Case Report
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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode with m.3243A>G variant involving the cerebellum and basal ganglia

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome is a maternally inherited mitochondrial disorder that usually affects the cerebral cortex and prevents high-energy demands from being met. Herein, we present the case of a male patient who rapidly developed multiple seizures, headaches, and altered mentality accompanied by severe metabolic acidosis and lactic acidosis. Initially, a brain imaging study confirmed stroke-like lesions (SLLs) only in the cerebellum. During follow-up, newly developed SLLs with lactic acidosis were observed in the basal ganglia (BG), cerebellum, and occipital lobe. The m.3243A>G variant had been found in the patient and MELAS was diagnosed, despite the BG and cerebellum being atypical locations for SLLs in MELAS. Since most cases of m.3243A>G variant MELAS show SLLs in the cerebral cortex, this case is unusual considering the location of the lesion. We emphasize that in the case of lactic acidosis accompanied by neurological symptoms, such as seizures, as in this case, MELAS should be included in the differential diagnosis, even if SLLs are observed in areas other than the cerebral cortex.

Key words: MELAS syndrome, Mitochondrial diseases, Cerebellum, Basal ganglia.

Introduction

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome is a progressive, destructive, maternally-inherited mitochondrial disorder. The majority of MELAS cases are attributed to an adenine-to-guanine pathogenic variant at the m.3243 position (m.3243A>G) of the mitochondrial genome (mtDNA) in the *MT-TL1* gene coding for $tRNA^{leu(UUR)}$ [1-3]. Stroke-like episodes (SLEs) are known to occur owing to development of stroke-like lesions (SLLs). Although the underlying mechanism is not precisely understood, several hypotheses, such as ischemic, metabolic, or neuronal hyperexcitability, have been suggested [4-7]. SLLs usually invade the cerebral cortex, which has high energy requirements; however, subtentorial lesions are rare [8]. Additionally, although mineral deposits such as calcifications are sometimes observed in the basal ganglia (BG), it is unusual for SLLs to invade the BG and white matter in MELAS with m.3243A>G, a common pathogenic variant [8,9]. We report a case of MELAS with m.3243A>G variant in which initial SLLs developed only in the cerebellum and later in the BG. This study was approved by the Dankook University Hospital ethical committee's Institutional Review

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Board (IRB number: 2022-10-005). The requirement to obtain informed consent was waived.

Case

A 13-year-old male patient presented to the emergency department (ED) with a sudden generalized motor seizure (GMS) and altered mental status. The patient complained of vomiting and nausea on the morning of admission. According to the report, the patient complained of headaches and dizziness before the seizure. After his first GMS, which lasted approximately 10 minutes, he developed two more GMSs during transport and one more in the ED, all of which stopped within 5 minutes. The level of consciousness in the ED scored six points on the Glasgow Coma Scale. The weight and height of the patient were 38.2 kg (5-10 percentiles) and 154 cm (10-25 percentiles), respectively. The initial blood pressure (BP) at the ED was 165/55 mmHg; however, after admission to the intensive care unit (ICU), it was 110/60 mmHg without treatment for high BP. His body temperature in the ED was 36.2°C; however, after admission to the ICU, it was 37.7°C.

He was born at full term with no remarkable perinatal history and no specific history, including seizures. His developmental history was considered normal based on developmental milestones described by his parents. At that time, his parents explained that no one in their family had neurological dysfunction. The initial arterial blood gas analysis revealed a pH of 6.89, pCO_2 of 44 mmHg, and HCO_3 of 8.4 mmol/L, indicating severe metabolic acidosis. The levels of lactate and ammonia in the blood were elevated to 19.1 mmol/L and 125 μmol/L, respectively. There were no specific findings in the complete blood count, except that the white blood cell count increased to 19,020 cells/mL. The levels of C-reactive protein and procalcitonin in the blood did not suggest an inflammatory response, and there were no specific abnormal findings regarding electrolytes. A cerebrospinal fluid (CSF) test was performed to differentiate infectious encephalopathy in the patient. The CSF opening pressure (13 cmH_2O) was appropriate to the reference range for age, and no specific findings were observed regarding white blood cells (0 μL), protein (30.7 mg/dL), and glucose (93 mg/dL). Electroencephalogram findings in the acute phase showed diffuse delta activity, and brain magnetic resonance imaging (B-MRI) revealed multifocal diffusion restriction in the bilateral cerebellar hemispheres (Fig. 1A). However, no specific stenosis was observed on brain magnetic resonance angiography (Fig. 1B). The patient was treated in the ICU for two days and underwent hyperosmolar therapy (HT) to control the increased intracranial pressure that may occur after status epilepticus, and antiseizure medication (ASM) was started. Fluid therapy and ASM was maintained during the 4 days after the patient was moved to the general ward; HT was tapered off. The lactate level (5.7 mmol/L) and NH3 level (42.3 μmol/L) improved, and pH (7.41) was normalized. Subsequently, the patient was discharged with symptomatic improvement. However, after 4 months, he was hospitalized again through the ED because of the development of status epilepticus with increased levels of lactate (12.1 mmol/L) and metabolic acidosis (pH 7.0). At the time of the second hospitalization, brain computed tomography showed no abnormalities

