

## An Unusual Cause of Stroke-Like Symptoms in an Elderly Patient

A 60-year-old man with a history of chronic kidney disease, type 2 diabetes mellitus and hearing impairment presented with short-term memory loss and slurring of speech. There was no neck stiffness, limb weakness, photophobia or sensory disturbances. He was afebrile and his vital signs were stable. No seizures were reported throughout the disease duration. On examination, he was found to have both expressive and receptive dysphasia, visual agnosia and apraxia.

Non-contrast-enhanced computed tomography (CT) of the brain (Fig. 1) revealed an ill-defined area of hypodensity in the left occipital and temporal lobes that traversed the left middle cerebral artery (MCA) and posterior cerebral artery (PCA). Magnetic resonance imaging (MRI) of the brain (Fig. 2) was performed to further characterise the lesion. Time-of-flight (TOF) magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) were also performed.

Cerebrospinal fluid (CSF) analysis revealed no evidence of pleocytosis. CSF lactate was also absent. Panel test for common causative agents of community-acquired encephalitis was negative. Serum lactate was, however, mildly elevated at 2.6 mmol/L (normal range, 0.7-2.1 mmol/L). Electroencephalography revealed waveform abnormalities in the left posterior occipital, parietal and temporal lobes.

What is the most likely diagnosis?

- A. Viral encephalitis
- B. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
- C. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- D. Acute left PCA infarct
- E. Status epilepticus

### Discussion

MELAS is one of the most common mitochondrial disorders with marked phenotypic and genetic heterogeneity. It is characterised by stroke-like episodes, encephalopathy with epileptic seizures, dementia, lactic acidosis and ragged red fibres in skeletal muscle.<sup>1</sup> Diabetes and sensorineural hearing loss were the most common systemic manifestations seen in our patient.<sup>1</sup> To date, 30 pathogenic variants of mitochondrial deoxyribonucleic acid (mtDNA) that cause MELAS have been reported.<sup>1</sup> The pathogenic *m.3243A>G* mutation located in the tRNA<sup>Leu(UUR)</sup> of the mitochondrial genome accounts for >80% of MELAS cases.<sup>1</sup> This point mutation disrupts mitochondrial protein translation and impairs respiratory chain function, leading to impairment of neuronal oxidative energy production and neuronal death.<sup>1</sup>

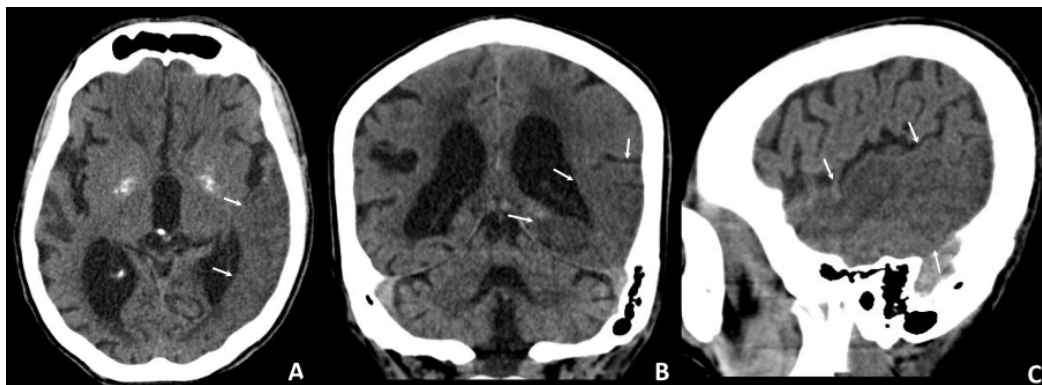


Fig. 1. Computed tomography of the brain. (A) Axial, (B) coronal and (C) sagittal images showed ill-defined hypodensities with loss of normal grey-white matter differentiation in the left occipital and temporal lobes (white arrows). This was associated with adjacent ventricular and cerebral sulcal effacement.

