

Late-onset mitochondrial encephalopathy with lactic acidosis and stroke-like episodes and the role of serial imaging

Robert Ambrogetti,¹ Ethan Kavanagh,² Khalid ElTayeb³

¹Internal Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK

²University Hospitals of Leicester NHS Trust, Leicester, UK

³Neurology, University Hospitals of Leicester NHS Trust, Leicester, UK

Correspondence to

Dr Robert Ambrogetti;
robert.ambrogetti1@nhs.net

Accepted 16 February 2024

SUMMARY

Mitochondria are essential for human metabolic function. Over 350 genetic mutations are associated with mitochondrial diseases, which are inherited in a matrilineal fashion. In mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), defective mitochondrial function and resultant impaired cellular energy production compromise vascular perfusion in affected tissues. Early diagnostic criteria suggested the diagnosis should be considered in those under 40. However, a broader range of phenotypes are now recognised, including those that present for the first time later in life. The primary presenting feature in MELAS is a stroke-like episode invariably resulting in patients undergoing neuroradiological imaging. We present a case of a woman with a first presentation of a stroke-like episode and seizures in her 40s who was eventually diagnosed with MELAS. We detail her clinical presentation, treatment and diagnosis, emphasising the role of serial imaging in her diagnosis.

BACKGROUND

Mitochondria are vital to human life, producing roughly 90% of the body's energy on a cellular level via oxidative phosphorylation (OXPHOS).¹ The prevalence of known mitochondrial disease in adults has been estimated to be around 12 per 100 000.² However, the prevalence may be higher in the general population as around 1 in 250 healthy adults have been found to carry pathogenic mitochondrial DNA at low levels.³ There are over 350 gene mutations known to cause mitochondrial disease.⁴ The m.3243A>G was first identified in a case of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) in 1990.⁵ The m.3243A>G MT-TL1 variant has since been found to be one of the most common pathological mitochondrial mutations and accounts for up to 80% of cases of MELAS.⁶ M.3243A>G MT-TL1 prevalence has been reported to be between 0.017% and 0.236% in adults.^{7 8} The transition of adenine to guanine at nucleotide 3243 in mitochondrial tRNA results in impaired protein formation and ultimately leads to defective formation of complexes 1, 3, 4 and 5 of the OXPHOS system.^{9 10} The resultant impairment in cellular energy production causes vascular lesions and compromised microvascular perfusion in affected tissues.^{10 11} We present a case of late-onset MELAS caused by the m.3243A>G MT-TL1 variant.

CASE PRESENTATION

A woman in her 40s presented to hospital with a history of gradual decline in her cognitive function and nocturnal seizure activity over the last 2 weeks. She was an independent non-smoker with no alcohol consumption who worked in child-care and as a nanny. There is no family history of mitochondrial disease. Her only other significant medical history was of intermittent migraines and long-standing sensorineural hearing loss previously attributed to a childhood measles infection, compounded by 18 years of playing in a band with minimal ear protection. CT scan of the head was performed in the emergency department for suspected stroke and showed bilateral basal ganglia calcification with no other intracranial findings. As a result, an MRI of the brain was performed by the stroke team. This MRI brain showed widespread cortical restricted diffusion in the right parieto-occipital region, suggested to be in keeping with postictal changes, as seen in [figure 1](#).

Given her symptoms and a raised white cell count with neutrophilia on presentation she was initially treated for bacterial and viral meningoen- cephalitis with ceftriaxone and aciclovir. However, her cerebrospinal fluid (CSF) biochemistry, viral panel, microscopy and culture were not in keeping with an infectious aetiology. Other than a raised lactate of 4.1 mmol/L on admission, her blood tests, autoimmune screen, infection screen and lumbar puncture results were unremarkable (CSF results: glucose=4.6, protein=0.42 (0.10–0.45), cultures=no growth, CSF PCR panel HSV1, HSV2, varicella-zoster, *Enterovirus* and *Parechovirus*=not detected by PCR, cytology=no significant inflammation and no malignant cell conclusion CSF—within normal limits). HIV1 and HIV2 tests were normal, and blood cultures did not grow any organisms. Her autoimmune encephalitis serum screen via indirect immunofluorescence was negative for antibodies to CASPR2, LGI1, AMPA1, AMPA2, GABAb, GABA A and NMDA antigens. Antinuclear antibodies and extractable nuclear antigens (Ro, La, U1RNP, RNP70, CENP, Jo-1, Scl-70) were negative. Antineutrophil cytoplasmic antibodies (ANCA) (immunofluorescence) were weakly positive at a lower titre (P-ANCA 1:40) with PR3 (<0.6 IU/mL) and Myeloperoxidase (<1.0 IU/mL) negative. A baseline electroencephalogram (EEG) showed no epileptiform activity with intermittent widespread slow waves in keeping with mild cerebral dysfunction. During this admission, a CT thorax, abdomen