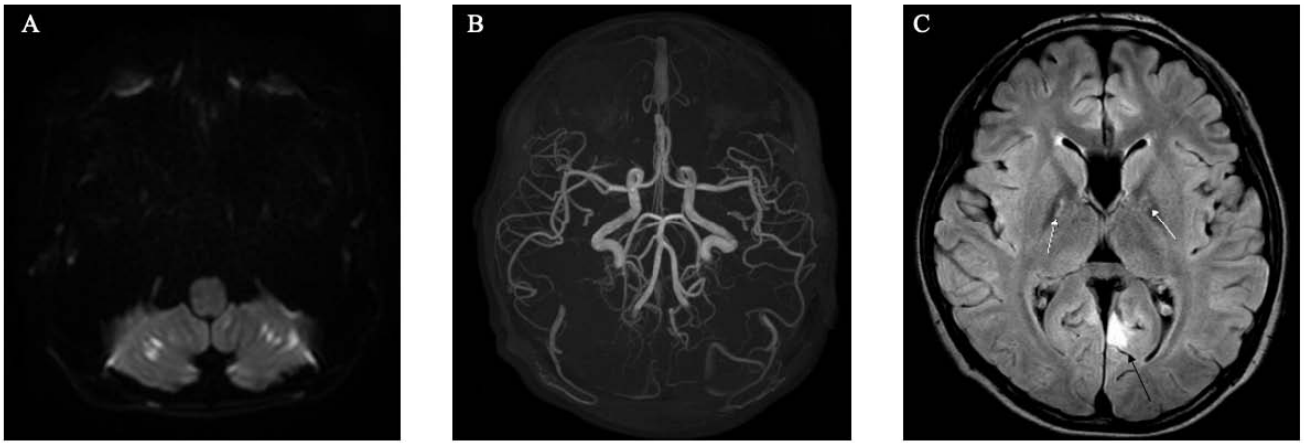

Fig. 1. B-MRI and MRA at the first SLE (A, B) and B-MRI at the second episode (C). In diffusion-weighted images obtained during the first SLE, we observed restrictions along the cerebellum folia (A). However, on MRA, stenosis could not be confirmed in any cerebral artery (B). A second SLE occurred 4 months later, and at that time, we observed newly developed SLLs in the occipital areas (black arrow) and in the globus pallidus (white arrows) in T2-FLAIR (C). B-MRI, brain magnetic resonance imaging; MRA, magnetic resonance angiography; SLE, stroke-like episode; SLLs, stroke-like lesions.

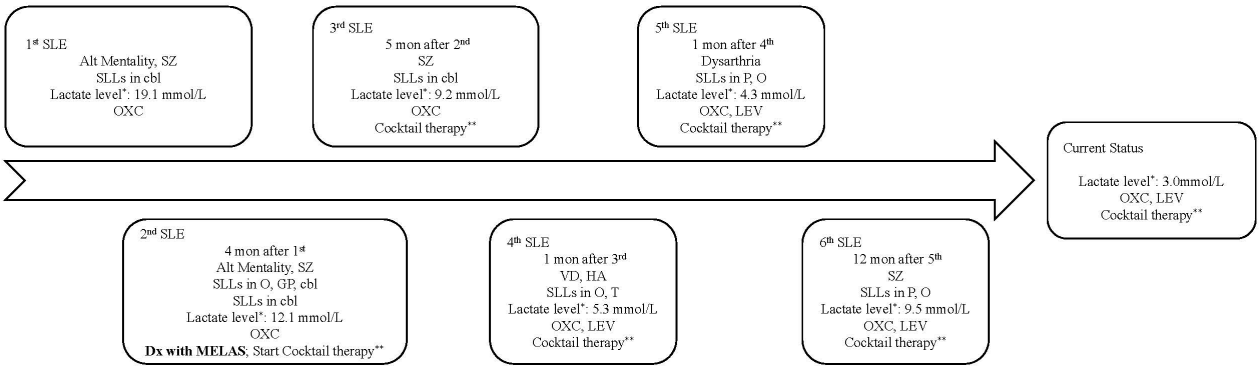

Fig. 2. Summary of stroke-like episodes (SLEs). The SLEs that occurred in this case are shown. MELAS was suspected in the second SLE and the final diagnosis was made by confirming the pathogenic variant m.3243A>G in the genetic test. *Serum lactate level was confirmed. **Cocktail therapy included L-arginine, L-carnitine, coenzyme Q10, thioctic acid, and vitamins. Alt, altered; cbl, cerebellum; Dx, diagnosis; GP, globus palidus; HA, headache; LEV, levetiracetam; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode; O, occipital lobes; OXC, oxcarbazepine; P, parietal lobes; SLLs, stroke-like lesions; SZ, seizure; VD, visual disturbance.