Answer: B

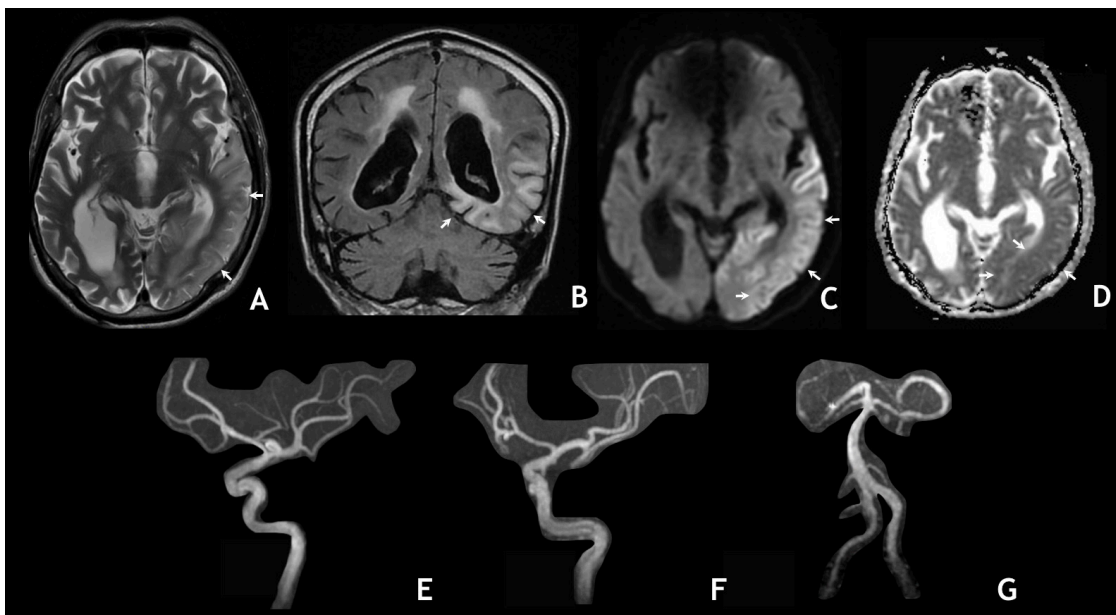


Fig. 2. Magnetic resonance images of the brain. (A and B) Axial T2-weighted and coronal fluid attenuated inversion recovery images, respectively, confirmed the presence of cortical and subcortical white matter hyperintensities (white arrows) in the left occipital and temporal lobes that encompassed the left middle cerebral artery and posterior cerebral artery. (C and D) Axial diffusion-weighted images showed gyriform pattern of increased signal (white arrows) with corresponding low signal on apparent diffusion coefficient map which is in keeping with diffusion restriction. (E to G) Three-dimensional time-of-flight images of the right internal carotid artery, left internal carotid artery and vertebrobasilar artery, respectively, demonstrate normal flow signal.

On CT imaging studies, cortical areas of decreased attenuation are seen and they often involve the parieto-occipital and parieto-temporal regions. These “metabolic strokes” often transcend the vascular boundaries and could involve the left MCA and PCA which was the case in our patient. Angiographic studies will show patent vessels in the affected area which is a crucial feature that differentiates MELAS from ischaemic stroke.

On MRI, these stroke-like lesions typically show T2 hyperintense signal with predominant involvement of the cortex.<sup>2</sup> Subsequent imaging studies will show a reduction of these lesions. They may also show complete resolution or develop into an area of atrophy with cortical signal alteration.<sup>3</sup> Variable diffusion characteristics of stroke-like lesions of MELAS have been described in the literature<sup>3</sup> and are possibly related to the combination of cytotoxic and vasogenic oedema. Diffuse cerebellar atrophy and leukoencephalopathy are rarely seen. The detection of a lactate peak that resonates at 1.3 ppm on proton spectroscopy may aid in the diagnosis of an underlying mitochondrial disease. However, it is not useful in the acute setting since a lactate peak may also be seen in ischaemic stroke.<sup>2</sup>

Our case was atypical for MELAS given the late onset of this condition in our patient. Over 90% of patients present with MELAS before the age of 40.<sup>1</sup> A review of the literature revealed only 5 cases of adult-onset MELAS with *m.3243A>G* mutation over the age of 40.<sup>1</sup> The reasons for the late onset of neurological symptoms in certain

patients with MELAS are unclear. Some researchers have suggested a correlation between mtDNA variant load and disease burden.<sup>1</sup> MELAS is characterised by a phenomenon known as heteroplasmy in which a high variability of the mitochondrial mutation load can be found in different individuals from the same family, various organs of an individual or different cells in the same organ.<sup>1</sup> Our patient presented with multiple vascular risk factors which made it difficult to exclude the possibility of an arterial ischaemic stroke. Lesions that cross vascular boundaries—which were seen in our patient—are not typical for an ischaemic stroke.

Viral encephalitis is an important consideration since it can present with imaging findings that are similar to those seen in MELAS. However, our patient was not clinically septic and remained afebrile throughout the disease duration. Panel test for common causative agents of community-acquired meningoencephalitis also did not yield a positive result. These findings rendered the diagnosis of viral encephalitis as highly unlikely. Herpes simplex virus encephalitis is the most common cause of fatal sporadic viral encephalitis. It is characterised by signal alteration in the cortical and subcortical regions of the bilateral fronto-temporal lobes, cingulate gyri and insula. In our patient, the absence of such involvement made herpes an unlikely diagnosis.

CADASIL should be considered in patients with stroke-like symptoms and cognitive deficits, especially in young and middle-aged adults. Subcortical lacunar infarcts and leukoencephalopathy are characteristic imaging features

of CADASIL and involve penetrating cerebral and leptomeningeal vessels. Due to the absence of these imaging features, late disease onset and absence of a positive family history, CADASIL was excluded in our patient.

