Adult onset MELAS Syndrome Presenting as A Mimic of Herpes Simplex Encephalitis

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Abtract

Purpose: Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome primarily affects the young and may not be considered first in an older adult with infection-like encephalopathy. Here, we present the case of a patient who suffered from the acute onset of fever, delirium, and epilepsy, mimicking herpes simplex encephalitis (HSE).

Case report: A 52-year-old woman with diabetes and end stage renal disease (ESRD) regularly took oral anti-diabetic drugs (OADs) and received hemodialysis. She presented with an acute onset of fever, delirium, and epilepsy, mimicking HSE. Further investigation showed a persistent elevated lactate level in the cerebrospinal fluid (CSF). A mitochondrial DNA analysis revealed a point mutation at nucleotide 3243.

Conclusion: The clinical presentation and imaging studies of MELAS in adults are variable and may mimic those of HSE. Antiviral therapy should be administered until the diagnosis of MELAS is definitive. Infection and metformin may have also precipitated MELAS manifestation in this patient. Clinicians should avoid potential mitochondrial-toxic drugs in these patients.

Key words: MELAS, herpes simplex, encephalopathy, temporal lobe

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INTRODUCTION

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a multisystem disorder with broad manifestations including myopathy, migraines, cortical blindness, hearing loss, epilepsy, diabetes mellitus, and renal dysfunction[(1-3)]. Variability in phenotypes and imaging presentations often confuse clinicians, especially in cases with late onset. Here, we report the case of one woman who was initially presumed to have herpes simplex encephalitis (HSE), but was subsequently proven to have MELAS syndrome.

CASE REPORT

A 52-year-old right-handed woman was brought to the

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emergency department due to the acute onset of bizarre behavior and cognitive decline, with preceding severe diarrhea and nausea 2 days before the presentation. No headaches, hallucinations, or involuntary movements were reported. The patient was a housewife who independently performed activities of daily living and took care of her in-laws. She had a medical history of end stage renal disease (ESRD) requiring renal transplant 10 years prior to the presentation, progressive sensorineural hearing loss for 17 years, type 2 diabetes mellitus for 5 years, and being a hepatitis C virus (HCV) carrier without cirrhosis. The patient's medications included tacrolimus 2 mg/day, sirolimus 1 mg/day, sitagliptin 100 mg/day, glimepiride 4 mg/day and metformin 1500 mg/day, and the latter was recently added one month prior. On examination, she had a fever and confusion without focal weakness or a sensory deficit. Her weight was 39 kg and height was 1.55 m, which was similar to other members of her family. She had a new onset of generalized tonic-clonic seizures (GTCS) soon after admission (<12 hours from arrival), with a total of three attacks in a cluster. Valproic acid 400 mg was immediately given every 8 hours, but the patient was in a stupor after the cessation of the convulsions.

A laboratory analysis found lactic acidosis (lactate 26 g/dl, pH of arterial gas 7.21, HCO_3 18.8), elevated C-reactive protein (CRP) levels (5.6 mg/L), and abnormal procalcitonin levels (2.67 ng/mL). All other biochemistry studies and serum drug levels were unremarkable. An emergent brain CT scan showed bilateral basal ganglia calcification without a recent infarct or hemorrhage. MRI using a 1.5 tesla imager demonstrated a left anterior temporal lesion with hyperintense signals on T2-weighted imaging (T2WI), hypointense signals on T1-weighted imaging (T1WI), and restricted diffusion along the cortex on diffusion weighted imaging (DWI) (Fig. 1a-d). The lesion did not enhance with gadolinium contrast. Surface electroencephalography (EEG) revealed periodic lateralizing epileptiform discharges in the left hemisphere, maximizing in the middle temporal areas (T3), with background slowing waves in the theta to delta range. Valproic acid was replaced with levetiracetam 500 mg every 12 hours, and the follow-up EEG showed no more seizures.

