

# Late-onset Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes Presenting With Auditory Agnosia

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**Introduction:** Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multisystemic mitochondrial disorder that usually presents in childhood. Patients can have a wide array of neurological symptoms when presenting with stroke-like episodes, and imaging characteristics during the episodes can overlap with different neurological disorders.

**Case Report:** A 61-year-old woman presented with communication difficulties consistent with auditory agnosia and was found to have bitemporal abnormalities on imaging that first raised the concern for herpes simplex virus encephalitis. Further work-up, in conjunction with the patient's past medical and family history, suggested a mitochondrial disorder. Mitochondrial full genome analysis revealed m.3243A > G variant in the *MT-TL1* gene, with 6% heteroplasmy in blood leading to a diagnosis of MELAS.

**Conclusions:** MELAS is a disorder with clinical variability. Neuro-imaging studies during stroke-like episodes in MELAS can provide significant clues to the underlying disorder. Although patients typically present in childhood, the first stroke-like episode can occur later in life in some patients, potentially related to a lower heteroplasmy level.

**Key Words:** MELAS, stroke, auditory agnosia

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## CASE REPORT

A 61-year-old right-handed woman with a history of severe bilateral sensorineural hearing loss presented with cognitive and communication difficulties. Three weeks before presentation, she developed intermittent fevers, nausea, and vomiting. While these constitutional symptoms improved within 1 week, her family reported that she appeared to be having auditory hallucinations. She was making paraphasic errors and had trouble with verbal communication to the point where she was solely using handwritten notes and text-messaging for communicating.

On presentation, the patient was afebrile and hemodynamically stable. All examination instructions and questions were delivered through written modality. Bedside evaluation by a speech-language pathologist revealed mild difficulty with verbal expression, reading and writing, and profoundly impaired auditory comprehension. She appeared to accurately respond to nonverbal sounds (clapping) presented outside of her visual field at varying loudness levels. Her communication difficulty seemed most consistent with auditory agnosia with mild evidence of aphasia. The patient's neurological examination, limited by her difficulty with communication, was otherwise normal.

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Her past medical history was notable for severe sensorineural hearing loss since her 50s, requiring bilateral hearing aids. She was chronically underweight, body mass index of 13 with average height (163 cm). She had migraine headaches requiring propranolol for headache prevention. She had a remote history of tobacco use, but no alcohol or substance abuse. Three of her 4 children had hearing loss requiring hearing aids in their 20s to 30s, one who passed away from a stroke in his 30s. Her other child had drug-resistant epilepsy.