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To cite: Ambrogetti R, Kavanagh E, ElTayeb K. *BMJ Case Rep* 2024;**17**:e259102. doi:10.1136/bcr-2023-259102

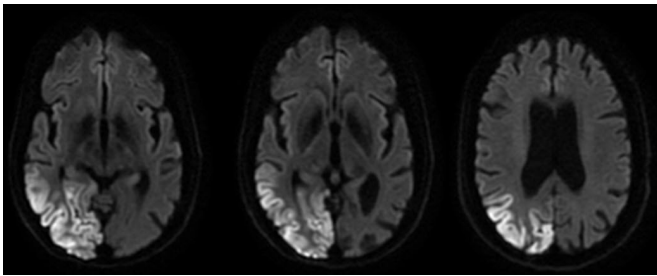


Figure 1 Initial MRI brain diffusion-weighted imaging (DWI) on first admission shows widespread cortical restricted diffusion in the right parieto-occipital region.

and pelvis showed a right adnexal cyst. Provisional diagnoses of posterior reversible encephalopathy syndrome (PRES) and autoimmune encephalitis were given. The patient was started on lacosamide and levetiracetam and completed a 5-day course of methylprednisolone. Although the patient showed some clinical improvement during a course of intravenous methylprednisolone, a normal CSF and negative autoimmune screen protein made autoimmune encephalitis less likely. Owing to the clinical improvement, absence of seizures and the patient's good functional independence, she was discharged with neurology outpatient follow-up. The patient remained seizure free and asymptomatic as an outpatient. A repeated MRI of the brain as an outpatient 5 months later showed the right-sided changes had now developed into encephalomalacia and gliosis with atrophic effect and moderate enlargement of the occipital horn of the lateral ventricle, as seen in [figure 2](#). Both the unilateral lesion and the incomplete reversibility were considered not in keeping with typical PRES.

Approximately 1 year later, the patient re-presented to the hospital with a 4-day history of intermittent self-resolving right upper limb focal motor seizures, a reduction in vision bilaterally and further cognitive decline. On examination, she was noted to be of short stature and slim build. She had left-sided homonymous hemianopia, reduced hearing in both ears, weakness in the right upper and lower limbs (Medical Research Council grading 4/5) and more than five beats of clonus bilaterally in the lower limbs. She did not have muscle pain or global muscle weakness. Ophthalmology review and visualisation of her retina excluded

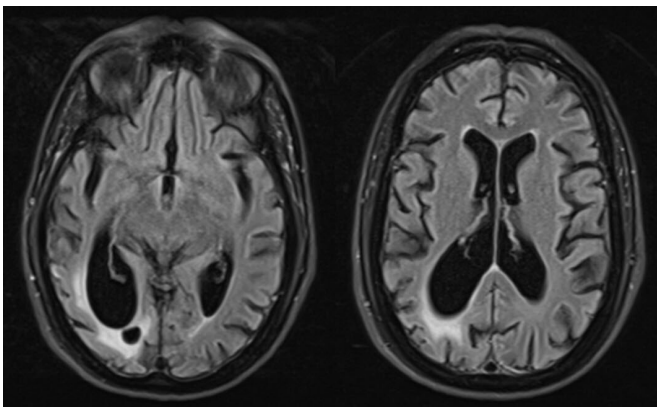


Figure 2 Outpatient MRI brain T2 turbo-spin-echo dark fluid sequence 5 months after initial MRI, showing previous areas of right temporo-occipital and parietal regions restricted diffusion and hyperintensity to have evolved into encephalomalacia and gliosis with atrophic effect and moderate enlargement of the occipital horn of the lateral ventricle.

