Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) in the older adult

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CASE HISTORY
A 70-year-old woman presented to the hospital’s general physicians with a 3-week exacerbation of pre-existing migrainous headache, speech and behavioural change. There was a 20-year history of slowly progressive bilateral sensorineural hearing loss, and a 10-year history of diabetes mellitus. On examination, there was marked receptive and expressive dysphasia, but no other abnormalities. She was afebrile. Her leucocyte count and inflammatory markers were normal. Uncontrasted CT scan of the brain showed bilateral temporal lobe low attenuation, more on the right side, with bilateral basal ganglia calcification (figure 1A, B). The lesions could not be characterised further as she could not tolerate MR imaging. Cerebrospinal fluid (CSF) examination was acellular, with normal protein and glucose. CSF lactate was elevated at 5.4 mmol/L (plasma lactate 2.8 mmol/L). Molecular genetic analysis identified an adenine to guanine mitochondrial DNA point mutation at nucleotide 3243 coding for the transfer RNA (Leu), consistent with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. The m.3243A>G mutant load in blood was 4%; in urine it was 23%. A detailed family history identified no other definite MELAS cases, though her mother, who died from stroke aged 64 years, may well have been affected, and one of her two daughters suffered from migraine.

DISCUSSION
Mitochondrial disorders comprise a heterogeneous group of disorders linked to mutations in mitochondrial DNA or nuclear mitochondrial maintenance genes. The most common disease-causing mtDNA mutation in MELAS is m.3243A>G, found in 80% of cases.1 The prevalence of m.3243A>G mutation was 10.2 per 100 000 in the adult Finnish population, but based on the assumption that all first-degree maternal relatives of a verified mutation carrier also harbour this mutation, prevalence increased to more than 16 per 100 000.2 Recent population-based studies suggest

She presented again 3 years later with a 2-week history of continuous migrainous headache, and worsening speech. She was afebrile. On examination, there was profound receptive and expressive dysphasia and a right homonymous hemianopia. Repeat CT brain suggested more extensive right temporal hypodensity and basal ganglia calcification (figure 1C, D). CSF examination was acellular with normal protein and glucose. CSF lactate was elevated at 5.4 mmol/L (plasma lactate 2.8 mmol/L). Molecular genetic analysis identified an adenine to guanine mitochondrial DNA point mutation at nucleotide 3243 coding for the transfer RNA gene (Leu), consistent with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. The m.3243A>G mutant load in blood was 4%; in urine it was 23%. A detailed family history identified no other definite MELAS cases, though her mother, who died from stroke aged 64 years, may well have been affected, and one of her two daughters suffered from migraine.
that the carrier rate of m.3243A>G mtDNA mutation is 1 in 400, and potentially all of these will develop hearing impairment. Unlike the common monosystemic mtDNA disease, Leber’s hereditary optic neuropathy, where haplotype analysis shows a small number of founder mutations, m.3243A>G has arisen many times independently, consistent with its detrimental effects. Our patient had a substantial load of the common m.3243A>g mutant in urinary epithelial cells (23%), with a lower level in blood (4%). In this as in many other mtDNA diseases there is a rough relationship between mutant load and symptoms. However, the load of mutant mtDNA often gives a poor reflection of the load in muscle and other tissues, because it falls with age. The mutant load in urinary epithelial cells usually lies between that in blood and muscle, and can be readily assayed by collecting urine samples. The level we documented lies within the range of mutant load in urinary epithelial cells from symptomatic individuals; however the precise value is a poor predictor because there are no longitudinal published data. Given the clinical presentation, we think that m.3243A>G mutation caused her symptoms.

The age at onset of symptoms in MELAS is highly variable but typically before the fifth decade.
are several published cases of MELAS diagnosed in patients older than 50 years (table 1). Our patient appears unusual in that her age at initial presentation to acute services was 70 years. An 80-year-old patient was mentioned in the radiographic findings of eight cases of MELAS, and the UK MRC Mitochondrial Disease Patient Cohort included a 74-year-old patient. Disease Patient Cohort. There are several published cases of MELAS diagnosed in patients older than 50 years (table 1). Our patient appears unusual in that her age at initial presentation to acute services was 70 years. An 80-year-old patient was mentioned in the radiographic findings of eight cases of MELAS, and the UK MRC Mitochondrial Disease Patient Cohort included a 74-year-old patient without the age at first presentation being specified.

