Magnetic Resonance Spectroscopy

Use in Monitoring MELAS Treatment

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Background: Sodium dichloroacetate has been used to treat patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Magnetic resonance spectroscopy (MRS) has been used to assess cerebral metabolism in MELAS, but to our knowledge, the findings of serial MRS studies performed after therapeutic intervention of stroke-like episodes have not been reported.

Methods: Proton MRS was serially used to measure brain metabolites in stroke-like regions and in clinically uninvolved brain regions in a patient with MELAS.

Patient: A patient with MELAS and a stroke-like episode clinically improved after treatment with sodium dichloroacetate. An elevated lactate-creatine ratio in the “stroke” region decreased on MRS studies after treatment. After a second episode, the lactate-creatine ratio increased from baseline in a region of the brain that was normal on magnetic resonance imaging scans.

Conclusions: To our knowledge, this is the first study to assess the response to treatment of a MELAS stroke-like episode and the first to show an increase in the lactate-creatine ratio in a brain region that was associated with a clinical abnormality, even though it appeared normal on magnetic resonance imaging. We conclude that MRS may help to monitor therapeutic efficacy in mitochondrial encephalomyopathies.

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Recent advances in molecular biology have increased our understanding of mitochondrial encephalomyopathies, including mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Because the course of MELAS is variable, with brain relapses that simulate strokes, treatment trials are difficult to assess. In vivo assessment of brain lactate concentration by brain proton magnetic resonance spectroscopy (MRS) may further our understanding of treatment efficacy. We describe a patient who was first diagnosed as having MELAS at the age of 40 years. Brain lactate levels were serially monitored by MRS and compared with serum lactate levels and clinical status before and after treatment with sodium dichloroacetate, which lowers both systemic and brain lactate levels by activating the pyruvate dehydrogenase complex. To our knowledge, the patient described herein is the first patient with MELAS studied serially with brain MRS during stroke-like episodes.

A short (155-cm), chronically underweight (34-kg), 40-year-old woman had a history of migraine headaches and Wolff-Parkinson-White syndrome. She presented with a 3-day history of a severe left-sided parieto-occipital headache. The neurological examination was remarkable for a partial right homonymous hemianopia associated with the complaint of “flashing lights” in the right visual field.

Brain T2-weighted magnetic resonance imaging (MRI) scans revealed a left parieto-occipital lobe hyperintense region, with normal findings on magnetic resonance angiography. Because of diagnostic uncertainty, a left temporal needle biopsy was performed and revealed edematous brain parenchyma. After other possible conditions were ruled out, a diagnosis of MELAS was supported by an elevated serum lactate level (4.0 mmol/L [36 mg/dL]; reference range, 0.4-1.8 mmol/L [3.6-16.2 mg/dL]). The presence of a mitochondrial...
3243 DNA mutation in a blood sample (39% mutant–wild-type ratio) confirmed the diagnosis of MELAS. Treatment with vitamins (ascorbic acid, phytonadione, and vitamin E), dexamethasone (8 mg/d), and coenzyme Q was started, but the patient's condition continued to deteriorate. She had periods of unresponsiveness, a Cheyne-Stokes respiratory pattern, and partial motor seizures involving her right arm and face. Respiratory acidosis ensued and mechanical ventilation was begun.

Serial brain MRI examinations were obtained, and at the fifth MRI scan, MRS data were acquired with the point resolved spectroscopy method (echo time, 144 milliseconds; repetition time, 1600 milliseconds) were scaled to correct for region-of-interest volume differences between examinations. The N-acetylaspartate–creatine (NAA/Cr) ratio improved as level of lactate decreased. Cho indicates choline; PPM, parts per million.

Figure 1. Magnetic resonance imaging spectra of the hyperintense region of the left brain before (A), during (B), 1 week after (C), and 3 weeks after (D) sodium dichloroacetate treatment show the decline in lactate (Lac) levels after treatment. Spectra acquired with the point resolved spectroscopy method (echo time, 144 milliseconds; repetition time, 1600 milliseconds) were scaled to correct for region-of-interest volume differences between examinations. The N-acetylaspartate–creatine (NAA/Cr) ratio improved as level of lactate decreased. Cho indicates choline; PPM, parts per million.

Figure 2. Arterial lactate concentration in millimoles per liter (open circles), brain lactate-creatine (Lac/Cr) ratio (closed circles), and N-acetylaspartate–creatine (NAA/Cr) ratio (squares). Metabolite ratios, derived from the spectra shown in Figure 1, show the decline in brain lactate levels after treatment with sodium dichloroacetate and a low level of N-acetylaspartate that gradually increases. Sodium dichloroacetate was administered for 19 days beginning 9 days after the first magnetic resonance spectroscopic (MRS) study. The rectangles on the horizontal axis indicate the time of sodium dichloroacetate therapy at 50 mg/kg per day (large rectangle) and 25 mg/kg per day (small rectangle).

Six days (Figure 1, A) and a low N-acetylaspartate–creatine (NAA/Cr) ratio of 0.51 (normal, 1.56; n = 4) in the edematous left parieto-occipital region (Figure 1 and Figure 2). An MRS study of the contra lateral unaffected parieto-occipital region of interest showed no measurable level of lactate but a reduced NAA/Cr ratio of 1.17.

