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Case Report

Neonatal methionine adenosyltransferase I/III deficiency with abnormal signal intensity in the central tegmental tract

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Abstract

Methionine adenosyltransferase I/III (MAT I/III) deficiency is characterized by persistent hypermethioninemia. The clinical manifestations in cases with MAT I/III deficiency vary from a complete lack of symptoms to neurological problems associated with brain demyelination. We experienced a neonatal case with MAT I/III deficiency, in which severe hypermethioninemia was detected during the newborn screening test. The patient gradually showed hyperreflexia, foot clonus, and irritability from the age of 1 month onwards, and his brain magnetic resonance imaging scans showed abnormal signal intensity in the bilateral central tegmental tracts. His neurological manifestations improved after the S-adenosylmethionine (SAMe) treatment, deteriorated after discontinuation of SAMe, and re-improved owing to re-administration of SAMe. He achieved normal neurodevelopment through SAMe and methionine restriction therapy. Lack of SAMe as well as severe hypermethioninemia were thought to contribute towards the clinical psychophysical state. Moreover, impaired MAT I/III activity contributed to the development of neurological disorder from the early neonatal period.

Keywords: Central tegmental tract; Hypermethioninemia; Methionine adenosyltransferase; S-adenosylmethionine

1. Introduction

Methionine adenosyltransferase I/III (MAT I/III) deficiency, caused by mutations in the *MAT1A* gene (10q23.1), is characterized by persistent hypermethioninemia without elevated tyrosine levels [1]. Although the clinical manifestations in cases with MAT I/III deficiency vary from a complete lack of symptoms to neurological problems associated with brain demyelination [2], most cases with moderate impairments in MAT I/III activity do not exhibit clinical manifestations.

We experienced a unique neonatal case with MAT I/III deficiency, in which severe hypermethioninemia was detected in the newborn screening test (NBST) and neurological lesions were observed in the neonatal period, and successful treatment was achieved using S-adenosylmethionine (SAMe).

2. Case report

A 1-month-old boy was admitted to the hospital for hypermethioninemia (134 μmol/L [2 mg/dL], cut-off

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67 μmol/L [1 mg/dL]) that was detected during a NBST. He was born at 39 weeks' gestation with weighed 2716 g. He and his mother had no medical problems during pregnancy and after birth. He had no significant family medical history. Two weeks after the NBST, the blood methionine level was re-analyzed and found to be elevated (998.3 μmol/L [14.9 mg/dL]) (Fig. 1A). He gradually presented hyperreflexia, foot clonus and irritability. Laboratory tests revealed no significantly abnormal findings except for elevated levels of serum soluble interleukin-2 receptor (sIL-2R) (1505 U/mL) (Supplemental data 1). Plasma amino acid analysis using high-performance liquid chromatography/mass spectrometry revealed hypermethioninemia (2049 μmol/L [30.6 mg/dL]) and mildly elevated blood homocysteine levels (38.7 μmol/L [523 μg/dL]) (Table 1). Although cardiac ultrasonography demonstrated normal cardiac function with normal regular heart beat and ejection fraction (68%), interventricular septum thickness was increased to 6 mm. At the age of 1 month, his brain magnetic resonance imaging (MRI) scans showed abnormal signal intensity with restricted diffusion in the bilateral central tegmental tracts (Fig. 2). Gene analysis identified a compound heterozygous mutation (c.812A > G [p.Y271C], c.1066C > T [p.R356W]) in the *MAT 1A* gene. He received methionine-free formula, and his blood methionine level decreased to normal (<67 μmol/L [1 mg/dL]) 23 days later. However, his hyperreflexia and irritability did not improve. Because some reports indicated that S-adenosylmethionine (SAMe) intake could be used to treat this kind of neurological disorder, he underwent SAMe supplementation from 3 months to 6 months of age. SAMe treatment improved these neurological symptoms, and his parents decided to take a treatment break. After the break, he again started exhibiting poor weight gain and irritability. Because the recurrence was suspected to have been caused by the discontinuation of SAMe treatment, we restarted treatment with SAMe, and he showed improvement again (Fig. 1B). He acquired head control at the age of 5 months. His auditory brainstem response was normal at 6 months.

