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CASE REPORTS

Adult-onset mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): A case report and review of its conventional and diffusion-weighted MRI features

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Abstract

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare mitochondrial neurodegenerative disorder characterized by stroke-like episodes, seizure, and lactic acidosis. The diagnosis of MELAS is often challenging due to its variable phenotypic manifestations and rarity of this disease. In this article, we report the case of a 38-year-old woman who presented with repeated seizures and clinical stroke-like symptoms. She had no positive family history, and lactic acidosis was only present in her initial episode. Magnetic resonance imaging (MRI) of the brain was also normal in her first presentation. However, subsequent scans due to new clinical events showed migratory stroke-like lesions that were hyperintense on T2/fluid attenuated inversion recovery (FLAIR) sequence and had restricted diffusion. They did not conform to vascular territories but had a predilection for posterior temporal, occipital and parietal regions. The radiological findings prompted the suspicion of MELAS, which diagnosis was confirmed with genetic testing. Here, we also reviewed the MRI features of MELAS from literature, in particular the diffusion-weighted sequence findings, as debate still exists on whether the apparent diffusion coefficient (ADC) signal should be high or low in these lesions. Our case highlights the importance of recognizing key imaging features of this rare and highly heterogenous disease. In addition to helping with earlier diagnosis, these imaging findings also provide more insight into the underlying pathophysiology of MELAS.

Keywords: MELAS; stroke-like lesions; mitochondrial disease; MRI restricted diffusion

INTRODUCTION

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare genetic disorder that leads to progressive neurological impairment. Around 80% of cases are caused by an m.3243A>G mitochondrial mutation.[1] Despite being well known for its classic triad of stroke-like episodes, seizure, and lactic acidosis, its phenotypic presentation is in fact highly variable.[2] The carrier frequency of m.3243A>G is 40-70 times higher than the disease prevalence, which implies that many of the carriers are asymptomatic or undiagnosed due to mild disease.[3,4] Only around 15% of m.3243A>G carriers present with MELAS, with the remainder associated with diabetes mellitus, hearing impairment, myopathy, ataxia, and others.[5] Therefore, the diagnosis of MELAS can be challenging in clinical practice.

We hereby present a case of MELAS in which typical neuroimaging findings were critical in helping with the diagnosis.

CASE REPORT

A 38-year-old woman was admitted for her first

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episode of generalized tonic-clonic seizure, following a prodrome of low mood, hand numbness and dizziness. She claimed to have unremarkable past health, except for contracting COVID-19 infection two months prior. Her condition deteriorated after admission, and she developed status epilepticus, requiring intensive care unit support for intubation and vasopressor for cardiovascular instability.

Blood tests revealed hyperammonemia (142 umol/L, reference 18-72 umol/L) and severe lactic acidosis (lactate 14.6 mmol/L, pH 6.92, bicarbonate 6.1 mmol/L, base excess -25.8 mmol/L), which rapidly normalized upon repeat blood sampling after resuscitation. Cerebrospinal fluid (CSF) analyses and autoimmune encephalitis panels were all normal. Electroencephalography (EEG) showed frequent background slowing down to 2-3Hz in bifrontal regions, but there were no sharp waves, spike-and-waves, or other epileptiform discharges. Magnetic resonance imaging (MRI) of the brain was normal. Metabolic screening revealed elevated serum pyruvate (0.23 mmol/L, reference 0.03-0.1mmol/L), and a lactate-to-pyruvate (L:P) ratio of 63, which suggested impairment of oxidative metabolism. Carnitine and urine organic acids were normal. Liver function tests, ceruloplasmin, toxicology and ultrasound of liver were also normal.

The patient was stabilized and discharged with phenytoin. However, four months later, she had a second seizure, and was re-admitted for left hand and facial twitching with preserved consciousness, which was preceded by left side weakness. She reported good drug compliance, which was confirmed by a phenytoin level within therapeutic range. Neurological examination showed mild left upper limb weakness only.

On further questioning, she claimed to have experienced hearing impairment for several years but did not seek medical advice. Audiogram performed later confirmed bilateral sensorineural hearing loss. She was noted to have a short stature of 151 cm (3rd-10th percentile)[6], and also exhibited psychiatric features including abnormal affect and labile mood.