Arterial ischaemic stroke is the most common aetiology for the acute onset of neurological deficits in elderly patients with cardiovascular risk factors. An acute ischaemic stroke is often seen on CT scans as a wedge-shaped, ill-defined hypodensity confined within vascular boundaries unlike the lesion seen in our patient which traversed the left MCA and PCA territories. The gyriform pattern of diffusion restriction seen in our patient was also unusual for an arterial infarct. An arterial infarct often demonstrates a wedge-shaped area of restricted diffusion on MRI. Cerebral infarcts secondary to venous thrombosis may cross arterial territories but they are often haemorrhagic, which was not the case in our patient.

Additionally, TOF MRA and MRV did not show arterial occlusion or dural venous sinus thrombosis.

Status epilepticus may result in transient MRI signal changes and swelling that are found predominantly in cortical grey matter, subcortical white matter and/or hippocampus. In our patient, the absence of seizures exclude the diagnosis of seizure-related changes observed in the MRI findings.

MELAS requires multidisciplinary management that supports mitochondrial function to prevent acute neurological deterioration and progressive neurodegeneration.<sup>1</sup> Genetic counselling also plays a crucial role in the management of patients with MELAS.<sup>4</sup> The clinical course is often unpredictable and is fraught with acute episodes and gradual deterioration.<sup>4</sup> In Figure 3, we described the diagnostic

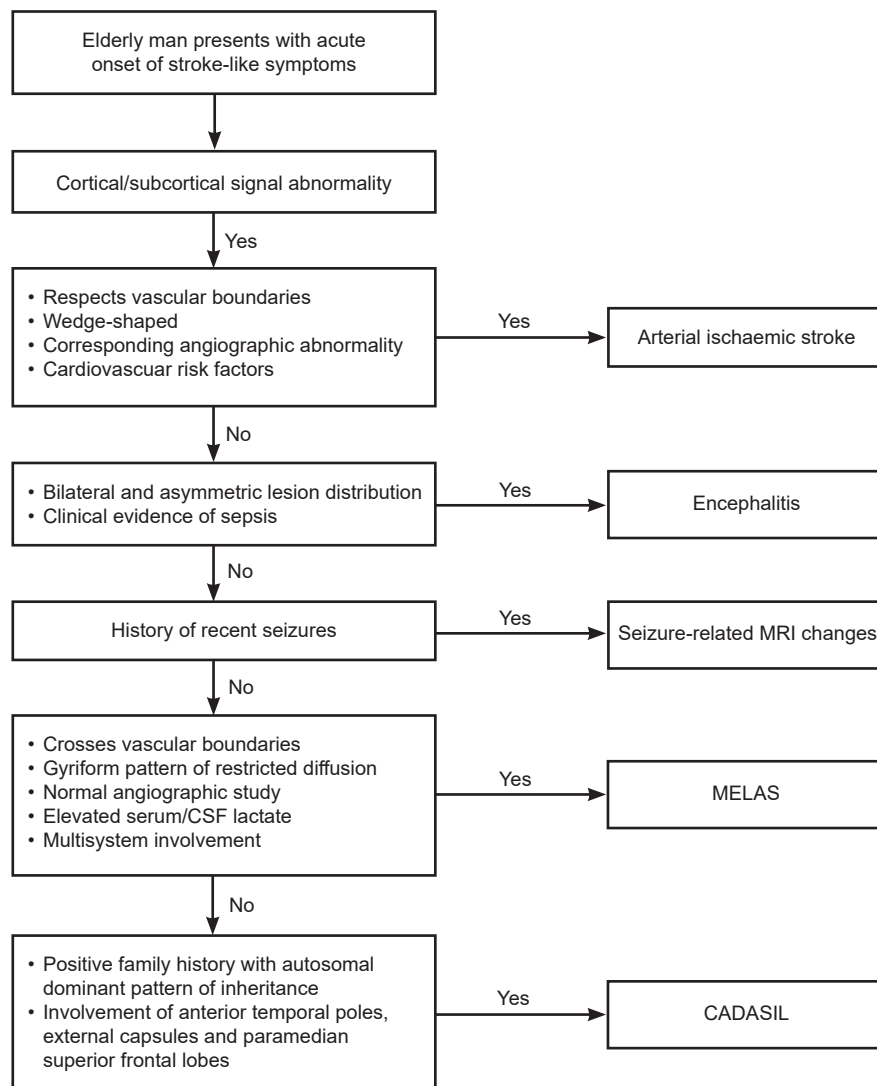


Fig. 3. Flow chart to diagnose cortical/subcortical lesion in an elderly patient presenting with stroke-like symptoms. CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF: Cerebrospinal fluid; MELAS: Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MRI: Magnetic resonance imaging

approach to identify the cortical/subcortical lesion in our patient who presented with stroke-like symptoms.

### Conclusion

Though rare, MELAS should be one of the differential diagnoses for cortical/subcortical lesions in elderly patients who present with stroke-like symptoms. This is especially true when atypical imaging features such as crossing of vascular territories and gyriform pattern of restricted diffusion are present. It is not always possible to make a definitive diagnosis based only on radiograph findings. A correlation with clinical information and a thorough exploration of family history must also be attempted.

### REFERENCES

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