

CASE REPORT

Uncommon mutation in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)

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Accepted 10 February 2017

SUMMARY

A 26-year-old man presented to the emergency department with new-onset generalised tonic-clonic seizures. His clinical picture suggested either autoimmune or infectious encephalitis while his brain imaging raised the possibility of a stroke. A detailed developmental and childhood medical history added suspicion of a mitochondrial defect to the differential. After several molecular genetic analyses, an uncommon mitochondrial mutation was confirmed, unequivocally consistent with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome.

BACKGROUND

It is increasingly recognised that mitochondrial disorders are more common than previously thought. The advent of improved diagnostic techniques has led to a global increase in patients diagnosed with mitochondrial disorders. Gorman *et al*¹ recently reported that among inherited neurological disorders, adult mitochondrial diseases are among the most prevalent, with one in 4300 adults being affected in the UK.

Patients with mitochondrial disorders still suffer from delays in diagnoses. General physicians are often not familiar with these disorders. The diagnosis of mitochondrial diseases is challenging because of wide variations in phenotypic expression and variable penetrance.²

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is one of the more common mitochondrial disorders. Over 30 mitochondrial DNA gene mutations have been reported to be associated with this syndrome.³

CASE PRESENTATION

A 26-year-old man presented with two episodes of generalised tonic-clonic seizures within a 4-hour period. He had no history of seizures. His presentation was preceded by a 10-day history of slurred speech followed by 'inability to read properly'. He also had headaches, nausea and vomiting of 2 months' duration.

He had a normal development apart from being a late walker. However, he was 'always clumsy' and stuttered. At age of 5 years, he was noted to have reduced social skills. He developed a phobia for bandages and disabled people and an aversion to specific smells.

When he was 6 years old, he had an episode of bilateral ptosis which was diagnosed as myasthenia

gravis. His acetylcholine receptor antibodies were negative and a CT thorax was non-contributory. He was treated with steroids and pyridostigmine. His symptoms completely resolved in 3 weeks and never reoccurred. At 18 years of age, he was diagnosed with Asperger's syndrome.

There was no family history of epilepsy but his sister was born with a rare form of dwarfism. She had a 'big head, swollen tummy, small limbs, and a congenital heart and lung disease'. She died soon after birth. He has three other siblings, all alive and well. He had three maternal cousins with type I diabetes. The patient was a non-smoker and did not consume alcohol.

On clinical examination, he was vague and mildly encephalopathic. He was afebrile, there was no rash and he had no palpable organomegaly. Pathologic findings included right-left disorientation and a right homonymous hemianopia. There was full albeit, somewhat saccadic eye movements. Strength in all four limbs was normal and reflexes were brisk but symmetrical. There were bilateral withdrawal responses on planter stimulation. On gait assessment he appeared to veer to the left hand side.

INVESTIGATIONS

Complete blood counts, renal, liver and thyroid profiles were normal. C-reactive protein (CRP) was raised to 100 mg/L (<5). CT brain showed left occipital and parieto-occipital hypodensities with mild oedema and some contrast enhancement. Cerebellar atrophy was also noted. EEG was normal.

cerebrospinal fluid (CSF) analysis reported no white cells, protein of 0.36 g/L (2–4) and glucose of 3.4 mmol/L (2–4). Gram stain was negative and no pathogens were cultured. CSF PCR for viral panel including herpes simplex virus type 1 and 2 (HSV1/2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV 6), enteroviruses and parvovirus were all negative.

MRI brain showed high signal changes in the left temporal, parieto and occipital lobes predominantly affecting the cortex and the deep white matter. Cerebellar atrophy was again noted. No postcontrast enhancement. (figure 1). Diffusion-weighted images were not carried out at initial presentation but on follow-up scan 3 months later minor restriction diffusion was noted. The imaging appearance raised the possibility of encephalitis. Ischaemia was also suspected although the abnormalities included anterior cerebral, middle cerebral and posterior cerebral artery territories.



