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MELAS Syndrome: Imaging and Proton MR Spectroscopic Findings

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PURPOSE: To evaluate imaging findings in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, strokes) syndrome for the presence and location of infarctions and the presence of lactate. **METHODS:** Eight patients were studied with MR (n = 8) and CT (n = 2). One patient underwent single-photon emission CT with technetium 99m hexamethyl-propyleneamine oxime and one patient had conventional catheter angiography. One fixed brain was studied with MR imaging. Five patients underwent single volume proton MR spectroscopy. Imaging studies were evaluated for atrophy, edema, and infarctions. Proton MR spectroscopy was visually analyzed for presence or absence of lactate. **RESULTS:** One patient showed a cerebral infarction, and later a second distant infarction developed. One patient showed a transient area of cortical edema. Two patients had small nonspecific periventricular white matter abnormalities and one patient had diffuse white matter hyperintensities. Two patients had nonspecific MR abnormalities (probably age-related changes), and two had normal MR findings. None had basal ganglia involvement. Proton MR spectroscopy showed presence of lactate in one case with transient cortical edema; in two cases with nonspecific (probably age-related) brain findings; and in two patients with normal MR findings. **CONCLUSIONS:** Patients with MELAS have a variety of MR findings. The fact that proton MR spectroscopy showed lactate in all five cases studied, regardless of MR findings, indicates that proton MR spectroscopy may be more sensitive in the detection of MELAS-associated abnormalities than MR imaging.

Index terms: Degenerative disease; Magnetic resonance, spectroscopy; Brain, magnetic resonance

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MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, strokes) syndrome is a group of inherited mitochondrial abnormalities that, in some patients, has been found to be caused by point mutations of mitochondrial DNA or mitochondrial RNA^{Leu}. MELAS is characterized clinically by strokes, strokelike events, nausea, vomiting, encephalopathy, seizures, short stature, headaches, muscle weakness, exercise intolerance, neurosensory hearing loss, and myopathy (1, 2). Invasive procedures that may help establish the diagnosis of MELAS include quantification of lactic acid in serum and cerebrospinal fluid (CSF), presence of ragged red fibers on muscle biopsy, and an increased number of mitochondria in endothelial cells of small cerebral arteries. Imaging studies demonstrate fluctuating abnormalities of gray and white matter predominantly in the occipitoparietal regions (3, 4). However, these findings are nonspecific and in the absence of clear-cut symptoms and laboratory results, the imaging features cannot be considered pathognomonic. Decreased regional cerebral blood flow as measured with IMP-^{123}I was noted in a small series of three patients with MELAS (5). Reduced uptake of this radiotracer was seen in the occipitoparietal regions. This finding is also nonspecific; perhaps single-photon emission computed tomography (CT) is suited better for follow-up of these patients than for screening. Hydrogen and ^{31}P magnetic resonance (MR) spectroscopy may show the presence of lactate and

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decreased phosphocreatine, respectively (1, 6). Phosphorus MR spectroscopy is a somewhat impractical clinical tool because it requires specially designed MR coils. Hydrogen MR spectroscopy is easier to perform, but in the previously cited study (1) only two patients with MELAS underwent this type of study. Hence, the data available concerning proton MR spectroscopy are limited.

Recently, we had the opportunity to evaluate nine patients with MELAS. We reviewed the imaging studies to determine whether the abnormalities seen were similar to those reported in the literature. We also perform proton MR spectroscopy to determine the presence of lactate and correlated it with imaging findings.

