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Case Report

Multimodal MR imaging in acute exacerbation of methylmalonic acidemia ☆,☆☆,★

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ABSTRACT

Methylmalonic acidemia (MMA) is a disorder of methylmalonic acid metabolism caused by impaired methylmalonyl CoA mutase. Neuroimaging shows symmetric hypodensity on CT, and T2 prolongation on MRI in the globus pallidus; however, there have been only a few reports on MR spectroscopy findings and no previous reports on arterial spin labeling (ASL), both of which could reflect neurochemical derangement in MMA. We herein report an 18-month-old Sri Lankan boy presented with severe acute exacerbation of MMA due to bacteremia of *Salmonella sp.* O7. MRI on the seventh day showed T1 and T2 prolongation with decreased diffusion in the bilateral globus pallidus. ASL revealed hyperperfusion in the bilateral globus pallidus. MR spectroscopy showed increased choline (Cho), myo-inositol (mIns), glutamine (Gln), and lactate (Lac) in the globus pallidus; and increased Gln and Lac in the white matter. The globus pallidus is the site of high energy demand around the age of 1 year. In severe acute exacerbation of MMA, increased anaerobic metabolism due to impaired mitochondrial function may lead to hyperperfusion in the globus pallidus to compensate for a disturbed energy supply. Increased Cho, mIns, and Lac in the globus pallidus may result from active demyelination, astrogliosis, and increased anaerobic metabolism. Increased Gln in the basal ganglia and white matter may reflect excitotoxicity.

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Introduction

Methylmalonic acidemia (MMA) is a disorder of methylmalonic acid metabolism caused by impaired methylmalonyl CoA mutase, which changes methylmalonyl CoA into succinyl CoA. Defect in methylmalonyl CoA mutase leads to the accumulation of methylmalonic acid and a clinical picture of MMA. Metabolic decompensation can be triggered by minor stress or infections, leading to mild to severe clinical manifestations, such as vomiting, dehydration, weight loss, hypothermia, convulsions, coma, multi-organ failure and even death [1].

CT and MRI show hypodensity and T2 hyperintensity in the bilateral globus pallidus in patients with MMA [2,3]; however, there have only been a few reports of MR spectroscopy and no report on arterial spin labeling (ASL). We here report MR spectroscopy and ASL in addition to MRI in an 18-month-old boy with MMA presenting with acute exacerbation, and present a possible pathomechanism.

Case report

An 18-month-old Sri Lankan boy presented with disturbance of consciousness (GCS, E1V1M1) after a day of fever and vomiting. He was transferred to our pediatric intensive care unit because of poor oxygenation and metabolic acidosis observed at the previous hospital. On admission, the patient remained unconscious and underwent tracheal intubation. According to the mother and child health handbook, his newborn screening in Japan revealed abnormal organic acid metabolism, leading to a diagnosis of MMA at a special children's hospital. Due to insufficient knowledge of Japanese, his parents could not understand his illness, nor visit the hospital regularly. After the last visit at 1 month, there was no history of further check-ups, nor a detailed developmental course. According to the parents, he presented no obvious motor delay, but in terms of language development, he only babbled and did not produce any significant words. He weighed 9.5 kg (-0.8 SD) and was 80.0 cm tall (-0.2 SD). Blood examination on admission showed hypoglycemia, below 30 mg/dL (normal range; 70-105), metabolic acidosis (pH 6.83 [normal range; 7.35-7.45], HCO^{3-} 3.2 mmol/L [21-28], BE -29.7 mmol/L [-2 to 3]) , hyperlactatemia (lactate 30 mg/dL [5-14]), and hyperammonemia (NH_3, 1101 μg/dL [12-66]). The blood glucose level normalized quickly after glucose infusion. Blood culture revealed bacteremia, *Salmonella sp.* O7. Brain CT showed symmetrical hypodensity in the globus pallidus (Fig. 1a). He underwent continuous hemodiafiltration (CHDF) and was treated with L-arginine and cargurumic acid. The hyperammonemia normalized on the second hospital day and CHDF was terminated on the third day. The patient was extubated on the sixth day when he exhibited spontaneous eye opening but poor visual pursuit. On the eighth day, the patient was transferred to a special children's hospital for management of MMA. Genetic testing later revealed a homozygous *MMUT* mutation, c.521T>C (p.Phe174Ser), confirming a diagnosis of MMA. One year after the onset, the patient was bedridden, continued to be tube fed, and was unable to utter words. No involuntary movements or convulsive seizures were noted.

