

# Diagnosis of adult-onset MELAS with suspected recurrent strokes: A case report

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**Abstract.** Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is caused by mutations in mitochondrial DNA and is one of the most common syndromes among the mitochondrial diseases. Clinical manifestations typically occur before the age of 40 years. The present study reports a case of MELAS with a mutation in the adenine to guanine conversion at mitochondrial genome 3243 in a 48-year-old woman who was suspected of suffering from recurrent strokes. Finally, the genomic analysis confirmed the diagnosis of MELAS. This case highlights the importance of considering MELAS as a potential cause of recurrent stroke-like events if imaging findings are atypical for cerebral infarction, even among middle-aged patients with vascular risk factors.

## Introduction

Mitochondrial diseases are a group of rare disorders associated with defects (mutations or deletions) in mitochondrial DNA (mtDNA) or nuclear DNA (1), with an estimated birth prevalence of 20 cases per 100,000 individuals (2). Due to the fact that mitochondria are major sources of energy in cells and are present in all tissues (except for red blood cells), clinical characteristics are depicted in tissues with high energy

demand, including the brain, skeletal muscle, cardiac muscle and endocrine system (2). The clinical manifestations, severity and prognosis of the different mitochondrial diseases vary. The diseases usually exhibit a series of symptoms and are correspondingly grouped into several syndromes (1). Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is one of the most common syndromes, with a prevalence as frequent as 1 in 6,000 (3). MELAS is typically characterised by mitochondrial myopathy, encephalopathy with stroke-like episodes, seizures and/or dementia, and lactic acidosis. The clinical manifestations of MELAS syndrome often occur before the age of 40 years (4).

The current study reports a case of MELAS with a mutation in the adenine to guanine conversion at mitochondrial genome 3243 (m.3243A>G), in which two stroke-like episodes damaged different cerebral hemispheres.

## Case report

A 48-year-old, right-handed female presented to the Affiliated Hospital of North Sichuan Medical College (Nanchong, China) with a sudden dysarthria in September 2021.

At 46 days before this hospital admission, the patient had suddenly developed weakness in the left limb and was unable to flexibly move the body. The condition of the patient had continued to worsen over the next 2 days, after which the patient experienced walking difficulties. There were no fevers, headaches or limb convulsions. The patient underwent magnetic resonance imaging (MRI) due to the symptoms and was suspected of having an ischemic stroke, for which treatment was administered.

At the age of 35, the patient had developed a hearing impairment, which resulted in the loss of hearing in the left ear and very poor hearing in the right ear. At the age of 43, the patient was diagnosed with type 2 diabetes, which was treated with acarbose. At the age of 45, a diagnosis of cardiomyopathy was made. The patient did not have any other ailments, such as headaches, seizures, dementia or mental illness. The mother of the patient, who was also diagnosed with diabetes in her 30s, died in her mid-50s due to unknown reasons. The brother of the patient, who was weak and suffered from diabetes, had died suddenly 3 years prior to the current admission and the cause of death was unknown. The father of the patient was still alive.

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On admission (day 1), a temperature of 36.5°C, a blood pressure of 112/70 mmHg, a pulse rate of 76 beats per min and a breathing rate of 20 breaths per min were recorded. The patient had a height of 148 cm and weighed 40 kg. The physical examination did not detect any other obvious abnormalities. The neurological examination revealed a loss of hearing in the left ear and very poor hearing in the right ear. Comprehension and reading ability were normal, whereas left limb movement and sensation were impaired, with a muscle strength level of 3.

Blood test results on admission were unremarkable, except for the fact that the serum lactic acid level was 3.42 mmol/l (normal range, 0.5–2.2 mmol/l), the blood glucose was 8.6 mmol/l (normal range, 3.85–6.11 mmol/l) and HbA1c was elevated at 7.2% (normal range, 4–6%). The brain MRI scan obtained on admission showed a decreased T1-weighted imaging signal and an increased diffusion-weighted imaging (DWI)/fluid-attenuated inversion recovery (FLAIR) signal in the right temporal and parietal lobes, which mainly affected the cerebral cortex with underlying subcortical oedema (Fig. 1). However, no significant abnormality was observed on magnetic resonance angiography (MRA) (Fig. S1).