As in this case, most patients presenting with MELAS have pre-existing diabetes mellitus, deafness or migraines due to m.3243A>G.

It is uncertain why neurological dysfunction is delayed in some patients with MELAS, but it may be that these patients’ brains have a lower mitochondrial mutation load. The pathophysiology of stroke-like episodes, a hallmark of this disorder, is unknown but may represent ‘metabolic strokes’ due to deficiency of adenosine triphosphatase, limited oxidative glucose metabolism, increased lactic acid production or mitochondrial angiopathy. The lesions do not necessarily conform to arterial territories nor do they resemble an ordinary small-vessel disease. Epilepsy, often status epilepticus, is strongly associated with stroke-like episodes, but the exact mechanism is not fully understood. Inhibition of mitochondrial oxidative phosphorylation leading to ATP deficiency may lead to increased neuronal excitability and epileptogenesis via several mechanisms. Migraine or migraine-like headaches in these patients may also reflect the stroke-like episodes. Pedigrees of patients with classical MELAS syndrome identify many members whose only manifestations are migrainous headaches.

The encephalopathy in association with temporal lobe changes on CT in this case was initially erroneously attributed to herpes simplex virus encephalitis, a specific issue previously noted in some case reports. Basal ganglia calcification, though not

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>Sex</th>
<th>Clinical features</th>
<th>Neuroimaging findings</th>
<th>Mutation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>M</td>
<td>Headaches, seizures, psychiatric symptoms, diabetes, deafness, normal serum lactate</td>
<td>Right and left temporal lesions</td>
<td>m.3243A&gt;G</td>
<td>Kisanuki et al 2006</td>
</tr>
<tr>
<td>53</td>
<td>F</td>
<td>Seizures, stroke-like episodes, lactic acidosis, ragged-red fibres</td>
<td>Focal brain lesions (no details given) but no basal ganglia calcification</td>
<td>m.3243A&gt;G</td>
<td>Ciuffaloni et al 1992</td>
</tr>
<tr>
<td>55</td>
<td>F</td>
<td>Encephalopathy, seizures, stroke-like episodes, headache, deafness, cognitive decline</td>
<td>Bilateral temporoparieto-occipital region</td>
<td>m.3243A&gt;G</td>
<td>Sharfstein et al 1999</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>Irritability, aphasia, ataxic gait, hearing deficit, convulsive status epilepticus, elevated serum and CSF lactate, ragged-red fibres</td>
<td>Left temporal lobe</td>
<td>Not specified</td>
<td>Vrettou et al 2013</td>
</tr>
<tr>
<td>59</td>
<td>M</td>
<td>Stroke-like episodes, encephalopathy, seizures, headache, exercise intolerance, fatigue, ragged-red fibres, elevated CSF lactate</td>
<td>Left temporal and later right temporoparieto-occipital lesion</td>
<td>m.3243A&gt;G</td>
<td>Kimata et al 1998</td>
</tr>
<tr>
<td>66</td>
<td>F</td>
<td>Encephalopathy, proximal myopathy, type 2 diabetes mellitus, sensorineural deafness, paroxysmal atrial fibrillation, supraventricular tachycardia, ischaemic cardiomyopathy, non-specific chronic elevation of alanine transferase</td>
<td>Left periventricular lacunar infarction, prominent calcification of pineal gland and basal ganglia</td>
<td>m.3243A&gt;G</td>
<td>Jones et al 2004</td>
</tr>
<tr>
<td>52</td>
<td>M</td>
<td>Stroke-like episodes, lactic acidosis, deafness, seizures, ragged-red fibres</td>
<td>High signal bilaterally in the occipital regions and right tempo-parietal region</td>
<td>m.13513G&gt;A</td>
<td>Hanna et al 1998</td>
</tr>
<tr>
<td>61</td>
<td>F</td>
<td>Stroke-like episodes, ragged-red fibres</td>
<td>NA</td>
<td>m.13513G&gt;A</td>
<td>Shanske et al 2008</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Episodic brain stem dysfunction, headache, severe lactic acidosis</td>
<td>Left cerebellar hemisphere, medulla, pons, and cerebral peduncles</td>
<td>m.13635C&gt;A missense mutation in (ND5) gene</td>
<td>Vanniarajan et al 2006</td>
</tr>
<tr>
<td>54, 59, 64, 69</td>
<td>Not stated</td>
<td>MELAS</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Minamoto et al 1996</td>
</tr>
<tr>
<td>52</td>
<td>M</td>
<td>Stroke-like episodes, seizures, complex partial status epilepticus, raised serum and CSF lactate, ragged-red fibres</td>
<td>Hypodense lesion in right parietal lobe posteriorly</td>
<td>Mutations not found in 3243, 8344, 3271, and 9957 as well as in the entire tRNA leucine (UUR) gene</td>
<td>Leff et al 1998</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes.
an uncommon incidental finding in neuroimaging, should lead clinicians to consider an underlying mitochondrial disorder in the presence of other appropriate clinical features (such as raised CSF lactate).22

