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Clinical Observations

Reversible White Matter Lesions During Ketogenic Diet Therapy in Glucose Transporter 1 Deficiency Syndrome

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ABSTRACT

BACKGROUND: Glucose transporter type 1 deficiency syndrome is caused by brain energy failure resulting from a disturbance in glucose transport. **PATIENTS:** We describe a 4-year-old boy with classical type glucose transporter type 1 deficiency syndrome with a heterozygous splice acceptor site mutation (c.517-2A>G) in the *SLCA2A1* gene. **RESULTS:** We initiated a ketogenic diet at 4 months of age. However, even though his condition was good during ketogenic diet therapy, multiple cerebral white matter and right cerebellum lesions appeared at 9 months of age. The lesions in the cerebral white matter subsequently disappeared, indicating that white matter lesions during diet therapy may be reversible and independent of the ketogenic diet. **CONCLUSIONS:** This is the first report of reversible white matter lesions during ketogenic diet therapy in glucose transporter type 1 deficiency syndrome.

Keywords: glucose transporter 1 deficiency syndrome, ketogenic diet, reversible brain lesions, magnetic resonance imaging

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Introduction

Glucose transporter 1 deficiency syndrome (GLUT1-DS), which is caused by brain energy failure resulting from a disturbance in glucose transport across the blood-brain barrier, exhibits clinically diverse symptoms including infantile-onset refractory epilepsy, acquired microcephaly, psychomotor retardation, and abnormal ocular movements.[1,2]

Although previous studies have already reported subcortical white matter lesions as a potentially useful finding for the diagnosis of GLUT1-DS, it remains unclear whether these lesions indicate brain cell damage, myelination delay, or something else. We describe a GLUT1-DS patient with multiple brain lesions on the cerebral white matter and cerebellum during ketogenic diet therapy. The cerebral white matter lesions spontaneously disappeared, which indicated that these lesions are reversible during ketogenic diet therapy and are independent of the therapeutic process in GLUT1-DS. This is the first report of GLUT1-DS with reversible multiple brain lesions during ketogenic diet therapy, which suggests the diverse significance of the affected central nervous system in this disease progression.

Case Report

This 4-year-old boy was born as a 3396-g infant of Japanese/Thai ancestry at term after an uneventful pregnancy and delivery. His family history was noncontributory. At 18 days of age, he exhibited atonic seizures accompanied by abnormal ocular movements. At 56 days of age, he was admitted to the hospital because of recurrent generalized tonic seizures. Intravenous diazepam and subsequent maintenance with rectal phenobarbital relieved the generalized seizures, but abnormal ocular movements and distal myoclonic movements persisted. Laboratory examinations revealed hypoglycorrhachia (25 mg/dL) and a low cerebrospinal fluid/blood glucose ratio (0.21). The cerebrospinal fluid lactate was normal limits. The boy was diagnosed with GLUT1-DS because of hypoglycorrhachia with normoglycemia on two independent occasions. At 61 days of age, we discontinued phenobarbital, which may have potentially inhibited the glucose transporter type 1 protein. At 67 days of

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age, he developed several generalized seizures; therefore, we immediately started classical ketogenic diet therapy with a formula-based ketogenic diet consisting of a 3:1 lipid/nonlipid ratio, resulting in the amelioration of seizures and abnormal ocular movements.

His height and weight during the first half year of his life grew on a mean curve and a +1 standard deviation (SD) curve of Japanese age-matched references, respectively. From 6 months of age, he exhibited low compliance for the ketogenic diet with caloric deprivation of 110 to 90 kcal/kg/day, which may have been because of his taste preferences, resulting in his body weight gradually decreasing on a +1 to −1 standard deviation (SD) curve of references by age 13 months. His serum β-hydroxybutyrate level was maintained over 4.5 mM, even during the period of caloric deprivation. Dietary instructions when he was age 14 months increased his calorie intake to 120 kcal/kg/day, which resulted in him catching up to a +1 SD curve of references by 18 months of age. His head circumference gradually decreased to a −2 SD curve of references from 5 months old. He finally exhibited normal gross motor development and verbal retardation at 4 years of age.

Interictal electroencephalography showed 2.5-Hz spike-wave discharges predominantly over the left occipital area before the ketogenic diet, with no paroxysmal discharge being noted after the ketogenic diet. Whole-brain F-18 fludeoxyglucose−position emission tomography at 14 months of age showed hypometabolism in the left medial temporal lobe and thalami, which corresponded to previously reported findings on GLUT1-DS.[3] The diagnosis of GLUT1-DS was finally confirmed by a heterozygous splice acceptor site mutation (c.517-2A>G) in the *SLCA2A1* gene at chromosome 1p34.2. An assessment using the splice-site prediction program (http://www.fruitfly.org/seq_tools/splice.html) revealed that the probability score for this variant was lower than that for the naturally occurring splice signal.

