

Cerebral blood flow and oxygen metabolism before and after a stroke-like episode in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

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Abstract

Cerebral blood flow and oxygen metabolism were examined in two patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) using positron emission tomography (PET). Regional cerebral blood flow (rCBF), regional cerebral oxygen metabolic rate (rCMRO₂) and regional oxygen extraction fraction (rOEF) were determined with the steady-state technique using oxygen-15-labeled tracers (¹⁵O₂, C¹⁵O₂ and C¹⁵O). Case 1, a 45-year-old woman, presented with abrupt onset of fluent aphasia. T2-weighted magnetic resonance imaging (MRI) showed a high signal intensity lesion in the left temporoparietal region. The first PET study on day 16 showed increased rCBF and decreased rCMRO₂ in the temporal region. In the second PET study, on day 35, rCBF in the temporal region had decreased. Case 2 was a 19-year-old male; the second son of Case 1. He complained of transient blurring of vision, and then generalized tonic–clonic convulsion occurred. A PET study six days before this stroke-like episode demonstrated increased rCBF in both frontal lobes and putamen, where MRI showed lesions after the episode. Focal hyperemia of the lesion antedated and lasted for at least sixteen days after the stroke-like episode in these MELAS patients. These stroke-like episodes appear to be the result of metabolic dysfunction in neural tissue, although the role of an ischemic vascular event cannot be ruled out. © 1998 Elsevier Science B.V.

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1. Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) was first described as a distinctive clinical syndrome in 1984 by Pavlakis et al. [14]. MELAS is clinically characterized by normal early development, periodic stroke-like episodes, nausea, vomiting, encephalopathy, seizures, short stature, headache, neurosensory hearing loss, muscle weakness, exercise intolerance and myopathy. Point mutations of mitochondrial tRNA have been found in most, but not all, MELAS patients [3,4,7]. However, whether stroke-like episodes in

MELAS are due to energy failure secondary to impaired oxidative metabolism [2,5] or to brain ischemia related to vascular abnormalities [1,12] has yet to be determined. Although mitochondrial abnormalities have been reported in arteries of the brain and muscles [12,17,21], but not in brain parenchyma [9,12], a recent study reported abnormal mitochondria in nerve cells [2]. Only a few studies have examined cerebral blood flow (CBF) in MELAS and the results of these studies are controversial [11,20]. We report positron emission tomography (PET) findings in two cases of MELAS; in one case, repeated PET studies with oxygen-15-labeled tracer were performed after a stroke-like episode and, in the other case, the same PET studies were performed a few days before a stroke-like episode.

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The implications for the mechanisms that precede stroke-like episodes in MELAS are also discussed.

2. Subjects and methods

We studied two patients with MELAS. PET studies were performed 16 and 35 days after a stroke-like episode in Case 1 and six days before a stroke-like episode in Case 2. Chronological changes in magnetic resonance imaging (MRI), related to the stroke-like episodes, were observed on both patients.

2.1. Case 1

A 45-year-old female was apparently normal until the age of 40, when sensorineural hearing loss and muscle weakness in the upper extremities were noticed. At the age of 45, she suddenly developed aphasia with predominantly sensory features, followed by an upper respiratory infection that lasted for several days. Neurological examination on admission showed mild right-side weakness of her face and arm, and muscular atrophy of the limbs. She was dysphasic. The concentrations of lactate (18.2 mg/dl; normal range, 4.0–16.0 mg/dl) and pyruvate (1.2 mg/dl; normal range, 0.3–0.9 mg/dl) in serum and in the cerebrospinal fluid (36.6 and 1.4 mg/dl, respectively; normal ranges, 9.0–25.0 and 0.6–1.2 mg/dl, respectively) were elevated. A biopsy specimen from the biceps brachii muscle showed scattered ragged red fibers by modified Gomori trichrome staining. Analysis of mitochondrial DNA (mtDNA) in peripheral leukocytes revealed an A–G transition at nucleotide 3243. Her dysphasia gradually improved and she returned to work three months later.