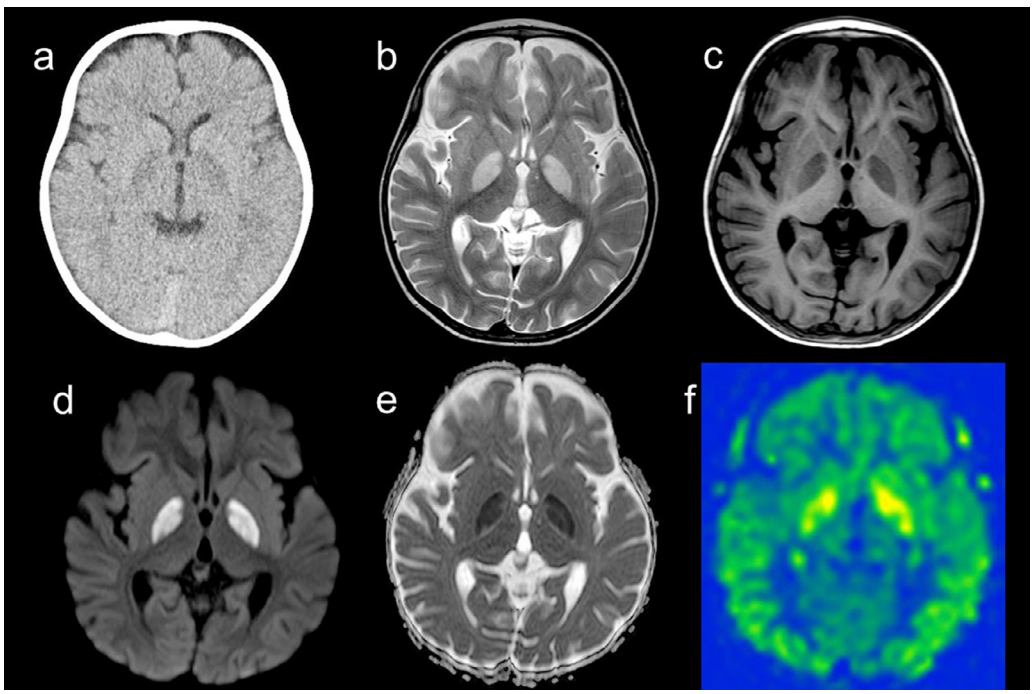

Fig. 1 – Brain CT on day 1 and MRI on day 7. CT (a) showed hypodensity lesions in the bilateral globus pallidus. T2-weighted (b) and T1-weighted (c) images show high and low signals in the bilateral globus pallidus, respectively. A diffusion-weighed image (d) reveals a high signal with reduced ADC (e) in the globus pallidus. ASL (f) shows hyperperfusion in the bilateral globus pallidus.