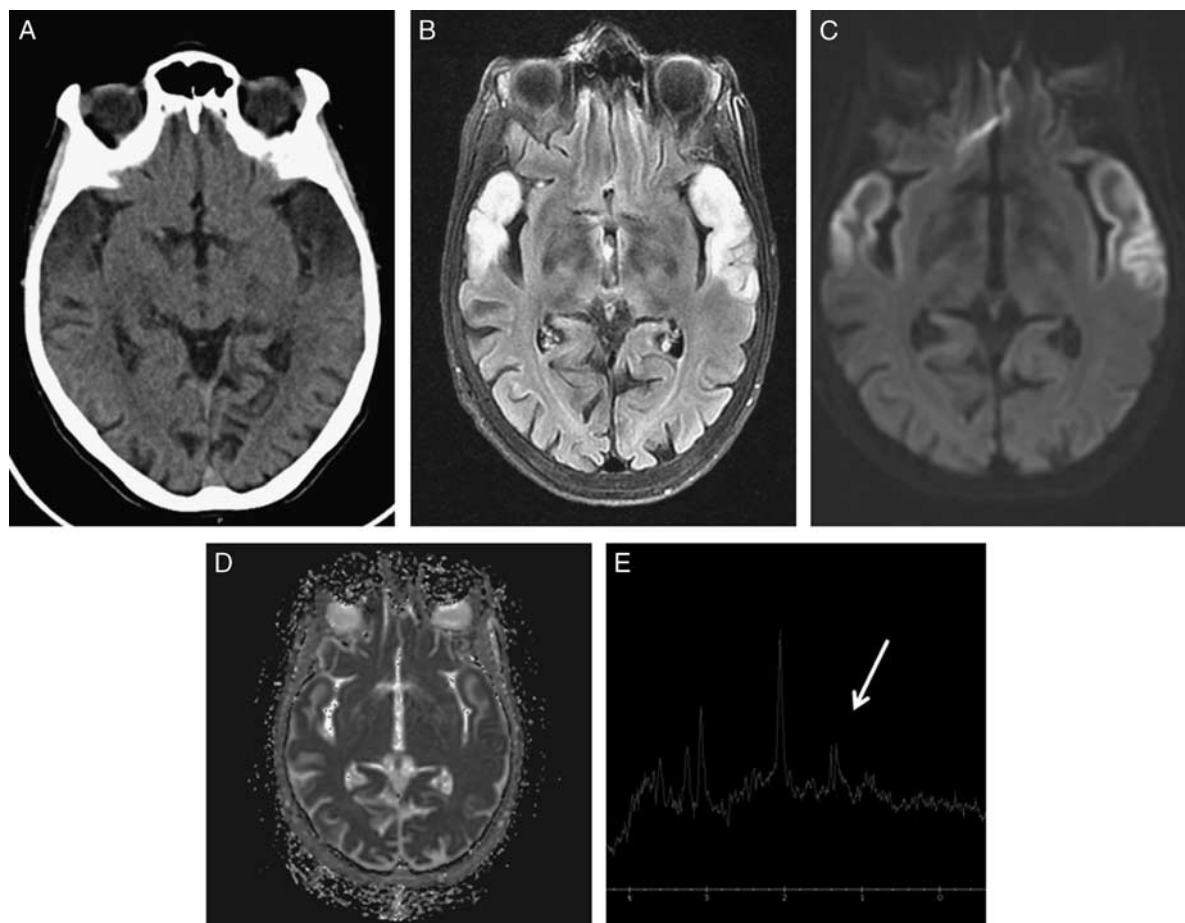
Brain computed tomography showed low attenuation changes in bilateral temporal lobes (Fig. 1A). Brain magnetic resonance imaging (MRI) (Figs. 1B–D) showed increased T2 and fluid-attenuated inversion recovery (FLAIR) signal abnormality in the lateral temporal lobes symmetrically, with sparing of the mesial temporal lobes, insula, and basal ganglia without gadolinium enhancement. There was restricted diffusion involving the cortex, with sparing of the white matter of the lateral temporal lobes and increased apparent diffusion coefficient (ADC) signal. Given high morbidity and mortality associated with herpes simplex virus encephalitis (HSE), treatment with IV acyclovir was initiated empirically. Initial cerebrospinal fluid (CSF) analysis revealed the following: total nucleated cells, 2 cells/mL (normal: 0 to 5); 2 erythrocytes cells/mL; protein, 68 mg/dL; glucose, 55 mg/dL. Bacterial and viral testing including herpes simplex virus polymerase chain reaction was negative and acyclovir was therefore discontinued. Despite the lack of clinical seizures, video electroencephalogram revealed frequent bilateral independent periodic discharges arising from the left and right temporal regions, as well as subclinical electrographic right temporal onset seizures. Levetiracetam was started, with resolution of electrographic seizures.

Given the patient's personal and family history of hearing loss, migraine, and seizures, a mitochondrial etiology was considered. Serum lactate and pyruvic acid levels were mildly elevated at 3.0 (normal: 0.6 to 2.3), and 0.21 mmol/L (normal: 0.08 to 0.16), respectively. CSF lactate was 4.2 mmol/L; CSF pyruvate, 0.2 mmol/L (normal: 0.06 to 0.19 mmol/L). MRI spectroscopy (MRS) revealed a prominent doublet lactate peak characteristic of mitochondrial cytopathies (Fig. 1E). A mitochondrial full genome analysis revealed m.3243A > G variant in the *MT-TL1* gene, a known pathologic mutation that causes mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), with 6% heteroplasmy in the blood. Further testing was considered to determine if the level of heteroplasmy is higher in other tissues (skeletal muscle) but the patient and family deferred further investigations as it was unlikely to change management. The clinical phenotype was consistent with MELAS. The patient was started on L-carnitine, L-arginine, and co-enzyme Q10. Evaluation for other systemic complications of MELAS was negative. The patient did gradually improve before dismissal from the hospital.

## DISCUSSION

MELAS is a multiorgan mitochondrial disorder with substantial clinical variability. This patient's late age of onset, auditory agnosia at presentation, initial imaging findings mimicking bitemporal HSE, and the low level of heteroplasmy in the blood are instructive findings.