Materials and Methods

Eight patients (seven female and one male; age range, 5 to 80 years) who presented with repeated strokelike episodes or seizures or were asymptomatic but had elevated lactic acid in CSF and serum (see clinical details in the Table) were evaluated with conventional noncontrast MR imaging (n = 7) using spin-echo sagittal and axial T1-weighted images (500/20/1 [repetition time/echo time/excitations) and axial and coronal T2-weighted images (2500–3000/30, 90/1). In one patient contrast-enhanced T1-weighted axial images also were obtained. Contrast CT with 10-mm-thick sections through the entire head was performed on two subjects. Single-photon emission CT study after ^{99m}Tc hexamethyl-propyleneamine oxime (HMPAO) administration was done in axial and coronal projections on one patient. Conventional cerebral plain-film angiography was performed in one case. One

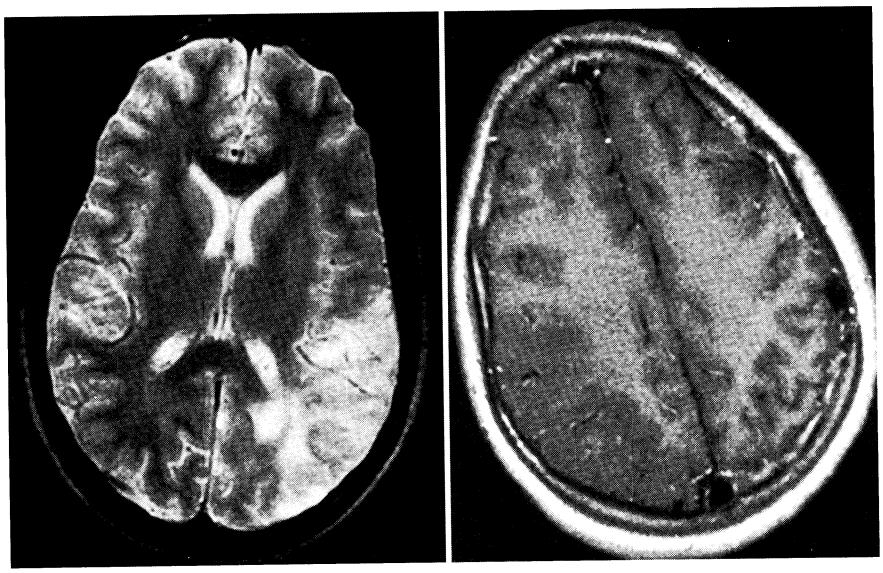
Clinical and imaging features in nine patients with MELAS

Case	Age	Sex	Clinical Symptoms	Imaging Studies	Proton MR Spectroscopy?	Initial Findings	1-Year Follow-up Clinical/Imaging
1	18 mo	F	Developmental delay; seizures	MR	No	Atrophy, diffusely high T2 signal in PVWM	Progressive developmental delay; microcephaly; seizures/stable
2	47 y	F	Unknown	Postmortem MR	No	PVWM focal High T2 signal	. . .
3	17 y	M	Permanent right- and left-sided weakness	MR/CT/Angiogram	No	L temporo-occipital infarct; negative angiogram	Stable/stable
4	16 y	F	Seizures	MR/CT single-photon emission CT†	Yes	Transient R occipital edema; lactate	Stable/stable
5	13 y	F	Transient ischemic attack*	MR/CT	No	Atrophy; nonspecific PVWM T2 signal abnormalities	Stable/stable
6	80 y	F	Transient ischemic attack*	MR	Yes	Atrophy; nonspecific PVWM T2 signal abnormalities; lactate	Stable/. . .
7	33 y	F	Transient ischemic attack*	MR	Yes	Tiny L occipital infarct; lactate	Stable/stable
8	60 y	F	Transient ischemic attack*	MR	Yes	Negative MR; lactate	Stable/. . .
9	5 y	F	Transient ischemic attack*	MR	Yes	Negative MR, lactate	Stable/stable

Note.—PVWM indicates periventricular white matter.

* Transient ischemic attacks were less than 24 hours in duration.

† Single-photon emission CT study was done with ^{99m}Tc HMPAO.



A B

Fig 1. Case 3. *A*, MR axial T2-weighted image (3000/90/1) shows a left temporooccipital subacute infarction involving both gray and white matter.