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At 4 years of age, he achieved a normal neurodevelopmental status, as evaluated using the Kyoto Scale of Psychological Development, even though his MRI findings revealed abnormal signal intensity in the bilateral cerebral white matter (Fig. 3).

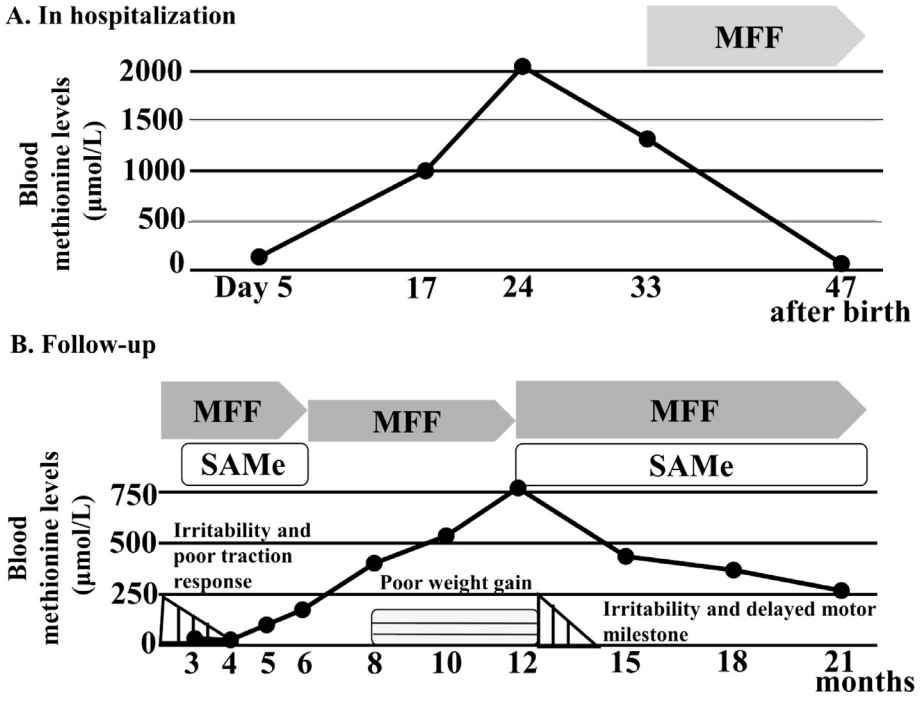

Fig. 1. Blood methionine levels and clinical course in methionine adenosyltransferase I/III deficiency. A. The patient's methionine levels decreased under methionine restriction therapy. B. Neurological manifestations improved with S-adenosylmethionine (SAMe) treatment (10 mg/kg/day). However, SAMe treatment was discontinued between the ages of 6 months and 1 year because of his parents' decision. After the break, poor weight gain and irritability, and increased blood methionine levels (1595 μmol/L [11.4 mg/dL]) after reduced methionine restriction were observed. At 1 year of age, his neurological symptoms recurred and SAMe treatment was restarted, resulting in improvement after 1 month. He could walk after acquiring normal postural refluxes including the parachute reflex and hopping reaction, at the age of 1 year and 3 months. MFF: methionine-free formula.

Table 1
Amino acids analysis upon the first medical examination.