The patient was empirically treated with intravenous

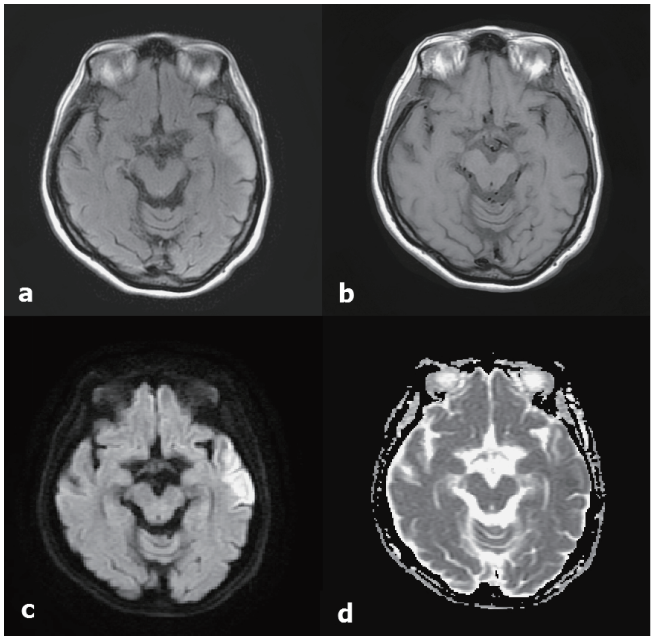

Figure 1. Brain 1.5-T magnetic resonance imaging (MRI) performed 2 days after admission showing a high signal lesion on T2-weighted imaging (a) and a low signal on T1-weighted imaging (b) in the left lateral temporal lobe. Both cortical and white matter are involved. On diffusion-weighted imaging (c), a high signal was seen in the cortical gyriform pattern, with an iso signal on apparent diffusion coefficient sequences (d) in the same region.

acyclovir for presumed HSE in a standard dose of 10 mg per kg for 21 days. An extensive infection and autoimmune workup including NMDA receptor antibody was unremarkable. The CSF studies showed leukocyte 15 cell/μL (neutrophil 87%), red blood cell (RBC) 10560 cell/μL, glucose 141 mg/dL (serum 170 mg/dL), protein 209 mg/dL, elevated lactate (60.1 mg/dL), a normal IgG index and no oligoclonal band. Stains or cultures of bacteria, tuberculosis, Cryptococcus, and syphilis were negative. Viral PCR and culture of the CSF to detect HSV-1, HSV-2, and VZV yielded negative results. However, consistent abnormal lactate levels in both serum and CSF were noted.

The patient's mental status gradually improved one week after treatment, although her cognitive dysfunction remained. Follow-up MRI one month later showed a partial regression of the previous lesion and an extension posteriorly to the left temporoparietal area (Fig. 2). Magnetic resonance spectroscopy (MRS) showed a moderate reduction of N-acetylaspartate (NAA), moderate elevation of choline complex, and the presence of a lactate peak. MELAS was confirmed by mitochondrial DNA point mutation at position 3243 (np-3243A>G). A detailed family history revealed migraines in her only daughter and a maternal history of diabetes and short stature. Q10 and L-arginine were started early, empirically, while awaiting the results of diagnostic testing. The patient was discharged in a relatively stable condition.

DISCUSSION

The variable clinical manifestations of MELAS make it difficult to receive an early diagnosis. The typical age of onset is before 20 years, with 1-6% of cases presenting after the age of 40 years[1-3]. Individuals frequently present with more than one initial manifestation, including seizures, headaches, vision loss, diabetes, and stroke-like episodes such as hemiparesis and hemianopia. Fever as the initial feature, however, accounts for less than 10% of cases[4]. In contrast, fever, seizures, acute mental dysfunction and headaches are the most prevalent symptoms of HSE[5]. Furthermore, immunocompromised HSE patients could have fewer prodromal symptoms and a more fulminant course compared to immunocompetent HSE patients[6]. Therefore, considering the age of our patient, a possible infectious episode, and her complicated medical history, a differential diagnosis was given for viral encephalitis, mitochondrial disease, and even autoimmune encephalitis.