B, Post–gadopentetate dimeglumine axial MR T1-weighted image (500/20/1) obtained 1 year after A shows nonenhancing infarct involving right posterior parietal region. Proton MR spectroscopy was not done in this case.

formalin-fixed brain (with histologic confirmation of mitochondrial encephalopathy) was evaluated with MR imaging (protocol was identical to in vivo MR studies). In this patient, skeletal muscle biopsy also was obtained. Four female patients were from a family with four generations of affected persons and prospectively underwent proton MR spectroscopy using point resolved surface coil spectroscopy localization technique, water elimination Fourier transform for water suppression (2000/272), and 256 signal averages. Shimming in all cases was no greater than 0.1 ppm. In four subjects with nonspecific MR findings, a 9 × 6 × 3-cm volume was obtained at the level of the superior aspect of the parietal lobes. This volume was composed mostly of white matter (centrum semiovale) but also included some adjacent cortex. This volume was taken because it is well known that involvement of the occipitoparietal regions is typical of patients with MELAS (1). The ventricular system was not included in these voxels. In the patient with transient right occipital edema (case 4), this region (3 × 3 × 3-cm proton MR spectroscopy volume) was sampled using the aforementioned parameters. Voxels did not encompass subcutaneous scalp fat. Imaging and proton MR spectroscopy studies were done in a 1.5-T unit, and all spectra were visually analyzed for the presence of lactate. Imaging studies were retrospectively analyzed for presence of atrophy and infarctions (including their location).

Results

Results from our imaging and proton MR spectroscopy studies are found in the Table. On initial MR imaging studies, only two patients (cases 3 and 4) showed large abnormalities involving the left temporooccipital region (infarct) and the medial right occipital lobe (edema) (Fig 1A). In one of these patients (case 3), a second infarct developed in the right posterior parietal region 1 year after the initial MR imaging study (Fig 1B). Two patients (cases 1 and 5) had diffuse cerebral atrophy that was considered disproportionate for their ages. One patient (case 1) showed diffuse abnormally increased signal intensity in the white matter of both cerebral hemispheres (Fig 2). Case 7 showed a tiny left occipital signal intensity abnormality on

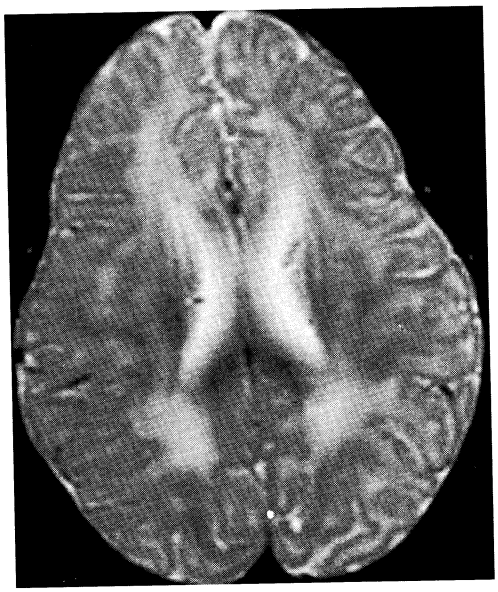


Fig 2. Case 1. MR axial T2-weighted image (3000/90/1) shows abnormal increased signal intensity in white matter, which is more pronounced in parietooccipital regions. Proton MR spectroscopy was not done in this patient.

T2-weighted MR images (Fig 3A). One 80-year-old patient (case 6) showed nonspecific white matter changes and atrophy, which were interpreted as age-related and probably not caused by mitochondrial cytopathy. Two patients (cases 8 and 9) had normal MR findings. In case 2, postmortem MR imaging (Fig 4) revealed small periventricular white matter focal abnormalities (antemortem study was not available in this case, which had been transferred to our institution for autopsy). Histologic findings in this case were microcystic changes and softening of the brain in the multiple areas of white matter abnormalities and a skeletal muscle biopsy showed ragged red fibers. CT in 2 cases (cases 3 and 4) showed findings identical to those seen on their MR studies. In one case, single-photon emission CT with ^{99m}Tc HMPAO injection showed a left temporal focus of decreased radiotracer uptake, but both CT and MR findings were normal in this region (Fig 5A). The right occipital lobe demonstrated normal radiotracer uptake, whereas MR imaging showed transient cortical edema. Conventional angiography was normal in one patient (case 3). Proton MR spectroscopy showed an abnormal peak at 1.3 ppm in all four patients from the one family with four generations of MELAS. In these four cases, MR findings were normal in two and nonspecific in the other two (cases 6 to 9). In another case, a right occipital infarction was sampled with proton MR spectroscopy and also showed an abnormal resonance at 1.3 ppm to the right of the water peak (Fig 5B). We have assumed that this resonance at 1.3 ppm represents lactate; however, proton MR spectra using an echo time of 136 milliseconds were not obtained (patients not able to tolerate scan time). Choline, creatine, and *N*-acetyl aspartate peaks were visually normal in all our patients.