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To cite: David J, Okiro JO, Murphy K, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-218133

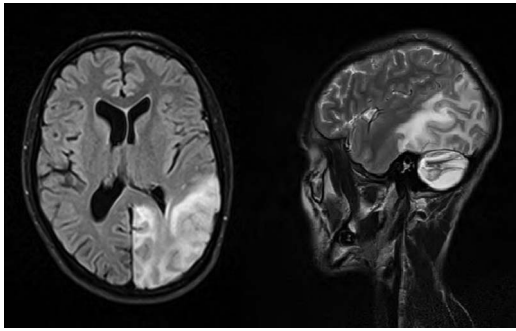


Figure 1 MRI on presentation. T2-fluid attenuation inversion recovery (FLAIR) sequence.

Normal laboratory investigations included antibodies against thyroid peroxidase (TPO), N-methyl-D-aspartate receptor (NMDA-R), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), gamma-Aminobutyric acid (GABA), glutamic acid decarboxylase (GAD), voltage-gated potassium channels-complex protein, antineuronal antibodies, serum immunoglobulins, protein electrophoresis, creatine kinase (CK), ACE, serology for lyme, HIV, and syphilis and vasculitic screen.

In the context of young-onset stroke and the unusual imaging appearance, a muscle biopsy was undertaken to rule out a mitochondrial disorder. This showed enhanced staining on Gomori trichrome, nicotinamide adenine dinucleotide hydrate (NADH) and cytochrome c oxidase (COX), suggesting an underlying mitochondrial dysfunction. However, on undertaking genetic analysis of the tissue, there were no large scale mitochondrial DNA rearrangements and the common mitochondrial DNA mutations were absent (m.3243A>G, m.8344A>G, m.8993T>G, m.8993T>C, polymerase gamma (POLG) mutation).

DIFFERENTIAL DIAGNOSIS

At the top of our differential diagnosis list was infectious encephalitis for which he was treated with acyclovir while we awaited the result of his CSF virology and culture. However, CSF viral panel was negative and no pathogens were detected. This excluded an infectious cause for his symptoms. Autoimmune encephalitis was also excluded with negative blood and CSF reports for a vast range of antibodies. Imaging suggested the possibility of stroke. However, there were atypical features: the stroke-like episode did not respect vascular territories, lack of vascular risk factors, the association with encephalopathy. This led us to consider the possibility of a mitochondrial disorder.

TREATMENT

For seizure control, the patient was started on lamotrigine. He was also initially treated with acyclovir. This had no effect on his encephalopathy and was subsequently discontinued following the negative CSF viral studies. As autoimmune aetiology was also suspected, he also had a trial of IVIG pending antibody results with no benefit. He maintained on antiepileptics and coenzyme Q 10 (based on the suspicion of a possible mitochondrial disorder).

OUTCOME AND FOLLOW-UP

Our patient improved and was discharged with minimal deficits. However, 3 months post discharge he was admitted with severe hiccups and vomiting refractory to antiemetics. General examination was normal but neurological examination revealed new-onset left-sided hemianopia and optic atrophy. No abnormality

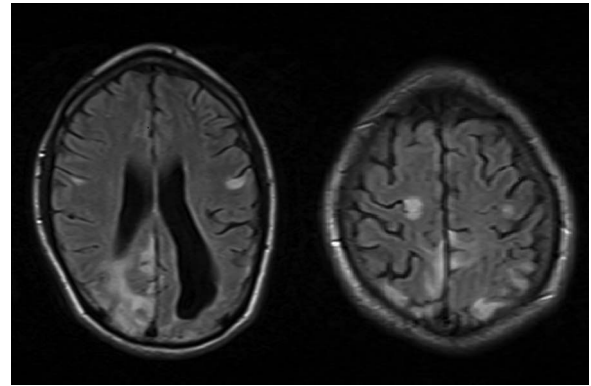


Figure 2 Repeat MR brain (FLAIR) during one of our patient's subsequent hospital admission's showing new areas of ischaemia not conforming to vascular territories.

was found on oesophago-gastro-duodenoscopy. Repeat MR images showed new areas of ischaemia, again not conforming to vascular territories (figure 2). Multiple subsequent admissions were characterised by encephalopathic changes and new changes on MRI. He subsequently presented with psychosis and suicidal ideations. He was admitted into the psychiatry unit following an attempted suicide. He was treated with antipsychotics.

