Received: 21 August 2023 | Revised: 27 October 2023 | Accepted: 11 November 2023

DOI: 10.1002/ccr3.8438

Clinical Case Reports Open Access WILEY

CASE REPORT

Elderly onset of MELAS carried an M.3243A>G mutation in a female with deafness and visual deficits: A case report

Lin Zijun | **Yi Xu** | **Yang Yujia** | **Xu Zhiqiang**

Department of Neurology, Army Medical Center of People's Liberation Army of China, Chongqing, China

Correspondence
Xu Zhiqiang, Department of Neurology, Army Medical Center of People's Liberation Army of China, Chongqing 400042, China.
Email: xzq881@163.com

Funding information
Science and Technology Innovation Special Project of Chongging Social Undertakings and Peoples Livelihood Guarantee, Grant/Award Number: cstc2017shmsA 130005; Science and Technology Innovation Training Project of Army Medical Center

Key Clinical Message

MELAS is a disorder with clinical variability that also responsible for a significant portion of unexplained hereditary or childhood-onset hearing loss. Although patients typically present in childhood, the first stroke-like episode can occur later in life in some patients, potentially related to a lower heteroplasmy level. It is crucial to consider MELAS as a potential cause of stroke-like events if age at presentation and symptoms are atypical, especially among middle-aged patients without vascular risk factors.

Abstract

MELAS syndrome (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) is a rare genetic condition that most patients develop stroke-like episodes before the age of 40. We report a 52-year-old female with a documented 40-year history of progressive sensorineural hearing loss, developed a visual field deficit and stroke-like events in her middle age who finally diagnosed was MELAS. The patient was started on vitamin E, L-carnitine, L-arginine, and coenzyme Q10 that gradually improved before dismissal from the hospital. This case highlights the importance of considering MELAS as a potential cause of stroke-like events if imaging findings are atypical for cerebral infarction, especially among middle-aged patients without vascular risk factors and an unusual cause of progressive sensorineural hearing loss.

KEYWORDS

case report, epilepsy, MELAS syndrome, mitochondria, stroke-like episodes, visual deficit

1 | INTRODUCTION

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multisystemic mitochondrial disorder that is one of the most common maternally inherited mitochondrial diseases that usually presents in childhood.[1] Patients with stroke-like episodes (MELAS) syndrome or maternally inherited diabetes and deafness (MIDD) syndrome (with 10% and 38% of m.3243A>G carriers, respectively) can have a wide array of neurological symptoms when presenting with stroke-like episodes, and imaging characteristics during the episodes can overlap

Graphical Abstract

with different neurological disorders. Moreover, its pleomorphic clinical manifestations and the fact that the maternal relatives carrying the same mutation may be asymptomatic or only oligosymptomatic make the diagnosis sometimes elusive.[2]

Herein, we report a 52-year-old Chinese female initially suspected of ischemic infarction who was ultimately diagnosed with MELAS. This case highlights the importance of considering MELAS as a potential cause of stroke-like events if imaging findings are atypical for cerebral infarction, especially among middle-aged patients without vascular risk factors. To achieve the correct diagnosis and launch appropriate management in time, a detailed medical history together with appropriate diagnostic laboratory investigations should therefore be collected.

2 | CASE PRESENTATION

A 52-year-old, right-handed female presented to the Army Medical Center of People's Liberation Army (Chong, China) with a sudden-onset visual deficit in September 2021. Approximately 40 years ago she began losing hearing in her left and then right ear, and her left ear had been completely deaf for the last 8 years. Prior testing revealed that the patient had sensorineural hearing loss, but the etiology could not be determined.

Ten days before this hospital admission, she presented with sudden-onset visual deficits, and the condition continued to worsen over 5 days. There were no fevers, headaches, or limb convulsions. There was a new lesion on magnetic resonance imaging (MRI). Diffusion-weighted MRI (DWI-MRI) showed a hyperintense area in the right temporo-parieto-occipital lobe and hippocampus (Figure 1A), which was hypointense on apparent diffusion coefficient (ADC) (Figure 1B) and hyperintense on fluid-attenuated inversion recovery (FLAIR) imaging (Figure 1C). However, computed tomography angiography (CTA) was normal on admission (Figure 1D). Echocardiography did not show any evidence of a cardiogenic embolism. Cervical and transcranial Doppler ultrasonography were normal.

