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## Comparison of conventional and diffusion-weighted MRI and proton MR spectroscopy in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events

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**Abstract** The mechanism of neurological disturbances in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is controversial. We studied 12 patients with MELAS using conventional and diffusion weighted MRI (DWI) and MR spectroscopy (MRS), to look at the physiopathology of the stroke-like events. Although conventional MRI showed lesions in all patients, DWI was more sensitive. One patient did not show high signal on DWI 48 h after a stroke-like episode, but MRS

demonstrated a lactate peak in left occipital lobe; 2 weeks after the attack, high signal was demonstrated on the right frontal lobe where MRS had shown a lactate peak. Our findings suggest a possible predictive ability of  $^1\text{H}$ -MRS, in showing early MELAS lesions and supports the hypothesis that mitochondrial metabolic dysfunction may precede abnormalities on DWI.

**Keywords** Mitochondrial cytopathy · Stroke-like episodes · Diffusion-weighted imaging · Magnetic resonance spectroscopy

### Introduction

MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events) is a mitochondrial disorder characterised by nausea, vomiting, seizures, headaches, diabetes mellitus, muscle weakness, exercise intolerance, sensorineural hearing loss, and sudden neurological deficits [1, 2]. Although these neurological disturbances strongly mimic those of stroke, their mechanism is unclear and they are therefore generally termed “stroke-like” events. Two main hypotheses have proffered brain involvement: angiopathy leading to ischaemia or and direct neuronal death resulting from mitochondrial impairment [3].

Although conventional MRI shows signal abnormalities indistinguishable from those seen in ischaemic stroke, newly developed MR techniques applied to the challenge of elucidating the physiopathology [4, 5]. We studied 12 patients with MELAS using conventional and diffusion-weighted MRI (DWI), and MR spectroscopy (MRS) and discuss the physiopathology of the stroke-like events.

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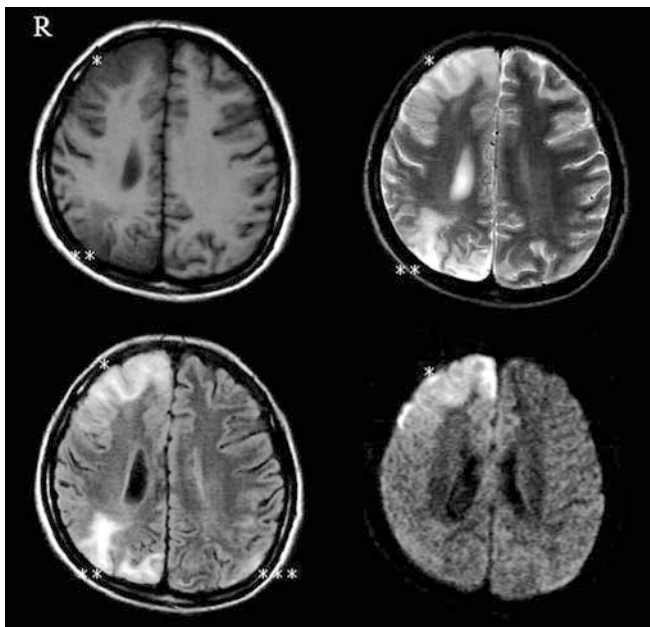
### Materials and methods

We studied 12 patients with MELAS, one man and 11 women, mean  $29.9 \pm 8.5$  years, clinically diagnosed as having MELAS and confirmed by DNA analyses to have tRNA<sup>Leu(UUR)</sup> A3243G point mutation [6, 7]. All were examined by a neurologist (Table 1) and had initial and follow-up MRI including DWI and MRS 2 weeks after a stroke-like episode.