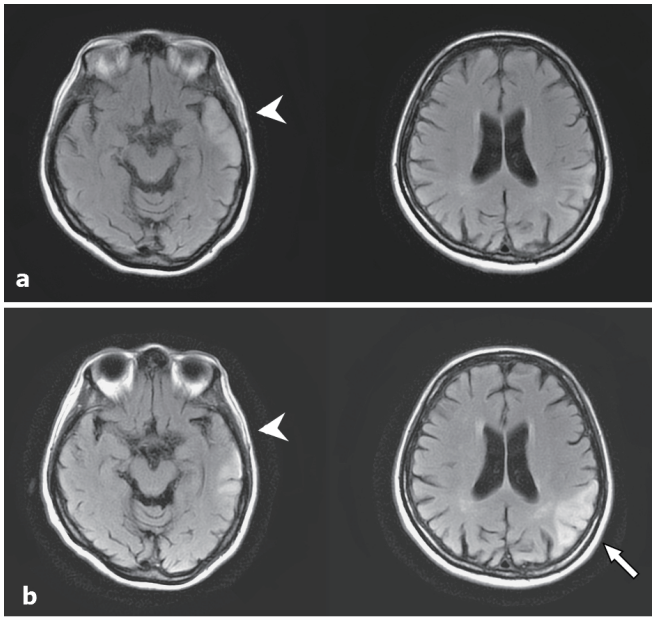

Figure 2. The follow-up MRI one month after (a) the first study (b), which shows spatial migration from the left temporal lobe to the parietal lobe. Partial regression of the lesion at the temporal pole (arrow head) with extension to the parietal lobe (long arrow) was seen. This unique interval feature is characterized in MELAS syndrome.

Table 1. Initial presentation and findings of herpes simplex encephalitis (HSE) mimics of proven MELAS patients in the English literature.

Reference	Age at onset/Sex	Clinical manifestation				Neuroimaging		CSF		
		History	Neurological presentation	Fever	Course	Side	Location	WBC (cells/μL)	Protein (mg/dL)	Glucose (mg/dL)
Sophia R, et al. 1999[7]	55/F	Hearing loss, ophthalmic herpes zoster infection	Headache, delirium, aphasia, seizure	N	2 acute events in 5 years	L	T, P	3	63	53
Hsu YC, et al. 2012[8]	47/M	Hearing loss, DM	Headache, delirium, seizure	Y	Acute	L, R	*	7750	431.8	35.8
Christopher G et al. 2013 [9]	36/M	Hearing loss, DM	Headache, aphasia, seizure	N	6 months	L, R	T	<5	65.8	*normal
Rubesh G, et al. 2014[10]	29/M	Hearing loss, DM	Headache, delirium, psychosis, seizure	Y	Acute	R	T, P	1	62	*
Chen, et al. 2018 (current patient)	52/F	Hearing loss, DM, ESRD	Delirium, seizure	Y	Acute	L	T	15	209	118

M: male; F: female; DM: diabetes mellitus; ESRD: end stage renal disease; L: left; R: right; T: temporal lobe; P: parietal lobe; CSF: cerebrospinal fluid; WBC: white blood cell; *: not described

Table 1 presents the data for our patient and previously reported patients with MELAS presenting as a mimic of HSE[7-10]. The other patients included three men and two women, for a mean age of 43 years with a range of 29 to 55 years. Three patients (including our case) had fever and acute neurological deficits. All of the patients had a history of hearing loss and eventually developed seizures. The imaging showed unilateral or bilateral temporal lobe involvement, which is also a characteristic lesion site of HSE. The CSF data did not show consistent results. All the cases received empirical antiviral therapy before confirming the diagnosis.

The typically illustrated imaging findings of MELAS exhibit localization in the parietal-occipital cortex that does not conform to the vessel territories[2,11]. Takahiro et al.[12] documented the gradual spatial progression to the region surrounding the lesion 2 to 3 weeks after the onset of initial symptoms in four MELAS cases. This unique feature was also seen in our case in the follow-up MRI (Fig. 2). However, distinguishing MELAS from HSE early in a unilateral isolated temporal lesion remains difficult. According to a study by Chow et al.[13] of 251 cases of temporal lobe encephalitis, bilateral involvement or lesions outside the limbic region (temporal lobe, insula, cingulate) were associated with lower odds of HSE. Calcification in the basal ganglia is another common finding in MELAS [11,13]. These features may aid in distinguishing between the two disorders. Yoneda et al. [14] first reported an increased signal on apparent diffusion coefficient (ADC) maps in the stroke-like region. The authors described that the average ADC (ADCav) ratio of the stroke region relative to the normal control side would increase 2 days after onset and decrease over 2 to 3 weeks. However, such an ADC ratio change was not observed in our patients, who received MRI within 2 days from admission.

Infection, drugs, and aging may have been

predisposing factors in our case. The onset of symptoms in this patient might have been provoked by a mismatch between energy requirements and the availability of the affected mitochondria exacerbated by febrile illness, dehydration and metformin use [2,15]. Metformin has a propensity to induce lactic acidosis in patients with MELAS syndrome; besides, the dose should be reduced in those with renal insufficiency[15-17]. Valproic acid is notorious for worsening seizures in patients with MELAS syndrome[18,19], probably via altering the fundamental structures of the mitochondrial membrane by inducing paroxysmal depolarization shifts and inhibiting cytochrome c oxidase [20-22].