Discussion

MELAS syndrome is not a single disorder, but rather an entity formed by a group of systemic abnormalities that share clinical symptoms. Thus, it is not surprising to find that it has many different imaging expressions. Classically, MR T2-weighted imaging in patients with MELAS shows increased signal intensity abnormalities involving both gray and white matter predominantly in the occipital and parietal lobes (1). These abnormalities may fluctuate, evolving into well-defined strokes or resolving completely. Also the basal ganglia may be involved in an isolated or symmetrical fashion making MELAS indistinguishable by MR imaging from other disorders such as Leigh disease (1). In our patient group, only two subjects had large cerebral abnormalities (Fig 1A). In one of these cases, right occipital cortical edema resolved on a follow-up MR study obtained 1 month later. In the second patient, a left occipital infarction developed and 1 year later, follow-up MR study showed a second infarction in a separate vascular territory (Fig 1B). In two instances (one in vivo and one postmortem), small white matter signal abnormalities were present (Figs 3 and 4). Two cases had normal MR findings and three had nonspecific findings of atrophy and periventricular white matter hyperintensities. In one case, single-photon emission CT showed decreased uptake in a region that was normal by MR and CT, but did not reveal an abnormality of radiotracer uptake in the region of edema in the right occipital lobe (Fig 5A). No follow-up imaging evaluation is available in that case, and it remains uncertain whether a stroke eventually developed in the region of abnormal radiotracer uptake (left temporal lobe).

MR spectroscopy of the brain has been used in the evaluation of mitochondrial disorders. In vivo ^{31}P MR spectroscopy has shown low phosphocreatine in patients with mitochondriopathies (6). In one series, half the patients with a mitochondrial cytopathy also had high inorganic phosphate (6). In that same series, ^{31}P MR spectroscopy was also sensitive enough to detect abnormal metabolites in patients without clinically evident brain symptoms (6). In a different study, proton MR spectroscopy in two of five patients with MELAS showed lactate (1). Presence of lactate on proton MR spectroscopy has been reported in other mitochondrial disorders and in cerebral infarctions (7–9). It is curious to note that lactate may return to normal in chronic lesions, a change probably related to washout of this metabolite (1). In our series, abnormal peaks at 1.3 ppm were assumed to represent lactate and were found in the five patients who underwent proton MR spectroscopy (Figs 3B, 5B, and 6). Lactate was present in one patient with a large infarction, in one case with just atrophy and nonspecific (probably age-related) white matter changes, in one case with a tiny signal intensity abnormality remote from the region sampled with proton MR spectroscopy, and in two cases that had normal