Conventional dual-echo fast spin-echo, FLAIR (fluid attenuated inversion recovery) images and DWI were obtained using a 1.5 tesla imager with a circularly polarised head coil. Standard conventional sequences were used. DWI was acquired using a spin-echo echoplanar sequence with diffusion-sensitising gradients switched in slice direction and three different values of  $b$ : 30, 300 and  $1.100 \text{ s/mm}^2$ . Sequential sampling of  $k$ -space was used with effective echo time 123 ms, bandwidth of 1250 Hz/pixel, and acquisition matrix  $128 \times 128$ , interpolated to  $256 \times 256$  during image calculation. The DWI sequence provided 20 contiguous 3 mm slices, field of view 230 mm; acquisition time for each sequence was 5 s.

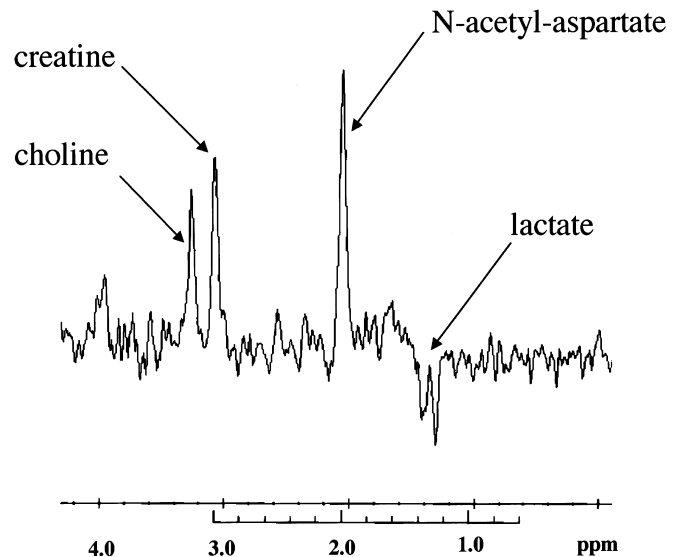
**Table 1** Clinical features

Patient	Age (years), sex	Duration of illness (years)	Neurological disturbances
1	29, male	10	Cortical blindness, recurrent hemiparesis
2	23, female	5	Cortical deafness, ataxia
3	32, female	5	Ataxia, myopathy
4	36, female	10	Recurrent hemiparesis, myopathy
5	26, female	7	Nystagmus, ataxia
6	34, female	8	Cortical deafness, ataxia
7	37, female	15	Ataxia, myopathy
8	29, female	5	Ataxia, recurrent hemiparesis
9	46, female	20	Cortical deafness, ataxia
10	16, female	2	Cortical blindness, ataxia
11	17, female	1	Hemiparesis
12	34, female	16	Ataxia, hemiparesis



**Fig. 1** Patient 1. On T2-weighted (*top right*) and fluid-attenuated inversion-recovery (FLAIR) (*bottom left*) images, high signal was observed in the right frontal (\*) and occipital lobe (\*\*) lobes. A left occipital lesion (\*\*\*) seen better on FLAIR. The right frontal occipital lesions were also visible on a T1-weighted image (*top left*), which suggested that they were relatively new. On diffusion weighted imaging (DWI) (*bottom right*), only a lesion in the left frontal lobe (\*) was visible, suggesting that it was the most recent

For MRS, we used axial FLAIR images were used to prescribe  $2 \times 2 \times 2$  cm<sup>3</sup> voxels, chosen to include affected and unaffected white matter, as judged from FLAIR images. The point-resolved spectroscopy localisation technique was used with parameters: TR 3000 TE 35 and 140 ms, 128 acquisitions. The spectroscopic data acquisition provides a water-suppressed proton spectrum over a range from 4.3 to 0.1 ppm. Chemical shifts were identified with the N-acetyl-aspartate resonance at 2.02, phosphocreatine and creatine at 3.05 and choline-containing compounds at 3.22 ppm [9]



