

MELAS and Reversible Vasoconstriction of the Major Cerebral Arteries

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Abstract

A 26-year-old woman was admitted due to an altered mental status and generalized tonic-clonic seizures. She had experienced chronic migraine-like headaches, progressive bilateral hearing loss, a short stature and nephrotic syndrome. Laboratory data showed elevated lactate and pyruvate levels. Brain MRI using diffusion-weighted imaging revealed a hyperintense lesion in the left temporal lobe. MR angiography revealed segmental stenosis at the C1 and M1-2 junction. A genetic study revealed a mitochondrial DNA A3243G point mutation. The patient's clinical symptoms and MRI/MR angiography (MRA) findings improved within four weeks. We herein discuss the possible pathophysiology involving both stroke-like episodes and reversible vasoconstriction.

Key words: stroke-like episode, mitochondrial encephalopathy, lactic acidosis, L-arginine, reversible cerebral vasoconstriction syndrome

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Introduction

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a subtype of mitochondrial encephalomyopathy. Stroke-like episodes (SE) are characterized by a variety of neurological symptoms, including headaches, homonymous anopsia, an altered mental status and seizures (1). Although the exact mechanism of SE remains unknown, it has been suggested that the pathophysiology of SE is based on mitochondrial angiopathy (2) and mitochondrial cytopathy (3, 4). Mitochondrial angiopathy is characterized by the accumulation of mitochondria within vascular endothelial cells and smooth muscle cells in cerebral small arteries and arterioles (2). Koga et al. found significantly lower levels of L-arginine in MELAS patients compared to those observed in control subjects and suggested that this phenomenon was caused by endothelial dysfunction. Koga also suggested that the mechanism of SE is related to ischemic conditions caused by impaired cerebral microcirculation resulting from decreased L-arginine and nitric oxide

production (5). On the other hand, involvement of the large cerebral arteries has rarely been reported (6, 11). We herein report a case of MELAS that presented with SE and reversible vasoconstriction of the proximal major cerebral vessels and discuss a review of the literature.

Case Report

A 26-year-old woman was admitted to our hospital due to headaches, nausea and fever that had started one day prior to admission, followed by an altered mental status and generalized tonic-clonic seizures. She had a long-standing history of episodic migraine-like headaches for which she did not take any medications, progressive bilateral hearing loss lasting for three years, a short stature and nephrotic syndrome that was diagnosed as minimal change disease based on the results of a kidney biopsy performed three years earlier. She had been taking oral prednisolone (15 mg/day) and mizoribine (300 mg every other day) for the treatment of nephrotic syndrome for three years. Her vital signs revealed a normal body temperature of 36.3°C, an elevated blood

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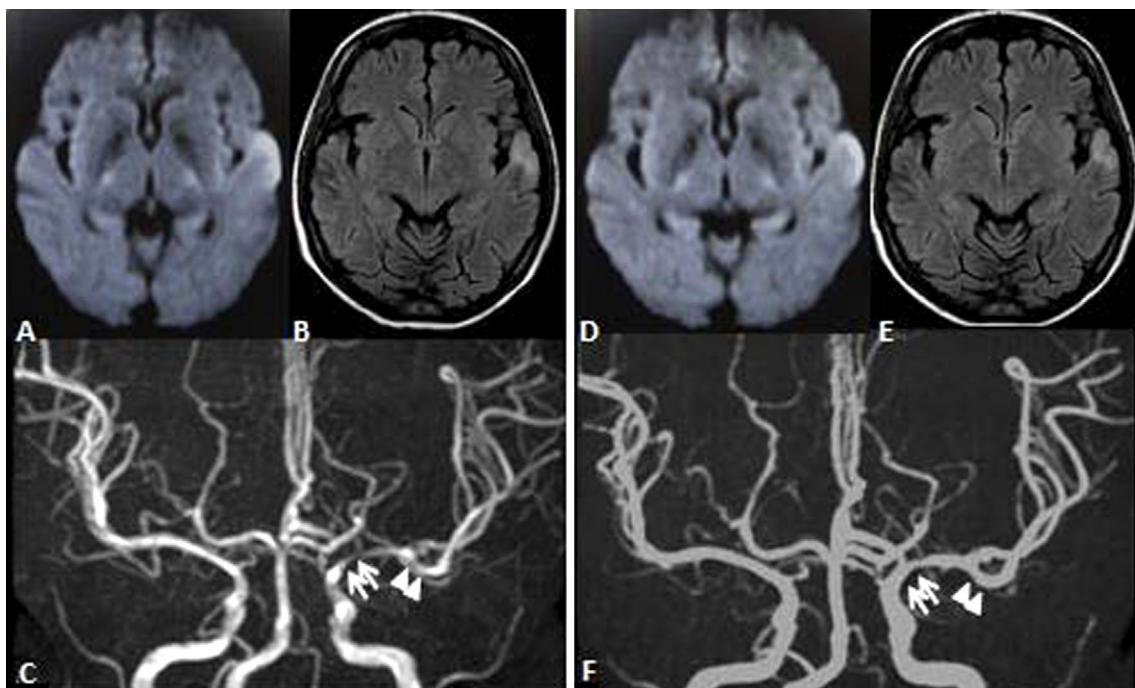


