Multi-slice Proton MR Spectroscopy and Diffusion-weighted Imaging in Methylmalonic Acidemia: Report of Two Cases and Review of the Literature

Ba-Chinh Trinh, Elias R. Melhem and Peter B. Barker

AJNR Am J Neuroradiol 2001, 22 (5) 831-833
http://www.ajnr.org/content/22/5/831

This information is current as of October 15, 2023.
Multi-slice Proton MR Spectroscopy and Diffusion-weighted Imaging in Methylmalonic Acidemia: Report of Two Cases and Review of the Literature

Ba-Chinh Trinh, Elias R. Melhem, and Peter B. Barker

Summary: Methylmalonic acidemia is an inborn disorder of amino acid metabolism that commonly presents with neurologic deficits. We present the results of multi-slice proton MR spectroscopy and diffusion-weighted imaging of the brain in two patients with methylmalonic acidemia. The findings consisted of restricted diffusion and elevated lactate in the globi pallidi, compatible with acute infarction (patient 1) and elevated lactate in CSF (patient 2).

Methylmalonic acidemia is an inborn disorder of amino acid metabolism that commonly presents with neurologic deficits. CT and MR imaging of the brain typically reveal atrophy, delay in myelination, and abnormalities in the basal ganglia, predominantly in the globi pallidi. To our knowledge, there has been only one report on proton MR spectroscopic (MRS) findings and no reports on diffusion-weighted imaging findings in patients with methylmalonic acidemia. In this report, we present the results of multi-slice proton MRS and diffusion-weighted imaging of the brain in two patients with methylmalonic acidemia.

Case Reports

Patient 1

A 16-month-old female patient presented with vomiting, lethargy, and upper limb tremor. She presented 6 months earlier with failure to thrive, dehydration, and metabolic acidosis. Organic acid analysis of urine revealed high levels of methylmalonic acid. In vitro skin fibroblast analysis confirmed that the methylmalonic acidemia was a result of a cobalamin synthesis defect. She remained well with protein restriction, carnitine supplementation, and alkalinization until this episode. In vitro skin fibroblast analysis confirmed that the methylmalonic acidemia was a result of a cobalamin synthesis defect.

Patient 2

A 14-year-old boy with methylmalonic acidemia attributable to mutase deficiency (mut–), diagnosed at 3 weeks of age, was admitted for fluctuating consciousness, hearing and visual loss, nystagmus, and clonus after an episode of upper respiratory tract infection. Blood tests revealed hypoglycemia, hyperammonemia, and elevated Lac levels. Organic acid analysis of urine was not performed during this admission. CT on the same day of admission depicted mild prominence of the cortical sulci and ventricular system. Brain MR imaging and mul-

Received August 21, 2000; accepted after revision December 5.

From the Russell C. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD.

Address reprint requests to Elias R. Melhem, MD, Department of Radiology, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287-2182.

© American Society of Neuroradiology
Fig 1. Patient 1. 
A, Symmetrical high signal intensity in the globi pallidi is demonstrated (*) on fast-FLAIR (8800/140/2200 [TR/TEeff/TI]) and T2-weighted FSE (5015/97 [TR/TEeff]) MR images. On the diffusion-weighted (10,000/100 [TR/TE]) (b = 1000 s/mm²) MR image, the lesions were mildly hyperintense anteromedially and markedly hyperintense posterolaterally (arrowheads). The ADCave map demonstrated symmetrical low signal intensity (restricted diffusion) in the posterolateral portions of the globi pallidi (arrowheads), consistent with acute infarctions. Other brain regions appeared normal, and no Lac was detected in CSF.

B, Single-voxel short-TE spectrum (2000/30 [TR/TE]) of the left globus pallidus shows decreased levels of NAA and increased levels of Lac compared with controls (not shown). Levels of other metabolites are within normal limits (Glu, glutamate and glutamine; ml, myo-inositol).