	Reference value (nmol/mL)	
Taurine	39.5–93.2	54.2
Aspartic acid	≦2.4	7.8
Hydroxyproline	≦21.6	82.3
Threonine	66.5–188.9	350.4
Serine	72.4–164.5	200.5
Asparagine	44.7–96.8	73.9
Glutamic acid	12.6–62.5	72.6
Glutamine	422.1–703.8	582.2
Sarcosine	TR	ND
α-Aminobutyric acid	ND	3.1
Proline	77.8–272.7	271.4
Glycine	151.0–351.0	233.9
Alanine	208.7–522.7	455.4
Citrulline	17.1–42.6	30.6
α-Aminobutyric acid	7.9–26.6	21.7
Valine	147.8–307.0	243.1
Cystine	13.7–28.3	15.5
Cystathionine	TR	ND
Methionine	18.9–40.5	2049
Isoleucine	43.0–112.8	86.9
Leucine	76.6–171.3	140
Tyrosine	40.4–90.3	100.6
Phenylalanine	42.6–75.7	49.9
γ-Amino β-hydroxybutyric acid	ND	ND
β-Alanine	TR	9.3
β-Amino-iso-butyric acid	TR	10.7
γ-Aminobutyric acid	ND	ND
Monoethanolamine	≦10.4	10.8
Homocystine	ND	ND
Histidine	59.0–92.0	93.3
3-Methylhistidine	≦5.0	ND
1-Methylhistidine	≦18.5	ND
Carnosine	ND	10.4
Anserine	ND	ND
Tryptophan	37.0–74.9	64
Hydroxylysine	ND	ND
Ornithine	31.3–104.7	129
Lysine	108.7–242.2	238.8
Arginine	53.6–133.6	121.8
Total AA	2068.2–3510.3	5644.8
NEAA	1381.6–2379.4	2349.4
EAA	660.0–1222.3	3295.4
BCAA	265.8–579.1	470
EAA/NEAA	0.40–0.63	1.4
BCAA/Total AA	0.11–0.18	0.08
Fischer ratio	2.43–4.40	3.12

AA: amino acids, NEAA: non-essential amino acids. EAA: essential amino acids, BCAA: branched-chain amino acids, ND: not detectable, TR:trace.

3. Discussion

To our knowledge, this is the first report on the development of neurological lesions in the neonatal period in a case of MAT I/III deficiency. We believe that impaired MAT I/III activity contributed to the development of a neurological disorder in the early neonatal period in our patient. The neurological manifestations improved after treatment with SAMe, deteriorated after the discontinuation of SAMe, and re-improved following the re-administration of SAMe. We believe that the lack of SAMe as well as severe hypermethioninemia, contributed to the clinical state in our patient.

Most cases of MAT I/III deficiency do not involve clinical complications, and p.R264H is the most commonly associated mutation. MAT I/III deficiency with the p.R264H mutation, even if heterozygous, causes mild hypermethioninemia (50–600 μmol/L) owing to a dominant negative effect.

Except for p.R264H, mutations in the *MAT 1A* gene are inherited in an autosomal recessive manner. They are believed to reduce or abolish MAT activity and