Figure 1. MRI finding of first stroke-like episode showing changes of stroke-like lesion between day 5 (A, B, C) and day 12 (D, E, F) on diffusion-weighted image (DWI; A, D), fluid-attenuated inversion recovery (FLAIR) images (B, E), and MR angiography (MRA)(C, F). Although DWI and FLAIR image showed only minimal improvement on day 12, MRA revealed significant recanalization of left C1 (arrows) and M1-2 transitional (arrowheads) segment.

pressure of 146/70 mmHg and tachycardia at 140 beats per minute. On physical examination, she was in a comatose state. The laboratory data showed high anion gap metabolic acidosis with elevated lactate and pyruvate levels. A CSF analysis did not show xanthochromia, an increased white blood cell count or the presence of proteins. Brain CT showed no evidence of subarachnoid hemorrhage or intracerebral hemorrhage. On day 4, brain MRI (1.5 tesla) using diffusion-weighted imaging (DWI) revealed a hyperintense lesion in the left temporal lobe. MR angiography (MRA) revealed segmental stenosis at the C1 and M1-2 junction (Fig. 1).

An electroencephalogram obtained on day 6 disclosed intermittent bilateral slow wave activity. Single photon emission computed tomography (SPECT) was not performed. Based on the clinical and radiological findings, we suspected mitochondrial diseases. A genetic study of the patient's peripheral blood leukocytes revealed a mitochondrial DNA A3243G point mutation. Initially, the patient was treated with intravenous diazepam and phenytoin. Her condition rapidly improved without seizure recurrence, and she regained consciousness within several days. Follow-up MRI revealed almost complete improvement in the stenotic arteries. The patient's condition continued to improve, and on day 26, she was discharged without any symptoms, except for a minimal headache. On day 27, cyclosporine A therapy was initiated (50 mg/day) to treat the nephrotic syndrome. On day 75, the patient's headache became worse, and she became unconscious again five days later. The trough level of cyclosporine A was 38 ng/mL. She was readmitted to our

hospital and treated with intravenous L-arginine and ubidecarenone. On day 84, DWI on brain MRI showed a large hyperintense area encompassing the right temporal and occipital lobes. The apparent diffusion coefficient (ADC) value of the lesion was significantly lower than that observed in the unaffected area. MRA revealed segmental stenosis at M1 and P1 (Fig. 2).

The patient remained unconscious for several days, then became very agitated. Her altered mental status persisted for a few days before she was discharged on day 120 (Fig. 3).

Follow-up MRI performed on day 118 showed improvement of the high intensity area on DWI. The ADC value became higher than that of the unaffected areas. MRA showed almost complete improvement in the stenotic segments. The patient continued to receive L-arginine and ubidecarenone after discharge and has been free of any neurological symptoms.