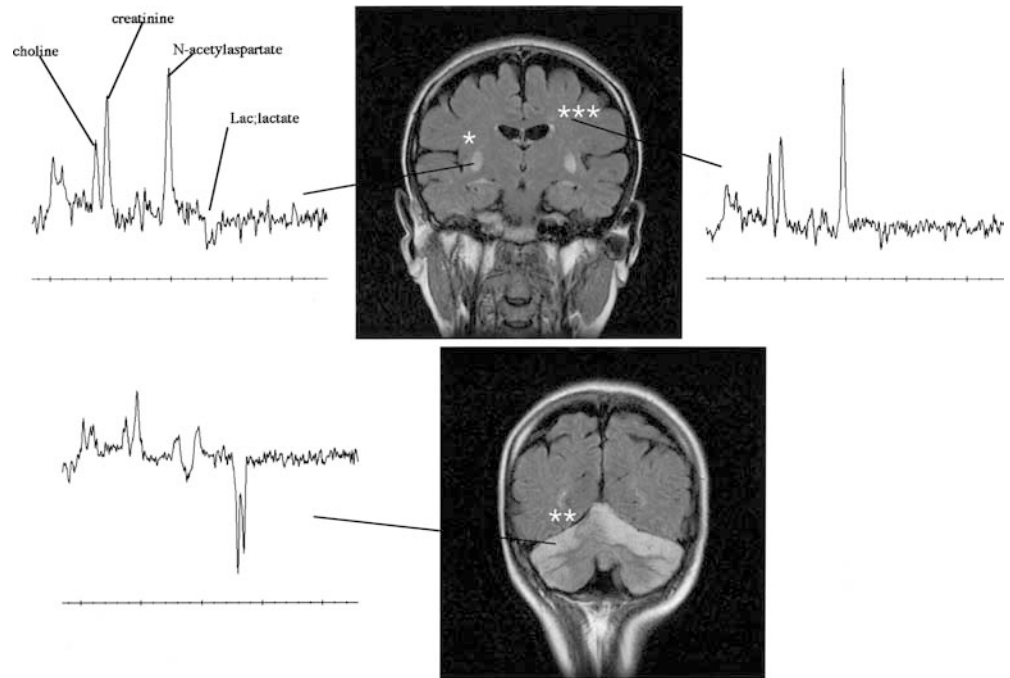
**Fig. 2** Patient 1. <sup>1</sup>H MR spectroscopy (MRS): chemical shifts were identified with the N-acetyl-aspartate resonance at 2.02, phosphocreatine and creatine at 3.05 and choline-containing compounds at 3.22 ppm

## Results

The T2-weighted fast spin-echo and FLAIR images (Fig. 1) showed abnormalities in all patients, FLAIR appearing more sensitive. When new lesions occurred, the brain appeared swollen on T1-weighted images, but this was not always clear. Lesions seen only on DWI were assumed to be new (Fig. 1) [10, 11].

MRS at TE 35 ms revealed a large doublet in recent lesions at 1.3 ppm, inverted at TE 140 ms, typical of lactate (Fig. 2). A lactate peak was clearly identified in the most recent lesions and less clearly in lesions known to be present before the first imaging study (Fig. 3). No lactate peak could be identified in a lesion in brain which appeared normal on initial MRI. It has been suggested

**Fig. 3** Patient 5. MRS. A lactate peak was clearly identified in the most recent lesion (\*) and less clearly in a relatively new lesion (\*\*); no lactate peak could be identified in a lesion normal on MRI (\*\*\*)

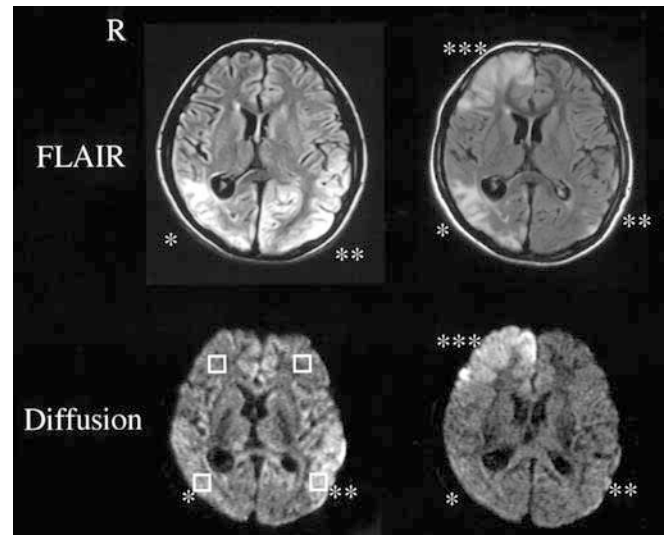


that these changes in lactate peaks are of diagnostic value in new stroke-like lesions [12, 13, 14]. However, our observations suggest that stroke-like lesions may show a lactate peak for a while after the episode.

