

Letter to the Editor

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes due to m.3243A > G mutation in a 76-year-old woman



ARTICLE INFO

Keywords:

Digital PCR

Elderly onset

Mitochondrial myopathy, encephalopathy,

lactic acidosis and stroke-like episodes

Non-convulsive status epilepticus

m.3243A > G

Dear Editor,

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) with m.3243A > G mutation is a common type of mitochondrial disease [1,2]. Most patients with MELAS develop stroke-like episodes before the age of 40, a criterion of MELAS [3]. However, increasing reports have demonstrated that elderly subjects (≥ 60 years old) may develop this mitochondrial encephalopathy [4,5]. Here, we report a 76-year-old woman who was previously healthy without any organ dysfunction related to mitochondrial abnormalities (except for a mild hearing disability) and developed encephalopathy accompanied by stroke-like episodes and non-convulsive status epilepticus (NCSE).

The patient visited a nearby hospital with her husband because she felt her hearing disability was worsening and became unable to communicate. Based on neurological deficits (including sensory aphasia and right unilateral spatial neglect) and a hyperintense area in the left temporal lobe on diffusion-weighted magnetic resonance imaging (DWI-MRI), she was diagnosed with ischemic stroke and started treatment with aspirin (100 mg/day) and edaravone (60 mg/day) in hospital. Nonetheless, she was transferred to our hospital four days later due to deterioration of her neurological symptoms. On admission to our hospital, her height and weight were 155 cm and 52.8 kg, and she exhibited high blood pressure (166/75 mmHg), normal heart rate (71 per minute and regular), and normal body temperature (36.3 °C). Her neurological deficits included impaired consciousness, sensory aphasia, right unilateral spatial neglect, and right central facial hemiparesis. Her laboratory data were mostly within normal limits. DWI showed a hyperintense area in the left temporo-parieto-occipital lobe (Fig. 1A), which was hypointense on apparent diffusion coefficient (ADC) (Fig. 1B) and hyperintense on fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 1C). The left middle cerebral artery (MCA) was slightly dilated on magnetic resonance angiography (MRA) (Fig. 1D), consistent with hyperperfusion in the lesion shown by arterial spin labeling (Fig. 1E). Electroencephalogram showed sharp waves in the left occipital region. Considering the possibility of recanalization after embolic occlusion of the left MCA and post-stroke epilepsy, we administered intravenous infusion of heparin (10,000 U/day) and

levetiracetam (1,000 mg/day) during the proofing process, although intravenous heparin is not recommended as an urgent anticoagulation therapy according to the guidelines [6]. We were unable to identify any embolic sources by electrocardiogram, including Holter monitor, carotid ultrasound, and transthoracic echocardiogram. On the 4th day of hospital, she further developed weakness in the right upper and lower limbs with enlargement of the lesion on CT. Magnetic resonance spectroscopy (MRS) showed a lactate peak in the lesion (Fig. 1F), while the lactate/pyruvate ratio (blood, 19.8 and cerebrospinal fluid [CSF], 21.6; cut-off value: 20) was increased in blood and CSF with a normal cell number (2/ μ l) and protein level (29 mg/dl), suggesting mitochondrial encephalopathy. During the course, we obtained information that her son had developed MELAS with m.3243A > G mutation at the age of 40. Although DNA sequencing using genomic DNA prepared from peripheral blood leukocytes did not detect any mitochondrial gene abnormalities (Fig. 1G), digital PCR revealed that 1.3% of her mitochondrial DNA had the m.3243A > G mutation (normal rate, < 0.1%) [7]. Thus, we diagnosed her with MELAS due to m.3243A > G mutation and started administration of L-arginine, ubidecarenone, ascorbic acid, fursultiamine, and levocarnitine. However, to manage the refractory NCSE, we ultimately required multiple antiepileptics, carbamazepine (200 mg/day), lacosamide (200 mg/day), and perampanel (8 mg/day) after sedation by midazolam with ventilation support. The follow-up MR images on the 41st day are shown in Fig. 1H. She was transferred to a rehabilitation hospital with sensory aphasia as a sequela.