2.2. Case 2

A 19-year-old male, the second son of Case 1, had a normal prenatal and perinatal history. By the age of three, delayed motor and language development were evident. From twelve to sixteen years of age, he had occasional generalized seizures, which had been treated with phenytoin and phenobarbital. A CT scan showed calcification in the basal ganglia. No epileptic seizures have been noted since the age of sixteen, but motor and cognitive impairment gradually progressed.

Neurological examination at nineteen years of age revealed mental retardation, impaired visual acuity, sensorineural hearing loss, muscle atrophy of the limbs and decreased tendon reflexes. His language function was preserved and he could walk with assistance. The concentrations of lactate (24.4 mg/dl; normal range, 4.0–16.0 mg/dl) and pyruvate (1.2 mg/dl; normal range, 0.3–0.9 mg/dl) in serum and in the cerebrospinal fluid (44.6 and 1.6 mg/dl, respectively; normal ranges, 9.0–25.0 and 0.6–1.2 mg/dl, respectively) were elevated. Muscle biopsy

revealed ragged red fibers, suggesting mitochondrial myopathy. Analysis of mtDNA in peripheral leukocytes revealed an A–G transition at nucleotide 3243. Starting nine days before the PET study, he had frequent infections of the upper respiratory tract, with a cough and fever. An electroencephalogram (EEG) eight days before the PET study showed generalized slowing and paroxysmal small spikes at the bilateral fronto-central region.

Six days after the PET study, the patient complained of transient blurring of vision, and then generalized tonic-clonic convulsion occurred. Convulsive status epilepticus and the clouding of consciousness continued for several weeks. A flaccid paralysis in the right upper and lower extremities appeared after this stroke-like episode. Cortical blindness and right hemiparesis persisted.

2.3. PET study

Informed consent was obtained from all of the subjects studied. They were required to lie still in the tomograph in a quiet darkened room with their eyes closed and covered with eyepatches. Regional cerebral blood flow (rCBF), regional cerebral oxygen metabolic rate (rCMRO₂), and regional cerebral blood volume (rCBV) were determined using C¹⁵O₂ (7.18±0.15 mCi/min×20 min), ¹⁵O₂ (15.5±2.4 mCi/min×20 min) and C¹⁵O (62.7±2.8 mCi/min±1 min), respectively. rCBV was calculated using the equation: rCBV=100 Ci/(0.85 Ca), where Ci and Ca are active concentrations in the tissue and arterial blood, respectively, and 0.85 is the ratio of hematocrit in the brain capillary to that in the large vessels [15]. The regional oxygen extraction fraction (rOEF) and rCMRO₂ were corrected for using rCBV [10]. PET images were obtained for horizontal planes with a slice thickness of 11 mm, taken at 6.5 mm intervals above and parallel to the orbitomeatal (OM) line (Headtome IV, Shimadzu, Japan, with a full width at half-maximum of 4.5 mm). Thus, fourteen planes were scanned between OM 0 and OM+91 mm. Regional values of rCBF, rOEF, rCMRO₂ and rCBV were obtained from the printout of matrix data. Round regions of interest (ROI) with diameters of 12–18 mm were taken in the cerebellum (eight right and left regions in the OM+12 and OM+18 planes), in the temporal cortex (eight regions in the OM+38–OM+57 planes), in the frontal cortex (eighteen regions in the OM+31–OM+77 planes), in the occipital cortex (six regions in the OM+38–OM+57 planes), in the parietal cortex (six regions in the OM+70 and OM+77 planes), in the putamen (four regions in the OM+38 and OM+51 planes), and in the thalamus (four regions in the OM+38 and OM+51 planes).

Measurements were evaluated based on deviation above or below the 95% confidence interval in the controls. Controls were seven normal subjects (mean age, 44±6 years).