The distinction is important because seizures are common in MELAS and meningoencephalitis and are typically treated with anticonvulsants. Sodium valproate is a commonly used anticonvulsant and is contraindicated in mitochondrial disorders because valproic acid inhibits oxidative phosphorylation in hepatic and cerebral mitochondria, impairing complex I of the respiratory chain.23 This leads to exacerbation of symptoms, especially seizures.24

In the largest cohort study of patients with biochemically or genetically confirmed mitochondrial disease associated with the m.3243A>G mutation, only half of patients exhibited a recognised classical phenotype, only 10% met the diagnostic criteria for MELAS and more than a quarter did not conform to any of the ‘classical’ syndromes. The authors suggested that, even without the classical phenotype, screening of patients with three or more of the following clinical features (and no other causative unifying diagnosis) will help to identify more cases: cardiomyopathy, deafness, developmental delay or cognitive decline, diabetes mellitus, epilepsy, gastrointestinal disturbance (constipation or irritable bowel syndrome), migraine, progressive external ophthalmoplegia and retinopathy. Others have warned of the need for a higher index of suspicion in the phenotype of the ‘thin, deaf, diabetic’.25 The natural history of the disease varies considerably. Generally, there is progressive cognitive and neurological impairment, worsening of MRI abnormalities and progressively increased CSF lactate levels over time.26 The annual mortality rate is 5–8%, but juvenile-onset cases can rapidly decline and have earlier mortality (median age from onset to death 6.4 years in juvenile compared with 10.2 years in adult onset).22

At present, there is no proven therapy to prevent, attenuate or treat established MELAS-related clinical episodes. Coenzyme Q10 (ubiquinone), L-arginine, dichloroacetate, creatine monohydrate, lipic acid, riboflavin, nicotinamide, sodium succinate, menadione (vitamin K-3), phylloquinone (vitamin K-1), ascorbate, exercise training and ketogenic diets have all been tried. Given the likely role of epilepsy in the pathogenesis, it is logical to treat seizures aggressively, even proactively. Despite the Cochrane review conclusion that there was “no clear evidence supporting the use of any intervention in mitochondrial disorders”, many centres now use L-arginine.

Once the diagnosis is established, the patient and family need genetic counselling. Mitochondrial disorders present a unique set of challenges. It is necessary to determine the most likely mode(s) of inheritance, explain difficult genetic concepts, provide psychological support and to look out for ‘soft signs’ in family members, such as migraines, seizures, mental retardation, gastrointestinal complaints, chronic fatigue and weakness.30 The clinician also needs to discuss the natural history of the disease, its untreatable nature and various complications (eg, cardiomyopathy, nephrotic syndrome, deafness, diabetes, gastrointestinal difficulties).

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REFERENCES