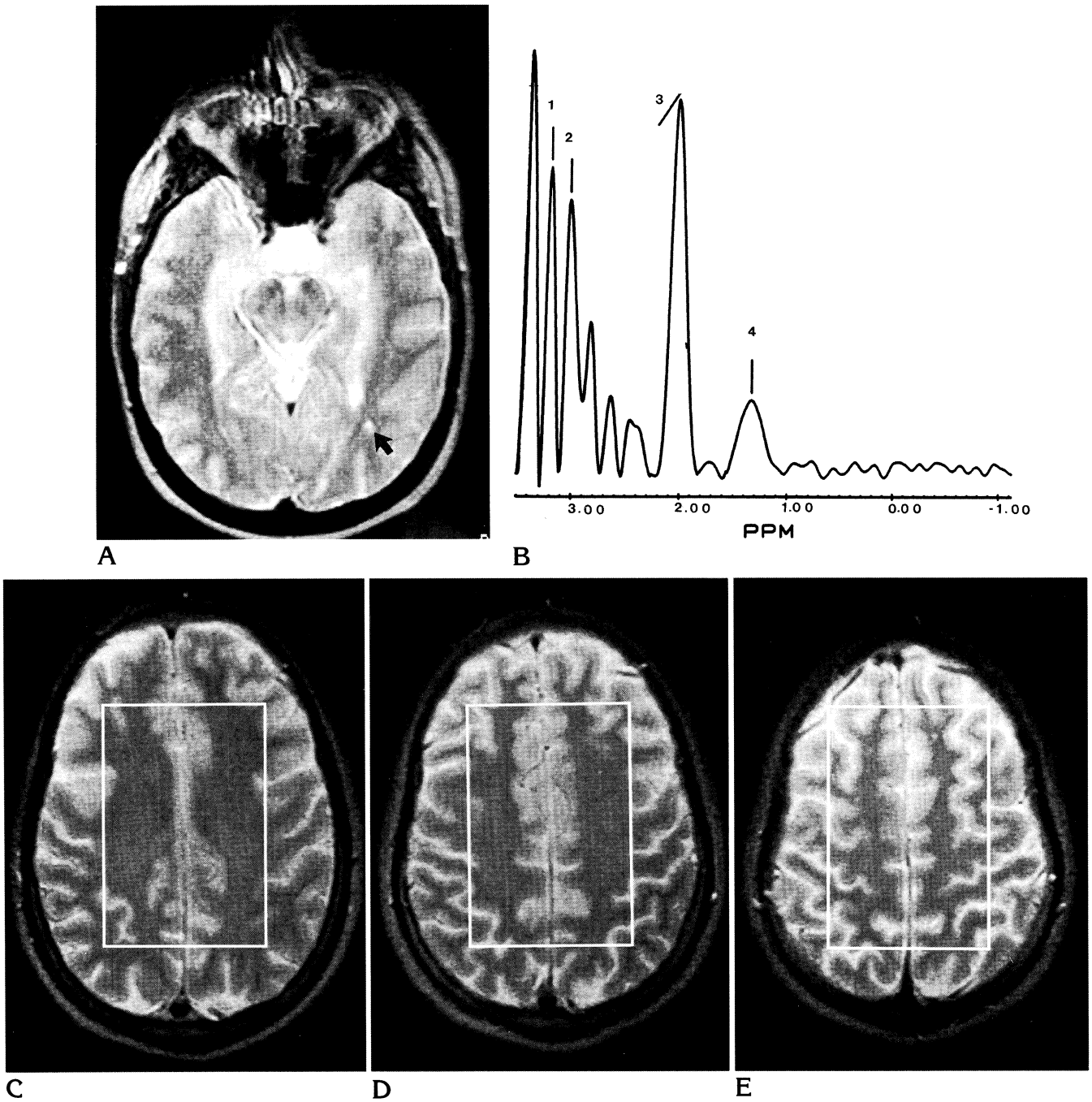


Fig 3. Case 7. *A*, MR axial T2-weighted image (3000/90/1) shows an incidental tiny left occipital signal intensity abnormality (*arrow*).

B, Proton MR spectroscopy spectrum shows peak (4) at 1.3 ppm presumed to represent lactate. 1 indicates choline; 2, creatine; and 3, *N*-acetyl aspartate.

C, Axial T2-weighted image shows lower section to contain voxel. Note that this section is above region of lateral ventricles, therefore contribution from lactate in CSF is unlikely.

D, Axial T2-weighted image at midvoxel level.

E, Axial T2-weighted image at superior aspect of voxel. Although no subcutaneous fat is in the voxel, contributions to the lactate peak from fat outside voxel limits cannot be excluded. Same voxel configuration is used in cases 6, 8, and 9.