Physical examination on admission revealed that the patient had short stature. She had a height of 1.58 meters and weighed 42.6 kilogram (kg). Blood pressure and heart rate were normal. Mental status testing revealed normal orientation, attention, concentration, memory, and language. However, she presented with communication difficulties consistent with auditory agnosia. Family and social histories were unremarkable. She had no vascular risk factors apart from mild dyslipidemia.

Routine hematological and cerebrospinal fluid tests were normal. Blood electrolyte sodium concentration was low, with a value of 130.0 mol/L (reference values, 137.0–147.0 mol/L). Serum concentrations of lactate were elevated, with values of 9.67 mol/L (reference values, 0.6–2.2 mol/L). The creatine kinase level was increased to 177.70 U/L (reference values, 26.0–140.0 U/L). Cerebrospinal fluid glucose was slightly elevated, with values of 5.03 mol/L (reference values, 2.5–4.5 mol/L), and the rest of the indicators were

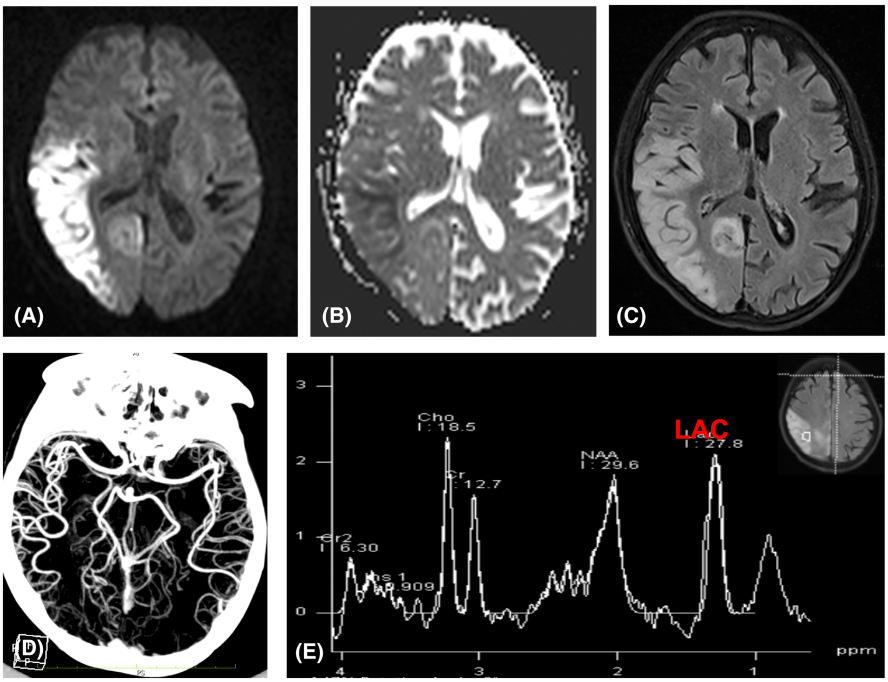

FIGURE 1 Diffusion-weighted images (DWI) (A) on admission showed a hyperintense area in the right temporo-parieto-occipital lobe, which is reflected as a hypointense area on apparent diffusion coefficient (ADC) (B) and a hyperintense area on fluid-attenuated inversion recovery (FLAIR) (C). Computed tomography angiography (CTA) was normal on admission (D). Magnetic resonance spectroscopy (MRS) (E) showed a lactate peak in the lesion. Lac, lactate; NAA, *N*-acetyl aspartate: Cho, choline; and Cr, creatinine.

normal. Electrophysiological report shows that bilateral ABR were abnormalities (prolonged latency of I, III, and V waves), prolonged latency of P300, the SEP of the left median nerve was abnormalities (the amplitude of the left N20 wave was significantly lower than that of the right side) and the SEP of bilateral posterior tibial nerve were abnormalities (bilateral P40 wave amplitude decreased significantly).