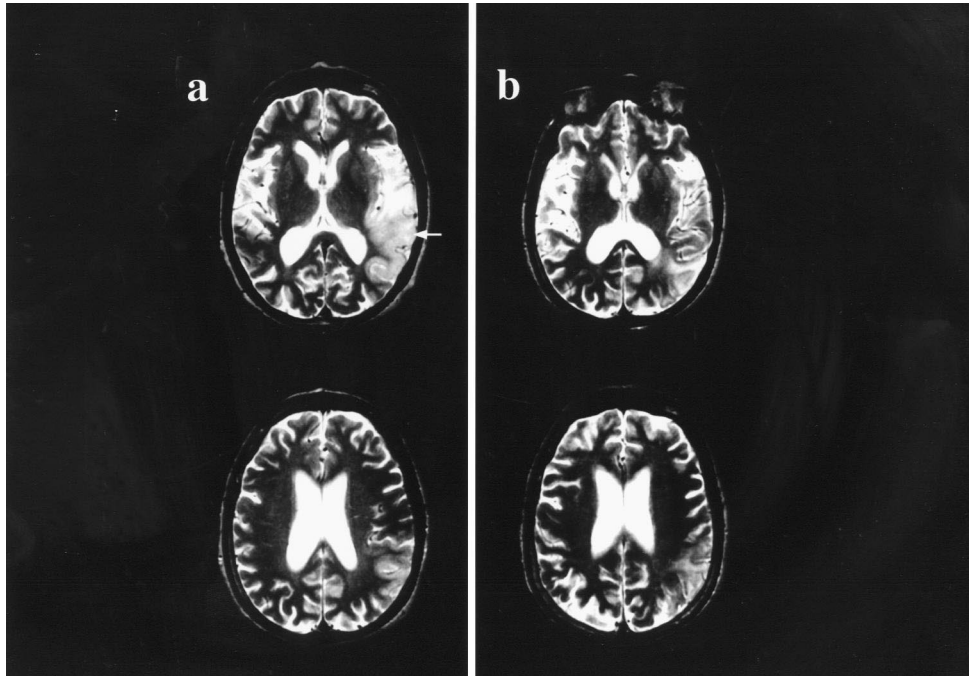


Fig. 1. Magnetic resonance imaging (MRI) in Case 1. T2-weighted axial MRI seven days after a stroke-like episode showed a high signal intensity lesion in the left temporoparietal region (arrow) (a). The lesion size decreased in subsequent MR images 34 days after onset (b).

3. Results

MRI findings are presented in Figs. 1 and 2, and PET studies in Figs. 3 and 4 and Table 1.

In Case 1, T2-weighted axial MRI seven days after onset showed a high signal intensity lesion in the left temporoparietal region (Fig. 1a). The first PET study was performed sixteen days after the stroke-like episode (Fig.

