Brief communication

Effect of long-term oral treatment with L-arginine and idebenone on the prevention of stroke-like episodes in an adult MELAS patient

A. Lekoubou\textsuperscript{a}, A.-E. Kouamé-Assouan\textsuperscript{a}, T.-H. Cho\textsuperscript{a}, J. Luauté\textsuperscript{b}, N. Nighoghossiana\textsuperscript{a}, L. Derex\textsuperscript{a,*}

\textsuperscript{a}Cerebrovascular Unit, hôpital neurologique Pierre-Wertheimer, hospices civils de Lyon, 59, boulevard Pinel, 69677 Bron, France

\textsuperscript{b}Rehabilitation Unit, hôpital Henry-Gabrielle, hospices civils de Lyon, 20, route de Vourles, 69230 Saint-Génis-Laval, France

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A B S T R A C T

Introduction. – Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a maternally-inherited multisystem disorder. Mitochondrial angiopathy mediated by nitric oxide, a metabolite of L-arginine, is among the proposed pathophysiologic mechanisms of stroke-like episodes (SLEs) in MELAS. There are very few reports on long-term prevention of SLEs with oral L-arginine and idebenone treatment in MELAS adult patients.

Case report. – A 38-year-old patient with MELAS and SLEs was treated with oral L-arginine and idebenone for 27 months. She remained free of attacks throughout the treatment period except when she stopped her treatment on two occasions during which she had recurrent cerebral metabolic attacks. The patient experienced no side effect of treatment with L-arginine and idebenone.

Conclusion. – Our observation suggests long-term safety and potential benefit of oral L-arginine and idebenone in the prevention of recurrence of SLEs in adult MELAS patients.

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R É S U M É

Introduction. – Le syndrome de MELAS est une maladie multisystémique a été suggéré dans des rapports ponctuels dont le pronostic est sévère. L’effet bénéfique de la L-arginine ou de l’idebenone (analogue du coenzyme Q10) sur la récidive des épisodes pseudovasculaires observée dans cette pathologie a été suggéré dans les rapports ponctuels mais on dispose de peu de données sur la tolérance et l’efficacité à long terme de ce type de traitement.

\textsuperscript{*} Corresponding author.
E-mail address : laurent.derex@chu-lyon.fr (L. Derex).

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1. Introduction

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a maternally-inherited multisystem mitochondrial disorder. There is a consensus that the cerebral stroke-like lesion (SLL) observed in MELAS represents a vasogenic edema (Finsterer, 2009). However, the pathophysiology of stroke-like episodes (SLE) in MELAS is not completely elucidated. Three main hypotheses have been proposed: (1) the SLE is due to mitochondrial angiopathy, (2) the SLE results from a local metabolic defect of the respiratory chain or oxidative phosphorylation, (3) the SLE results from focal neuronal hyperexcitability which leads to increased energy demand (Finsterer, 2009). It has been shown that intravenous L-arginine may improve the symptoms of SLEs during the acute phase (Koga et al., 2005). When given orally during interictal periods, L-arginine reduces both the severity and the frequency of SLEs in children (Koga et al., 2005). Idebenone is a synthetic analogue of coenzyme Q10 which serves as an electron carrier and may improve mitochondrial oxidative metabolism (Finsterer, 2009). Data on long-term safety and efficacy of oral L-arginine and idebenone therapy on SLEs in adult MELAS patient are scarce. We report the clinical and imaging course of an adult female MELAS patient treated with oral L-arginine and idebenone therapy over 27 months.