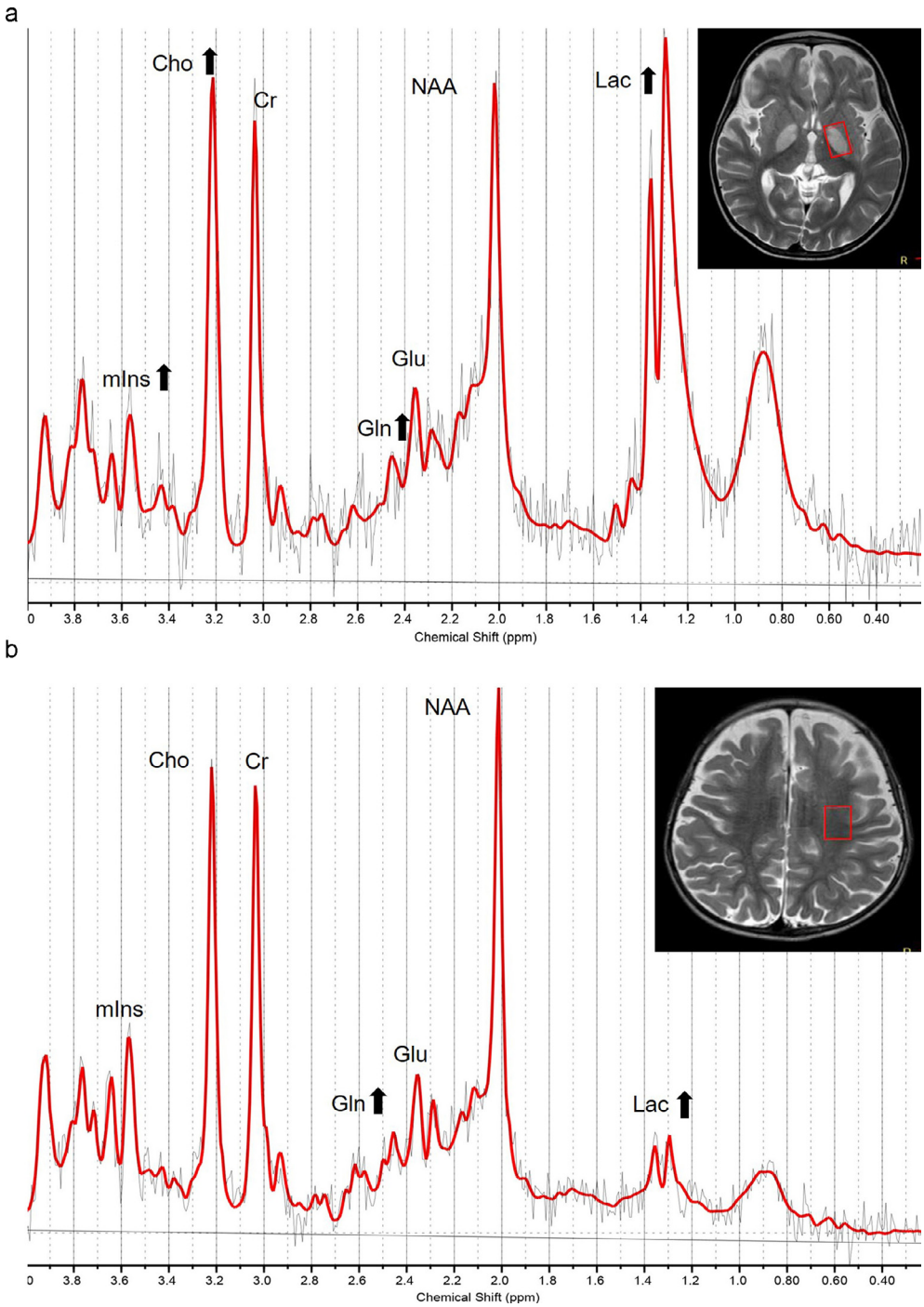

Fig. 2 – MR spectroscopy on day 7. The ROI of the white matter and basal ganglia is shown in the T2-weighted image. MR spectroscopy in the globus pallidus (a) shows increased Lac/Cr, Cho/Cr, mIns/Cr, and Gln/Cr, with normal levels of NAA/Cr, and Glu/Cr. MR spectroscopy in the white matter (b) shows high Gln and mildly increased Lac, with normal levels of NAA, Cho, mIns, and Glu. ROI, region of interest; Cho, choline; Cr, creatine; Gln, glutamine; Glu, glutamate; mIns, myo-inositol; NAA, N-acetylaspartate. A value exceeding the mean ± 2 SD was regarded as abnormal and is shown in bold, over the mean + 2 SD being shown as ↑, and under the mean - 2 SD as ↓.

MRI, MR spectroscopy, and ASL

Brain MRI was performed with a 3.0T scanner on the seventh day. T1- and T2-weighted images showed low and high signal lesions, respectively, with reduced diffusion in the bilateral globus pallidus (Figs. 1b-e). MR spectroscopy was performed in the left fronto-parietal white matter and globus pallidus (voxel size of 1.5 × 1.5 × 2.0 cm). Point-resolved spectra were obtained using TR of 5000 msec, TE of 30 msec, and number of excitations of 32. Quantification of metabolites in the white matter was performed using the water scaling method of LCModel (35.88 mol/L and T2 of 80 msec for default value of water proton density and T2 value) [4]. Spectroscopic data in the globus pallidus were semi-quantatively evaluated by the ratio of creatine (Cr), because high proton and prolonged T2 values in the basal ganglia may lead to underestimation of the metabolite concentration shown on LCModel. A value exceeding the mean ± 2SD for age-matched controls is regarded as abnormal. MR spectroscopy in the globus pallidus (Fig. 2a) showed increased choline (Cho)/Cr (0.45; age-matched control, 0.26 ± 0.02 [mean ± SD]), myo-inositol (mIns)/Cr (0.53; age-matched control, 0.45 ± 0.03), glutamine (Gln)/Cr (0.96; age-matched control, 0.51 ± 0.05), and Lac/Cr (1.90; not observed in controls), with normal N-acetylaspartate (NAA)/Cr (1.00; age-matched control, 1.06 ± 0.07), and glutamate (Glu)/Cr (1.27; age-matched control, 1.17 ± 0.06). MR spectroscopy in the white matter (Fig. 2) revealed high Gln (3.55 mM/L; age-matched control, 2.10 ± 0.28 mM/L [mean ± SD]) and mildly increased Lac (1.53 mM/L, not observed in controls) with normal levels of NAA, Cho, mIns, and Glu.