We also made a new observation. In a patient with cortical blindness we found two lesions in the occipital lobes in the first images, clearly visible on FLAIR, but only one lesion, presumably newer, was more clearly visible on DWI; it showed increased apparent diffusion coefficients (ADC). FLAIR images obtained 2 weeks later showed a new lesion in the right frontal lobe. On DWI only this lesion, with an increased ADC could be detected and the two older lesions were not visible (Fig. 4). MRS at the time of the first MRI showed lactate peaks in the left occipital lobe, where MRI showed a lesion. However, a lactate peak was also detected in the right frontal lobe, which seemed normal on the first MRI but showed a new lesion on the second (Fig. 5, Table 2).

## Discussion

The focal neurological deficits of abrupt onset of MELAS are clinically indistinguishable from strokes [15]. MRI classically shows signal change in both grey and white matter, predominantly in the occipital and parietal lobes, which strongly mimic infarcts. However, their distribution does not usually follow vascular territories and pathological studies do not show lesions of

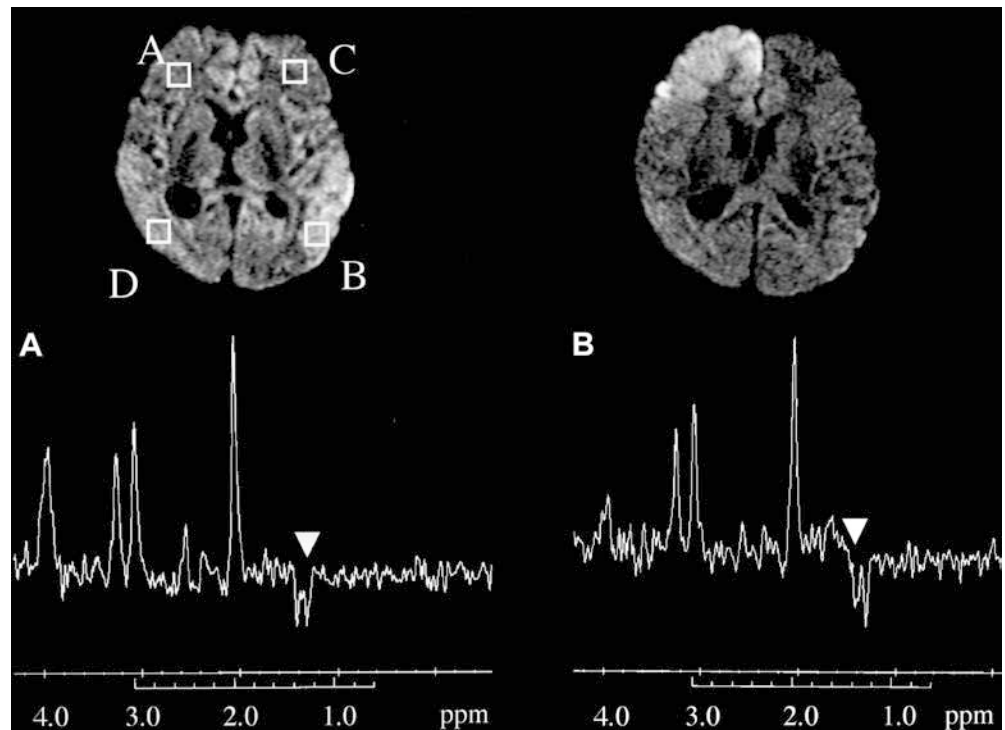


**Fig. 4** Patient 1. Serial MRI. The images on the right were obtained 2 weeks after those on the left. The lesion which appeared first (\*) on FLAIR (*top left*) but not on DWI (*bottom left*), while the second lesion (\*\*) was clearly visible on both. We placed four regions of interest (ROI) in the frontal and occipital lobes (*bottom left*). After 2 weeks, a third lesion in the frontal lobe (\*\*\*) was clearly visible on FLAIR (*top right*) and on DWI (*bottom right*). The first and second lesions were no longer visible on DWI, but were still seen on FLAIR

the major cerebral vessels. Fluctuating lesions on MRI are also characteristic (Fig. 4) [16].