2. Case report

A 38-year-old unemployed woman was admitted to the Lyon University stroke unit in November 2007 after the acute onset of disorientation, behavioral and speech disturbances. Except for migraine without aura, she had experienced no previous neurological symptoms including hearing loss, visual disturbance, muscle pain or weakness. There was no history of neurological or muscular disease in her parents or siblings as well. She was the mother of two children aged 8 and 12 years respectively. Her younger son was affected by speech disturbances but no medical evaluation had been performed. During the initial clinical assessment, she had a brief (30 seconds) left-sided tonic head deviation during which she remained unresponsive to verbal and painful stimuli. No focal motor deficit was observed and she had a symmetrical response to painful stimuli. There was a right Babinski sign. She had no neck stiffness, facial drop, papillary abnormality or ophtalmoplegia. She was afebrile. The patient had a short stature (155 cm) and low body weight (40 kg). Brain MRI performed on admission (Fig. 1) revealed a left cortical temporoparietal and insular hyperintense lesion both on Diffusion-Weighted Imaging (with an increased Apparent Diffusion Coefficient) and Fluid Attenuated Inversion Recovery (FLAIR) sequences without any arterial systematisation, consistent with vasogenic edema. Angiographic sequences showed no arterial or venous occlu-
sion. She became more confused and lethargic but had no recurrent seizure on Levetiracetam 500 mg twice daily. Control brain MRI at day 5 showed an extension of the hyperintense lesions with new lesions of the left occipital cortex and pulvinar (Fig. 2). Transesophageal echocardiography, 72-hours Holter ECG, and abdominal and chest CT were normal. CSF analysis showed normal cell count, protein and glucose levels. PCRs for Herpes Simplex Virus and enteroviruses yielded negative results. Bacteriological cultures and serological studies for HIV-1 and 2 viruses, hepatitis C and B viruses and Borrelia burgdorferi were all negative. Serum angiotensin converting enzyme level was normal and no cryoglobulin was found. Blood homocysteine, ammonium and urinary porphyrins were normal. Venous lactate was raised (3820 µmol/L, normal 500–1700 µmol/L) as well as branch amino acids plasmatic dosage (valine 252 µmol/L, normal 142–239 µmol/L, isoleucine 100 µmol/L, normal 22–78 µmol/L). While L-arginine plasmatic level was normal (46 µmol/L, normal 27–108 µmol/L), citrulline (10 µmol/L, normal 19–39 µmol/L), aspartate (4 µmol/L, normal 7–22 µmol/L), histidine (15 µmol/L, normal 47–101 µmol/L) and hydroxyproline (5 µmol/L, normal 11–37 µmol/L) were low. Genetic study revealed an A3243G mitochondrial DNA (mtDNA) mutation in the blood (heteroplasmy rate of the mutation: 15%). Oral L-arginine (0.375 g/kg daily, total daily dose = 15 g) and idebenone (270 mg daily) were started in December 2007. The Newcastle Mitochondrial Disease Adult scale (NMDAS) (Schaefer et al., 2006) on initiation of treatment was 54/145. The patient was transferred to a rehabilitation unit in December 2007 with persistent confusional state and delusions of persecution. Her clinical status gradually improved over the following months. In May 2008, the patient still exhibited action slowing but was well-oriented and had no residual behavioral disturbance. No deficit of memory, language, visuo-spatial or executive functions was noted. The patient was finally discharged home at the end of May 2008 on Levetiracetam (750 mg twice daily), oral L-arginine (15 g daily) and idebenone (270 mg daily). NMDAS score was 25/145. She presented with visual impairment and recurrent confusional state 10 days after she had stopped taking L-arginine and idebenone. She was readmitted to the stroke unit where neurological examination showed left hemiparesis and left hemianopsia (NMDAS score = 36/145). Brain MRI revealed new lesions involving the right parietal, temporal and occipital cortex (Fig. 3). Treatment with L-arginine and idebenone was reintroduced at the same dosage. Despite some residual visual and language impairments, the patient remained independent for most daily activities until October.
2008 when left hemianopsia worsened and the patient developed a left hemibody sensory deficit 48 hours after a second treatment discontinuation (NMDAS score = 36/145). MRI showed an extension of the lesions to the right pulvinar and marked bilateral parietal and occipital atrophy (Fig. 4). Oral L-arginine and idebenone were reintroduced at the same dosage. While on oral L-arginine and idebenone, cognitive impairment gradually improved and no recurrent epileptic seizure occurred. At the most recent clinical assessment in March 2010, compliance to oral L-arginine and idebenone therapy was good. No side effects were reported. The patient scored 24/145 on the NMDAS. She was orientated with a well-adapted behaviour but exhibited persistent action slowing, constructional apraxia, left hemianopsia and sensory deficit. She had neither aphasia nor memory disturbances. She was autonomous for daily activities including walking, dressing and eating.

3. Discussion

In our patient, diagnosis of MELAS was made by identification of an A3243G mtDNA mutation in the blood with a low heteroplasmy rate of the mutation (15%). A higher heteroplasmy rate could have been observed through urine analysis of epithelial cells or muscle biopsy but such analyses were not performed (McDonnell et al., 2004).

This observation highlights the safety and potential benefit of long-term oral treatment with L-arginine and idebenone in adult MELAS patients with SLEs. The symptoms of our patient improved significantly while on treatment and discontinuation of oral L-arginine and idebenone was systematically associated with reappearance of symptoms and worsening of MRI lesions. Overall, after 27 months of treatment, the cognitive functions of our patient improved significantly.

The rationale for using L-arginine in MELAS is that it is a substrate for nitric oxide synthase, which produces nitric oxide, stimulating guanosylcyclase, and thereby reducing the neurologic consequences of SLEs (Kerr, 2009). A study has shown improved regional cerebral blood flow on Single Photon Emission Computerized Tomography after the intravenous or oral administration of L-arginine in MELAS patients with stroke-like symptoms (Koga et al., 2006). In addition, L-arginine may reduce the neuronal hyperexcitability seen in MELAS as it is a precursor of agmatine, a neurotransmitter that selectively blocks the N-methyl-D-aspartate subclass of glutamate receptor channels (Yang and Reis, 1999). Case studies have also suggested that idebenone, at doses ranging from 90 to 270 mg daily, may improve clinical symptoms and prevent SLEs in MELAS patients (Ikejiri et al., 1996; Napolitano et al., 2000).

Reports on the long-term oral treatment with L-arginine and idebenone in adult MELAS patients are rare as studies have usually included children and adolescents (Koga et al., 2005; Koga et al., 2006). In the largest series, 24 MELAS patients (mean age 19.6 ± 12.5 years) with a total of 34 SLEs were enrolled in a study comparing the efficacy of oral L-arginine and idebenone in the prevention of SLEs in a large series of adult MELAS patients. Ultimately, only randomized controlled trials may demonstrate safety and efficacy of these oral treatments in MELAS patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