The parameters for 3D-ASL were as follows: TR/TE, 8000/11.0 ms; post labeling delay, 1500 ms; FOV, 240 × 240 mm; slice thickness, 6 mm; NEX, 4; number of slices, 14; and total scan time, 5 minutes 4 seconds. ASL revealed hyperperfusion in the bilateral globus pallidus (Fig. 1f).

Discussion

We for the first time present detailed MR spectroscopic findings with increased Cho, mIns, Gln, and Lac; and ASL showing hyperperfusion in the globus pallidus in the acute exacerbation phase of MMA.

It has been reported that the globus pallidus is specifically injured in MMA [2,3]. The reasons for this are considered to be the following. The globus pallidus is considered to be a site of high energy demand during development, around the first year of life [3]. In MMA, the activity of methylmalonyl CoA mutase is reduced, resulting in the accumulation of methylmalonic acid, which acts as a competitive inhibitor to succinate dehydrogenase, a key enzyme in mitochondrial aerobic oxidation. This process leads to mitochondrial dysfunction and increased anaerobic metabolism. The globus pallidus is, therefore, considered to be susceptible to cytotoxic edema caused by an inadequate energy supply due to mitochondrial dysfunction, which leads to reduced diffusion on diffusion-weighted images. A similar mechanism may be responsible for the marked elevation of lactate in the basal ganglia region observed on MR spectroscopy.

Cerebral blood flow in the acute exacerbation phase of MMA has not been previously reported on SPECT and ASL. ASL is an MR method without contrast enhancement for detecting perfusion abnormalities [5]. As mentioned above, there is a marked energy deficiency in the globus pallidus during acute exacerbation of MMA due to mitochondrial dysfunction [6]. It is reasonably considered that hyperperfusion in the globus pallidus observed on ASL may compensate for energy depletion. In the acute phase of Leigh's encephalopathy, a mitochondrial disorder with progressive neurodegeneration, hyperperfusion observed on ASL has also been reported in the basal ganglia [7], for which a compensatory mechanism has also been postulated.

MR spectroscopy showed increased Cho (a marker for myelin membranes) and mIns (a marker for astrocytes) in the basal ganglia, which may have resulted from destruction of the myelin sheath (active demyelination) and reactive astrogliosis, respectively, due to an inadequate energy supply. On the other hand, there are the following explanations for the high Gln. In the central nervous system, ammonia is consumed in astrocytes during the conversion of Glu to Gln. Therefore, in hyperammonemia, such as urea cycle disorders, Gln accumulates in astrocytes to detoxify ammonia, which is observed on MR spectroscopy [8]. In addition, Cho and mIns are generally reduced in hyperammonemia [8]. In the present case, however, both Cho and mIns were elevated, and MR spectroscopy was performed on the seventh day, that is, 4 days after normalization of serum ammonia. These facts suggest that a mechanism other than hyperammonemia could be considered for the high level of Gln. Glu toxicity has been postulated in various diseases including acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [9]. MR spectroscopy in AESD shows acute Glu elevation (days 1-4) changes to subacute Gln elevation (days 4-12), as observed in the present patient on the seventh day. Glu excitotoxicity may be, therefore, involved in the pathogenesis of acute exacerbation of MMA.

In conclusion, multimodal MR imaging in acute exacerbation of MMA revealed neurochemical derangement, that is, marked energy depletion due to mitochondrial dysfunction resulting in T2 prolongation, reduced diffusion, hyperperfusion on ASL, and high Lac on MR spectroscopy in the globus pallidus. Increased Gln on MR spectroscopy suggests that Glu excitotoxicity may be involved in the pathomechanism.

Patient consent

A written informed consent was obtained from the parents for publication of this report.

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