Initial magnetic resonance imaging (MRI) at 2 months showed no abnormal lesions (Fig 1A). After we started ketogenic diet therapy, MRI at age 9 months showed not only normal myelination on the genu of the corpus callosum, but also new T2 high-intensity lesions on the deep white matter with occipital dominancy. At age 14 months, MRI revealed additional brain lesions on the subcortical white matter (Fig 1B) and right cerebellum (Fig 2A,B) even though diet therapy had been successfully maintained. T1-weighted images and diffusion-weighted images showed normal signal intensities. Proton magnetic resonance spectroscopy was performed to acquire localization spectra for the abnormal T2 lesions on the left occipital lobe at 18 months of age. Absolute metabolite concentrations using an LCModel (L.A. Systems Inc., Tokyo, Japan) revealed a markedly lower N-acetylaspartate peak, higher choline peak, and slightly higher myo-Inositol and glutamate-glutamine peaks than those of the reference values.[4] Follow-up MRIs revealed an improvement in the lesions on the subcortical and deep white matter at 18 months of age, and their disappearance at 3.5 years (Fig 1C), except for the cerebellar hemisphere lesion.

Discussion

We present a boy with classical GLUT1-DS exhibiting reversible white matter lesions during ketogenic diet therapy in early infancy. Although ketosis was maintained at an appropriate level, multiple high-intensity T2 white matter lesions appeared even after normal myelination was achieved. These lesions caused a markedly decreased N-acetylaspartate, increased choline, and slightly increased myo-inositol and glutamate-glutamine on magnetic resonance spectroscopy, suggesting neuronal damage and glial proliferation. These findings are consistent with demyelination and secondary axonal degeneration.[5]

Abnormal T2 high-intensity lesions have been reported in the subcortical white matter in some patients with GLUT1-DS (Table).[6-8] However, these reports were limited to those before starting ketogenic diet therapy in GLUT1-DS patients, and T2 high-intensity lesions had resolved in one patient after introducing ketogenic diet therapy.[6] There have been no reports of MRI changes after starting a ketogenic diet. Thus this is the first report of reversible white matter lesions after initiating a ketogenic diet in GLUT1-DS patients.

High intensity T2 lesions were observed in our patient 6 months after successfully introducing a ketogenic diet. The recommendation for a ketogenic diet for GLUT1-DS patients emphasizes that serum β-hydroxybutyrate levels should be maintained in the 4- to 5-mM range for optimal brain nourishment.[2] The ketogenic status in this patient was also being maintained over the recommendation level when brain lesions appeared. Additional brain lesions subsequently appeared without the recurrence of seizures or

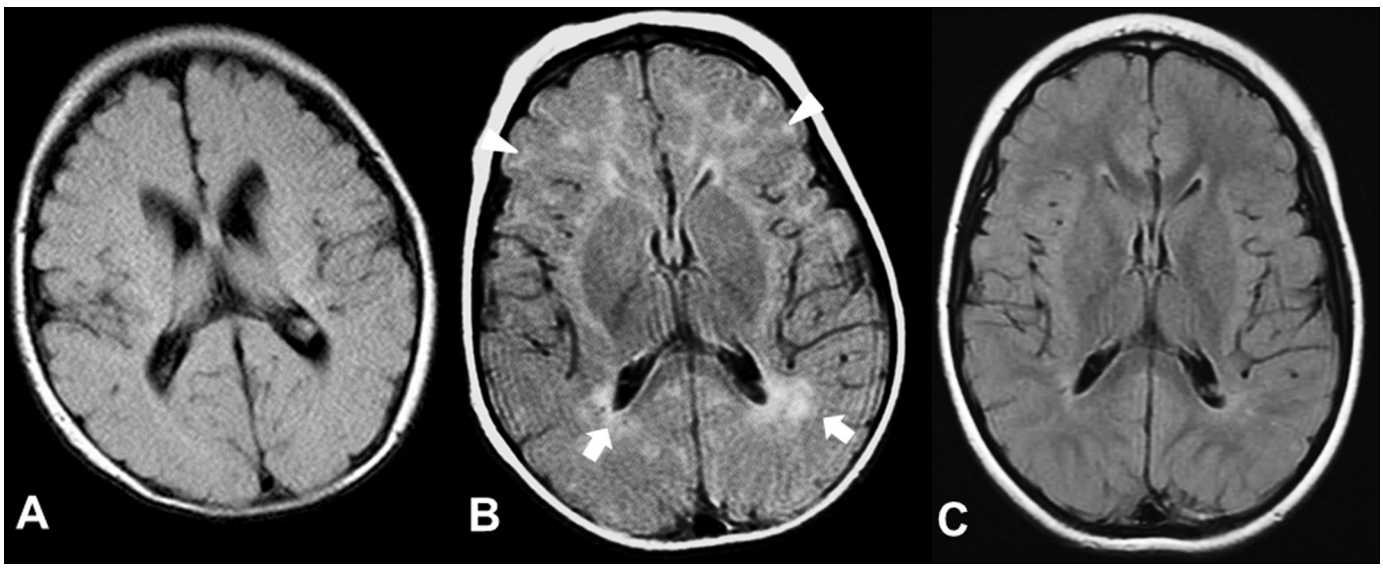

FIGURE 1.
Axial fluid-attenuated inversion recovery (FLAIR) images (repetition time [TR]/echo time [TE] 8000/110) obtained at 2 months old (A), and FLAIR images (TR/TE 10000 /110) obtained at 14 months old (B) and 3.5 years old (C). FLAIR images at 14 months old showed T2 high intensity lesions on the subcortical (arrow head) and deep white matter (arrow).