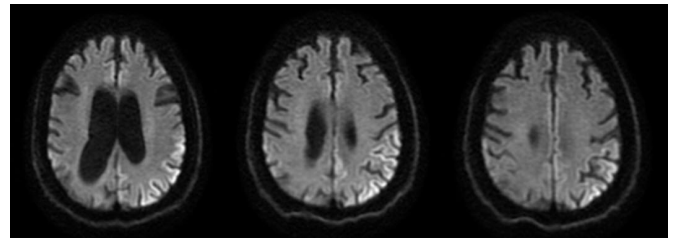


Figure 3 MRI brain diffusion-weighted imaging (DWI) taken on the second admission, approximately 1 year after the initial MRI brain, showing new regions of left parietal cortical diffusion restriction.

retinitis pigmentosa. Her routine blood tests, creatine kinase and CSF viral and bacterial studies on this admission were again unremarkable other than a slightly elevated serum lactate of 2.1 mmol/L (CSF glucose 7.5 mmol/L, CSF protein 0.36 g/L (0.10–0.45), CSF red blood cells=233, white blood cells=0, Gram stain=no organism seen, cultures=no growth). CSF cytology on this occasion was also reported as normal (CSF cytology—normal, no inflammatory cells and no malignant cells). Baseline EEG on this admission showed excess slow wave activity in a widespread distribution, which was at times more pronounced over the right temporal and parietal regions. No epileptiform activity was seen. MRI brain on this admission showed mature juxtacortical damage in the right parieto-occipital and posterior temporal lobes with gliosis, encephalomalacia with new gyriform diffusion restriction and T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity in the left parietal and occipital cortex, as seen in [figure 3](#).

A repeated MRI brain during this second admission showed new lesions on the left parietal diffusion restriction with T2/FLAIR hyperintensity, resolution of left occipital and parietal changes with mature posterior cerebral volume loss on the right occipital region. The migratory changes in a parietal/temporal/occipital fashion were more in keeping with an atypical MELAS in the context of gyriform-restricted diffusion. Given the serial MRI findings, history and exclusion of other more common differentials, a diagnosis of late-onset MELAS was suspected. MELAS was subsequently confirmed by genetic testing, which revealed an m.3243A>G MT-TL1 pathogenic variant with a 27% level of heteroplasmy in the blood-derived DNA sample. With the diagnosis confirmed with genetic tests from serum samples, further testing with muscle biopsy was not necessary. The patient showed clinical improvement with uptitration of antiepileptic medications and was discharged with follow-up.

INVESTIGATIONS

Stated above.

DIFFERENTIAL DIAGNOSIS

The clinical history, examination and imaging suggested an encephalopathic process. The initial differential included infective, autoimmune, metabolic, medication or drug toxicity, postictal state and hereditary causes. Metabolic and toxic aetiology was considered less likely from the outset as there was no obvious source of metabolic derangement or causative medication.

The patient initially appeared to show some improvement during a course of methylprednisolone, which suggested that there may have been an underlying inflammatory or autoimmune condition. However, with a weakly positive P-ANCA (1:40) of uncertain significance and an otherwise normal autoimmune screen, CSF protein, negative CSF cultures and viral

panels all indicated that infective and autoimmune processes were less likely.

Based on initial MRI brain imaging and history, a working diagnosis of PRES was considered. However, with no risk factors for PRES, the unilateral nature of lesions on imaging and the lack of reversibility over time, PRES became less likely.

Serial MRI brain imaging showed the development of new lesions bilaterally of differing ages. Her case was reviewed in the neurology and neuroradiology multidisciplinary team meeting, where differential diagnoses, including MELAS, postictal changes, limbic encephalitis and infectious causes such as prion disease and herpes, were discussed. With no myoclonus or EEG features consistent with prion disease, this diagnosis was considered less likely. The migratory changes on MRI in the distribution of the temporal, parietal and occipital lobes with gyriform restricted diffusion in the context of a now prolonged relapsing remitting temporal nature of symptoms and examination findings were thought to be more in keeping with MELAS than other previously mentioned differentials.

Previous basal ganglia calcification on CT was noted. However, in this case, the basal ganglia and cerebellum (areas often affected in MELAS) were not acutely affected on repeat MRI imaging. Muscle biopsies were initially requested. However, the diagnosis was confirmed with serum genetic testing, which revealed an m.3243A>G MT-TL1 mutation consistent with MELAS. Family history is usually important in the diagnosis of hereditary conditions. However, the patient's parents and siblings are healthy and not known to have any significant medical history or features convincing of mitochondrial disease. No genetic testing has been performed on her family members to date. However, the patients' parents were not known to have any medical significant medical history other than epilepsy that was attributed to head injury. Hence, the investigatory process and serial imaging became more important in reaching the diagnosis.