Discussion

Our patient has SE complicated by reversible vasoconstriction of the proximal major cerebral arteries. Major cerebral artery involvement has been rarely reported in patients with MELAS. We considered other causes of vasospasm, including subarachnoid hemorrhage and reversible cerebral vasoconstriction syndrome (RCVS) (7). Based on the results of the cerebrospinal fluid (CSF) analysis and brain CT, we clearly ruled out the possibility of subarachnoid hemorrhage (7). There have been no reported cases of RCVS complicated by SE. Strenuous exercise and febrile illnesses that

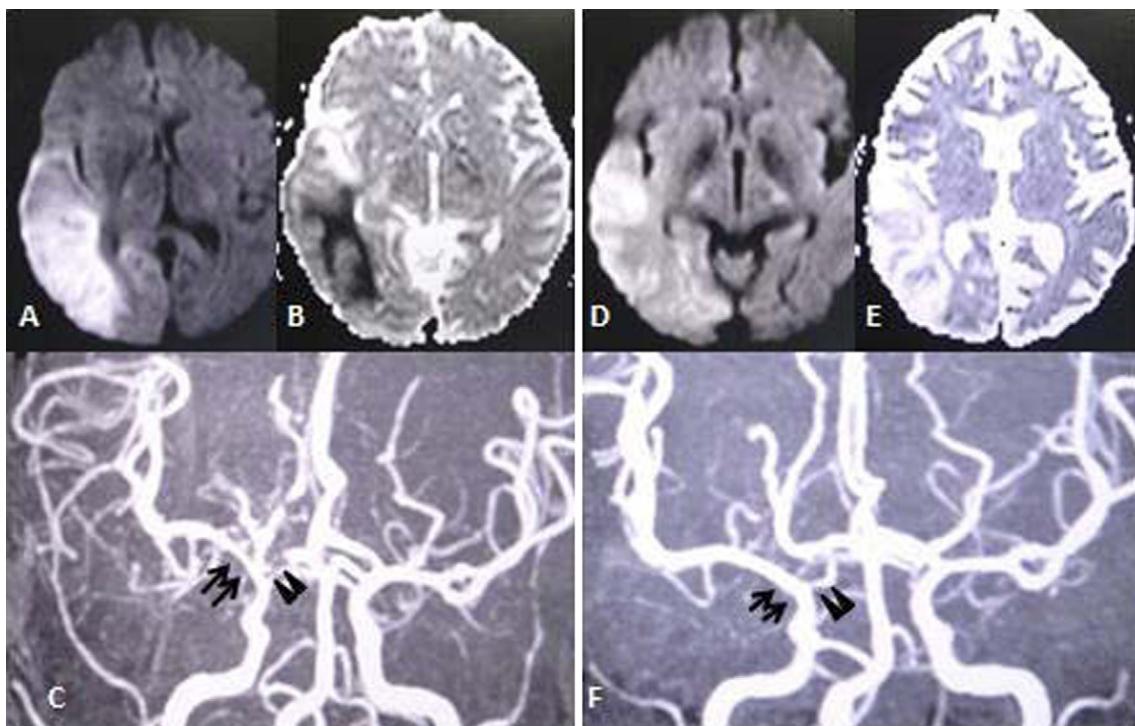


Figure 2. MRI finding of second stroke-like episode, showing changes of stroke-like lesion between day 84 (A, B, C) and day 118 (D, E, F) on diffusion-weighted image (DWI; A, D), apparent diffusion coefficient (ADC) maps (B, E), and MR angiography (MRA)(C, F). DWI showed improvement of high intensity lesion and ADC value became higher than that of unaffected area from lower value. MRA revealed recanalization of right M1 (arrows) and P1 (arrowheads) segment.