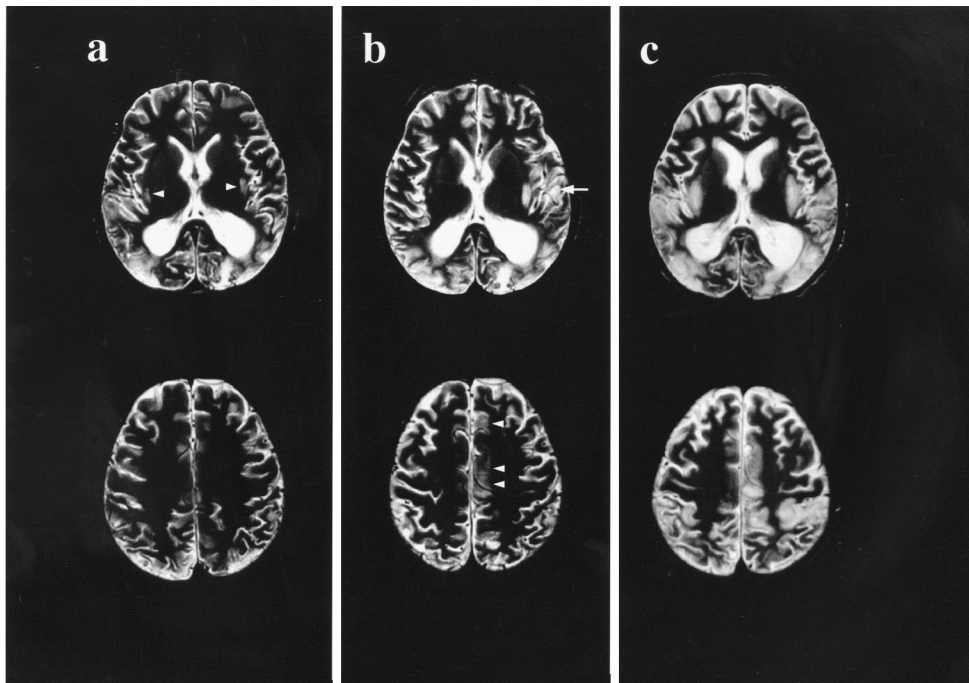


Fig. 2. Magnetic resonance imaging (MRI) in Case 2. T2-weighted axial MRI sixteen days before the stroke-like episode showed high signal intensity areas in both occipital regions and small high intensity lesions in both putamen (arrow head) (a). Eight days after the stroke-like episode, MRI showed new lesions in the left frontal (arrow head), temporal lobes (arrow) and an extended left putaminal lesion (b). Fifty-nine days after onset, the lesions extended to the bilateral temporal, frontal lobes, and putamen (c).

