Cystathionine \(\beta\)-synthase (CBS) deficiency, well known as classical homocystinuria, is a rare autosomal recessive inborn error of homocysteine and sulfur metabolism. CBS converts homocysteine to cystathionine. The clinical features of untreated CBS deficiency include myopia, ectopia lentis, mental retardation, skeletal anomalies resembling Marfan syndrome, and thromboembolic events. Cerebral white matter lesions (CWMLs), identified in magnetic resonance imaging (MRI), are related to various clinical conditions including ischemia, inflammation, demyelination, infection, a tumor, and metabolic disorders such as phenylketonuria. The presence of CWMLs is, however, believed to be a very rare condition in CBS-deficient patients. Herein, we report reversible CWMLs associated with hypermethioninemia caused by poor protein restriction and betaine therapy in a 21-year-old male with pyridoxine-nonresponsive CBS deficiency. T2-weighted images (T2WI) and fluid-attenuated inversion-recovery (FLAIR) images showed diffuse high signal intensity in subcortical areas extending to the deep white matter. Diffusion-weighted images (DWI) showed high signal intensity, while apparent diffusion coefficient (ADC) map demonstrated decreased ADC value in the lesions. The course of improvement after correct methionine restriction was successively followed by brain MRI. The CWMLs had regressed at 1 month after restriction, and disappeared after 5 months. ADC values were very low before proper methionine restriction, but normalized after 2 months. Use of betaine in the presence of elevated plasma methionine may increase the risk of reversible CWMLs in some CBS-deficient patients.

Keywords: apparent diffusion coefficient; betaine; cystathionine \(\beta\)-synthase deficiency; homocystinuria; reversible cerebral white matter lesions

Introduction

Cystathionine \(\beta\)-synthase (CBS) deficiency, well known as classical homocystinuria, is a rare autosomal recessive inborn error of homocysteine and sulfur metabolism. CBS converts homocysteine to cystathionine. The clinical features of untreated CBS deficiency include myopia, ectopia lentis, mental retardation, skeletal anomalies resembling Marfan syndrome, and thromboembolic events (Mudd et al. 2001). This disorder is a target disorder of newborn screening in Japan. CBS requires pyridoxal phosphate as a cofactor. Thus, pyridoxine-responsive patients have been treated with pyridoxine. In pyridoxine-unresponsive patients, homocysteine levels are controlled by a protein-restricted diet and betaine therapy (Mudd et al. 2001). Betaine has been used to lower homocysteine levels, because betaine acts as a methyl donor, thereby stimulating homocysteine remethylation to methionine.

Cerebral white matter lesions (CWMLs), identified in magnetic resonance imaging (MRI), are related to various clinical conditions including ischemia, inflammation, demyelination, infection, a tumor, and metabolic disorders such as phenylketonuria (Anderson and Leuzzi 2010). The presence of CWMLs is, however, believed to be a very rare condition in CBS-deficient patients. There are only a few reports of CBS-deficient patients with reversible CWMLs (Yaghmai et al. 2002; Devlin et al. 2004; Vatanavicharn et al. 2008). We report on a CBS-deficient patient with hypermethioninemia during betaine therapy. The patient showed CWMLs, and the betaine therapy was discontinued. The lesions were completely reversed after methionine restriction despite reintroduction of betaine.
Case Presentation

The case was a 21-year-old male diagnosed with pyridoxine-nonresponsive CBS deficiency by newborn screening followed by enzyme assay. CBS activity in his fibroblasts was reduced to 0.05 mmol/mg protein/h (normal range 4.57 ± 2.53). He was treated with a methionine-restricted diet using a special formula (methionine-free milk; Meiji S-26). Oral betaine administration was started at 2 years of age. His mental development was normal and his neurologic examination was unremarkable. Compliance with the methionine restriction therapy was good up to 19 years. His blood methionine levels were stable between 22.7 and 72.4 μM (normal range 18.9-40.5 μM) for 2 years. However, after he started to live apart from his family in another city, his blood methionine levels were elevated and remained between 678.1 and 1,142.4 μM for 2 years. Compliance with oral betaine supplementation had been good until his admission.