Nine days after the first MRS study, sodium dichloroacetate was administered intravenously (50 mg/kg per day for 13 days, then 25 mg/kg per day for 6 days) and the arterial lactate level decreased (Figure 2). Focal seizure activity ceased, and the patient's need for mechanical ventilation gradually decreased to 8 h/d. After 5 days of sodium dichloroacetate treatment, an MRS study of the affected occipital lobe showed a decreased lactate-creatine (Lac/Cr) ratio (Figure 1, B, and Figure 2). A further decrease in the Lac/Cr ratio was noted 1 week after the sodium dichloroacetate treatment ended (Figure 1, C, and Figure 2), and the NAA/Cr ratio slowly improved (Figure 1, D, and Figure 2). The patient was discharged to a rehabilitation facility 5 weeks after discontinuation of the sodium dichloroacetate treatment. Her neurological examination showed a persistence of the right visual field defect.

Six weeks after discharge, she was readmitted with headache, nausea, and a new onset of cortical blindness. More MRI and MRS studies were obtained (Figure 3). The MRI scan showed the persistence of the left parieto-occipital lesion and a normal right parieto-occipital region. The left occipital NAA/Cr ratio had increased to 1.09, with a stable Lac/Cr ratio of 0.46. An MRS study of the clinically affected right occipital lobe, which had a normal appearance on MRI, revealed a low NAA/Cr ratio of 1.13 and an elevated Lac/Cr ratio of 1.28. Intravenous sodium dichloroacetate therapy was re instituted, and the patient's vision returned, with only the right field defect persisting after 5 days. She refused further MRI or MRS assessment but continued intravenous sodium dichloroacetate therapy. After she went home, she used a respirator at night and had no further neurological events. She died 1 month later of progressive respiratory insufficiency. An autopsy was not performed.
Our patient presented with an acute left occipital lesion that progressed, resulting in a mass effect and clinical obtundation. A diagnosis of MELAS was confirmed by mitochondrial mutation analysis. Clinically, the patient did not respond to treatment with steroids, coenzyme Q, or vitamins. Clinical improvement after treatment with sodium dichloroacetate was accompanied by decreases in arterial and brain lactate levels. After treatment, brain lactate levels remained low, while serum lactate levels increased. After a second strokelike episode, sodium dichloroacetate treatment was again associated with clinical improvement.

Experience with sodium dichloroacetate treatment of MELAS is limited. One study showed that sodium dichloroacetate treatment can ameliorate some biochemical abnormalities in patients with mitochondrial encephalomyopathies, including 1 patient with MELAS. Those patients were studied at baseline without clinical decompensation. In contrast, muscle energy metabolism in patients who were receiving sodium dichloroacetate, as measured with phosphorus MRS, remained abnormal. One patient with MELAS improved clinically after treatment with sodium dichloroacetate, and another continued to become demented despite treatment with sodium dichloroacetate.

Our patient presented twice with an acute cerebral focal mitochondrial decompensation. The clinical improvement that occurred soon after sodium dichloroacetate was administered suggests a cause-and-effect relationship. Since the course of MELAS is relapsing and remitting, we cannot exclude a chance association between the sodium dichloroacetate treatment and the clinical and biochemical improvement. However, our patient initially presented with a relentless downhill course before the diagnosis was confirmed. The initiation of sodium dichloroacetate therapy was temporally associated with a clinical reversal of neurological symptoms, both initially and after a relapse.

The possible sodium dichloroacetate–related improvement may be a result of improved pyruvate dehydrogenase complex function. In mitochondrial disease, pyruvate dehydrogenase complex activity is probably decreased owing to an elevated reduced nicotinamide adenine dinucleotide–oxidized nicotinamide adenine dinucleotide ratio. Since the mutation in MELAS is heteroplasmic, improved pyruvate dehydrogenase complex activity might increase lactate oxidation by mitochondria with wild-type DNA. This would reduce tissue lactate concentrations and enhance energy metabolism. Furthermore, the reduced lactate concentrations may ameliorate secondary toxic effects of a lower pH level.

In mature brain, N-acetylaspartate is found exclusively in neurons. In our patient, a low NAA/Cr ratio suggests neuronal damage in both MRI-abnormal and MRI-normal regions of interest. The presence of a low NAA/Cr ratio, and an elevated level of lactate, in an MRI-normal area suggests that comparing the MRS findings in an abnormal region with those of a control MRS study of a normal region may be misleading. In our patient, the NAA/Cr ratio did improve in the left occiput over the weeks of serial MRS examinations, suggesting some reversibility of neuronal damage.

Several of the results presented herein are similar to those in other published studies, including the low NAA/Cr ratio that occurred immediately after a strokelike episode, followed by a gradual recovery of the NAA/Cr ratio; the decrease in blood lactate levels and in the brain Lac/Cr ratio with sodium dichloroacetate treatment; and the improved clinical status with sodium dichloroa-
etate treatment after clinical decompensation. However, to our knowledge, this is the first report showing the usefulness of MRS in monitoring the response to treatment following a strokelike episode. A novel finding is the high Lac/Cr ratio found during a MELAS strokelike episode in a brain region that appears normal on MRI scans but is associated with a clinical abnormality. The patient before the strokelike episode had no lactate peak in that hemisphere. As such, the initial MRS Lac/Cr ratio did not predict the strokelike episode in this patient.

We conclude that (1) MRS is a potentially useful tool in assessing treatment (Lac/Cr ratio) and in evaluating neuronal integrity (NAA/Cr ratio) in MELAS and (2) MRS is more sensitive than routine MRI in acute evaluation of strokelike episodes. Sodium dichloroacetate therapy may improve acute cerebral exacerbations, but our 1 case does not confirm a therapeutic effect. Further studies will elucidate the utility of MRS in both prophylactic and acute MELAS treatment trials.

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REFERENCES