The typical age of onset of MELAS is in childhood (ages 2 to 10 y), with fewer cases with delayed onset between ages 10 and 40 years, and only 1% to 6% presenting after age 40.<sup>1,2</sup>



**FIGURE 1.** Neuroimaging: noncontrast computed tomography of the head (A) shows extensive hypodense changes within the temporal lobes corresponding with extensive T2 signal abnormality on T2 fluid-attenuated inversion recovery imaging (B). Associated restricted diffusion (C) involving the cortex with relative sparing of the white matter of the lateral temporal lobes was also noted with increased apparent coefficient diffusion signal (D). Single-voxel proton magnetic resonance spectroscopy (E) of the left basal ganglia demonstrates a lactate doublet (arrow) at 1.3 ppm.

Multisystemic dysfunctions of MELAS include myoclonus, cerebellar ataxia, optic atrophy, oculomotor abnormalities, pigmentary retinopathy, nephropathy, gastrointestinal changes, cardiomyopathy, cardiac conduction abnormalities, diabetes mellitus and other endocrine disturbances, muscle weakness, neuropathy, and psychiatric manifestations.<sup>3,4</sup> Stroke-like episodes in MELAS are characteristically associated with focal manifestations such as hemiparesis, hemianopia or cortical blindness.<sup>3,4</sup> Seizures can also be a manifestation of stroke-like episode in MELAS.<sup>3</sup>

Our patient's first stroke-like episode was of acute auditory agnosia at age 61. While peripheral sensorineural hearing loss is common in MELAS, rare cases of auditory agnosia in MELAS due to bitemporal lesions have been reported.<sup>5</sup> Bilateral cortical lesions of the primary auditory cortex (Heschl gyrus, Brodmann areas 41 and 42) can lead to profound hearing deficits, even cortical deafness.<sup>6</sup>

Patients can have unilateral or bilateral lesions, which typically do not conform to vascular territories. Posterior cerebrum, including occipital and parietal regions, is most frequently involved, though lesions can also occur in the temporal lobe and rarely, the cerebellum.<sup>3,4,7</sup> With stroke-like episodes in MELAS, restricted diffusion can be seen on diffusion-weighted

MRI while the ADC can be decreased, increased, or normal.<sup>8</sup> Therefore, ADC imaging can be helpful when differentiating between acute ischemic strokes and stroke-like episodes in MELAS as the cytotoxic edema from acute ischemic strokes leads to reduced ADC values.<sup>8</sup> MRS identified a lactate peak in our patient. MRS is an imaging modality which provides chemical information.<sup>9</sup> Lactate elevation is a prominent MRS signal abnormality in mitochondrial disorders, but can also be seen in other neurological diseases, such as strokes or seizures.<sup>9</sup>

The MRI characteristics at presentation mimicked some of the changes that can be seen in HSE. HSE is the most common cause of infective focal encephalitis worldwide and is frequently associated with temporal lobe abnormalities on imaging, typically unilateral or bilateral asymmetric.<sup>10</sup> Neuroimaging features against the diagnosis of HSE included symmetric temporal involvement with sparing of mesial temporal lobes and insula. Given overlap in imaging characteristics between HSE and MELAS, HSE has been considered in other cases of MELAS.<sup>11</sup>

Our patient had a pathogenic mutation in the *MT-TL1* gene m.3243A > G, the most common mutation found in MELAS, accounting for 80% of cases.<sup>2</sup> This mutation affects the functional level of tRNA that is normally involved in mitochondrial protein synthesis.<sup>3</sup> Of particular interest in our patient was the

6% heteroplasmy found in the blood. Because heteroplasmy in disorders of mitochondrial DNA can result in varying tissue distribution of mutated mitochondrial DNA, the level of pathogenic variant may be low or undetectable from leukocytes.<sup>12</sup> Interestingly, prior studies have found a correlation between increasing age of presentation and decrease in heteroplasmy, which is especially relevant in this patient.<sup>13</sup> For less invasive tissue sampling, saliva or urine could be tested for heteroplasmy level.<sup>13</sup>

This case highlights the significant clinical variability that can be seen among patients with mitochondrial disorders such as MELAS. Given our patient's atypical age at presentation and symptoms, a thorough history-taking and diagnostic evaluation proved instrumental in leading to a final diagnosis. In this particular case, mitochondrial disorder was clinically suspected with revelation of a positive maternal family history, prior sensorineural hearing loss, seizure, bilaterally symmetrical temporal lobe lesions, and new onset auditory agnosia.

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