Repeat lactate was noted to be raised to 3.60 mmol/L (0.5–2.2). As there was still a high index of suspicion for MELAS, further DNA samples were sent for entire mitochondrial genome sequencing. This revealed MT-ND5 (13513G>A) mutation at 59% level of heteroplasmy in his muscle. Unfortunately, we did not perform analysis on other tissues during initial investigation. Analysis was undertaken on his mother to determine whether his mutation was maternally inherited or had occurred de novo. It was discovered that his mother harbours the same mutation at a heteroplasmy level of 8% in her urine. No mutation was detected in her blood.

DISCUSSION

MELAS is a progressive multisystem disorder with onset of clinical manifestations usually in childhood or early adulthood. However, late onset is common.⁴ Children generally develop normally but may be short for their age.^{4 5} Early on, patients may begin to develop seizures, recurrent headaches, anorexia and recurrent vomiting caused by lactic acidosis.⁵ It is not uncommon for patients to have multiple stroke-like episodes which may be accompanied by signs of encephalopathy such as seizures.⁶ These episodes are often preceded by nausea, vomiting and headache. Ischaemic changes are often located in the parieto-occipital region and do not conform to vascular territories.⁷

Other clinical features may include cardiomyopathy, deafness, developmental delay or cognitive decline, diabetes mellitus, gastrointestinal disturbance (constipation and/or irritable bowel syndrome), migraine, progressive external ophthalmoplegia, retinopathy,³ exercise intolerance, muscle weakness⁵ and psychiatric manifestations.⁸

By far the most frequent mutation associated with MELAS is m.3243A>G of the MT-TL1 gene which accounts for about 80% of cases.⁷ The frequency of this mutation in the general population is about 1:15 000.⁹

The diagnostic criteria described by Hirano *et al*⁶ in 1992 proposed that the syndrome should be suspected by the 'three invariant criteria: (1) stroke-like episode before age 40 year; (2)

encephalopathy characterised by seizures, dementia or both and (3) lactic acidosis, ragged-red fibres (RRF) or both.’ Supportive criteria included normal development, recurrent headache and vomiting.⁶

Subsequent identification of the genetic causes of MELAS revealed striking variability in phenotypic expression.¹⁰ A 2013 study, which examined 129 MELAS patients with confirmed gene mutations suggested that diagnoses could be missed if it is only suspected in patients with the ‘classic syndrome.’³

Our patient presented with several features suggestive of MELAS including stroke-like episodes, seizures, encephalopathy, headaches and vomiting. Although initial lactate levels were normal, repeat testing demonstrated lactic acidosis.

While the most frequently reported phenotype associated with the m.13513G>A gene mutation identified in our patient is Leigh’s syndrome, the mutation is also reported in 10% of MELAS cases.^{11 12} According to Shanske *et al*,¹¹ MELAS patients carrying the 13513G>A gene mutation (as opposed to the more common A3243G mutation) tend to present at a relatively later age and frequently have no family history. Long before central nervous system involvement becomes apparent, deafness, Wolff–Parkinson–White Syndrome and ophthalmic manifestations, including optic atrophy, cataracts and ptosis can often be observed.^{13 14} The latter observation is interesting in the context of our patient who presented with bilateral ptosis at the age of 6 years which was misdiagnosed as myasthenia gravis. In fact, the widely varied clinical presentations in patients with MELAS often lead to initial misdiagnoses as myasthenia gravis, epilepsy, cerebral infarction, encephalitis, gastrointestinal or heart diseases, resulting in inappropriate therapies and delayed treatment opportunity.^{2 5 9 10 15}

We can only speculate as to the cause of death of our patient’s sister. It is likely that she inherited the same mutation making metabolic acidosis or cardiac arrhythmia possible explanations for her sudden demise at 4 hours old.