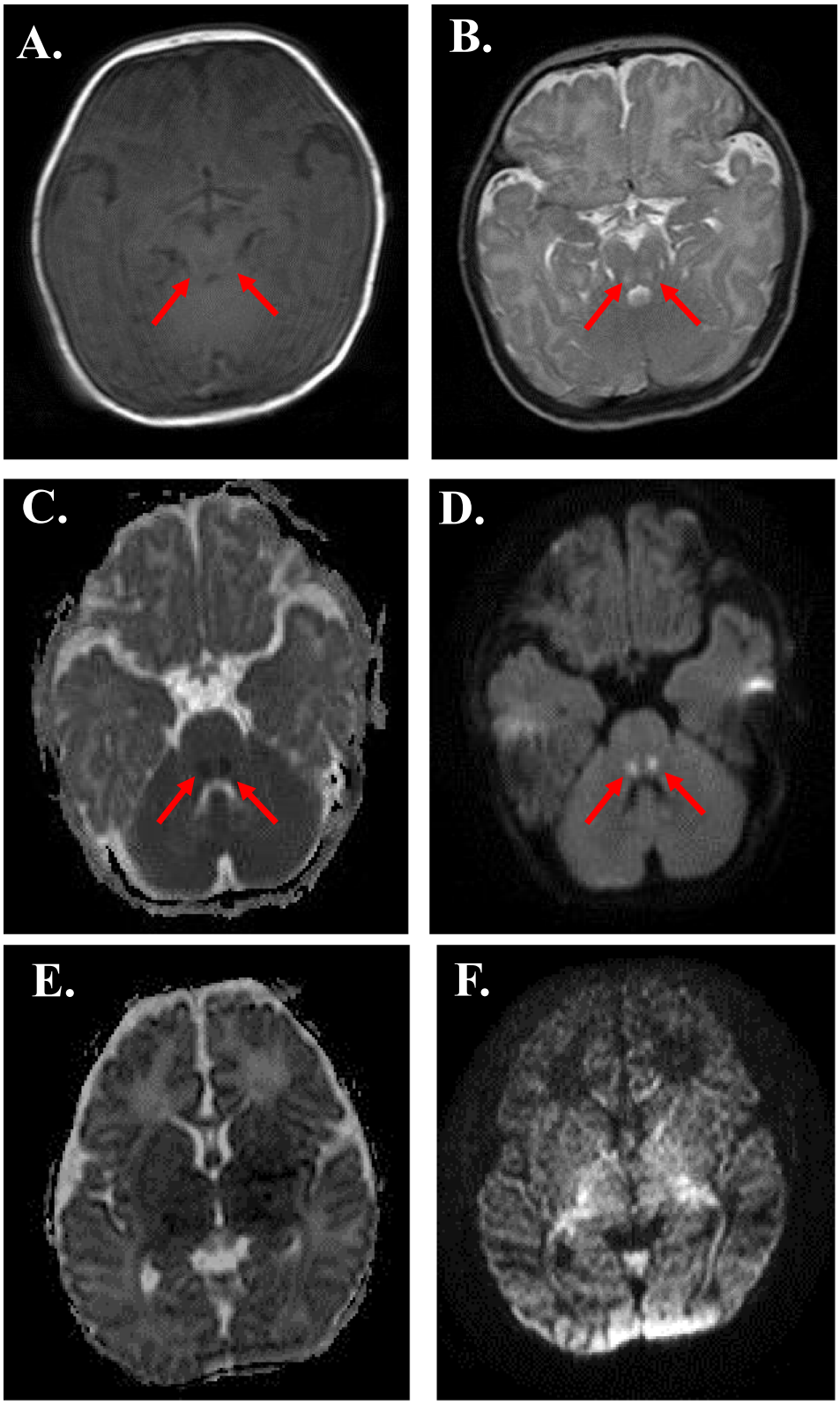

Fig. 2. Brain magnetic resonance imaging (MRI) at 37 days after birth. MRI revealed a low signal intensity on T1-weighted imaging (A: T1WI), a high signal intensity on T2-weighted imaging (B: T2WI), a low signal intensity on the apparent diffusion coefficient map (C: ADC, 0.5×10^{-3} mm^2/s), and a high signal intensity on diffusion-weighted imaging (D: DWI, b = 1000), in the bilateral central tegmental area (arrows). The bilateral cerebral white matter showed no significant abnormal signal intensity on the ADC (E) and DWI (b = 3000) (F).