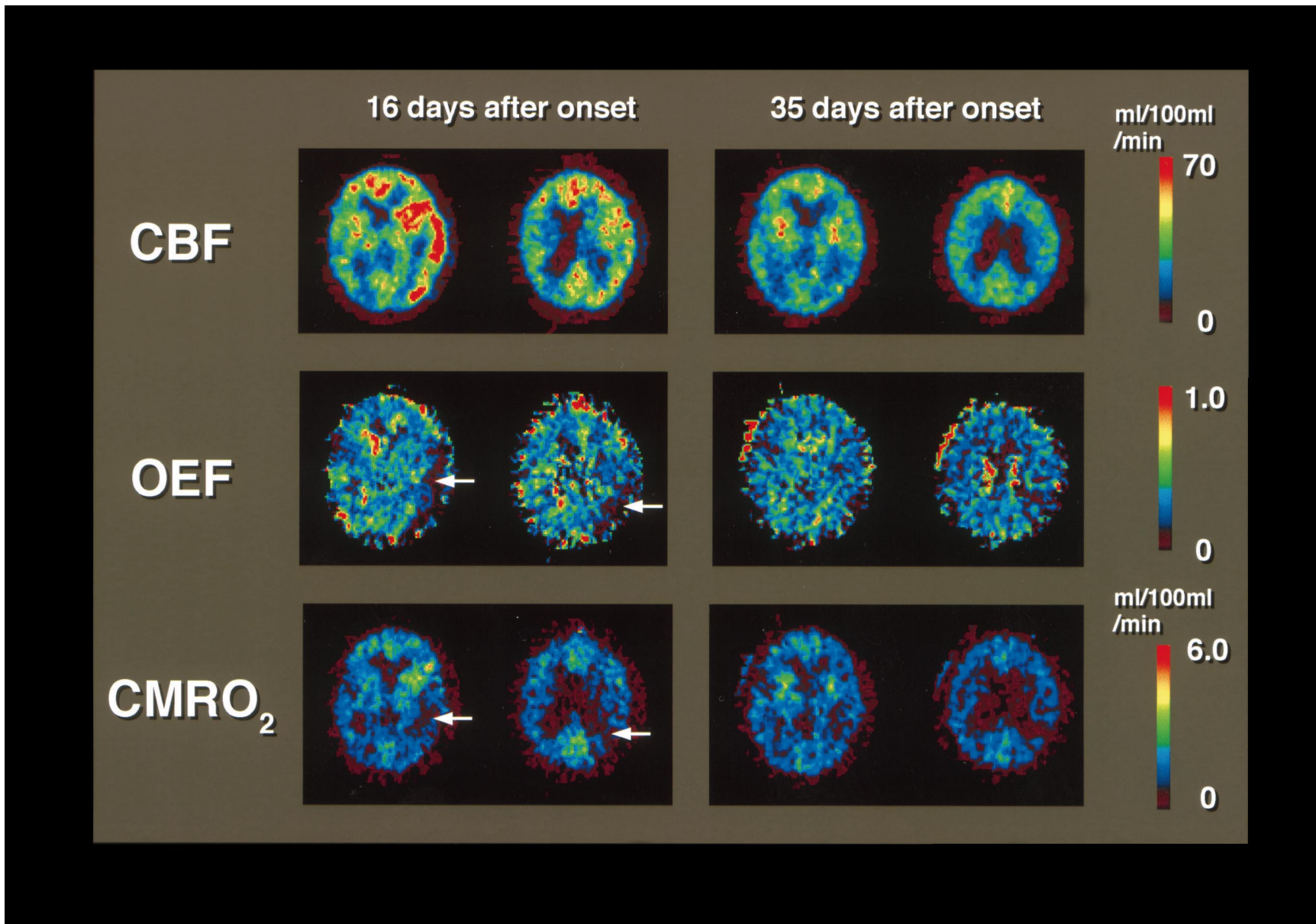


Fig. 3. PET images in Case 1. A PET study sixteen days after the stroke-like episode (left) demonstrated increased rCBF (top) in the left temporal lobe. rCMRO₂ (middle) and rOEF (bottom) had generally decreased, especially in the left temporoparietal lobes (arrow). A PET study on the 35th day (right) demonstrated decreased rCBF generally (top), and rCMRO₂ remained decreased in all areas (middle). rOEF had decreased in most regions compared with controls (bottom).