The patient was empirically treated with intravenous butylphthalide (dose of 200 mg per time, three times a day) and oral aspirin (dose of 100 mg, once a day) to address a possible cardiogenic cerebral embolism. Dynamic electrocardiogram and echocardiography did not show any evidence of a cardiogenic embolism. The condition of the patient was improved after ~1 week and they were discharged from the hospital.

At 2 days before the current admission, the family members had observed that the speech of the patient lacked clarity, with a slow response. Due to the fact that the patient had been discharged from the hospital only 1 month earlier due to ischemic stroke, the family members were worried about a recurrence. The patient was admitted to hospital for emergency treatment due to recurrent ischemic strokes.

On readmission (46 days after the initial stroke), the physical examination resembled the previous examination. The neurological examination demonstrated that the patient exhibited a clear mind, poor higher neurological function (orientation, memory and calculation functions), dysarthria and other obvious abnormal neurological signs.

The blood tests did not reveal any significant changes from the first admission. However, the MRI analysis showed a new lesion, a decreased T1-weighted imaging signal and an increased DWI/FLAIR signal in the left temporal, parietal and occipital lobes (Fig. 2). In addition, there was a reduction in the area covered by the old lesion in the right temporal and parietal lobes compared with the previous month. The MRA analysis was still normal (no significant change from 1 month ago).

Therefore, the presence of the combination of diabetes, hearing impairment, short stature, good cerebrovascular status and lack of evidence of cardiogenic embolism indicated the requirement for a genome analysis (mitochondrial gene sequencing, positive genetic testing for the mitochondrial DNA mutation) performed by Kindstar Global (Beijing) Technology, Inc., which demonstrated a m.3243A>G mutation (Fig. S2), thus confirming the presence of MELAS syndrome.

The patient was treated with L-carnitine (1,000 mg/day), vitamin B1 (100 mg/day) and vitamin B12 (100 mg/day), and the diabetes treatment regimen was adjusted. The symptoms

gradually improved, after which the patient was discharged from the hospital. The medication was well tolerated, and no adverse events occurred. At the last follow-up (6 months after discharge), the Modified Rankin Scale (5) was scored as 3, which indicated residual cognitive deficits. Follow-up was performed once every 3 months for 1 year. Electromyography, nerve conduction and muscle biopsy tests were not performed during the disease course, as these studies could not be conducted due to a lack of consent from the patient and their family. After the genetic analysis, the daughter of the patient was also determined to have an m.3243A>G mutation, whereas no mutation was present in the father of the patient.

## Discussion

This case highlights the importance of considering MELAS as a potential cause of recurrent stroke-like events when imaging findings are atypical for ischemic stroke, even among middle-aged patients with vascular risk factors. The patient in the present study was middle-aged, had diabetes and had two stroke-like episodes; however, the imaging findings were not consistent with the symptoms of ischemic stroke, and recurrent stroke was not considered past this point. This inconsistency triggered the completion of a mitochondrial gene analysis.

Although MELAS syndrome is a matrilineal inherited disorder, some sporadic cases also exist. The incidence of MELAS syndrome is slightly higher in males than in females. Moreover, the onset of MELAS syndrome is usually between 2 and 31 years, whereas the onset after 40-years-old is extremely rare (4,6). In the present study, the patient was 48-years-old before MELAS onset, which is a relatively rare occurrence. The existence of a family history, as well as the early deaths of the mother and brother of the patient (likely from the same disease), and the presence of an m.3243A>G mutation in the daughter, were demonstrated via the mitochondrial gene analysis. Although there are specific mutations that are typically associated with MELAS (m.3243A>G and m.3271T>C), MELAS is a polygenetic disorder associated with at least 29 specific point mutations. A number of mutations, especially those involving protein subunits, have been implicated in other mitochondrial syndromes [such as Leber's hereditary optic neuropathy, Leigh Disease and myoclonic epilepsy with ragged-red fibers (MERRF)] (5,7). This combination of different diseases caused by a single mutation and polygenic mutations coexist in polygenic syndromes, thus leading to a bewildering variety of features of mitochondrial disease (5).