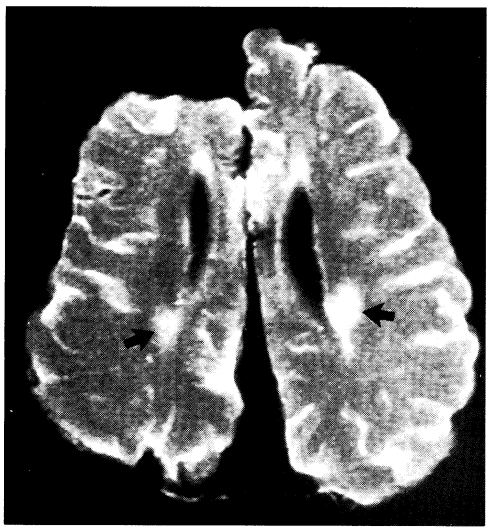


Fig 4. Case 2. Postmortem (fixed brain) axial MR T2-weighted image (3000/90/1) shows abnormal areas of high signal intensity (*arrows*) in periventricular white matter.

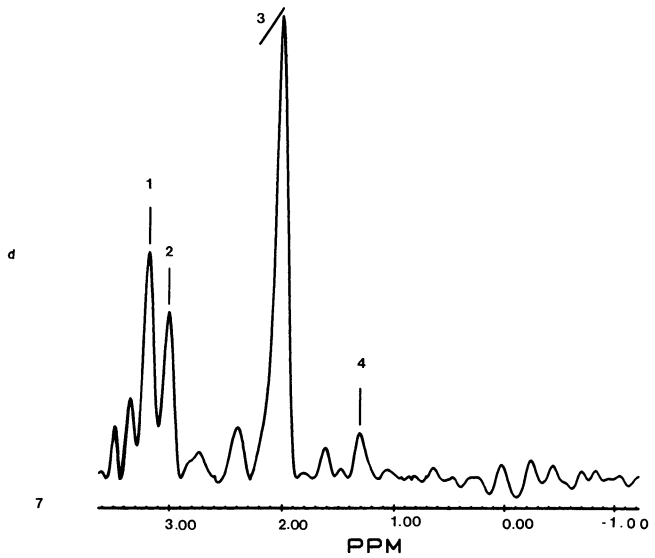


Fig 6. Case 9. Proton MR spectrum shows weak peak (4) at 1.3 ppm presumed to represent lactate. MR images (not shown) were normal in this case. 1 indicates choline; 2, creatine; and 3, *N*-acetyl aspartate.

brain MR findings. In the family with four generations affected, only the youngest one had clinical symptoms of MELAS, but lactate was present by proton MR spectroscopy in all of the studied members. Visually the peak for lactate in our cases was small. We have no clear explanation for this appearance. Lactate inverts at an echo time of 136 and that finding further corroborates (although not in a definite manner) the presence of lactate. A second, albeit remote, possibility is that the peak seen at 1.3