Cerebrospinal fluid lactate concentrations were not measured. MRI spectroscopy (MRS) revealed a prominent lactate peak characteristic of mitochondrial cytopathies (Figure 1E). Electroencephalogram recording showed frequent epileptiform discharges in the posterior regions. Therefore, the presence of the combination of hearing impairment, short stature, seizures, stroke-like episodes, good cerebrovascular status, and lack of evidence of cardiogenic embolism indicated the requirement for genome analysis. Mitochondrial full-genome analysis revealed the m.3243A > G variant in the MT-TL1 gene, with 6% heteroplasmy in blood leading to a diagnosis of MELAS. The clinical phenotype was consistent with MELAS. A deltoid muscle biopsy showed ragged-red fibers (RRFs) on modified Gomori trichrome stain, strongly succinate dehydrogenase-positive blood vessels, and some citocrome coxidase–negative fibers.

The patient was started on vitamin B1 (300 mg/day), L-carnitine (200 mg/day), L-arginine (1000 mg/day), and coenzyme Q10 (1500 mg/day). The patient gradually improved. The muscle strength recovered, and there were residual psychotic symptoms or aphasia on discharge.

3 | DISCUSSION

Pavlakis et al. first reported MELAS in 1984.[1] The diagnosis of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is sometimes elusive owing to heteroplasmy.[2] Childhood is the typical age of onset of MELAS, with 65–76% of affected individuals presenting at or before the age of 20 years. Only 5%–8% of individuals present before the age of 2 years and 1%–6% after the age of 40.[3] The disease is mostly acquired by maternal inheritance, and genetic testing is required for diagnosis. The most common mutation is the A3243G point mutation of mitochondrial deoxyribonucleic acid, which accounts for approximately 80% of MELAS patients.[3] MELAS is a polygenetic disorder associated with at least 29 specific point mutations. Mutations involving protein subunits have been implicated in other mitochondrial syndromes, such as Leber's hereditary optic neuropathy, Leigh's disease, and myoclonic epilepsy with ragged-red fibers (MERRF).[4]

The clinical manifestations of MELAS syndrome are diverse. Stroke-like episodes are one of the cardinal features of MELAS syndrome that occur in 84%–99% of affected individuals.[5] Seizures are another feature of MELAS, occurring in up to 70% of MELAS patients older than 50 years.[6] Researchers analyzed the clinical characteristics of MELAS and found that the main neurological symptoms were epileptic seizures, hemiplegia or partial numbness, cortical blindness or hemianopia, headaches, mental retardation or dementia, exercise intolerance, and sensorineural deafness. Nonneurological symptoms included a short stature, hirsutism, fever, vomiting, and kidney damage.[7] The clinical manifestations of the present patient included epileptic seizures, stroke-like episodes, motor intolerance, cortical blindness or hemianopia, sensorineural deafness, and short stature.

Although the pathogenesis of stroke-like episodes in MELAS has not been fully elucidated, it may be due to an energy production failure in central nerve cells caused by mitochondrial dysfunction with a mismatch of perfusion and metabolism. Perfusion and substrate delivery are intact, but defects in the electron-transport chain cause production failure of adenosine triphosphate with an exaggeration of anaerobic glycolysis that may progress to seizures and neuronal death. This energy production failure could explain blindness, cell membrane over-discharge, and the lack of time correlation between blindness and EEG.[8] Differentiation between epilepsy-induced cortical blindness and mitochondrial dysfunction generating epilepsy and cortical blindness is difficult. We think that, in our case, the mechanism of cortical blindness is probably multifactorial.

Brain MRI can show a wide range of abnormalities that are not compatible with the distribution of blood supply. The temporoparietal lobe and occipital lobe are most likely affected, without mass effect in most cases.[9] Muscle pathological biopsy is helpful in the diagnosis of patients with suspected MELAS. Gomori staining of frozen sections of muscle biopsy shows RRF and a number of degenerated mitochondria.[10] Mitochondrial disease was suspected in our patient due to the combination of stroke-like episodes, seizures, fluctuations in symptoms, newly presented lesions on MRI indicating cortical laminar necrosis and an elevated venous lactic acid level at rest. The diagnosis of MELAS was subsequently confirmed through genetic testing and deltoid muscle biopsy.