We diagnosed the patient with MELAS due to m.3243A > G mutation, based on the following findings: 1) stroke-like episodes; 2) characteristic brain images in the temporo-parieto-occipital lobe; 3) increased lactate concentration in peripheral blood and CSF and the brain lesion shown by MRS; and 4) a history of her son developing MELAS with m.3243A > G mutation [8]. Since MELAS is a maternally inherited disorder [9], it is certain that she harbored the m.3243 > G mutation, although there remains a possibility that her son harbored a de novo mutation [10].

It is surprising that she had been almost healthy until the age of 76, because it is believed that MELAS usually develops around the age of 40 [1–3]. Indeed, her son had developed MELAS before her, at the age of

<https://doi.org/10.1016/j.jns.2020.116791>

Received 3 February 2020; Received in revised form 3 March 2020; Accepted 18 March 2020

Available online 19 March 2020

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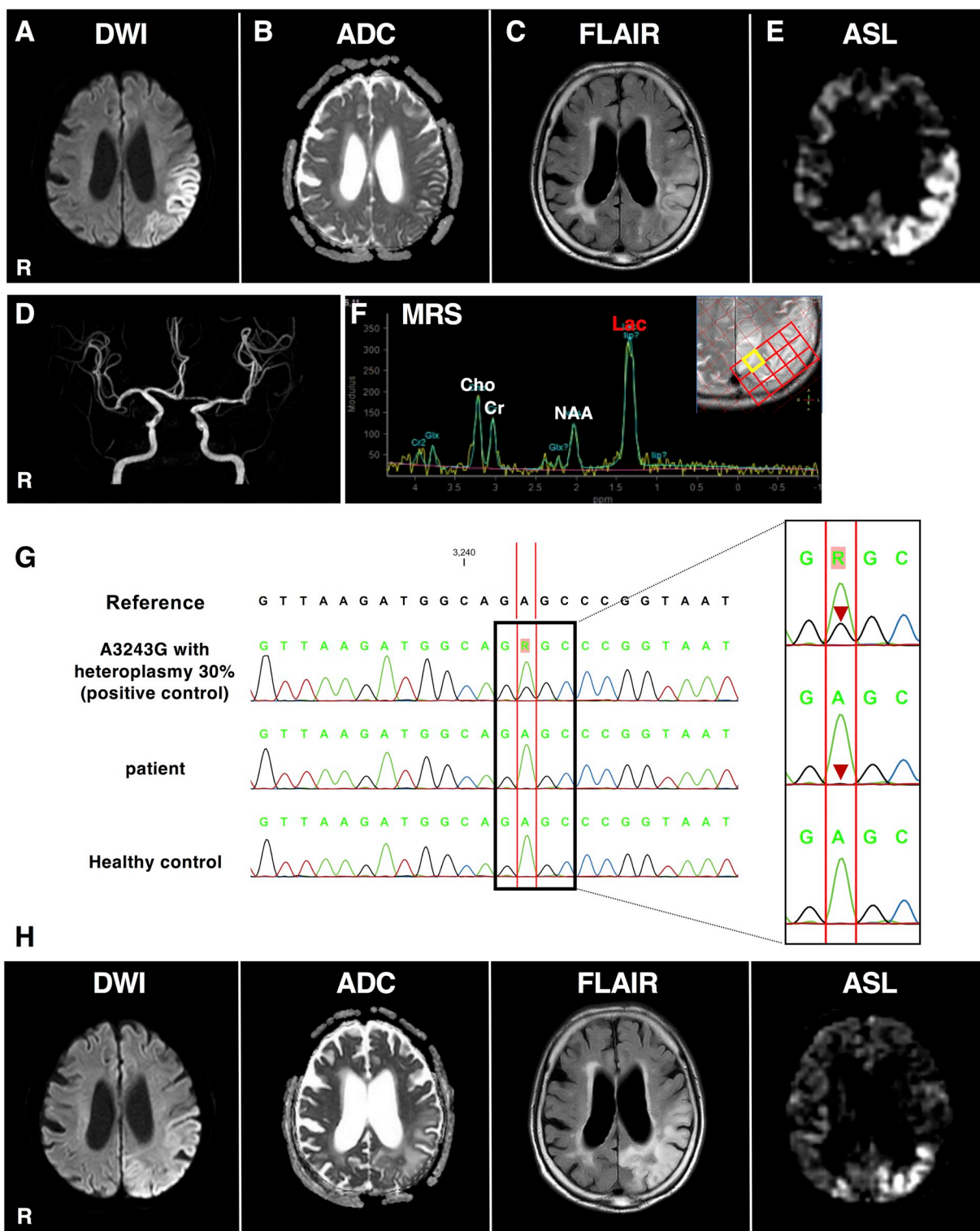