Blood lactate and ammonia levels were normal in this admission. Transaminase level was mildly elevated. Computed tomography (CT) of the brain revealed a new right parietal hypodensity (Figure 1). MRI of the brain done on day 6 confirmed a T2/fluid attenuated inversion recovery (FLAIR) hyperintensity at the right peri-sylvian fissure, associated with restricted diffusion, leptomeningeal enhancement, and mild gyriform cortical swelling. FLAIR hyperintensity was also present at the right thalamus, extending to the right cerebral peduncle with mild contrast enhancement (Figure 2).

EEG this time showed right temporal sharp waves with evolution into spike-and-wave morphology that spread to the right parietal region. Levetiracetam was added in view of the breakthrough seizure and ictal discharges on EEG. Lumbar puncture and autoimmune encephalitis panels were repeated, but results were again normal. Young stroke workup including thrombophilia screen, autoimmune markers, homocysteine, 24-hour electrocardiography and echocardiogram were all normal, except for a mildly elevated glycated hemoglobin (HbA1c) of 6.6. Her family history was reviewed, which was negative for seizure, stroke, diabetes mellitus, hearing impairment, and other neurological diseases.

Cerebral CT angiogram performed on day 13 showed no cerebral venous sinus thrombosis or other vascular pathologies. However, worsening of the right peri-sylvian cerebral white matter edema was observed. Repeat MRI brain on day 24 showed improvement of the right peri-sylvian and right thalamic lesions. However, new T2/FLAIR signals were seen at the right temporo-occipital lobe, which were associated with restricted diffusion, mild edema and gyriform contrast enhancement (Figure 3).

Overall, imaging findings showed multifocal relapsing-remitting lesions that were of non-vascular distribution but had a predilection for posterior temporal, occipital and parietal involvement. Despite a normal lactate level in this episode and a negative family history, the typical radiological appearance prompted the

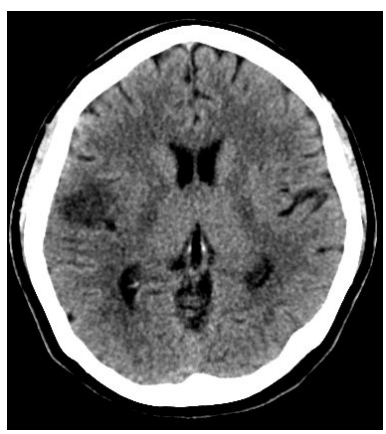

Figure 1. Brain CT scan showing new right parietal hypodensity

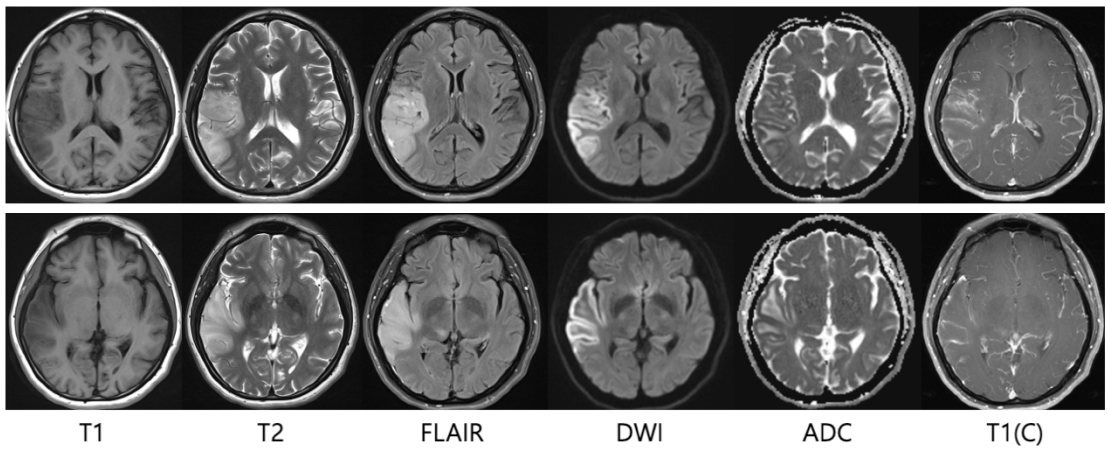

Figure 2. First set of brain MRI scan in second admission, showing right peri-sylvian and right thalamic lesions (FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted image; ADC, apparent diffusion coefficient; T1(C), T1 contrast).

