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LETTER TO THE EDITOR

L-Arginine prevents stroke-like episodes but not brain atrophy: a 20-year follow-up of a MELAS patient

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Dear Editor,

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) usually presents with stroke-like episodes (SLEs), progressive encephalopathy, lactic acidosis, migraine headaches, exercise intolerance, and multisystem involvement [1]. SLEs represent the clinical signature of MELAS with a relapsing-remitting pattern [1]. The prognosis of MELAS is determined by the frequency and severity of SLEs, the progression of diffuse encephalopathy, and the involvement of multiple systems. The pathogenesis of SLEs has not been fully elucidated, but recent investigations have found that SLEs are metabolic stroke driven by seizure activity, and other non-ischemic cellular mechanisms may be involved [2]. Meanwhile, growing evidence has indicated that nitric oxide (NO) deficiency occurs in MELAS syndrome and can contribute significantly to endothelial cell dysfunction [3]. Arginine supplementation has been reported to decrease the frequency and severity of SLEs [4]. We report a 20-year follow-up of a MELAS patient to determine the effect of long-term oral arginine administration on various aspects of the clinical presentation.

Case report

A 17-year-old woman was hospitalized in May 2001 complaining of migraine headache, seizures, and hemiparesis of the right limbs. One month previously, she had a fever accompanied by a throbbing headache, which lasted approximately 3 days. Then, she presented with transient hallucinations and right extremity convulsions. Viral encephalitis was suspected, but cerebral spinal fluid (CSF) analysis revealed a normal white blood cell count and protein level. Antiviral antibodies against several viruses including herpes, rubella, cytomegalovirus, and Epstein-Barr virus were negative. Furthermore, antiviral medication was ineffective. Three days previously, she experienced acute attacks of hemiparesis and hemianopsia on the right side. A neurologic examination revealed right hemiparesis and defects in the right visual field. She had a history of pre-excitation syndrome, and radiofrequency ablation was conducted 3 years before her presentation. The patient reported fatigue and exercise intolerance from childhood, although full-term delivery and normal development were recorded. Her mother experienced hearing loss at a young age. On examination, she was 1.5 m in height and weighed 40 kg. Magnetic resonance imaging (MRI) of the brain revealed hyperintense lesions centered in the cortex and subcortical white matter of the left occipital, temporal, and parietal lobes on T2-weighted and FLAIR sequences (Fig. 1a, b). Electroencephalography (EEG) showed focal spikes and wave complexes with a slowing of background activity. The cerebral angiogram was normal. Her lactic acid level was elevated to 3.4 mmol/l (normal 0.5–1.6 mmol/l) in the blood and 4.8 mmol/l in the CSF (normal < 3 mmol/l). A vastus lateralis muscle biopsy showed numerous ragged red fibers (RRF) and succinate dehydrogenase reactive vessels (SSV) (Fig. 2). Mitochondrial DNA analysis of a peripheral blood leukocyte sample yielded an m.3243A>G mutation with a 35% mutation load, which confirmed the diagnosis of MELAS. Oral medications and cofactors included levetiracetam (500 mg twice a day), coenzyme Q10 (50 mg three times a day), vitamin C (100 mg three times a day), vitamin B_1 (30 mg three times a day), and vitamin B_2 (30 mg three times a day). The patient gradually returned to baseline 10 days later. In the

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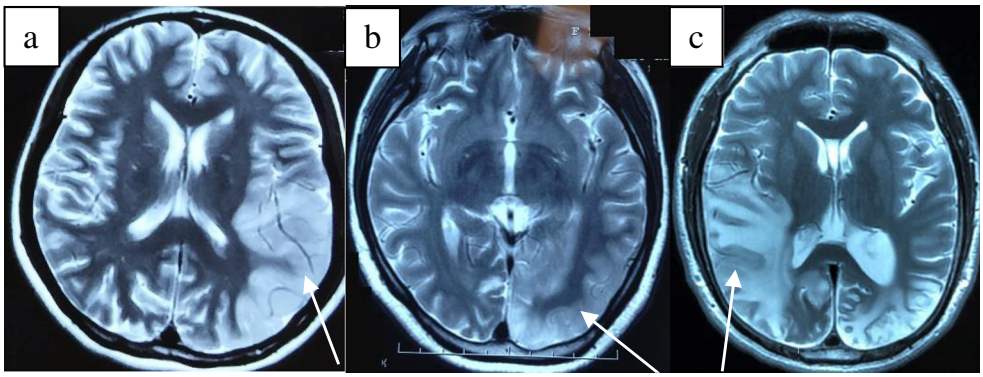