TREATMENT

The patient was initially treated for meningoencephalitis with ceftriaxone and aciclovir. Further to this, she completed a 5-day course of intravenous methylprednisolone in light of a suspected autoimmune aetiology. Her seizures were initially controlled with an antiepileptic regimen of lacosamide (150 mg two times per day) and levetiracetam (500 mg two times per day). Clobazam (750 mcg once a day) was added with good effect for further seizure control on her second admission. The treatment options of MELAS are limited. Once the diagnosis of MELAS was established, the focus of treatment was supportive in nature with an emphasis on good seizure control and optimising quality of life. Our patient did not have children and was not planning to start a family.

OUTCOME AND FOLLOW-UP

The patient has not had any further hospital admissions, has remained clinically stable and has been followed up as an outpatient.

DISCUSSION

We have reported a case of late-onset MELAS caused by the m.3243A>G MT-TL1 mutation. This mutation has been shown to manifest clinically in multiple organs including the eyes, ears, brain, endocrine organs, myocardium, intestines, kidneys, muscles and nervous system.^{10 12} Organ involvement, clinical manifestation, the timing of disease onset and severity are determined by the proportion of mutated mitochondria

within cells and specific distribution of tissues affected.¹⁰ The fluctuating levels of abnormal mitochondrial DNA in specific cells and tissue distribution are accounted for by heteroplasmy and random segregation of mitochondrial DNA during cell division.^{4 12 13} Varying degrees of loss and gain of function in mitochondrial proteins in cells of different tissues may also play a role in disease severity.¹⁴ The most typical feature is stroke-like episodes. Other common features are headaches, cognitive decline, seizures, lactic acidosis, short stature, motor weakness and cortical vision loss.^{12 15} The m.3243A>G mutation can be associated with various clinical phenotypes ranging from early death to late-onset disease and individuals who are asymptomatic carriers.¹⁰ This mutation is known to cause other mitochondrial syndromes, including myoclonus epilepsy with ragged red fibres, maternally inherited diabetes and deafness and chronic progressive external ophthalmoplegia.¹⁶ Various overlaps between syndromes have also been observed.^{12 15 16} A significant proportion of patients with the m.3243A.G mutation have a phenotype that does not meet the accepted criteria for these classical mitochondrial syndromes. These can include asymptomatic carriers, non-syndromic multisystem subtypes, isolated sensorineural hearing loss, isolated myopathy, retinopathy or nephropathy.^{10 13 16-20} As a result, the disease course, diagnosis and prognosis can be challenging to navigate. After neurological disease, cardiac pathology has the most impact on prognosis in patients with MELAS.²¹ Multisystem involvement and specifically the significance of cardiac involvement can be overlooked in clinical practice.

Early diagnostic criteria suggest that MELAS should be suspected if there are stroke-like episodes before the age of 40 years, encephalopathy with seizures and dementia or both with lactic acidosis and/or ragged red fibres on muscle biopsy. The diagnosis is considered confirmed if there are also two of the following: normal early development, recurrent headaches or recurrent vomiting.²² A broader range of phenotypes are now recognised, including those with onset after the age of 40 years, such as in our case.^{23 24} In the UK, best practice guidelines recommend genetic testing of serum for mitochondrial diseases such as MELAS as a confirmatory test.⁴ However, diagnosis of MELAS caused by the 3243A-G mutation with blood samples has been shown to be difficult, as mutational load decreases over time in the serum and in some cases is undetectable.^{25 26} The amount of heteroplasmy in blood samples has been shown to decrease by ~1% per year and up to 29% over time with ageing.²⁵⁻²⁹ Hence, genetic testing of serum samples in older patients can be associated with higher false negative rates.^{28 29} It has been noted that mutant mitochondrial DNA remains at higher levels in non-dividing tissues such as skeletal muscle, urinary epithelium and hair.^{25 26} Hence, in cases where the suspicion of MELAS remains high despite indeterminate serum results, further genetic testing of such tissues should be considered, especially in older patients.^{4 25 26} Some authors suggest that urinary epithelial cell sampling replaces muscle biopsy as the gold standard as it is less invasive, and the associated mutational load has the highest correlation with disease severity.^{25 26}

Given the challenging nature of clinical diagnosis and the need for molecular diagnosis, many patients with stroke-like episodes are initially diagnosed with ischaemic stroke, infectious encephalitis, autoimmune encephalitis and vasculitis.³⁰ This can lead to a delay in the diagnosis. As the primary presenting feature is a stroke-like episode, invariably, patients with MELAS undergo neuroradiological imaging.³¹ The radiological features of MELAS syndrome can vary significantly. However, the most common findings are stroke-like lesions which do not conform