Discussion

The amino acids isoleucine, valine, methionine, and threonine are normally catabolized successively to propionic acid, methylmalonic acid, and succinic acid. The conversion of methylmalonic acid to succinic acid requires an enzyme, methylmalonyl-CoA mutase, and a coenzyme, adenosylcobalamin. Deficiency of the mutase enzyme (complete, mut0; partial, mut–) or of the cobalamine coenzyme (cblA through cblF) results in accumulation of methylmalonic acid (4). The pathophysiology of brain lesions in patients with methylmalonic acidemia is attributed to inhibition of succinate dehydrogenase, an enzyme essential for mitochondrial aerobic glucose oxidation, by high levels of methylmalonic acid (5). The globi pallidi are particularly sensitive to mitochondrial dysfunction, and are thus prime targets for injury. This is further supported by the frequent involvement of the globi pallidi in patients with congenital succinate dehydrogenase dysfunction. Energy depletion is partially compensated for by anaerobic glycolysis, with a resultant increase in the production of Lac.

All types of methylmalonic acidemia are transmitted by autosomal recessive mode. The incidence, as derived form a neonatal screening program, is one in 48,000 live births (6). The actual occurrence, however, is estimated to be one in 25,000 live births (6). Patients with methylmalonic acidemia usually manifest in the first year of life with vomiting, feeding difficulties, lethargy, dehy-
Brain CT and MR imaging reveal prominence of ventricles and sulci and a delay in white matter myelination (2). In the largest published series on brain imaging findings in methylmalonic acidemia (2), four of 23 patients had symmetrical globi pallidi infarcts similar to our first patient. One patient had increased T2 signal in the putamina bilaterally, which disappeared on a follow-up study performed 3 weeks later. These basal ganglia changes were found in patients over 2 years old and did not seem to correlate with patient compliance or severity of clinical symptoms (2).

Single-voxel proton MRS of the basal ganglia has been previously reported in three patients: one with cystic lesions in the globi pallidi, one with abnormal signal in the basal ganglia bilaterally, and one with normal MR imaging results (3). Decreased NAA was found in the two patients with basal ganglia changes on MR images, consistent with neuronal loss (3). Unlike our cases, Lac was not detected in any of the three patients (3).

Our first case demonstrated bilateral lesions in the globi pallidi, which were consistent with acute (posterolateral portions) and subacute (anteromedial portions) infarction. The diagnosis of infarction was supported by reduced ADC_{ave} and increased Lac in the involved regions and the appearance of hypodensity in the globi pallidi on follow-up head CT scans. Brain infarctions have also been demonstrated by autopsies performed on patients who died of methylmalonic acidemia (7). It is important to emphasize that the reduction in ADC_{ave} is most likely due to bioenergetic failure and not vascular compromise (normal MR angiogram of the circle of Willis).

In our second case, MR imaging was normal, and multi-slice proton MR spectra showed normal metabolism within brain parenchyma. However, there was a large increase in Lac in CSF spaces. The origin of this CSF Lac is unclear; however, we speculate that a constant low level of anaerobic glycolysis due to reduced Krebs cycle flux may have occurred in brain parenchyma, with subsequent transport and accumulation of Lac in the CSF (8). High levels of CSF Lac without concomitant elevated brain Lac has been observed in several neuropathologic abnormalities, including certain mitochondrial diseases and HIV-associated encephalitis. Although the mechanism of elevated CSF Lac remains to be determined, it is possible that measurements of CSF Lac levels achieved using MRS may be helpful in predicting the risk for brain parenchymal injury, and for noninvasively monitoring the effects of therapy. The absence of CSF Lac in our first patient may have been due to complete clearance by the time of MRS imaging (6 days after admission), and the persistence of elevated Lac in the globi pallidi may have been the result of impaired transport from the infarcted area into CSF. This case further illustrates one advantage of multi-slice proton MRS over single-voxel spectroscopy in evaluating metabolic diseases of the brain. Previous MRS study of methylmalonic acidemia (3) used single-voxel localization techniques that did not include coverage of CSF spaces. In contrast, multi-slice MRS allows spatial encoding of large amounts of brain parenchyma as well as CSF spaces in a single scan.

Conclusion

In methylmalonic acidemia, multi-slice proton MRS and diffusion-weighted brain imaging findings can range from abnormalities limited to the CSF spaces (elevated Lac) without parenchymal involvement to acute infarction in regions sensitive to mitochondrial dysfunction (globi pallidi). Multi-slice proton MRS can cover regions of metabolic abnormalities unsuspected on anatomic MR imaging.

References

5. Wajner M, Coelho JC. Neurological dysfunction in methylmalonic acidemia is probably related to the inhibitory effect of methylmalonate on brain energy production. J Inherit Metab Dis 1997;20:761–768