Patients with mitochondrial disease may have visual loss (homonymous hemianopic defects or cortical

blindness.) not ascribable to optic nerve or retinal dysfunctions, but rather a reflection of the disruption of the retro chiasmal visual pathways. The mitochondrial disease most consistently associated with retrochiasmal visual loss is MELAS.[11]

Hearing loss may appear long before stroke-like episodes and could be easily neglected by patients during history taking, especially for the elderly.[12] As in this case, a careful investigation of medical history should be emphasized. In addition, studies have shown that the frequency of mitochondrial DNA mutations is related to the age of onset, indicating that patients with a low-frequency mutation may present at an older age.[10] Therefore, the low-frequency mutation in our patient might explain her late onset of disease.

4 | CONCLUSION

Patient's atypical age at presentation and symptoms in our case highlights the significant clinical variability that remand when encountering middle-aged patients with stroke-like episodes, imaging findings are atypical for cerebral infarction and without vascular risk factors, MELAS stands out as a possible culprit in clinical practice. Meanwhile, given that mitochondrial diseases are responsible for a significant portion of unexplained hereditary or childhood-onset hearing loss, it is crucial to consider mitochondrial disease as an important diagnosis for patients experiencing progressive hearing loss without any other accompanying symptoms. To prevent delays in treatment, a detailed medical history should therefore be collected before starting with the appropriate laboratory investigations to reach a correct diagnosis.

AUTHOR CONTRIBUTIONS

Lin Zijun: Formal analysis; writing – original draft; writing – review and editing. **Yi Xu:** Formal analysis. **Yang Yujia:** Writing – original draft. **Xu Zhiqiang:** Resources; supervision.

ACKNOWLEDGMENTS

Thanks to Professor Zhiqiang Xu to this review and continued support.

FUNDING INFORMATION

Science and Technology Innovation Training Project of Army Medical Center (Grant No. 2019CXICBOI4), and Science and Technology Innovation Special Project of Chongqing Social Undertakings and Peoples Livelihood Guarantee (Gran No. cstc2017shmsA 130005).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

HUMAN AND ANIMAL RIGHTS AND INFORMED CONSENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Lin Zijun https://orcid.org/0000-0002-5409-5004

REFERENCES

1. Pavlakis SG, Phillips PC, DiMauro S, de Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a distinctive clinical syndrome. *Ann Neurol*. 1984;16(4):481-488.
2. Dimauro S, Tay S, Mancuso M. Mitochondrial encephalomyopathies: diagnostic approach. *Ann N Y Acad Sci*. 2004;1011:217-231.
3. El-Hattab AW, Adesina AM, Jones J, et al. MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab*. 2015;116(1–2):4-12.
4. Wong LJ. Pathogenic mitochondrial DNA mutations in protein-coding genes. *Muscle Nerve*. 2007;36(3):279-293.
5. Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. *Biochim Biophys Acta*. 2012;1820:619-624.
6. Aurangzeb S, Vale T, Tofaris G, Poulton J, Turner MR. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) in the older adult. *Pract Neurol*. 2014;14(6):432-436.
7. Chen H, Hu Q, Raza HK, et al. An analysis of the clinical and imaging features of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). *Somatosens Mot Res*. 2020;37:45-49.
8. Chakrabarty S, Govindaraj P, Sankaran BP, et al. Contribution of nuclear and mitochondrial gene mutations in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. *J Neurol*. 2021;268(6):2192-2207.
9. Bhatia KD, Krishnan P, Kortman H, Klostranec J, Krings T. Acute cortical lesions in MELAS syndrome: anatomic distribution, symmetry, and evolution. *AJNR Am J Neuroradiol*. 2020;41(1):167-173.

10. Goodfellow JA, Dani K, Stewart W, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: an important cause of stroke in young people. *Postgrad Med J*. 2012;88(1040):326-334.
11. Al-Enezi M, Al-Saleh H, Nasser M. Mitochondrial disorders with significant ophthalmic manifestations. *Middle East Afr J Ophthalmol*. 2008;15(2):81-86.
12. Vandana VP, Bindu PS, Sonam K, et al. Audiological manifestations in mitochondrial encephalomyopathy lactic acidosis and stroke like episodes (MELAS) syndrome. *Clin Neurol Neurosurg*. 2016;148:17-21.

How to cite this article: Zijun L, Xu Y, Yujia Y, Zhiqiang X. Elderly onset of MELAS carried an M.3243A>G mutation in a female with deafness and visual deficits: A case report *Clin Case Rep*. 2024;12:e8438. doi:10.1002/ccr3.8438