At 21 years of age he initiated aspirin to prevent cerebral infarction, and at the same time complained of mild headaches. Brain MRI and magnetic resonance angiography (MRA) showed no evidence of vascular obstruction or stenosis. However, T2-weighted images (T2WI) and fluid-attenuated inversion-recovery (FLAIR) images showed diffuse high signal intensity in subcortical areas extending to the deep white matter. Diffusion-weighted images (DWI) showed high signal intensity, while apparent diffusion coefficient (ADC) map demonstrated decreased ADC value in the lesions (Fig. 1). He was admitted to our hospital for further evaluation and treatment.

On admission (at 21 years of age), his neurological examination had no abnormalities. Routine laboratory studies on blood and urine were normal. Amino acids analysis showed elevated plasma methionine level (904.2 μM) and total homocysteine (tHcy, 166.5 μM; normal range 3.7-13.5 μM). Lumbar puncture showed an opening pressure of 18 cmH₂O of cerebrospinal fluid (CSF), but was otherwise normal. CSF methionine and tHcy were 115.9 μM (normal range 1-5 μM) and 1.4 μM (normal range 0.04-0.13 μM) (Isobe et al. 2010). Magnetic resonance spectroscopy (MRS) imaging showed normal lactate and creatine. Single photon emission computed tomography (99m Tc-ECD SPECT) revealed diffuse blood flow reductions of the CWMLs.

Based on these findings, intracellular edema associated with hypermethioninemia was considered a cause of the CWMLs. His estimated methionine intake was approximately 1,000-2,000 mg/day before admission. To reduce the methionine level, methionine restriction was prescribed strictly (natural protein: 30 g/day; protein from methionine-free milk: 37.8 g/day; estimated total methionine intake:

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Fig. 1. MRI findings on admission.
MRI (T2WI, FLAIR, DWI) showed diffuse high-intensity signal in the cerebral white matter. The ADC value of the site was low. MRI and MRA of the brain showed no evidence of vascular obstruction or stenosis.
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~400 mg/day) and oral betaine was stopped. His headache frequency was decreased gradually after methionine restriction, and the methionine level was decreased to 147.3 μM on the 8th hospital day. However, his plasma tHcy gradually increased to 262.9 μM on the 8th hospital day. Thus, oral betaine supplementation was restarted carefully at 5 g/day on the 13th hospital day. Thereafter, plasma concentrations of methionine and tHcy were stable, at 190.2 μM and 136.7 μM, respectively, on the 18th hospital day. He was discharged on the 30th hospital day, and his protein restriction and oral betaine therapy were continued with good compliance.

Brain MRI and MRS imaging were performed to monitor the treatment process (Fig. 2). We followed the CWMLs by successive MRI at 17 years of age with good compliance with methionine restriction and betaine therapy, at 19 years of age at the beginning of elevated plasma methionine level with poor compliance with the therapy, at just before and after admission, and at 2 weeks, 1 month, 2 months, and 5 months after methionine restriction. No CWMLs were detected in the first two MRIs. However, ADC values at the genu of the corpus callosum and left frontal horn of the lateral ventricle were already decreased at 19 years of age. At 1 month after admission, brain MRI (T2WI, FLAIR, DWI) showed regression of the CWMLs, while these abnormal findings disappeared almost completely 5 months later. ADC values were elevated gradually in response to treatment and normalized after 2 months. MRS imaging showed no significant changes of lactate and creatine. Two months after methionine restriction, his headache disappeared almost completely.

Discussion

Herein, we present a CBS-deficient patient who developed CWMLs. Although he had been treated with protein restriction and betaine, his plasma methionine level was elevated to 678.1-1,142.4 μM for 2 years because of poor compliance with a methionine restriction diet. After reintroduction of strict diet therapy and discontinuation of betaine, his clinical headache was improved. Although betaine therapy was then reintroduced, his CWMLs gradually improved.