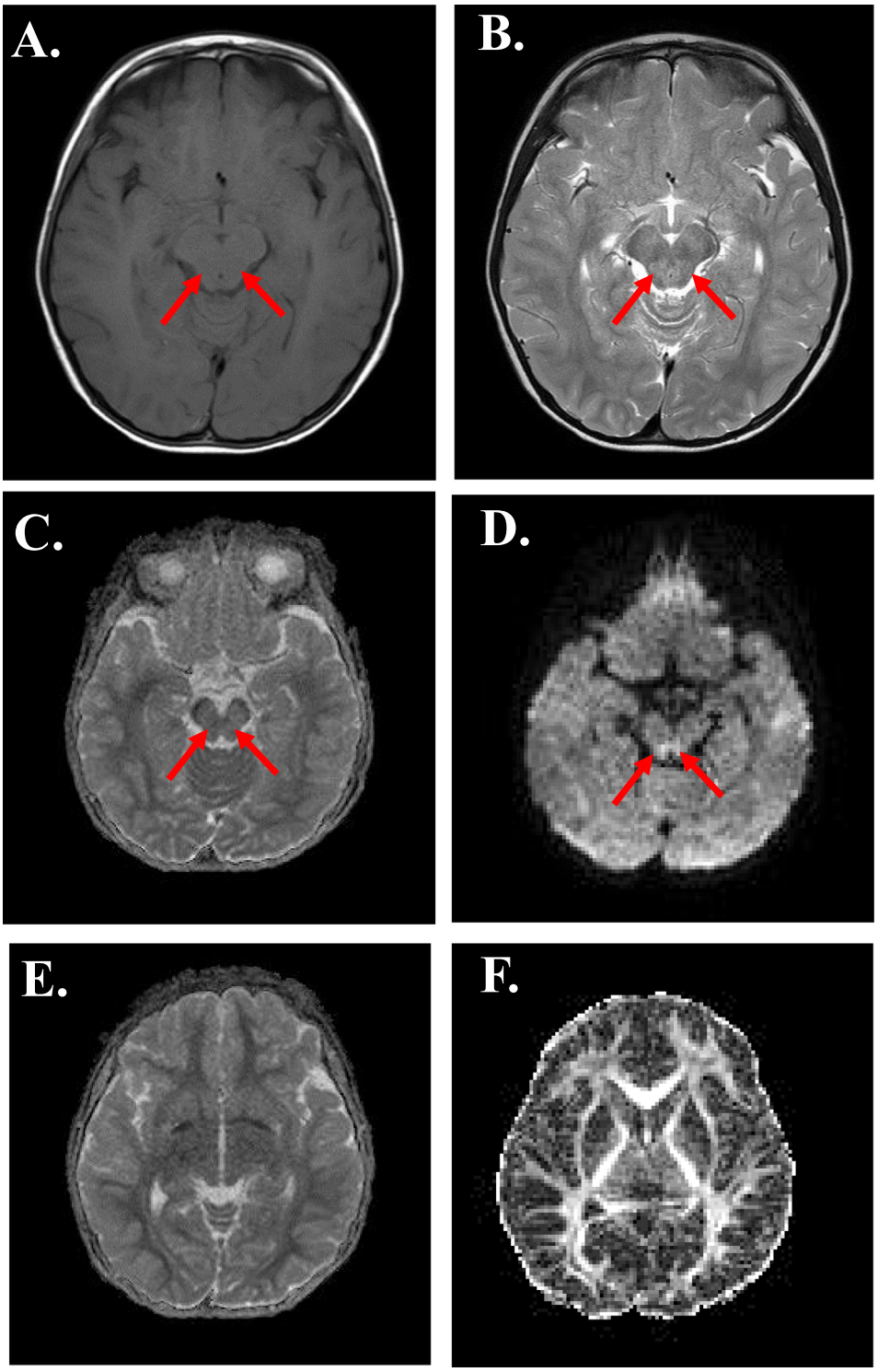

Fig. 3. Brain magnetic resonance imaging (MRI) at 4 years and 6 months during treatment with SAMe. The low signal intensity in the bilateral central tegmental area on T1-weighted imaging (A: T1WI) and the apparent diffusion coefficient map (C: ADC) improved at this stage; however, the high signal intensity on T2-weighted imaging (B: T2WI) and diffusion-weighted imaging (D: DWI, b = 1000) persisted. Moreover, the bilateral cerebral white matter, in particular the anterior commissure, showed a low signal intensity on the ADC (E) and a high signal intensity on DWI (b = 3000) (F).

result in severe hypermethioninemia (600–2500 μmol/L) [3]. Loss of MAT activity likely leads to the development of brain demyelination owing to the lack of SAMe production, which is required for the maintenance and production of the myelin structure [4]. SAMe acts as the major methyl donor for transmethylation reactions,

especially during the synthesis of two myelin phospholipids, phosphatidylcholine and sphingomyelin. It has been reported that SAMe treatment rescues demyelination in some patients with severe MAT I/III deficiency [5].