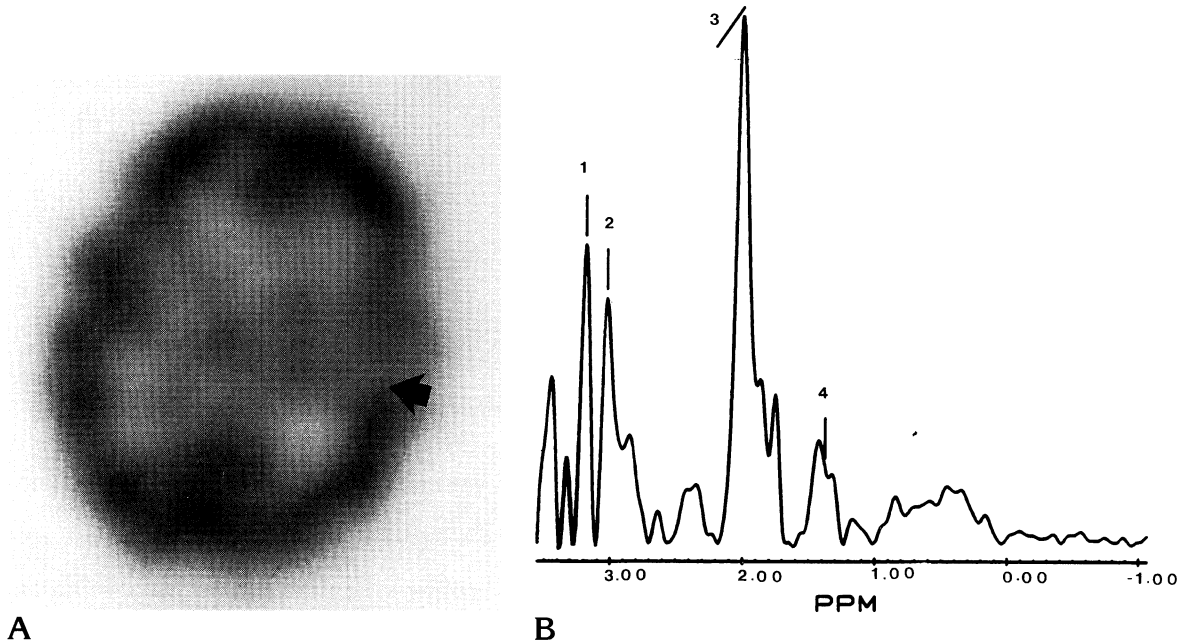


Fig 5. Case 4. *A*, Axial image from 99mTc-HMPAO single-photon emission CT study shows decreased uptake in left temporal region (*arrow*). MR images (not shown) showed transient right occipital edema in this patient. The left temporal region was normal by CT and MR imaging.

B, Proton MR spectrum in area of right occipital edema shows a peak at 1.3 ppm (4) presumed to represent lactate. Resonances between 1.0 and 0.0 ppm may represent contamination from scalp fat outside the volume. 1 indicates choline; 2, creatine; and 3, *N*-acetyl aspartate.

ppm resonance in our patients represents contaminants from abnormal lipid breakdown. In our experience abnormal lipid metabolites simultaneously produce resonances at 0.8 and 1.2 ppm; these were present only minimally (if at all) in our cases. Therefore, we believe that the resonance seen at 1.3 ppm represents mostly lactate; however, it could be mildly broadened by contamination of fat lying outside the confines of the voxel sampled. A third possibility is that the peak seen is an admixture of lactate from the brain and from CSF in the ventricles. Because no large CSF-containing structure (obviously there were some cortical sulci containing CSF included) was sampled, we believe that there is no significant lactate contribution from CSF, which is known to contain higher levels of lactate than normal brain parenchyma. We have sampled similar parts of the brain in 10 healthy persons for a different experiment (10), using almost identical imaging parameters as those used here, and found no resonances corresponding to lactate.

Obviously, the presence of abnormal cerebral metabolites in asymptomatic patients could conceivably lead to early treatment in the future and closer follow-up. The presence of lactate also could be used to separate acute and subacute infarctions from chronic ones when conventional imaging is unclear. Another potential use of proton MR spectroscopy is as a screening device when a mitochondrial cytopathy is suspected. At this time there is no successful treatment for lactic acidosis. Dichloroacetate may help by reducing the serum concentration of lactic acid. The role of proton MR spectroscopy in the follow-up of patients receiving experimental medications also remains to be determined. As seen in our cases, despite normal or near-normal MR imaging, proton MR spectroscopy showed lactate in all cases, indicating that it is a powerful and sensitive tool.

In summary, the imaging findings of MELAS in our study group were nonspecific, with only 1 patient (12%) showing large infarctions involving gray and white matter. No basal ganglia abnormalities were seen. These observations support that MELAS is a group of disorders, which have many imaging expressions. Despite normal and nonspecific MR findings in four patients, proton MR spectroscopy showed increased presumed lactate. Lactate was also present in the area of cerebral edema in another patient. This suggests that proton MR spectroscopy may reveal the presence of lactate even when the MR findings are unremarkable and in the future may be used as a screening tool in patients suspected of having mitochondrial cytopathy.

Acknowledgments

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