This report showed successive MRI of CWMLs. There are only three other reports of CWMLs in CBS-deficient patients (Yaghmai et al. 2002; Devlin et al. 2004; Vatanavicharn et al. 2008). These cases showed improvement of the lesions by follow-up MRI done after 4 months (Yaghmai et al. 2002) and 6 months (Devlin et al. 2004) after proper treatment, while MRI was re-examined only after 5 years in the other case (Vatanavicharn et al. 2008). By successive MRI in our case, we found that the lesions were not improved at 2 weeks after reduction of blood
methionine levels to less than 200 µM, but had improved by 1 month. Similar to two previous reports (Yaghmai et al. 2002; Devlin et al. 2004), the lesions in our patient almost completely disappeared after 5 months. Our findings suggest that it takes at least longer than 2 weeks to improve MRI-defined CWMLs after proper treatment. Reduced ADC values in CWMLs are considered to reflect intramyelinic edema (Vermathen et al. 2007). Since ADC values in white matter were decreased in the presence of hypermethioninemia before CWMLs became apparent and were improved before CWMLs were disappeared after proper methionine restriction, ADC value was a very sensitive marker for CWMLs caused by hypermethioninemia.

Reversible CWMLs have also been reported in other amino acid disorders including phenylketonuria (Anderson and Leuzzi 2010). High plasma phenylalanine level may compete other neutral amino acids transport to brain (Pietz et al. 1999), resulting in neutral amino acids deficiency. In patients with phenylketonuria, ADC values in CWMLs and the corpus callosum correlate negatively with blood phenylalanine concentrations (Kono et al. 2005; Vermathen et al. 2007), as observed in our CBS-deficient patient. However, the exact pathogenesis of intramyelinic edema remains poorly understood. Vacuolating myelinopathy (Tada et al. 2004), disturbance of Na⁺K⁺-ATPase activity (Kono et al. 2005), and intracellular accumulation of a hydrophilic metabolite that increases intracellular water content (Leuzzi et al. 2007) were discussed as causes of intramyelinic edema. Since betaine functions as an intracellular osmolyte, while amino acids such as methionine and homocysteine are also hydrophilic metabolites, increased concentrations of these metabolites may increase intracellular water content as suggested by Leuzzi et al. (2007).

All the reported CBS-deficient patients who developed reversible CWMLs with hypermethioninemia used betaine when CWMLs became apparent (Yaghmai et al. 2002; Devlin et al. 2004; Vatanavicharn et al. 2008). Two of them had episodes of morning headaches with emesis and CWMLs on MRI just 3 months after restarting betaine (Yaghmai et al. 2002) and at 4 weeks just after starting betaine (Devlin et al. 2004). The former showed an elevation of methionine to 3,037 µM after betaine therapy, while the latter case showed methionine elevated to 1,190 µM. In both patients, betaine was not reintroduced thereafter and it was considered responsible for the CWMLs. A patient with methionine adenosyltransferase I/III deficiency was also reported to develop a reversible CWMLs when betaine was used for hypermethioninemia (Tada et al. 2004). Thus, there is suggestive evidence that betaine therapy can trigger CWMLs in some patients, although many patients have been treated with betaine without such adverse events. In our patient, betaine was used for more than 10 years, although the dose was increased from 5 to 7.5 g/day 1 year before the episode. This increase in betaine may have triggered the CWMLs in conjunction with elevated plasma methionine (approximately 1,000 µM). However, it should be noted that despite reintroduction of betaine (5 g/day) after a reduction in his plasma methionine level to less than 200 µM, there were no further adverse effects in our patient and his CWMLs improved and disappeared. Thus, betaine alone was unlikely to be responsible for the lesions.

In summary, use of betaine in the presence of elevated plasma methionine levels may increase the risk of reversible CWMLs in some CBS-deficient patients. A methionine restriction diet should be introduced to reduce plasma methionine levels prior to starting betaine therapy.

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Conflict of Interest

The authors declare no conflict of interest.

References