Notably, our patient presented early on with multiple behavioural issues, low mood and was also diagnosed with autism at the age of 18 years. He also had an episode of psychoses. The literature suggests a strong association between mitochondrial disease and psychiatric disorders in particular major depression, psychoses and anxiety.^{16 17} Fattal *et al*¹⁸ reported that psychiatric symptoms preceded the diagnosis of a mitochondrial disorder by an average of 7.5 years in their cohort of 36 patients. It has also been postulated that autism spectrum disorders may be an early clinical presentation of patients with mitochondrial disease.^{8 19} However, most studies have not been able to implicate any specific gene variant in association with psychiatric manifestations.¹⁶

Although the pathologic mitochondrial variant is present in all tissues in mitochondrial diseases, there is heteroplasmy (mutant load) where by various tissues have different levels of mutant mtDNA. Our patient had a heteroplasmy of 59% in his skeletal muscle sample. On literature review of cases of Leigh’s syndrome (LS), a mitochondrial disease which has also been associated with the MT-ND5 mutation m.13513G>A, we found a wide range of heteroplasmy levels reported in muscle tissues. Shanske *et al*¹¹ found that in nine patients with LS and the m.13513G>A mutation the degree of heteroplasmy ranged between 41% and 89%.²⁰ In a study by Sudo *et al*²¹ out of 84 patients with LS, the six who had the m.13513G>A mutation had their level between 42% and 70%. Chol *et al*²² found an average of 90% mutant load in three patients with LS while Kirby *et al*²³ reported a lower heteroplasmy of <50% in three patients. Van Karnebeek *et al* reported varying levels of

heteroplasmy in a family with the m.13513G>A mutation. Their index case, a 10-year-old female who was diagnosed with MELAS had a muscle heteroplasmy of 30%. She had a very similar clinical presentation to our patient albeit presenting at a younger age. Her younger sister, a 1-day-old, had 66% heteroplasmy in a postmortem liver tissue. She died of fatal acidosis. Their asymptomatic mother had 7% in her urine.¹⁴ Our patient’s asymptomatic mother harboured 8% heteroplasmy in her urine and also he had a sister who passed away hours after birth but at that time her tissues were not tested for mtDNA mutations. No correlation has been found between mutant load and clinical phenotypes in the m.13513G>A mutation.

No disease modifying treatment has been found for mitochondrial disease. However, a trial of coenzyme Q 10 in our patient was considered as it may be beneficial in individuals who have defects of coenzyme Q 10 biosynthesis.²³ While there are limited treatment options for patients with MELAS, making the correct diagnoses enables physicians to avoid unnecessary investigations, harmful inappropriate therapies, anticipate complications, treat secondary symptoms and most importantly, refer the patient for genetic counselling.

Our case highlights the fact that the diagnosis of MELAS (and mitochondrial diseases in general) is often delayed as patients may initially present with non-specific symptoms and signs that do not fulfil the ‘classic’ diagnostic constellation. In clinical practice, most suspected patients are only screened for common mutations. The diagnosis in our patient was confirmed only when the whole mitochondrial genome was analysed in the context of a negative initial screen for mitochondrial mutations.

Learning points

- ▶ Even with the major advances in diagnostics and increasing awareness of mitochondrial diseases, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) remains a challenge to diagnose and manage.
- ▶ MELAS, like other mitochondrial disorders, is characterised by diverse phenotypic expressions, some of which may be non-specific. This often leads to misdiagnoses.
- ▶ A stroke-like episode in a young patient in whom the changes do not respect vascular territories should raise suspicion for MELAS particularly in the context of headaches, vomiting, encephalopathy and/or seizures.
- ▶ Behavioural and psychiatric disorders including autism spectrum are common in mitochondrial disorders and can precede the other manifestations of the disease by several years.
- ▶ A negative family history does not exclude the diagnoses of a mitochondrial disorder. MELAS is caused by multiple pathogenic gene mutations which might not all be included in initial screening gene panels. In cases where there is a high index of suspicion whole mitochondrial genome sequencing should be considered.

Contributors JD contributed in discussion, learning point, references. JOO contributed in summary, background, case presentation, investigations, treatment, outcome and follow up, consent, gathering case data. ME contributed in discussion, background, learning point, differential diagnosis, overview. KM contributed in case title, summary, case presentation, investigations, differential diagnosis treatment, outcome and follow up, overview.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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