The clinical manifestations of MELAS syndrome are diverse. However, stroke-like episodes are one of the cardinal features of MELAS syndrome that occur in 84–99% of affected individuals (8). Researchers analysed 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. Non-neurological symptoms included a short stature, hirsutism, fever, vomiting and kidney damage (9). The clinical manifestations of the present patient included motor intolerance, hemiplegia, sensorineural deafness and a short stature. In addition, the patient case was complicated with diabetes, which is not uncommon in patients with MELAS.

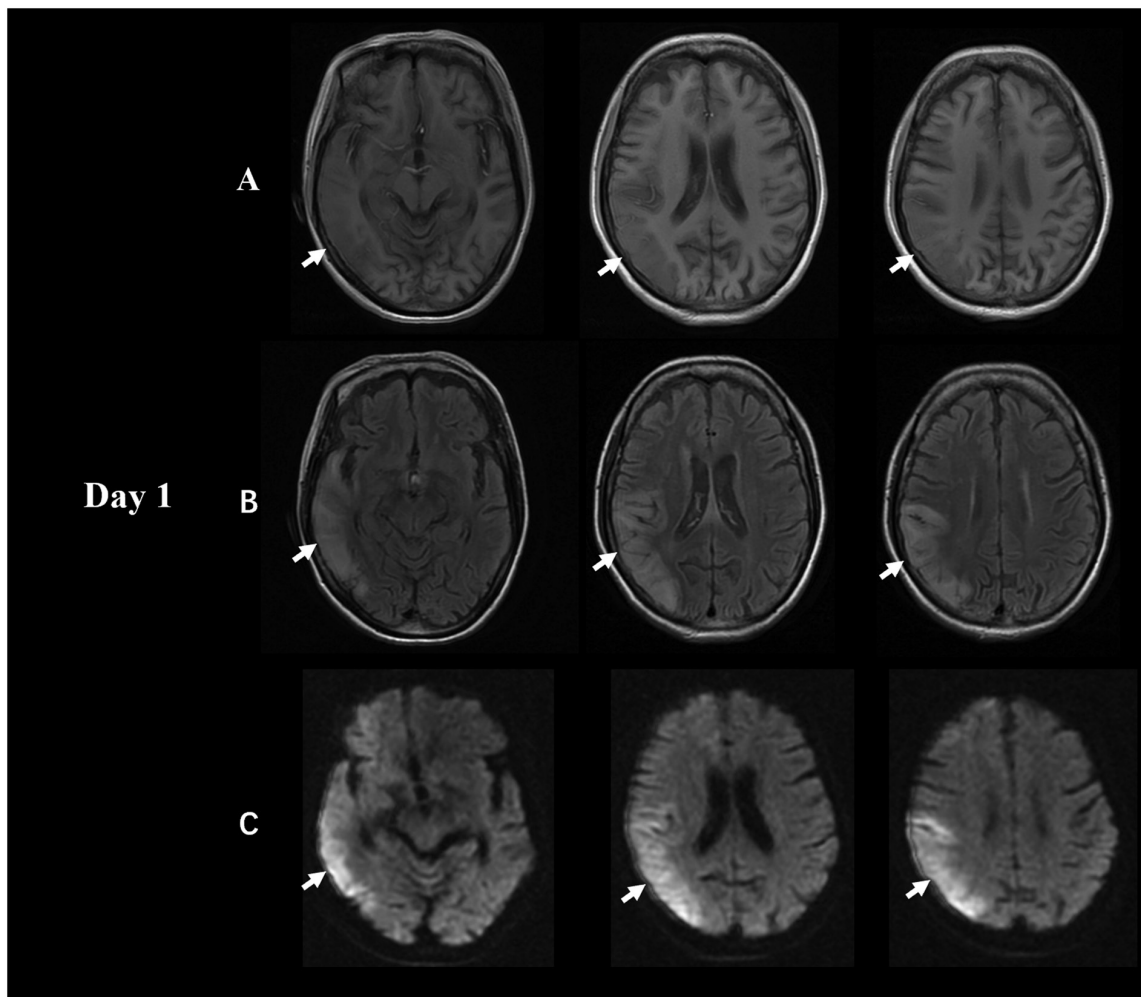


Figure 1. Brain MRI scans obtained after the first stroke-like episodes. Brain MRI scans obtained on the first admission (day 1) showed (A) a decreased T1-weighted imaging signal and increased (B) fluid-attenuated inversion recovery and (C) diffusion-weighted imaging signals in the right temporal and parietal lobes, which mainly affected the cerebral cortex with underlying subcortical oedema (arrows). MRI, magnetic resonance imaging.

This is due to the fact that the m.3243A>G mutation can not only cause neurological and muscular system lesions, but is also one of the most common pathogenic point mutations of mtDNA mutation in diabetes, and diabetes often precedes the neurological symptoms (9). In addition, the present patient had cardiomyopathy, and an m.3243A>G mutation is also a cause of cardiomyopathy. In total, >30% of MELAS patients have heart conditions (10). Thus, the clinical manifestations of MELAS are often diverse and are often misdiagnosed.

The preliminary screening of MELAS usually requires a neuroimaging examination and laboratory biochemical tests. Pathological biopsy is an important diagnostic tool, whereas genetic testing is the gold standard for the diagnosis of MELAS (11,12). Furthermore, lactic acid levels in the blood and cerebrospinal fluid are often