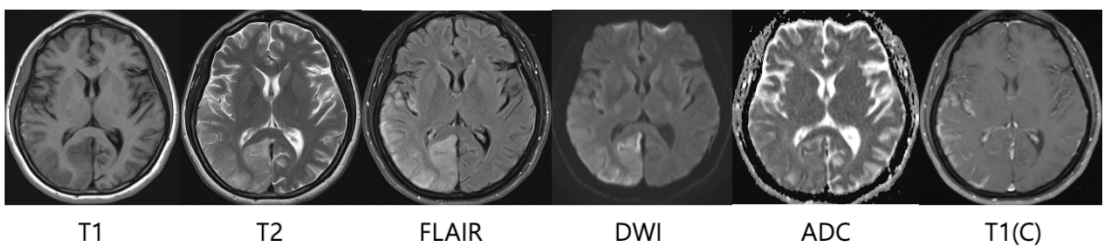

Figure 3. Second set of brain MRI scan in second admission, showing migratory lesions to posterior part of right temporo-occipital lobe with regression of previous right peri-sylvian lesion (FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted image; ADC, apparent diffusion coefficient; T1(C), T1 contrast).

suspicion of MELAS. Genetic test was performed, and confirmed a heteroplasmic m.3243A>G mitochondrial mutation (estimated heteroplasmy level 30% and 80-90% on blood and urine sample respectively), consistent with the diagnosis of MELAS.

The patient was prescribed coenzyme Q10, arginine, multi-vitamins, and L-carnitine. Levetiracetam was continued while phenytoin was tapered off due to its possible mitochondrion-toxic effect and liver derangement.[7] Genetic counselling was also provided to the patient and her family members. However, patient continued to develop stroke-like episodes with stepwise deterioration in cognition. Her latest brain MRI scan, which was done 4 months after the diagnosis (i.e. 8 months after the first presentation), showed new left parieto-occipito-temporal lobe involvement with regression of the previous right peri-sylvian and right parieto-occipito-temporal lobe lesions (Figure 4).

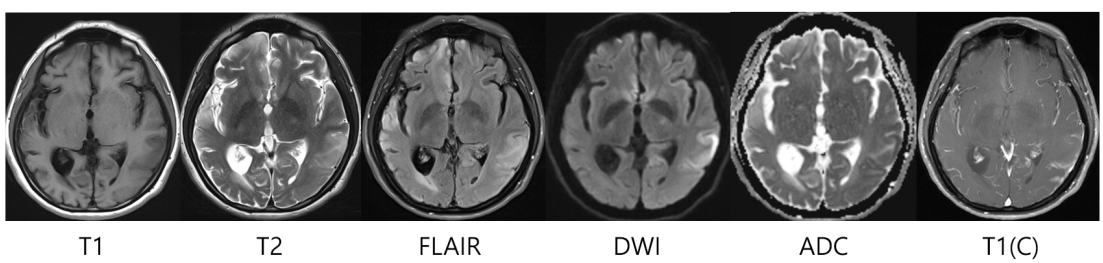

Figure 4. Brain MRI scan 4 months after diagnosis, showing new lesion over left parieto-occipito-temporal lobe with regression of previous right brain lesions (FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted image; ADC, apparent diffusion coefficient; T1(C), T1 contrast).

DISCUSSION

Mitochondrial stroke-like episode refers to a subacute, evolving brain syndrome driven by seizure activity in genetically determined mitochondrial disease.[8] Both clinical and radiological features can mimic acute ischemic stroke and other pathologies, leading to diagnostic difficulty. Several MRI features are characteristic of MELAS which can help with the diagnosis in atypical cases.