Fig. 1 MR images of T2-weighted sequences. **a**, **b** Hyperintense lesion centered in the cortex and subcortical white matter of left occipital, temporal, and parietal lobes in 2001 (showed by white arrows). **c** New right temporal lesion with high signal in 2003 (showed by white arrow). The original lesions of left occipital lobe became obsolete and atrophy

following days, the patient visited the local hospital four times for recurrent headaches and seizures despite continuous use of levetiracetam. At least five SLEs with hemiparesis, hemianopsia, or acute psychosis were reported during hospitalization. New-onset right occipital and right temporal lesions with confluent high T2-weighted and FLAIR signals were found successively on MRI (Fig. 1c). These episodes gradually resolved, but some residual symptoms remained.

In March 2008, L-arginine was administered intravenously (0.5 g/kg/day) for 5 days when the last SLE attacked and was administered orally (0.2 g/kg/day) thereafter. The patient underwent routine follow-up. No additional SLEs occurred, and the last epileptic seizures occurred on July 27, 2008. In January 2009, the dose of levetiracetam was lowered to 250 mg twice a day. No seizures or strokes were reported thereafter. The patient had no impairment in her basic or instrumental activities during daily living, though she reported difficulty with word finding, short-term memory decline, imbalance, generalized fatigue, and emotional abnormalities. In January 2010, a routine examination revealed diabetes mellitus, hematuria, and proteinuria. An increased blood creatinine level and a decreased 24-h creatinine clearance rate confirmed renal insufficiency. Levetiracetam was discontinued. Subcutaneous injection of insulin was prescribed to control blood glucose. Although the patient continued taking L-arginine, coenzyme Q10, and multivitamins orally, she developed deafness in 2011. The hearing loss gradually worsened, and she required hearing aids. Between 2011 and 2017, her gait, balance, coordination, and cognition worsened gradually, but no additional episodes of epilepsy or stroke were reported. Meanwhile, MRI revealed a progressive volume loss of the brain parenchyma without new lesions (Fig. 3).

In January 2017, the patient's condition deteriorated rapidly after an upper respiratory infection. Laboratory tests showed renal failure, liver dysfunction, and severe hypoalbuminemia. Although active symptomatic treatment and nutritional support were administered, her condition continued to deteriorate. Thereafter, pleural and abdominal effusion appeared, and she died of respiratory distress, metabolic acidosis, and multiple organ failure.

Discussion

This patient had characteristic SLEs, seizures, migraine headache, progressive encephalopathy, and multiple system involvement. MELAS was definitively diagnosed by a combination of clinical and neuroimaging findings, elevated lactate levels in the blood and cerebral spinal fluid, RRF on muscle biopsy, and a pathogenic m.3243A>G mutation.

Mitochondrial "cocktails" are widely used in clinical practice, including vitamins and cofactors [1, 5]. Due to the high

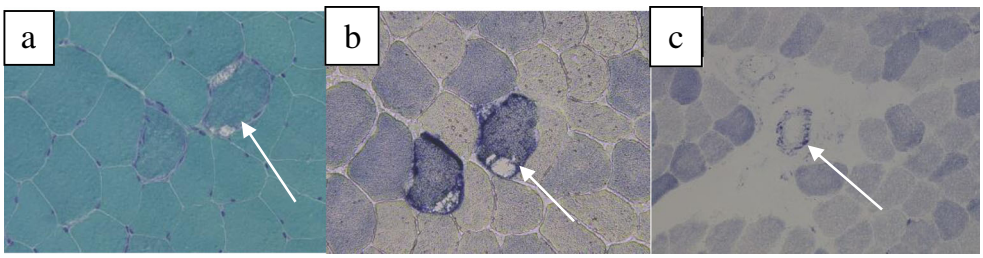

Fig. 2 Gomori trichrome stain (**a**) showed two ragged red fibers. Stain for SDH activity showed that these two RRF were SDH-positive fibers in blue (**b**) and a SDH-positive vessel (**c**). All showed by white arrows