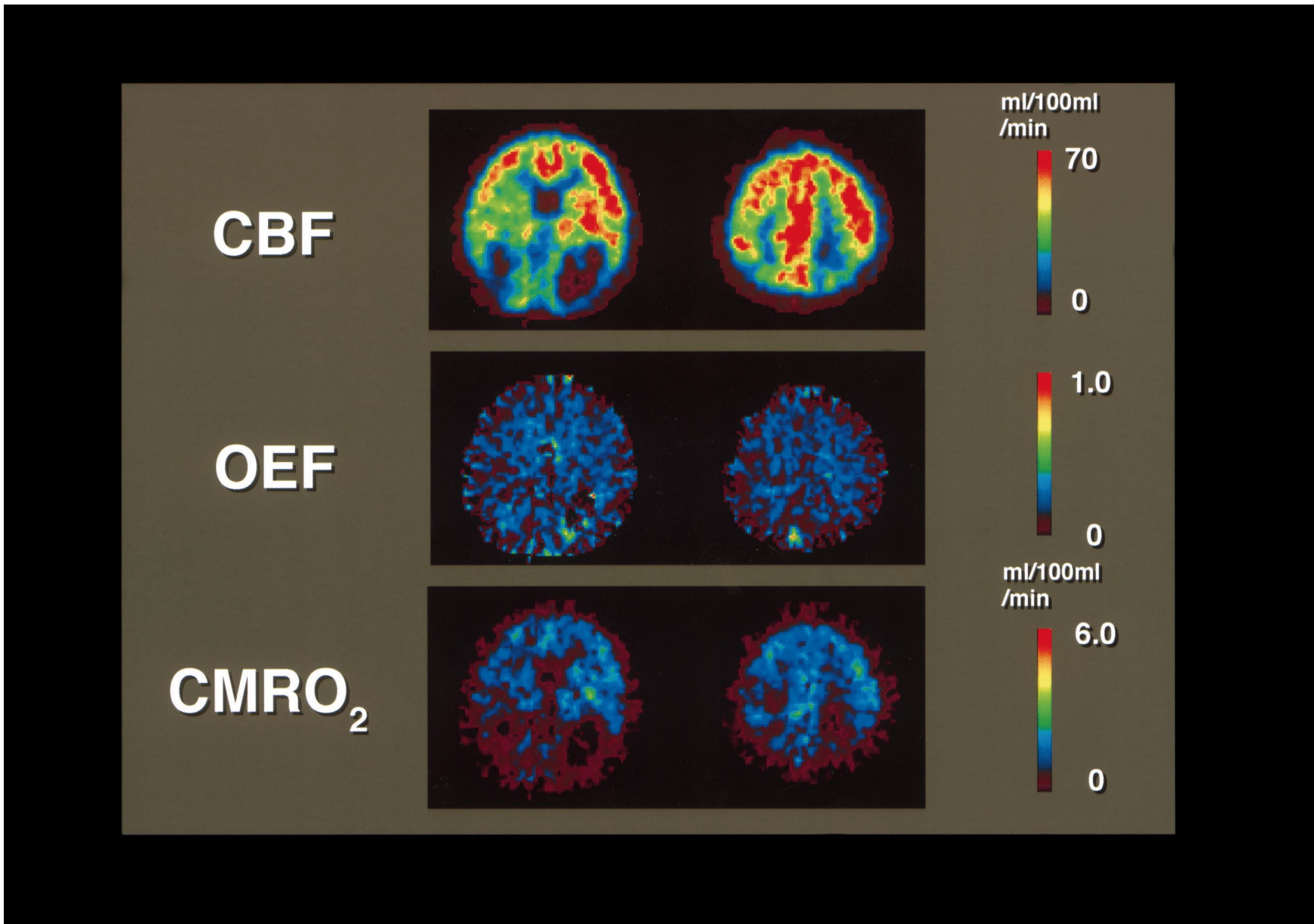


Fig. 4. PET images in Case 2. rCBF (top) had increased in both frontal lobes and putamen, while it had decreased in both occipital lobes: rCMRO₂ (middle) and rOEF (bottom) were evenly decreased.

Table 1

Regional cerebral blood flow (rCBF), cerebral oxygen metabolic rate (rCMRO₂) and oxygen extraction fraction (rOEF) in patients with MELAS and in normal controls