such as mineral (calcium or iron) deposition, but B-MRI showed new lesions in the occipital cortex and bilateral globus pallidi (Fig. 1C). We suspected MELAS in this patient. At this time, we heard that his mother's brother died suddenly as a young child due to an unknown etiology. We conducted a genetic test that revealed the pathogenic mutation, m.3243A>G. Based on these results, we confirmed the diagnosis of MELAS. We then prescribed cocktail therapy comprising L-arginine, L-carnitine, multi-vitamins, including thiamine and coenzyme Q10. Although there were intermittent hospitalizations after cocktail therapy, the lactate level was maintained below 10 mmol/L, and he was not in a life-threatening condition that required intensive care. In addition, 6 months after starting cocktail therapy, the pH level was maintained at ≥7.3 even at the time of hospitalization. The patient experienced four more SLEs (Fig. 2).

Discussion

Mitochondria are double-membrane organelles that generate much of the cellular supply of adenosine triphosphate (ATP) via aerobic respiration. Owing to mitochondrial dysfunction, the mitochondria fail to produce enough ATP to meet the high energy demands associated with the nervous system or heart in mitochondrial diseases [1,10]. Mutations in the nuclear DNA or mtDNA are the most crucial etiologies of mitochondrial diseases [1,2]. SLEs are usually accompanied by symptoms including headaches, vomiting, and seizures in MELAS. Classic SLEs are defined as those caused by classical SLLs located in the energy-dependent cortex (mainly in the temporal, parietal, or occipital regions) and are characterized by continuous lobular edematous lesions that extend along the cerebral cortex and are not coincident with the vascular territory [1,8,11]. Non-classic SLEs are defined as those attributable to non-classical SLLs and tend to extend beyond the cortical regions, or affecting infratentorial areas such as the cerebellum [8]. Cerebellar involvement has been reported in patients diagnosed with MELAS; however, cases of cerebellar involvement from the outset are very rare [8,12,13]. The cerebellum has a lower glucose metabolism than the cerebral cortex; therefore, SLLs are thought to occur relatively less frequently. There are few cases in which only the cerebellum is initially invaded [14].

In the present case, the laboratory test results showed increased lactate levels and metabolic acidosis, which are suggestive of MELAS. However, brain imaging showed SLLs only in the cerebellum, which is unusual in MELAS. In subsequent episodes, laboratory test results were consistent with the finding of MELAS, and newly discovered SLLs in brain imaging began to suggest MELAS. In addition, the pathogenic variant was identified as m.3243A>G in the genetic test, which enabled the final diagnosis of MELAS. After diagnosis of MELAS, the patient was prescribed supplements containing antioxidants. Afterwards, the patient was in a non-life-threatening condition, and the pH level was maintained above 7.3.

In cases with non-specific symptoms, such as headache and seizures, it is challenging to diagnose MELAS before the imaging evidence is clear because there are various etiologies that may explain those symptoms. However, a previous study reported that non-classic SLEs were more likely to be observed in children than in adults, possibly due to differences in brain energy metabolism between children and adults [8,15]. Therefore, if a patient has non-specific symptoms with non-classic SLEs, early diagnosis may be difficult, as was in our case.

There are reports that SLLs may occur in different areas depending on the pathogenic variants that can cause MELAS. It has been reported that minerals such as calcium can be deposited in the BG, and in a previous study, SLLs of the BG were reported in the m.13513G>A variant [4,8,9,16]. In comparison, it was rare to confirm whether the m.3243A>G variant invaded the BG, and it is important to differentiate lesions occurring in the BG, which have many systemic pathologies [4,8,17]. Although cerebellar involvement was observed in m.3243A>G MELAS in previous reports, we report a case of MELAS with involvement of SLLs in the cerebellum as well as in the BG and cortex, in which the pathogenic variant of m.3243A>G was identified [8,12,13]. The mechanisms by which SLEs are caused by each pathogenic variant are not clearly understood. According to a recent study by Klein Gunnewiek et al. [2], the pathogenic variant may show neuron-associated mitochondrial dysfunction, as well as structural and functional impairments including reduced dendritic complexity, reduced synapses, reduced neural activity, and impaired network synchrony. This report suggests that, even in MELAS, a mitochondrial disorder, SLLs can occur anywhere in the brain, not just a specific area. Additional studies are required in the future to investigate the association between pathogenic variants and classical/non-classical SLLs and to understand the mechanism of MELAS. It is also necessary to research its association with the extended neuronal network rather than the associations with specific brain areas.

Since in this case, in MELAS with the pathogenic variant of m.3243A>G, only the cerebellum was initially involved, and new lesions were later identified in the BG, we emphasize that it is necessary to suspect MELAS even if non-classic SLLs appear on brain imaging, especially in children with neurological abnormalities accompanied by lactic acidosis.

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Authors' Contributions

Drafting the article: CK. Revision and supervision: Jeesuk Yu. All authors reviewed and edited the paper.

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