CONCLUSION

The clinical presentation and imaging studies of MELAS in adults are variable and can mimic those of HSE. Antiviral therapy should be administered until the diagnosis of MELAS is definitive. Infection and metformin may have also precipitated MELAS manifestation in this patient. Once a mitochondrial disorder is suspected, clinicians should avoid potential mitochondrial-toxic drugs, such as metformin and valproic acid.

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REFERENCES

1. Pavlakis SG, Phillips PC, DiMauro S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: a distinctive clinical syndrome. Ann Neurol. 1984;16:481-488.
2. Hirano M, Pavlakis SG. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS): current concepts. J Child Neurol. 1994;9:4-13.
3. Ciafaloni E, Ricci E, Shanske S, et al. MELAS: clinical features, biochemistry, and molecular genetics. Ann Neurol. 1992;31:391-398.
4. Ayman WE, Adekunle MA, Jeremy J, Fernando S. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. Molecular Genetics and Metabolism. 2015;116:4-12
5. Tzu-CL, Ching PT, Chih LY, et al. Encephalitis in Taiwan: A Prospective Hospital-Based Study. Jpn. J. Infect. Dis. 2003;56:193-199.
6. Ik L. Tan, Justin C. McArthur, Arun Venkatesan, Avindra Nath. Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. Neurology. 2012;79(21).
7. Sophia RS, Mark FG, Richard BL, Elfrida SM. Adult-onset MELAS presenting as herpes encephalitis. Arch Neurol. 1999;56:241-243
8. Hsu YC, Yang FC, Perng CL, Tso AC, Wong LJ, Hsu CH. Adult-onset of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome presenting as acute meningoencephalitis: A case report. The Journal of Emergency Medicine. 2012;43(3):163-166
9. Christopher G, Philippe D, Philip VD, Guido W. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome mimicking herpes simplex encephalitis on imaging studies. J Comput Assist Tomogr. 2013 March/April;37(2)
10. Rubesh G, Badr EAD, Thattoli CV. Led astray: MELAS initially misdiagnosed as herpes simplex encephalitis. Acta Neurol Belg. 2014 December
11. Sue CM, Crimmins DS, Soo YS, et al. Neuroradiological features of six kindreds with MELAS tRNA(Leu) A2343G point mutation: implications for pathogenesis. J Neurol Neurosurg Psych. 1998;65:233–240.
12. Takahiro I, Fumihiko S, Shinichi K, Norihiro S. Slowly progressive spread of the strokelike lesions in MELAS. Neurology. 2003;61:1238-1244
13. Felicia CC, Carol AG, Heather S, Dongxiang X, Sharon M, Richard W, Arun V. Use of Clinical and Neuroimaging Characteristics to Distinguish Temporal Lobe Herpes Simplex Encephalitis From Its Mimics. Clinical Infectious Diseases. 2015;60(9):1377–83
14. Yoneda M, Maeda M, Kimura H, et al. Vasogenic edema on MELAS: a serial study with diffusion-

weighted MR imaging. Neurology. 1999;53:2182–2184.
15. D.M. Sproule, P. Kaufmann. Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. Ann. N. Y. Acad. Sci. 2008;1142:133–158.
16. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010;(1):CD002967
17. Heaf J. Metformin in chronic kidney disease: time for a rethink. Perit Dial Int. 2014;34:353-7.
18. C.W. Lam, C.H. Lau, J.C. Williams, Y.W. Chan, L.J. Wong. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. Eur. J. Pediatr. 1997; 156:562-564.
19. C.M. Lin, P. Thajeb. Valproic acid aggravates epilepsy due to MELAS in a patient with an A3243G mutation of mitochondrial DNA. Metab. Brain Dis. 2007;22:105-109.
20. Altrup U, Gerlach G, Reith H, Said MN, Speckmann EJ. Effects of valproate in model nervous system (buccal ganglia of Helix pomatia). Epilepsia. 1992; 33:743-759.
21. Ponchaut S, Van HF, Veitch K. Valproate and cytochrome c oxidase deficiency. Eur J Pediatr. 1995;154:79.
22. Lam CW, Lau CH,Williams JC, Chan YW,Wong LJ. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. Eur J Pediatr. 1997;156:562–564.