analysed during biochemical tests, as mitochondrial dysfunction in patients with MELAS syndrome results in enhanced anaerobic fermentation and increased lactic acid production. The present case analysis revealed that the patient had increased lactic acid levels. However, a variety of factors, such as exercise, hypoxia and improper sample collection and storage, can affect the blood lactic acid level, which can lead to an increase in the lactic acid reading and a corresponding incidence of false-positives.

Although lactic acid and pyruvate minimum exercise tests are often used in clinical practice to understand mitochondrial function, there is still no test standard. Other diseases with mitochondrial involvement may also have similar positive results, thus leading to false-positive results. It has been indicated that the lactate/pyruvate ratio is meaningful only when the lactic acid level is elevated to a certain level (>2.5 mmol/l) (12).

The characteristic neuroimaging areas involved in MELAS do not conform to the classical vascular distribution and are asymmetric; they mainly involve the temporal, parietal and occipital lobes. Furthermore, they are limited to the cortical areas or involve subcortical white matter and can migrate, fluctuate or even disappear over time (13). Acute cranial MRI shows a decreased T1 signal and increased T2, FLAIR, and DWI signals in cerebral cortical and/or subcortical white matter lesions, whereas the corresponding ADC shows equal or decreased signals (14). In the present patient, brain MRI showed a large lesion in the right temporal and parietal lobes at first onset (Fig. 1). However, the second brain MRI showed a large area of fresh lesions in the left temporal, parietal and occipital lobes 1 month later, and the old lesion on the right side was smaller than before (Fig. 2). These lesion fluctuations at different times were also consistent with the imaging characteristics of MELAS.