Fig. 1. A, Diffusion-weighted images (DWI) on admission showed a hyperintense area in the left temporo-parieto-occipital lobe, which is reflected as a hypointense area on apparent diffusion coefficient (ADC) (B) and a hyperintense area on fluid-attenuated inversion recovery (FLAIR) (C) imaging. D, Magnetic resonance angiography showed slight dilatation of the left middle cerebral artery, consistent with hyperperfusion shown by arterial spin labeling (ASL) (E). “R” indicates right. F, Magnetic resonance spectroscopy (MRS) showed a lactate peak in the lesion (yellow ROI). Lac, lactate; NAA, N-acetyl aspartate; Cho, choline; and Cr, creatinine. G, DNA sequencing of mitochondrial DNA. Patient with 30% heteroplasmy of m.3243A > G (as a positive control) (top), present patient (middle), and normal control (bottom). Magnified sequences from 3242 to 3245 are shown on the right-hand side. H, The follow-up MR images on the 41st day. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

40. Nevertheless, there are an increasing numbers of reports of MELAS in elderly subjects (≥ 60 years old) [4], with the highest reported age being 70 [5]. To the best of our knowledge, our case is the oldest

patient with MELAS reported in the literature. It is thought that the juvenile form of MELAS is severer than the adult form, probably due to higher mutational loads and greater energy demands [5]. Thus, it is

uncertain why some patients develop an initial MELAS at higher ages. There are two possible explanations: abnormal mitochondria with m.3243A > G may accumulate in cells with ageing [11]; or alternatively, the function of normal mitochondria may be reduced with ageing and become unable to compensate for abnormal ones despite its low mutational load [9,12].

Another important issue is that regular DNA sequencing was unable to detect any mitochondrial gene mutations, including m.3243A > G, due to the very low mutational load in peripheral leukocytes. Nonetheless, digital PCR could detect as little as 1.3% of m.3243A > G [7]. Similar issues can occur in other mitochondrial disorders, because they exhibit heteroplasmy with different mutational loads in each cell and tissue. It is reported that mutational loads over 90% may cause cellular dysfunction in cases of MELAS with m.3243A > G [12]. Therefore, we speculate that nearly 90% of mitochondria in the injured brain of the present case harbored the mutation. Because brain or muscle biopsies are invasive and distressful, digital PCR using blood, urinary sediments, and buccal mucosa may be useful for detecting the presence of common mitochondrial mutations, such as m.3243A > G, particularly in elderly subjects [7,13]. In this context, we should note that mutational loads are usually higher in order of urinary sediments, buccal mucosa, and blood [13]. We might not have been able to diagnose her with MELAS without a family history or performing digital PCR. There may be a considerable numbers of elderly cases unrecognized as MELAS with m.3243A > G, because the mutation is highly penetrable (at least 16 to 236 per 100,000 [14]). We should note that subjects harboring m.3243A > G mutations may develop MELAS at any age.

Declaration of Competing Interest

The authors disclose no potential conflict of interests.

Acknowledgements

We thank Rachel James, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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