Serial Diffusion Imaging in a Case of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes

Charalampos Tzoulis, MD; Laurence A. Bindoff, MD, PhD

Background and Purpose—Most diffusion MRI studies of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode stroke-like lesions report high- or normal-apparent diffusion coefficient, and this has been used to differentiate stroke-like lesion from ischemic stroke. There are, however, 3 recent reports of restricted diffusion in the acute phase of the stroke-like lesions. The purpose of our study was to investigate this apparent paradox.

Methods—We performed 9 serial MRI covering 2 stroke-like episodes in a 36-year-old man with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode caused by the common mitochondrial DNA mutation 3243A>G.

Results—We found clear evidence of initial restricted diffusion in the stroke-like lesions, which gradually evolved to high-apparent diffusion coefficient as lesions aged. Evolution was, however, asynchronous with both high- and low-apparent diffusion coefficients temporally coexisting.

Conclusions—Our findings suggest that cytotoxic edema does occur early in the course of a stroke-like lesions and that its presence or, conversely, the absence of vasogenic edema, should not weaken the possibility of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode in favor of ischemic stroke. (Stroke. 2009;40:e15-e17.)

Key Words: brain imaging ■ cerebral infarct ■ diffusion-weighted imaging ■ imaging ■ mitochondria

MRI performed during a mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode (MELAS) commonly reveals high T2 signal intensity lesions with a predilection for the posterior cortex.1 Diffusion-weighted imaging (DWI) shows high signal in the acute phase that normalizes progressively over time.2-5 Most studies also report increased apparent diffusion coefficient (ADC) in the acute phase of the stroke-like episode (Table), and this has been used to distinguish stroke-like lesions (SLL) from ischemic lesions.1,2,5-9 However, at least 3 cases of low SLL ADC have been reported.3,4,10 We performed multiple sequential MRI examinations covering 2 stroke-like episodes in a patient with MELAS to investigate the diffusion properties and evolution of the SLL.

Patients and Methods
A 36-year-old man with the common 3243A>G MELAS mutation underwent serial MRI during 2 stroke-like episodes. The first was characterized by confusion, headache, abdominal discomfort, increasing hearing loss, and generalized tonic-clonic seizures. Approximately 2 years later, he was readmitted with 10-day history of increasing hearing loss, headache, confusion, and receptive aphasia. His condition gradually improved and he was discharged with residual cortical deafness and aphasia.

Nine MRI examinations were performed before, during, and after both stroke-like episodes. MRI was performed in a Siemens Magnetom Symphony 1.5-T scanner with 30-mT/m gradients and a General Electric Sigma Excite 3-T HDX scanner with 40-mT/m gradients. Sequences included T1 (with and without gadolinium), T2, and T2 fluid-attenuated inversion recovery (FLAIR)-weighted. Diffusion imaging was performed with b values of 0, 500, and 1000; based on these, ADC maps were constructed.

Results
MRI performed 4 years before stroke-like episode 1 for investigation of impaired hearing was unremarkable. Eight days after the onset of stroke-like episode 1, MRI showed a large edematous, gyral, cortical, and subcortical right temporoparietal lesion with high T2 signal intensity, low T1 signal intensity, and mild, diffuse enhancement with gadolinium. DWI showed the lesion had inhomogeneously hyperintense signal with areas of pronounced DWI hyperintensity showing low ADC, whereas areas only mildly hyperintense on DWI corresponded to normal or high ADC (Figure 2).

Three days later we found spatial progression of the lesion, which now involved most of the right occipital lobe. New lesions (1 to 3 days old) invariably exhibited low ADC, whereas several areas with previously low ADC had evolved...
to normal or high ADC. A small area of gyriform cortical T1 hyperintensity was now evident in the anterior part of the superior temporal gyrus, consistent with cortical laminar necrosis (Figures 1 and 2).

