Reversible Leukoencephalopathy in a Man with Childhood-onset Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome

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Abstract:
A 49-year-old Japanese man had shown developmental delay, learning difficulties, epilepsy, and slowly progressive gait disturbance in elementary school. At 46 years old, he experienced repeated drowsiness with or without generalized convulsions, and hyperammonemia was detected. Brain magnetic resonance imaging detected multiple cerebral white matter lesions. An electroencephalogram showed diffuse slow basic activities with 2- to 3-Hz \(\delta\) waves. Genetic tests confirmed a diagnosis of hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. Leukoencephalopathy was resolved following the administration of L-arginine and lactulose with a decrease in plasma ammonia levels and glutamine-glutamate peak on magnetic resonance spectroscopy. Leukoencephalopathy in HHH syndrome may be reversible with the resolution of hyperammonemia-induced glutamine toxicity.

Key words: HHH syndrome, leukoencephalopathy, MRS, magnetic resonance spectroscopy, hyperammonemia, glutamine toxicity

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Introduction

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome (OMIM: 238970) is a rare autosomal recessive urea cycle disorder (UCD) caused by biallelic pathogenic variants in the \(SLC25A15\) gene, which encodes ornithine translocase (1, 2). The exact incidence of HHH syndrome is unclear but is estimated to be less than 1:2,000,000 (3). To our knowledge, only 15 Japanese patients with HHH syndrome have been reported in the literature (4-13). Patients with HHH syndrome show various neurological symptoms, such as intellectual disability, epilepsy, pyramidal dysfunction, and ataxia (1, 2). They also develop encephalopathy associated with hyperammonemia, as seen in other types of UCDs (1). In HHH syndrome, brain magnetic resonance imaging (MRI) detects abnormalities, such as mild cerebral and cerebellar atrophy, white matter changes (14, 15), cystic lesions and calcifications (14), and diffuse brain edema (16). However, to our knowledge, no studies using magnetic resonance spectroscopy (MRS) have investigated the effects of therapeutic intervention on abnormal radiological findings in patients with HHH syndrome.

We herein report the improvement of leukoencephalopathy by L-arginine and lactulose administration and reduction in the glutamine-glutamate (Glx) peak on MRS in a 49-year-old man with childhood-onset HHH syndrome.

Case Report

A 49-year-old Japanese man with healthy, consanguineous parents had displayed developmental delay, learning difficulties, and slowly progressive gait disturbance during elementary school. He had no history of perinatal complications or...
any neurological diseases in his family. He presented with convulsions and was diagnosed with epilepsy at 11 years old. Despite his dropping out of ambulatory treatment, the epileptic episodes disappeared.

At 18 years old, his intelligence quotient evaluated using the Tanaka-Binet test was 49. After graduating from a high school for disabled students, he started work but retired after a month because of poor relationships with his colleagues. He subsequently lived at home with his mother. At 46 years old, he entered a group home, where he experienced repeated drowsiness with or without generalized convulsions. He was admitted to another hospital, and antiepileptic drugs (levetiracetam and lacosamide) were administered.

At that time, brain MRI showed multiple high-intensity lesions in the cerebral white matter on fluid-attenuated inversion recovery (FLAIR) imaging sequence (Fig. 1A). Hyperammonemia was detected for the first time. However, no intervention for hyperammonemia was started at this time. Transient drowsiness, with or without convulsions, occurred about once a month. At 49 years old, he was admitted to our hospital.

On a physical examination, no abnormal findings were noted. On a neurological examination, he was slightly disoriented (Glasgow Coma Scale, E4 V4M6). The Mini-Mental State Examination (MMSE) score was moderately decreased (22/30). Apart from a small voice, the cranial nerves were normal. Asterixis, mild spasticity, and brisk tendon reflexes without weakness were observed in the upper limbs. A lower limb examination demonstrated spasticity and weakness (i.e. ilio-hippocampal and hamstring muscles, 4/4; tibialis anterior muscle, 2/2; and other muscles, 5/5; on the Medical Research Council Scale [range, 0-5]) with exaggerated tendon reflexes, ankle clonus, and pathological reflexes. Cerebellar ataxia and dysautonomia were absent. While he was able to walk without aid, his gait was spastic and unstable.