A heterozygous (c.812A > G [p.Y271C], c.1066C > T [p.R356W]) mutation in the *MAT 1A* gene was detected in our patient. A previous study involving a patient with a homozygous R356W mutation (severe and predicted to disrupt ionic interaction) reported significantly low activities of both MAT and tripolyphosphatase, which led to severe hypermethionemia (≥1000 μmol/L) [6]. The p.Y271C mutation is novel and located in exon 7, which contains many reported mutations leading to severe hypermethioninemia. Our patient exhibited lesions of abnormal signal intensity in the central tegmental tract one month after birth. In the report by Tada et al. [7], a male patient with MATI/III deficiency, whose disease was misdiagnosed to cystathionine β synthase (CBS) deficiency, demonstrated T2 prolongation in the symmetric central tegmental tract in the brain MRI at the age of 3 years old. During infancy, his condition was managed with methionine-restricted diets and oral betaine. He developed mildly decreased appetite and sleepiness in the daytime after the pyridoxine treatment was started at the age of 2.5 years. However, these clinical symptoms and MRI findings improved after the discontinuation of betaine and pyridoxine treatments. Therefore, although the administration of betain worsened hypermethioninemia, the patient did not present neurological symptoms. However, the further addition of pyridoxine treatment led to the manifestation of neurological symptoms. Moreover, Stabler et al. [8] reported a neonate with MAT I/III deficiency whose misdiagnosed to CBS deficiency became apneic and unresponsive, and required respiratory support after administration of pyridoxine but improved dramatically after discontinuation of pyridoxine.

This suggests that the incorrect administration of pyridoxine in MAT I/III deficiency reduces methionine levels in the blood and brain by activating CBS, which in turn reduces SAMe in the brain and worsens neurological symptoms.

In the current case, neurological symptoms were observed when blood methionine levels decreased due to the administration of methionine-free formula without supplementation with SAMe. Additional administration of SAMe during methionine restriction contributed to reduced neurological symptoms and controlled blood methionine levels. We could not determine whether the abnormal signal intensity on brain MRI one month after birth was due to neuronal edema or demyelination in the bilateral central tegmental area. Brain MRI repeated at the age of 4 years and 6 months revealed a persistent abnormal signal intensity in the same regions, though the findings indicated some degree of alleviation. Moreover, because the bilateral cerebral white matter also showed abnormal signal intensity, similar to that in the central tegmental tract, we presume that this abnormal signal intensity was likely correlated withedema in the neural fibers, and also included myelinic edema.

Braverman et al. [9] reported cases with severe hypermethioninemia presenting abnormal signal intensity in the dorsal brain stem, and the high methionine level itself was considered a causative factor for brain edema. Moreover, Chien et al.'s report [10] showed that most patients with mean plasma methionine levels of 800 μmol/L or more developed central nervous system abnormalities, suggesting that such levels of hypermethioninemia had adverse effects on the brain. Moreover, most patients with hypermethioninemia (200–1600 μmol/L) had mean plasma SAMe levels of 60–100 nmol/L, which are either considered normal or are close to normal levels (93 ± 16 nmol/L) [10]. However, Young et al. demonstrated that in rats, brain SAMe concentrations tend to decrease after the administration of high methionine doses, suggesting that severe hypermethioninemia contributes to decreasing SAMe levels in the brain [11]. In light of these lines of evidence, we considered that both severe hypermethioninemia and decreased SAMe levels in the brain could have contributed to the neurological manifestations observed in the present case.

The toxicity of severe hypermethioninemia in psychopathological symptoms remains controversial [12]. Our patient showed normal neurodevelopment and the neurological manifestation improved owing to the SAMe treatment. Therefore, in cases of severe MATI/III deficiency, a combination of controlling blood methionine levels and SAMe treatment are important and contribute to improving neurological symptoms. However, brain MRI may reveal persistent abnormal signal intensity in the cerebral white matter despite these treatments being provided.

In conclusion, we described a neonatal MAT I/III deficiency with abnormal signal intensity in the central tegmental tract. The patient's neurological symptoms improved after SAMe treatment but deteriorated after SAMe was discontinued. Both methionine restriction and SAMe treatment are important and effective in treating MAT I/III deficiency accompanied by severe hypermethioninemia.

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