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Case Report

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome mimicking herpes simplex encephalitis: A case report ☆

Wen-Gao Zeng, MD[a,1], *Wan-Min Liao, PhD*[b,1], *Jue Hu, PhD*[a,*], *Su-Fen Chen, MD*[a], *Zhen Wang, PhD*[a,*]

[a] *Department of Neurology, Changsha Central Hospital, Yuhua District, Changsha, China*
[b] *Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, 430030, China*

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ABSTRACT

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome presents with the features of herpes simplex encephalitis (HSE), which is rare and has been described in only a few case reports. Our case describes a 17-year-old female with no significant previous medical history presenting with an acute onset of fever, headache, and epilepsy, similar to HSE. Computed tomography of the brain showed bilateral basal ganglia calcification. Magnetic resonance imaging demonstrated gyriform restricted diffusion with T2-weighted images prolongation. Further investigation showed elevated blood lactate concentration at rest. Hence, MELAS was suspected and the diagnosis was confirmed by the presence of a nucleotide 3243 A→G mutation in the mitochondrial DNA. The clinical presentation and imaging studies of MELAS are variable and may mimic those of HSE. Infection may have also precipitated MELAS manifestation in this patient. Laboratory features, such as elevated lactate, basal ganglia calcification, and gyriform restricted diffusion may be helpful in identifying patients with MELAS.

Abbreviations: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; HSE, herpes simplex encephalitis; NGS, next-generation sequencing; CoQ10, coenzyme 10; DNA, deoxyribonucleic acid; CT, computed tomography; MRI, magnetic resonance imaging; T2WI, T2-weighted image; T1WI, T1-weighted image; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; MRA, magnetic resonance angiography; NMDA, N-methyl-D-aspartate; HS-CRP, high-sensitivity C-reactive protein; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; CJD, Creutzfeldt-Jakob disease; FLAIR, fluid attenuated inversion recovery.

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* Corresponding authors.
E-mail address: 41269745@qq.com (Z. Wang).

[1] These authors contributed equally to this work and should be considered co-first authors.

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Background

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a maternally inherited multisystemic disorder caused by mutations of mitochondrial DNA. MELAS is characterized by recurrent stroke-like episodes, migraine-like headaches, focal or generalized seizures, vomiting, short stature, sensorineural deafness, cognitive decline and muscle weakness in most cases [1]. There may be variable clinical presentations of MELAS, but to our knowledge, there are few cases resembling viral encephalitis [2–9]. Here, we report the case of a young woman harbouring the typical MELAS mutation presenting an acute onset mimicking the clinical and neuroimaging features of herpes simplex encephalitis (HSE). This case report follows the CARE Guidelines [10].

Case presentation

A 17-year-old Chinese woman was admitted to this hospital with acute onset of fever, headache, generalized seizure, nausea, vomiting, hallucinations, and personality change. She was a student with no significant past medical histor and showed normal development. Her family history was negative for neuromuscular or neurodegenerative disorders.

A physical examination revealed a height of 153 cm, a body weight of 45.4 kg, a body temperature of 37.1°C, a heart rate of 68 bpm, and a blood pressure of 110/60 mm Hg. She was alert but unable to follow any commands. There was decreased spontaneous speech output as well as verbal perseveration. She was periodically agitated. Cranial nerves were unremarkable. Results of motor and sensory nerve examinations appeared to be normal, although difficult to obtain due to poor cooperation.

Routine blood test and chemistry analysis were unremarkable, including liver, renal, and thyroid function. Neither erythrocyte sedimentation rate nor C-reactive protein was elevated. Autoimmune markers were negative, including antinuclear antibodies, anti-double-stranded DNA (anti-dsDNA) antibodies, rheumatoid factor, and antineutrophilcytoplasmic antibodies (ANCA). Brain computed tomography (CT) scan revealed bilateral basal ganglia calcification, atrophy of the left hemisphere, and areas of low attenuation in the right temporo-parieto-occipital regions (Fig. 1). Fig. 1 Cranial MRI demonstrated high signal changes in the right temporo-parieto-occipital lobes, predominantly affecting the cortex and the deep white matter on T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) images, not conforming to vascular territories (Fig. 2). Fig. 2 These lesions were hyperintense on diffusion weighted images (DWI) with decreased apparent diffusion coefficient (ADC) values, which was suggestive of cytotoxic edema. Atrophy of the left hemisphere was again noted. No postcontrast enhancement. Brain magnetic resonance angiography (MRA) was normal. The MRI findings were interpreted initially as the manifestation of HSE. The cerebrospinal fluid (CSF) studies showed leukocyte 5×10^6/L (range 0–5×10^6/L), glucose 3.13 mmol/L (range 2.5–4.4 mmol/L), and protein 0.475 g/L (range 0.15–0.45 g/L). Gram stain was negative. Bacterial cultures of the CSF were negative. CSF extensive workup for autoimmune encephalitis (including anti-N-methyl-D-aspartate receptor, anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor 1/2, anti-Leucine-rich glioma-inactivated 1, anti-contactin-associated protein 2, and anti-gamma aminobutyric acid class B receptor) was negative. Detection of herpes simplex virus DNA in the CSF by polymerase chain reaction (PCR) was not available.