MRI, performed 58 days after onset, showed significant regression of the lesion with atrophy and retraction. There was minor residual hyperintensity on DWI, whereas lesional ADC was uniformly increased. There was significant enlargement of the T1 gyriform cortical hyperintensity (Figures 1 and 2). Imaging at 120 and 251 days and ≈2 and 3 years after the onset of stroke-like episode 1 showed progressive regression of the T2 hyperintensity and further focal atrophy with ex vacuo ventricular enlargement. DWI signal returned to baseline early, whereas the ADC remained, in parts, elevated 3 years after ictus. The T1 cortical hyperintensity gradually regressed and was only barely visible by 2 years (Figure 2).

Thirteen days after the clinical onset of stroke-like episode 2, MRI revealed a new cortical and subcortical T2 hyperintensity in the left temporal lobe. Diffusion findings were similar to those found in stroke-like episode 1, and again an inverse association was seen between the degree of DWI hyperintensity and ADC. T1 showed hypointensity, swelling, and sulcal effacement. Follow-up MRI 11 months later showed significant regression of the signal abnormalities and atrophy. DWI was isointense and, in parts, hypointense, whereas lesional ADC was normal and, in parts, high (Figure 2).

**Discussion**

Restricted water diffusion in the brain is thought to represent cytotoxic edema and is associated with states of cellular energy deprivation such as ischemia/hypoxia, prolonged epileptic activity, and severe hypoglycemia.\(^{1,12}\) Whereas the exact mechanism involved in SLLs are unknown, several theories have been proposed, including primary neuronal mitochondrial dysfunction causing direct energy insufficiency, vascular mitochondrial dysfunction leading to neuronal ischemia, and a unifying neurovascular mechanism.\(^{1}\) Irrespective of the primary pathogenic event, neurons within SLL are assumed to be energy-deprived and, from this, one would predict the occurrence of cytotoxic edema and restricted diffusion in the acute phase of the lesion.

Our findings suggest initial neuronal energy insufficiency causing cytotoxic edema and low ADC, and subsequent development of extracellular edema that gradually increases the ADC. As lesions expand and new areas become involved, the 2 processes overlap temporally, producing a mixture of cytotoxic and vasogenic edema and conversely low and high ADC.

The reason why ADC findings vary in reported SLL remains unknown, but one possible explanation is the time interval between stroke-like episode onset and MRI.

### Table. Reported Diffusion Imaging Findings in MELAS SLE

<table>
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<tr>
<th>Author</th>
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*ADC normalized in some SLL, while it remained elevated in others. H indicates high signal or ADC; L, low signal or ADC; N, normal signal or ADC; NR, not reported; SLE, stroke-like episode.

Interval indicates time (in days) from reported SLE onset to MRI.

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**Figure 1.** A, Coronal FLAIR 11 days after stroke-like episode 1 onset. B, Sagittal T1 58 days after stroke-like episode 1 onset.
studies reporting low ADC have a short onset-MRI interval, and follow-up shows gradual ADC increase within days to weeks (Table). Some studies reporting normal or high ADC also have short intervals (Table). This apparent contradiction may, however, reflect the difficulties with precisely defining onset of a SLL. An SLL develops more slowly than ischemic stroke and may not initially produce symptoms severe enough to prompt medical attention. It is possible to speculate that in at least some of the cases reporting early increased ADC, the lesions may have already evolved over several days before clinical presentation.

In conclusion, our findings strengthen the view that cytotoxic edema does occur early in the course of a stroke-like episode. Therefore, its presence or, conversely, the absence of vasogenic edema, should not weaken the possibility of MELAS in favor of ischemic stroke. The distribution of the SLL, showing a predilection for the temporal, parietal, and occipital areas and spanning vascular borders, should alert the clinician to the possibility of SLL. Furthermore, in contrast to acute ischemic infarcts that show little, if any, spatial progression, SLL tend to evolve and expand in size during the first few days to weeks after onset.

Disclosures
None.

References
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