The physiopathology of MELAS remains unclear but two main hypotheses have been put forward [10]. The

**Fig. 5** Patient 1. MRS: the top right image was obtained 2 weeks after the top left. ROI were placed on the DWI in the frontal (*A, C*) and occipital (*B, D*) lobes. A stroke-like lesion was visible in *B* but was not in *A*. However, MRS showed lactate doublets (*arrow-heads*) in both (preceding DWI abnormalities), but not in *C* or *D*



**Table 2** Visibility of lesions on MRI. *T1*-, *T2*-weighted spin-echo *FLAIR* fluid-attenuated inversion recovery *DWI* diffusion-weighted images *lactate peak* MR spectroscopy

Patient	Clinically new lesions					Lesions not new clinically				
	T1-weighted	T2-weighted	FLAIR	DWI	Lactate peak	T1-weighted	T2-weighted	FLAIR	DWI	Lactate peak
1	+	+	+	+	+	+	+	+	-	-
						-	+	+	-	±
2	+	+	+	+	+	+	+	+	-	-
						-	+	+	-	±
3	+	+	+	+	+	-	+	+	-	-
4	+	+	+	+	+	-	+	+	-	-
5	+	+	+	+	+	-	+	+	-	-
						+	+	+	+	+
6	+	+	+	+	+	-	+	+	-	-
7	+	+	+	+	+	-	+	+	-	-
8	+	+	+	+	+	-	+	+	-	-
9	+	+	+	+	+	-	+	+	-	-
10	+	+	+	+	+	-	+	+	-	-
11	+	+	+	+	+	-	+	+	-	-
12	+	+	+	+	+	-	+	+	-	-

vascular hypothesis holds that metabolic damage to the endothelium leads to small-vessel occlusion and secondary neuronal death [2]. The defect in neuronal metabolism hypothesis states that mitochondrial dysfunction results in anaerobic metabolism and neuronal death from acidosis [17].

Oppenheim et al. [9] reported a patient with MELAS in whom MRI 2 days after a stroke-like episode showed subcortical high signal on FLAIR but normal to high

ADC. DWI displays regional mobility of protons and it is claimed that it can help distinguish between cellular and extracellular oedema. In general, in ischaemic infarcts, intracellular diffusion of protons is restricted or reduced, giving dark areas on ADC maps. Oppenheim et al. therefore concluded that increased diffusion supported the metabolic rather than the ischaemic hypothesis. Experimental and human studies suggest that increased ADC reflect cellular oedema, whereas

decreased ADC correspond to an increase in the extracellular space [18, 19, 20, 21]. Our observations are in agreement with previous reports and suggest that increased signal on DWI supports the metabolic rather than the ischaemic hypothesis.

Although decreased ADC in early stroke lesions can be a landmark of developing ischaemic strokes, MRI, including DWI, can not predict the occurrence of stroke [22, 23]. One of our patients (Fig. 5), showed a lactate peak in an area appearing normal on DWI; a lesion was, however, evident in the same area on DWI 2 weeks later.

This seems to suggest a possible predictive ability of  $^1\text{H}$ -MRS, in showing MELAS lesions in an early phase and supports the hypothesis that mitochondrial metabolic dysfunction may precede signal change on DWI, although the latter can show ischaemic injury within an hour of symptom onset in human ischaemic stroke [24]. There is thus a possibility that metabolic change detected by  $^1\text{H}$ -MRS precedes abnormal diffusion. We therefore believe that a combination of DWI and MRS may be used for detecting stroke-like attacks at an early stage.

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