In this clinical setting, the patient was treated with intravenous acyclovir for presumed HSE as long as the laboratory results were in progress. Fever, headache and vomiting subsided, but personality change and irritability remained constant. Next-generation sequencing of CSF was used for the detection of pathogens, however, the result was negative. Differential diagnosis includes infarct, HSE, mitochondrial encephalomyopathy, Creutzfeldt-Jakob disease (CJD), and status epilepticus. The lack of affected family members could not exclude the genetic etiology of the disease. A lumbar puncture for CSF can detect CJD and other prions. There was no cortical ribboning or elevated protein in the CSF, making CJD less likely. MRI characteristically shows hyperintensity on DWI and FLAIR with a predilection for the parietal, temporal, and occipital cortex, without conforming to a single vascular territory, which is a hallmark finding of MELAS.

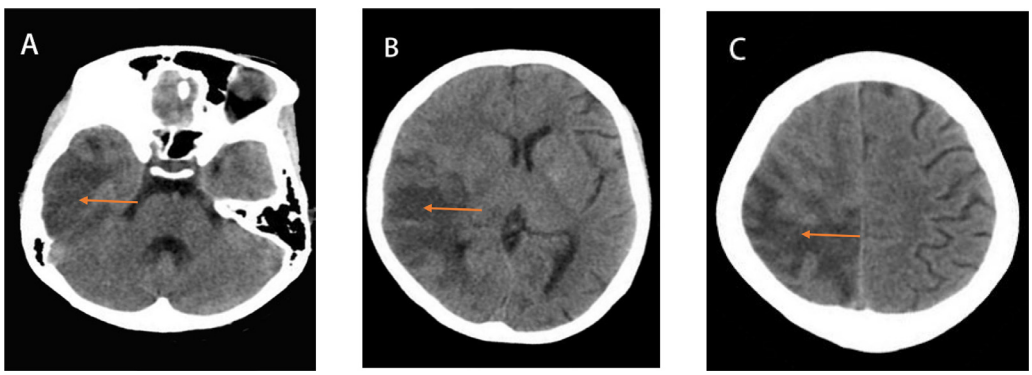

Fig. 1 – CT scan shows bilateral basal ganglia calcification (B), atrophy of left hemisphere (B, C), and an area of low attenuation in the right frontal, parietal, and temporal lobes (A, B, C).

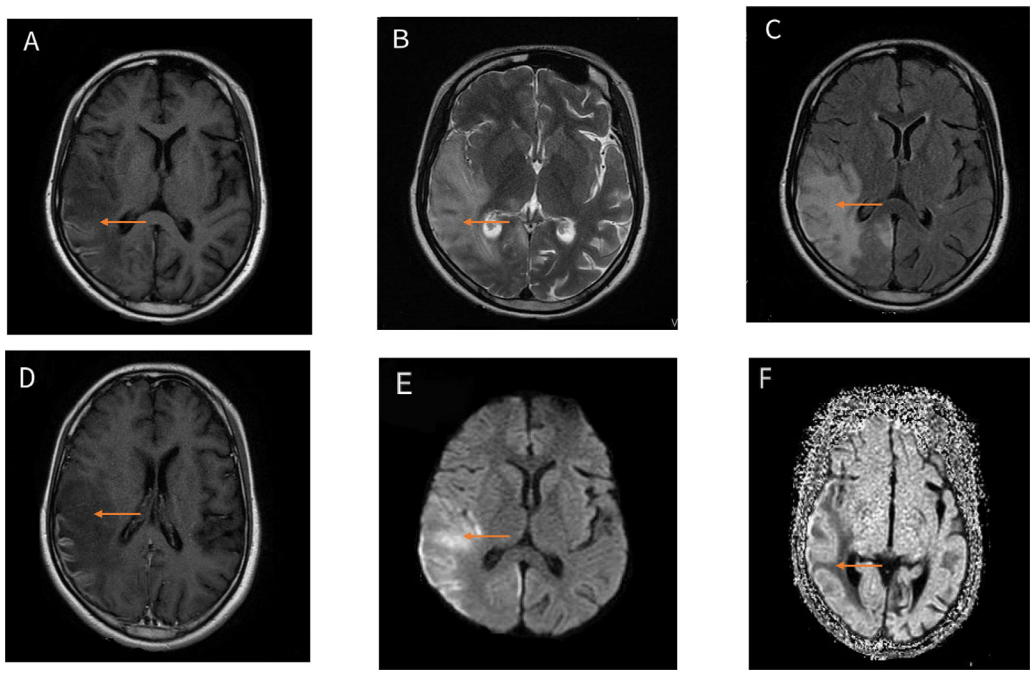

Fig. 2 – There is mild left cerebral atrophy (A–E). Gyriform restricted diffusion is observed in the right temporo-parieto-occipital cortex, (arrows) on axial DWI (E). Associated gyral swelling. Hypointense signal (arrows) is seen on T1WI (A), hyperintense signal on axial T2W (B) and FLAIR (C). No enhancement is seen in this region on post-contrast axial T1W image (D). There is low signal on ADC (F).