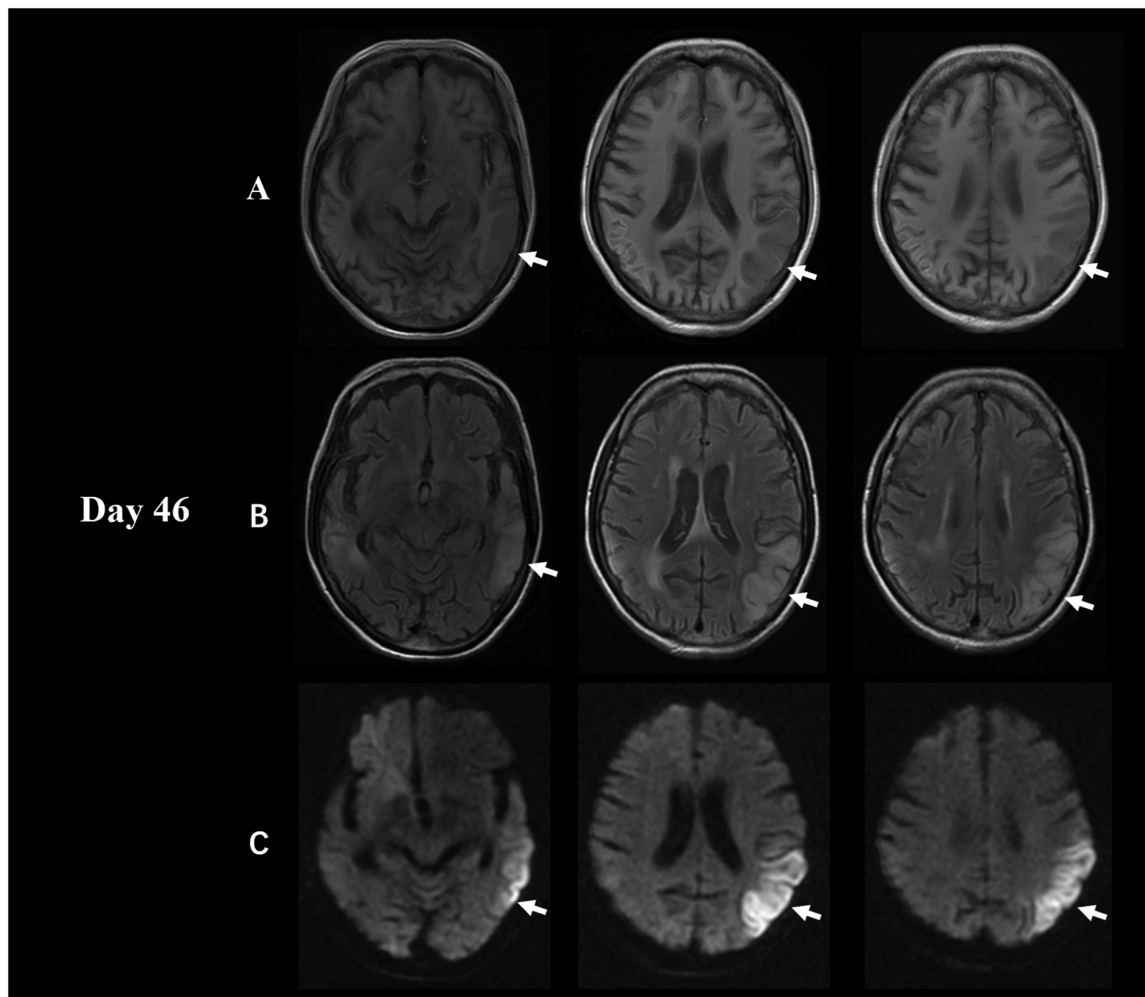


Figure 2. Brain MRI scans obtained after the second stroke-like episodes. Brain MRI scans obtained on the second admission (day 46) showed (A) a decreased T1-weighted imaging signal and increased (B) fluid-attenuated inversion recovery and (C) diffusion-weighted imaging signals in the left temporal, parietal and occipital lobes (arrows). MRI, magnetic resonance imaging.