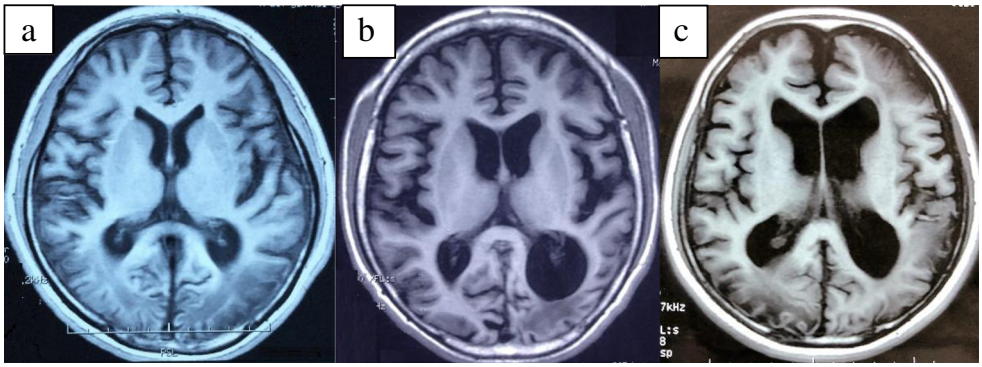

Fig. 3 MR images of T1-weighted sequences in 2005 (**a**), 2011(**b**), and 2016 (**c**). Progressive diffuse brain atrophy presented with widened and deepened cerebral sulcus and enlarged ventricles over time

morbidity and mortality of SLEs, arginine has gained increasing clinical use since 2005 [4]. In addition to the mostly accepted non-ischemic neurovascular cellular mechanisms, emerging hypotheses include alterations of nitric oxide (NO) homeostasis due to potential inhibition of endothelial NO synthase (eNOS) activity and low levels of plasma L-arginine and L-citrulline in MELAS patients. Supplementation with L-arginine could increase NO production, improve endothelial function, and reduce the incidence and severity of SLEs [3, 4]. This therapy was approved by our patient during the approximately 20-year follow-up based on a comparison of the frequency of SLEs before and after L-arginine use. However, evidence for the long-term effects of L-arginine on other manifestations of MELAS remains scarce. Despite continuous L-arginine supplementation, the patient's general condition gradually worsened, including her cognition, mental condition, and extent of multisystem involvement. Meanwhile, diffuse brain atrophy became more remarkable. She died of multiple organ failure. We tentatively put forward that long-term usage of L-arginine had little effect on this patient's progressive encephalopathy, brain atrophy, and multiple organ dysfunctions.

To our knowledge, this is the longest follow-up of a MELAS patient treated with L-arginine. Several insights into oral arginine use in MELAS were gained. First, this observation highlighted the probable benefit of long-term oral L-arginine for reducing the frequency of SLEs. Second, L-arginine had little effect on the prevention of progressive brain atrophy. Third, no adverse effects were reported during 10 years of L-arginine use, highlighting the safety of long-term supplementation.

However, these conclusions were achieved mainly by the combination of a single case report and a literature review, and MELAS is complicated by diverse symptoms and an unpredictable but progressive course. Therefore, larger numbers of patients and randomized, double-blind clinical trials are needed to clarify the potential role of L-arginine in all aspects of MELAS syndrome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. El-hattab AW, Adesina AM, Jones J, Scaglia F (2015) MELAS syndrome: clinical manifestations , pathogenesis , and treatment options. Mol Genet Metab 116(1–2):4–12. https://doi.org/10.1016/j.ymgme.2015.06.004
2. Iizuka T, Sakai F, Suzuki N, Hata T, Tsukahara S, Fukuda M, Takiyama Y (2002) Neuronal hyperexcitability in stroke-like episodes of MELAS syndrome. Neurology 59(6):816–824. https://doi.org/10.1212/WNL.59.6.816
3. El-Hattab AW, Emrick LT, Chanprasert S, Craigen WJ, Scaglia F (2014) Mitochondria: role of citrulline and arginine supplementation in MELAS syndrome. Int J Biochem Cell Biol 48(1):85–91. https://doi.org/10.1016/j.biocel.2013.12.009
4. Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Tanabe Y, Fujimoto S, Matsuishi T (2005) L-arginine improves the symptoms of stroke-like episodes in MELAS. Neurology 64:710–712
5. DiMauro S, Hirano M, Schon E A (2000) Mitochondrial encephalomyopathies: therapeutic approaches. [Review] [75 refs]. Neurol Sci 21(5:Suppl) Suppl-8