	rCBF (ml/100 ml/min)				rCMRO ₂ (ml/100 ml/min)				rOEF			
	Case 1 (1st)	Case 1 (2nd)	Case 2	Controls	Case 1 (1st)	Case 1 (2nd)	Case 2	Controls	Case 1 (1st)	Case 1 (2nd)	Case 2	Controls
Right frontal	41.6	32.5 ^b	51.3 ^a	42.6±5.3	1.76 ^b	1.76 ^b	1.48 ^b	3.06±0.26	0.30 ^b	0.38	0.19 ^b	0.41±0.05
Left frontal	45.9	32.9 ^b	56.5 ^a	43.1±4.4	2.24 ^b	1.78 ^b	1.59 ^b	3.07±0.31	0.35 ^b	0.39	0.19 ^b	0.41±0.04
Right parietal	35.9 ^b	30.5 ^b	41.6	45.7±6.3	1.79 ^b	1.51 ^b	1.16 ^b	3.47±0.36	0.35 ^b	0.36 ^b	0.19 ^b	0.43±0.04
Left parietal	38.7 ^b	29.2 ^b	45.9	46.2±7.0	1.07 ^b	1.14 ^b	1.34 ^b	3.45±0.38	0.21 ^b	0.28 ^b	0.20 ^b	0.43±0.04
Right temporal	33.3 ^b	27.2 ^b	30.1 ^b	47.6±6.6	1.53 ^b	1.58 ^b	0.84 ^b	3.46±0.24	0.33 ^b	0.43	0.20 ^b	0.42±0.05
Left temporal	56.0 ^a	29.4 ^b	27.7 ^b	48.0±7.9	1.11 ^b	1.38 ^b	0.96 ^b	3.56±0.30	0.16 ^b	0.33 ^b	0.23 ^b	0.43±0.05
Right occipital	30.2 ^b	27.8 ^b	29.9 ^b	42.5±6.4	1.72 ^b	1.59 ^b	0.94 ^b	3.37±0.43	0.41 ^b	0.41 ^b	0.23 ^b	0.46±0.04
Left occipital	36.9 ^b	29.3 ^b	25.5 ^b	42.5±4.8	1.45 ^b	1.70 ^b	0.76 ^b	3.43±0.38	0.29 ^b	0.42 ^b	0.22 ^b	0.47±0.05
Right putamen	44.8	40.2 ^b	59.0 ^a	50.1±6.9	1.73 ^b	2.02 ^b	2.02 ^b	3.52±0.55	0.28 ^b	0.37	0.23 ^b	0.40±0.04
Left putamen	44.0 ^b	39.9 ^b	66.5 ^a	53.1±9.0	2.22 ^b	1.91 ^b	2.17 ^b	3.66±0.36	0.38	0.34 ^b	0.22 ^b	0.40±0.05
Right thalamus	38.1 ^b	32.1 ^b	42.5	42.3±7.6	1.65 ^b	1.69 ^b	1.36 ^b	2.85±0.47	0.31 ^b	0.37	0.21 ^b	0.36±0.05
Left thalamus	44.0	29.5 ^b	47.8	45.8±9.3	2.07 ^b	1.66 ^b	1.79 ^b	2.76±0.41	0.34	0.41 ^a	0.25 ^b	0.36±0.04
Right cerebellum	39.8 ^b	30.2 ^b	47.9	51.1±9.4	1.88 ^b	1.98 ^b	1.77 ^b	3.58±0.65	0.34 ^b	0.47 ^a	0.24 ^b	0.41±0.04
Left cerebellum	45.3	32.1 ^b	47.0	53.1±11.2	2.05 ^b	2.03 ^b	1.62 ^b	3.67±0.84	0.32 ^b	0.45	0.22 ^b	0.40±0.06

^aAbove and ^bbelow the 94% confidence interval in controls.

3a). rCBF had decreased in most areas in the right hemisphere and in the left occipitoparietal lobes and putamen, but had increased in the left temporal lobe compared with the controls. rCMRO₂ had markedly decreased in all areas, particularly in the left temporal area (1.11 ml/100 ml/min compared with 3.56±0.30 ml/100 ml/min in controls) and parietal area (1.07 ml/100 ml/min compared with 3.45±0.38 ml/100 ml/min in controls). rOEF had also decreased in almost all areas, particularly in the left temporal area (0.16 compared with 0.43±0.05 in controls) and parietal area (0.21 compared with 0.43±0.04 in controls). On subsequent MRI 34 days after onset, the high signal intensity lesion in the left temporoparietal area had decreased in size (Fig. 1b). The second PET study was performed 35 days after the episode (Fig. 3b). rCBF had markedly decreased in all areas including in the left temporal lobe where rCBF had increased in the first PET scan. rCMRO₂ remained decreased in all areas and rOEF decreased in most regions compared with controls.