Multifocal stroke-like lesions (SLL) are typically present in MELAS and do not conform to vascular territories. A predilection for posterior temporal, occipital and parietal involvement can be observed.[9] Occasionally, the thalamus may also be involved as in our patient.[10] Although MELAS is a metabolic disease, brain lesions are usually asymmetrical. The non-vascular distribution may be explained by the hypothesis of neuronal hyperexcitability, which suggests that the disease is mediated by ictal activity instead of being a purely vascular event.[11] According to literature, basal ganglia calcification may also be present.[12]

SLL show T2/FLAIR hyperintensity associated with restricted diffusion on MRI. The restricted diffusion is usually in a gyriform pattern and appears several days after symptom onset.[13] Signal intensity is high in diffusion-weighted imaging (DWI) whereas apparent diffusion coefficient (ADC) signal is variable. Early studies have described high ADC signal in most cases and this feature was conventionally used to differentiate SLL from genuine ischemic stroke lesion.[14] The high ADC signal reflects the presence of vasogenic edema, which was purported as the underlying mechanism of SLL.[15] However, recent reports have identified more cases with low or normal ADC signal, which was due to the presence of cytotoxic edema.[16-18] Moreover, ADC signal has been shown to evolve from low to high with time.[16,18-20] This may account for the discrepancy in ADC findings due to variable timing of the MRI scan acquisition, given the often subacute nature of these stroke-like episodes. The acute SLL in our patient showed gyriform cortical ADC hypointensity with adjacent subcortical ADC hyperintensity, a pattern similar to what was described by Xu *et al*.[17]

Another distinguishing feature in MELAS is the migratory spreading pattern of SLL.[9] These lesions tend to appear in various stages of evolution. SLL will either resolve, progress, or result in residual tissue loss on serial imaging.[18] The end result of SLL evolution is independent of the ADC profile according to a large series study.[18] This mixture of lesions in different stages may also explain the variable ADC findings due to coexistence of cytotoxic and vasogenic edema.[16] In our patient, the latest MRI showed regression of the previous right peri-sylvian and right parieto-occipito-temporal lobe lesions. DWI signal was normalized with some residual T2/FLAIR and ADC hyperintensity. There was also mild widening of the right peri-sylvian fissure which signified possible tissue loss.

Magnetic resonance spectroscopy (MRS) is another useful imaging modality which analyzes metabolites in brain tissue non-invasively. MRS typically shows an elevated lactate peak and reduced N-acetylaspartate (NAA) in MELAS.[21] These metabolite alterations may also be present in MELAS patients with normal brain MRI scan.[22] Similar to MRI findings, MRS abnormalities are also time-dependent in the disease course of MELAS. Studies have found that lactate elevation in MRS is highly sensitive in MELAS patients with acute neurological symptoms[23], and it correlates with CSF lactate level.[24] MRS was not performed in our patient as the diagnosis was confirmed by genetic testing soon after her second presentation.

The clinical manifestation of MELAS is remarkably heterogenous.[2] Various diagnostic criteria for MELAS have been proposed. For example, a Japanese group suggested a definitive diagnosis to be made by fulfilling two clinical findings of stroke-like episodes in category A (e.g. presence of acute focal brain lesion on neuroimaging); plus two evidences of mitochondrial dysfunction in category B (e.g. high plasma or CSF lactate).[25] In our patient, even though she had normal MRI brain in the first presentation and normal plasma lactate level in the second presentation, these did not invariably exclude the diagnosis of MELAS as the clinical suspicion was high. The reason for the absence of lactic acidosis in our patient's second presentation may be accountable by delayed presentation, as the blood test was performed around 17 hours after symptom onset and the blood abnormalities can be transient. Lactic acidosis was also reported to be present in 94% of MELAS patients only[26], which means some patients may not have this feature. Retrospectively, if our patient's first CSF sample had been tested for lactate and showed an elevated level, the diagnosis of MELAS may have been considered earlier.

Our patient's blood L:P ratio was noted to be markedly raised in the first episode. This ratio

is an indicator of the equilibrium status between product and substrate of the reaction catalyzed by lactate dehydrogenase, reflecting the cytoplasmic oxido-reduction state. When cellular respiration is impaired, as in the case of MELAS, pyruvate and reduced forms of oxido-reduction coenzymes (NADH, FADH2) predominate, shifting the equilibrium to increase lactate production and result in a raised L:P ratio.[27] Mitochondrial diseases which decrease acetyl-CoA, which is required in ammonia detoxification, lead to secondary hyperammonemia.[28] This explains why our patient's hyperammonemia in her first episode normalized once lactatemia improved. Our patient also had deranged liver function in the second episode, which may be due to hepatopathy that has been reported in MELAS and other mitochondrial disorders.[29] Their liver biopsy findings were usually of fatty degeneration.[30]

DISCLOSURE

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