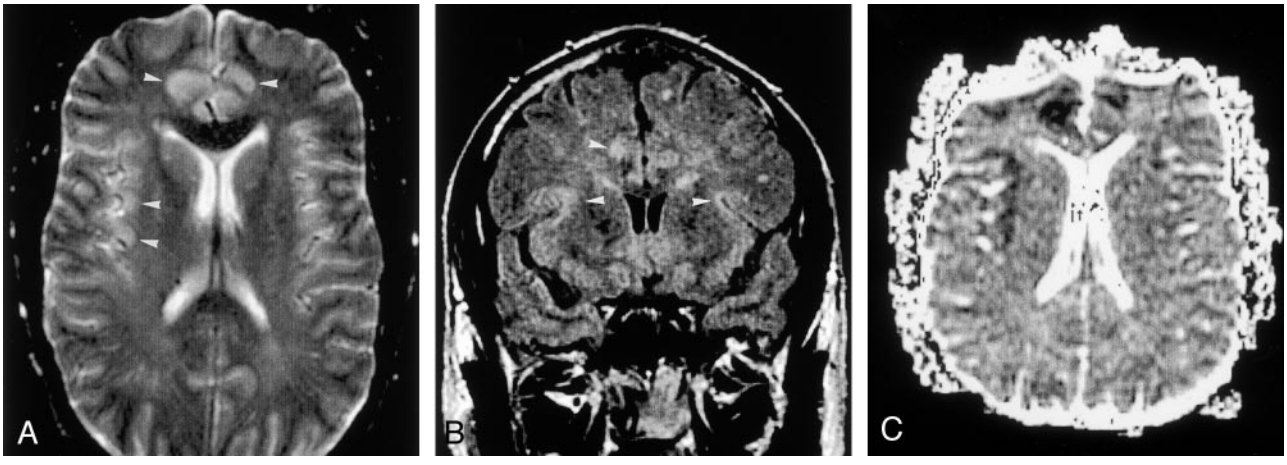

FIG 3. MR imaging in patient 3 obtained 10 days after the onset of symptoms.
A, Spin-echo image (2500/80/1) of the brain demonstrates swelling and T2 prolongation in the cingulate gyri and the right insular cortex (*arrowheads*).
B, Coronal fluid-attenuated inversion recovery image (10,000/140/2200) image shows hyperintense lesions in the right cingulate gyrus and bilateral insulae (*arrowheads*), with foci of hyperintensity in the left cerebral white matter.
C, Apparent diffusion coefficient map reveals reduced diffusion in the bilateral cingulate gyri, in the entire right insular cortex, and in the most anterior aspect of the left insular cortex.

of high levels of ammonia results in the conversion of large amounts of glutamate to glutamine mediated by glutamine synthetase, mainly in astrocytes. This theory suggests that the accumulation of large quantities of glutamine may 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). Further support for this theory is the fact that cerebrospinal glutamine concentrations in patients with OTCD are extraordinarily high during hyperammonemic encephalopathy. Proton MR spectroscopy has also demonstrated high glutamine concentrations in patients with hyperammonemic encephalopathy (3, 12).

Pathologically, symmetric cystic lesions at the gray matter–white matter junction, especially in the sulcal depth of the frontal, parietal, hippocampal, and insular regions, are early lesions in patients with hyperammonemic encephalopathy (13, 14). Such perisulcal lesions are strongly associated with diminished cerebral perfusion in the setting of elevated intracranial pressure (15), a condition found in hyperammonemic

encephalopathy. However, explaining the regional variations of the cortical lesions seen on MR images in late-onset OTCD as relatively mild perisulcal ischemic insults is difficult. More likely, the cingulate gyrus and insular cortex may seem to be particularly vulnerable to hyperammonemic-hyperglutaminergic encephalopathy, with the perirolandic and occipital cortex being relatively resistant.

Prolonged hyperammonemic coma is associated with impairment of intellectual function and notable parenchymal injury (16). Therefore, early diagnosis and treatment are essential to prevent chronic impairment. Previously reported cases have shown that cortical lesions seen on MR studies of patients with hyperammonemic encephalopathy may resolve completely (9), or they may result in mild atrophy in the cingulate gyrus or insular cortex after treatment (8, 10). These findings indicate that early changes are reversible and suggest that early treatment minimizes or completely prevents the neurologic sequelae. Knowledge of the MR findings of hyperammonemic encephalopathy may help to expedite the diagnosis and treatment, especially for the atypical late-onset OTCD.

Conclusion

We herein described brain MR imaging findings in three patients with acute hyperammonemic encephalopathy due to late-onset OTCD. MR images revealed injury to the cortex, especially the cingulate gyrus and insular cortex, with sparing of the perirolandic and occipital cortices. We speculate that that the cingulate gyrus and insular cortex may be particularly vulnerable to hyperammonemic-hyperglutaminergic encephalopathy, with the perirolandic and occipital cortices being relatively resistant. Knowledge of the MR findings may help to expedite the diagnosis and treatment of hyperammonemic encephalopathy.

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