In Case 2, T2-weighted MRI sixteen days before the stroke-like episode demonstrated high intensity areas in both occipital regions and small high intensity lesions in both putamen (Fig. 2a). A PET study was performed six days before the stroke-like episode (Fig. 4, Table 1). During the PET study, the patient was perfectly clear mentally and no acute cerebral symptoms were observed. rCBF had decreased in occipitotemporal lobes, but had increased in frontal lobes on both sides (right, 51.3 ml/100 ml/min; left, 56.5 ml/100 ml/min and right, 42.6±5.3 ml/100 ml/min; left, 43.1±4.4 ml/100 ml/min in controls) and putamen (right, 59.0 ml/100 ml/min; left, 66.5 ml/100 ml/min and right, 50.1±6.9 ml/100 ml/min; left, 53.1±9.0 ml/100 ml/min in controls). rCMRO₂ and rOEF had markedly decreased in all areas compared with the

controls. Eight days after the stroke-like episode, T2-weighted MRI showed new lesions in the left frontal, temporal lobes and extended left putaminal lesion (Fig. 2b). Fifty-nine days after onset, high signal intensity lesions extended to the bilateral frontal, temporal lobes, and putamen (Fig. 2b). In subsequent MR images, the lesions gradually decreased in size.

4. Discussion

The PET findings in the present cases with MELAS showed that rCBF increased before and after stroke-like episodes. Previous studies have reported a hyperemic state after a stroke-like episode in MELAS [11,13,19,22]. Focal hyperemia is common to the early stage of all cases of brain damage when arteries are not occluded. Cerebral angiography has revealed dilatation of cortical arteries, capillary brush and early venous filling in affected cerebral cortices during stroke-like episodes in MELAS patients [6], and the chronological fluctuation of the vasomotor response to CO₂ has been documented in a patient with MELAS after a stroke-like episode [5]. Ooiwa et al. [13] found vasodilation localized in the affected cerebral cortex without any reduction in rCBF in MELAS patients during the 3–72 h after onset of a stroke-like episode, using dynamic and xenon-enhanced CT. In this regard, hyperemia after the stroke-like episodes in MELAS may pathophysiologically differ from luxury perfusion after ischemic stroke, in which ischemia is the primary event. Similarly, in Case 1, sixteen days after the stroke-like episode, rCBF had increased in the region corresponding to the abnormal MRI signal. Although ictal rCBF is increased several fold [8], it is unlikely that frequent or continuous seizures caused hyperemia in our patients,

because seizures were absent throughout the course in Case 1 and before the stroke-like episode in Case 2. During the PET studies, both patients were mentally clear and no acute cerebral symptoms were observed. Epileptic discharges on EEG were not observed before or after PET scanning in Case 1, nor before eight days of the PET study in Case 2.

An important finding in Case 2 is that focal hyperperfusion was demonstrated six days before the stroke-like episode in the region where high signals appeared thereafter on MRI. Similarly, recent studies have shown cerebral hyperperfusion antedating a stroke-like episode in MELAS [16,18]. Rodriguez et al. [16] reported a case who showed diffuse cerebral hyperperfusion with ^{133}Xe planar rCBF nine years before a stroke-like episode. A PET study case was also reported where the reduction in CMRO₂ was not associated with CBF reduction in all areas eight months before a stroke-like episode [18]. Thus, the hyperemia may be caused by vasodilatation due to a passive response to tissue acidosis resulting from impaired oxidative metabolism. On the other hand, the second PET study performed 35 days after the stroke-like episode in Case 1 demonstrated generalized hypoperfusion. Suzuki et al. [20] also reported a case with MELAS in whom a SPECT study after a stroke-like episode demonstrated a low perfusion area that corresponded to a lesion demonstrated by MRI. The reduction in rCBF in the chronic phase may be a secondary phenomenon coupled with impaired oxygen utilization in brain tissue. However, the possibility that mitochondrial angiopathy [12] may in part play a role in the pathogenesis of hyperperfusion or hypoperfusion cannot be excluded.

In conclusion, although rCBF, rCMRO₂ and rOEF are generally decreased in MELAS patients, rCBF is increased in the region where the MRI lesion appears before and after a stroke-like episode.

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