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to typical vascular territories.³¹ These lesions are typically seen in the occipital and parietal lobes. On MRI brain the lesions typically appear hyperintense on T2 weight and FLAIR sequences and can show restricted diffusion in the acute phase.³¹ Over time, these lesions can lead to atrophy and gliosis, as seen in this case. Other common findings on neurological imaging are generalised or focal brain atrophy and basal ganglia calcifications.³¹ Unfortunately, the neuroradiological features are variable, often non-specific and can be seen in many neurological conditions.³¹ Our patient had repeated MRI brain scans over a period of approximately 1 year. The aforementioned neuroradiological features were observed to be acute, chronic, bilateral and migratory with fluctuating course, which, with the clinical history, aided the diagnosis of a late-onset/atypical MELAS. Our case highlights the utility of serial MRI brain scans as a non-invasive, yet effective method of aiding the diagnosis of atypical or late-onset cases of MELAS or neurological mitochondrial disease.

There is no curative or definitive treatment for MELAS. As a result, management is centred around symptom control and maintaining quality of life.³² Management often involves a multidisciplinary team approach to address the various clinical manifestations of the disease.³² The systems affected and the degree of impairment will dictate the type of multidisciplinary team involvement. Input from respiratory, cardiac, ophthalmological, endocrine, and genetic subspecialties and nutritional, audiological and rehabilitative services are often required.³³ Many patients with MELAS suffer from epilepsy. There are no specific guidelines for seizure control in MELAS. Choice of antiepileptic regimen is usually selected based on the type of seizures, patient gender, age, comorbidities, potential side effects, drug interactions and patient preference.^{11 34 35} The first choice of monotherapy for seizures in MELAS is usually lamotrigine or levetiracetam.^{34 35} In our case, an antiepileptic drug regimen of lacosamide and levetiracetam was initially effective. Later, the addition of slow titration of low-dose clobazam for seizure control also proved effective. In female patients such as ours it is important to consider the teratogenicity of antiepileptic medication. Lamotrigine and levetiracetam are considered to have the least teratogenic effect.³⁶ Sodium valproate has previously been reported to cause worsening of symptoms and precipitate attacks of seizures in patients with MELAS.³⁷ The deleterious effects of sodium valproate in patients with MELAS are mediated through its inhibitory effects on the mitochondrial OXPHOS.³⁸ Hence, sodium valproate and other antiepileptic drugs with inhibitory effects on mitochondrial function like phenobarbital, carbamazepine, oxcarbazepine, phenytoin, ethosuximide, topiramate, gabapentin and vigabatrin should be avoided in patients with MELAS.³⁸

Mitochondrial disorders result in more oxidative stress and can be associated with reduced levels of certain micronutrients and amino acids (eg, creatine, folate and carnitine). Hence, supplementation with combinations of antioxidants and vitamins (including multivitamins, coenzyme Q10, creatinine, L-carnitine, folate and B complex vitamins) can be considered. However, their effectiveness has not been established.^{11 39}

Mitochondrial DNA is inherited in a matrilineal fashion. Hence, males affected with MELAS cannot pass on the condition.⁴⁰ For young female patients with MELAS family planning is particularly important. There are several reproductive options available for patients with MELAS, including prenatal diagnosis (PD), preimplantation genetic diagnosis (PGD) and mitochondrial replacement therapy (MRT).⁴⁰ PD via villous sampling or amniocentesis allows for the diagnosis of pathological mitochondrial DNA in the fetus. Similarly, PGD allows for the selection of

embryos with low variant load. However, for both PD and PGD, determining the significance of mitochondrial variant loads at such early stages requires specialist interpretation on a case-by-case basis.⁴⁰ MRT can prevent or reduce the transmission of mitochondrial disease by replacing variant mitochondrial DNA from a healthy donor.^{4 41}

Learning points

- ▶ Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) can present for the first time in older age. MELAS and mitochondrial disease should be kept in the differential diagnosis in patients with typical symptoms and radiological findings regardless of age.
- ▶ In atypical presentations of MELAS, serial MRI brain imaging can play an important role in the diagnosis.
- ▶ Serum m.3243A>G MT-TL1 variant load does not correlate with disease severity and is more prone to give false negative results, especially in older patients.

Contributors RA, EK and KE were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms, and critical revision for important intellectual content. RA, EK and KE gave final approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from next of kin.

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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