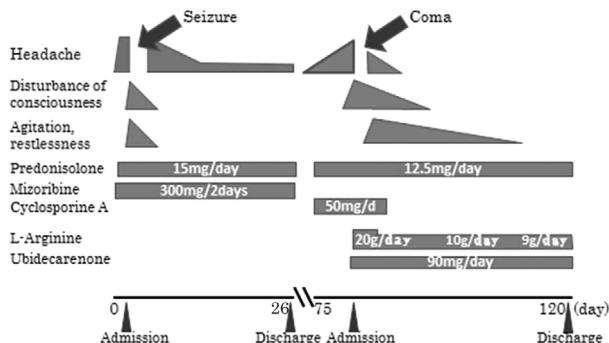


Figure 3. Clinical course of the two stroke-like episodes.

can induce SE are usually not associated with RCVS (7, 8). Although the patient was prescribed cyclosporine, which can cause posterior reversible encephalopathy syndrome (PRES) (9) and cerebral vasospasms (10), before the second episode of SE, the trough level of the drug was low, and this cannot explain the occurrence of the first episode of SE. In addition, patients with RCVS almost always present with “thunderclap headaches” or severe acute headaches (pain that peaks within a few minutes), which were absent in our case (7, 8). Upon reviewing the literature, we found an interesting relationship between the location of stenotic arteries and SE. As shown in Table, in all of the cases (1), stenotic arteries were present ipsilateral to the site of the brain lesions responsible for SE and (2) the location of SE was within the vascular territory of the stenotic arteries.

We believe that this finding indicates a possible relationship between reversible vasoconstriction and SE in this case. As described above, the pathogenesis of SE is thought to involve mitochondrial angiopathy (2) and mitochondrial cytopathy (3, 4). According to Koga et al., the mechanism of SE involves an ischemic condition caused by impaired cerebral microcirculation that stems from decreased nitric oxide production (6). On the other hand, relationships between vasospasm and dynamic changes in many neurohumoral factors, including nitric oxide, have been suggested (12, 13). The clinical response to L-arginine observed in our case further supports the role of nitric oxide as a key factor in the pathogenesis of SE and vasospasm (14). Large vessel involvement in patients with SE has rarely been reported (6, 11). Ohama et al. reported marked accumulation of mitochondria in the cell bodies of smooth muscle cells and endothelial cells in cerebral arteries. This abnormality is most prominent in the arterioles and small arteries and less frequent and severe in larger arteries (2). These findings may be related to the rare involvement of major cerebral arteries. Our patient experienced two episodes of SE. The first episode followed a benign course, and the patient achieved almost complete recovery within several days. The size of the lesion was also relatively small. On the other hand, the second episode followed a more protracted course with a persistent altered mental status and headache. The size of the lesion was much larger than that observed in the first episode. This suggests that the presence of vasospasm does not necessarily

Table. Clinical and Radiological Features of Our Case and a Previous Report

	Our case (First episode)	Our case (Second episode)	Noguchi et al. (11)
Age of onset (year)	26	26	8
Sex	Female	Female	Male
Headache	+	+	+
Fever	+	-	-
Seizure	+	-	-
Disturbance of consciousness	+	+	+
Hemianopsia	-	-	+
Site of stroke-like lesion	Left temporal lobe	Right temporal and occipital lobe	Right temporal and occipital lobe
Site of vascular stenosis	Left C1 Left M1-M2	Right P1 Right M1	Right P2
Reversibility of stenosis	+	+	+
Mitochondrial DNA mutation	A3243G	A3243G	A3243G

indicate a severe attack. Although it is difficult to explain exactly why our case was complicated by vasoconstriction, inherent vascular reactivity may be related, considering the patient's past history of severe pregnancy-induced hypertension and chronic migraine-like headaches that became exacerbated before menstruation. Both of these conditions occasionally complicate vasospasm of the cerebral vessels and brain ischemia (7, 8). A limitation of this case report is the poor imaging resolution of MRI/MRA. Although we obtained a thorough history, other factors playing a role in the induction of vasospasm in this case may have been missed. Because the finding of vasospasm in this case is extremely rare, the majority of cases of SE may not involve this pathophysiological process.

Conclusion

In this article, we presented a case of MELAS associated with SE and reversible vasoconstriction of the major cerebral vessels. The exact mechanisms underlying vasospasm remain unknown. The chronology and location of the vasospasm indicates a possible relationship between SE and reversible vasoconstriction in this case. Accumulating similar case reports is needed to clarify the underlying pathophysiology.

The authors state that they have no Conflict of Interest (COI).

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