Tests for a complete blood count, the hepatorenal function, glucose, and C-reactive protein showed no abnormalities. The plasma ammonia level was elevated (176 μg/dL; normal range, 12-66). A plasma amino-acid analysis showed high levels of glutamine, ornithine, and citrulline at 1031 (range, 420-700), 559 (range, 0-100), and 51.2 (range, 17-43) nmol/mL, respectively. Brain MRI showed cerebral white matter lesions with progression of cerebral atrophy (Fig. 1B). A high signal of globus pallidus on T1-weighted imaging was unapparent. MRS of the white matter lesion of the right semi-ovale center detected high peaks of Glx at 19.3 ppm (Fig. 1D). Spinal MRI showed no abnormalities. Single-photon emission computed tomography detected a diffuse decrease in perfusion, except to the cerebellum. An electroencephalogram (EEG) conducted while awake showed diffuse slow basic activities with 2- to 3-Hz δ waves without epileptic activities (Fig. 2A), suggestive of encephalopathy. No motor potentials were evoked in the upper or lower limbs on transcranial magnetic stimulation. Sanger sequencing revealed a homozygous nonsense variant in SLC25A15 (NM_014252.3:c.535C>T: p.Arg179*). This SLC25A15 gene variant has been reported as a pathogenic variant in the HHH syndrome (1), thereby confirming the diagnosis of HHH syndrome.

A protein-restricted meal of 1 g/kg/day did not decrease the plasma ammonia levels (i.e. 205 μg/dL [before breakfast], 282 μg/dL [1 h after breakfast], and 287 μg/dL [1 h after dinner]). Upon increasing the dose of oral L-arginine (from 3 to 6 g/day) and lactulose, the plasma ammonia levels decreased to the normal range (57.2±9.4 μg/dL [mean ± standard deviation]) with disappearance of disorientation, seizure, and asterixis. The apparent slow basic activities in the EEG were resolved with treatment, although the frequency of the α wave was approximately 8 Hz (Fig. 2B). After 2 months of treatment with L-arginine and lactulose, brain MRI showed resolving leukoencephalopathy associated with mild progression of cerebral atrophy (Fig. 1C). Furthermore, MRS detected a decreased Glx peak associated with an improvement in leukoencephalopathy, eight months after starting the treatment (Fig. 1E). The MMSE score increased slightly (24/30).

**Discussion**

We herein report an adult patient with childhood-onset HHH syndrome who demonstrated reversible leukoencephalopathy following the administration of L-arginine and lactulose, despite a lack of appropriate therapy for over 35 years. Furthermore, this is the first report of a decrease in the Glx peak on MRS with the resolution of hyperammonemic leukoencephalopathy in HHH syndrome.

The pathophysiology of abnormal brain MRI findings in HHH syndrome has not been elucidated. White matter lesions, similar to those observed in HHH syndrome, have been described in patients with other UCDs, such as ornithine transcarbamylase deficiency (OCTD) (17, 18). Takehashi et al. reported an increased Glx peak on MRS in four of six patients with OCTD (18). Furthermore, they showed decreased and increased Glx peaks on MRS accompanied by improved and exacerbated clinical severity, respectively (18). However, they did not describe changes in the white matter lesions on MRI in detail (18). An increased Glx peak supposedly reflects hyperammonemia-induced glutamine accumulation in the brain, which induces astrocyte enlargement (19) and cerebral edema (20). In our patient, improvement in both the cerebral white matter lesions observed on MRI and the encephalopathic symptoms following intervention for hyperammonemia may have been due to the resolution of hyperammonemia-induced glutamine toxicity. The mild progression in cerebral atrophy, despite an improvement in leukoencephalopathy, may be partly due to the resolution of both astrocyte swelling and brain edema. The deterioration of cerebral atrophy prior to intervention for hyperammonemia may have been due to intense hyperammonemia-induced glutamine toxicity.

The prognosis of HHH syndrome varies remarkably from...
may respond to treatment and show a decrease in leukoencephalopathy. In the cerebral white matter of adults. In our experience, even adult HHH syndrome patients with long-standing disease are not completely understood, especially in patients who receive treatment (1, 21). Treatment outcomes have varied from mild neurological involvement to severely disabling disease, with or without treatment (1, 21). Treatment outcomes have not been elucidated, especially in patients who receive delayed intervention in adulthood. In our experience, even adult HHH syndrome patients with long-standing disease may respond to treatment and show a decrease in leukoencephalopathy.

**Conclusion**

We encountered an adult patient with childhood-onset HHH syndrome who showed improvement in leukoencepha-
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