The patient was treated with intravenous acyclovir for presumed HSE in a standard dose of 10 mg per kg and levetiracetam 500 mg twice per day for her generalized seizure. Fever, headache, and vomiting subsided, but personality change and irritability remained constant. Next-generation sequencing of CSF was used for the detection of pathogens; however, the result was negative.

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. Calcification in the basal ganglia can be of significant value in narrowing the differential diagnoses.

Given her headache, vomiting, short stature, seizures, calcification in the basal ganglia and MRI findings MELAS was suspected. A blood gas analysis showed her blood lactate concentration was elevated at 9.0 mmol/L at rest (range 0.5–2.2 mmol/L). A blood test for MELAS mutations was undertaken and she was positive for the 3243 A→G mutation at a level of 62.7% heteroplasmy.

Coenzyme Q10 and L-arginine were started. The patient was discharged in a relatively stable condition.

Discussion and conclusion

Most of the patients with MELAS presenting as a mimic of HSE reported previously did not have fever [2,3,5,6,11].

We present a febrile patient with an initial clinical presentation consistent with HSE. The suspected diagnosis of HSE was given by typical clinical aspects (fever, headache, confusion, seizures) and mainly by neuroradiological features of unilateral and bilateral temporal and insular involvement [4,7–9].

Fever is a relatively rare initial manifestation, accounting for less than 10% of MELAS cases [1]. In contrast, over 90% of patients with HSE have fever [12]. Examination of the CSF typically shows a lymphocytic pleocytosis, increased number of erythrocytes, and elevated protein. The gold standard for establishing the diagnosis is the detection of herpes simplex virus DNA in the CSF by PCR [13], which was not available in our case. Of note, false-negative PCR test for HSV may occur early in the disease [14]. The absence of fever and lack of prominent alteration in consciousness in the presence of a normal CSF cell count help distinguish MELAS from typical HSE [4]. It should be noted, however, a normal CSF profile can occur early in the course of the HSE [15,16]. Increased CSF and serum acid lactic may be helpful.

The MRI findings in our patient were also suggestive of HSE. Temporal lobe lesions that are considered strong evidence for HSE [12] can also be prominent in MELAS [5]. Classic imaging features of HSE include DWI hyperintensity and T2/FLAIR hyperintensity in the mesiotemporal and orbitofrontal lobes and insula [14]. MELAS shows that the affected areas in neuroimaging are asymmetric and do not correspond to classic vascular distribution, involve predominantly the temporal, parietal, and occipital lobes, and can be restricted to cortical areas or involve subcortical white matter [1]. The lesions are hypodense on CT and hyperintense on T2-, DWI and FLAIR images and often show a slowly progressive spread [14]. Cal-

cification in the basal ganglia, as in our case, is another common finding in MELAS, which may help to distinguish it from HSE. Gieraerts et al [2]. proposed that diffusion restriction present in some parts of the lesions but not throughout the entire lesions, which could be an important sign in the differential diagnosis with HSE. However, in 2/11 HSE patients with MRI performed both 56 days after symptom onset, FLAIR showed more brain areas involved when compared with DWI [17]. The ADC values of the lesions of MELAS are reported as a mild increase, unchanged, or mild decrease [18]. Brain MRA is typically normal, whereas magnetic resonance spectroscopy shows decreased N-acetylaspartate signals and accumulation of lactate, however, this is not always the case. A characteristic lactate peak is not specific to mitochondrial disease and can also be found in vascular stroke, hypoxic-ischemic injury, and infection, although it was found to correlate with the degree of the neurological impairment in individuals with MELAS. Morphological MR sequences might fail in differentiating between MELAS and HSE because signal characteristics may overlap.

MELAS syndrome in adults may present as an atypical form of HSE and should be added to the list of neurologic diseases that can mimic HSE. Elevated CSF and/or serum acid lactic and basal ganglia calcification are helpful in identifying patients with MELAS. The mtDNA mutation can be easily detected in blood and urine without need for invasive procedures such as muscle biopsy. Therefore, this molecular genetic test should be performed and the lactate level measured when the patients do not respond to antiviral drugs.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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