Muscle pathological biopsy is an important basis for the diagnosis of patients with suspected MELAS. Gomori staining of frozen sections of muscle biopsy shows ragged-red fibres (RRF) and a number of degenerated mitochondria. Furthermore, glycogen staining also shows an accumulation of fat and glycogen. The positive staining of the vascular wall of the muscle tissue with subrinic acid dehydrogenase and the crystalloid inclusion bodies under an electron microscope are helpful in the diagnosis of MELAS (15). However, these pathological manifestations are not solely present in MELAS, but can also appear in MERRF and Kearns-Sayre syndrome, especially in early childhood. In addition, due to the fact that it is an invasive examination, the acceptance rate is low. The patient and the family in the present case study were not willing to approve a muscle biopsy. Nonetheless, muscle biopsy is useful in cases where there are no mutation bases or during the investigation of other mitochondrial disorders.

Mitochondrial DNA analysis is a diagnostic assay of decisive significance, and urine-derived DNA testing is now available in clinical practice, which is replacing the use of muscle-derived DNA, due to the fact that the critical test in investigating mitochondrial disorders is to establish the genetic mutation, rather than necessarily demonstrating

muscle pathology (15). Currently, the detection of gene mutation sites is the gold standard for the diagnosis of MELAS syndrome. Although the most common cause of MELAS is m.3243A>G mutation, MELAS can also be caused by a variety of other mtDNA and nuclear gene mutations. In recent years, nearly 20 types of MELAS-related mtDNA point mutations have been found, including m.3243A>G, m.3252A>G, m.3291T>C, m.3271T>C, m.3995A>G and m.3959G>A. Approximately 80% of patients with MELAS syndrome have the m.3243A>G mutation of the mtDNA tRNA leucine gene site (16). Similar to these results, the patient and daughter in the present study also had the same point mutation.

To date, there is no specific treatment for MELAS syndrome, and symptomatic treatment is often applied in clinical practice. Diet changes can reduce the production of endogenous toxic metabolites. Specifically, a high-protein, high-carbohydrate and low-fat diet compensates for impaired gluconeogenesis and reduces fat breakdown. Valproic acid should be avoided in the treatment of seizures due to its deleterious effects on mitochondrial function. Moreover, metformin should be avoided in individuals with MELAS syndrome due to its propensity to cause lactic acidosis (16,17). The current patient had diabetes but was fortunate to have been treated with acarbose. In addition, ATP,

coenzyme Q10 and large doses of B vitamins can reduce blood lactate and pyruvate levels. L-carnitine can improve energy metabolism and promote lipid metabolism. Furthermore, symptomatic treatments are used for heart disease, seizures, cranial hypertension and diabetes. Although a number of limitations exist for the current treatment of MELAS, gene therapy remains an attractive research direction. Stem cell-derived mitochondrial transplantation has been shown to play an important role in metabolic rescue (18), which offers hope for the treatment of MELAS. An earlier onset and increased incidence of clinical symptoms corresponds to a worsened prognosis (19). Therefore, early diagnosis and early intervention are particularly important, which may improve the patient prognosis.

In conclusion, in patients with recurrent stroke, there is a need for careful analysis of the occurrence and development of the disease, and the past medical history and family history of the patient, and a careful interpretation of the imaging characteristics. Indeed, the aforementioned clinical manifestations and imaging features are not specific to MELAS. Other potential conditions to consider include subacute ischemic stroke, progressive multifocal leukoencephalopathy, herpetic encephalitis, posterior reversible encephalopathy syndrome and vasculitis. Therefore, mitochondrial DNA testing may be important in determining whether a patient has MELAS. At present, the treatment of MELAS is still symptomatic. If the ultimate outcome is to be improved, future therapeutic research should consider an improvement in the potential of cell therapy-based mitochondrial restoration, especially stem cell therapy for MELAS.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

FY and SP were equal contributors in writing the manuscript. FY, QP and SP analysed and interpreted the patient data regarding the series of MRI data. FY and SP confirm the authenticity of all the raw data. All of the authors have read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Written consent was obtained for publication from the patient's legal representative (husband).

### Competing interests

The authors declare that they have no competing interests.

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