Journal of Neurology (2019) 266:245–246
https://doi.org/10.1007/s00415-018-9090-6

LETTER TO THE EDITORS

Whether NO-precursors are truly beneficial for stroke-like episodes remains unsolved

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Received: 7 October 2018 / Accepted: 8 October 2018 / Published online: 15 October 2018

Dear Sirs,

With interest we read the article by Koga et al. [1] about a study of 10, respectively, 13 patients with MELAS due to the mtDNA mutation m.3243A > G who received intravenous, respectively, oral L-arginine to treat an acute stroke-like episode (SLE) or to prevent the recurrence of a SLE, respectively. We have the following comments and concerns.

A major shortcoming of the study is that heteroplasmy rates of the mtDNA variant m.3243A > G were not considered in the interpretation of the results. We should be informed if the therapeutic effect was dependent on heteroplasmy rates in the muscle, hair follicles, skin fibroblasts, buccal mucosa cells, lymphocytes, or urinary epithelial cells. Heteroplasmy rates may strongly influence the phenotype of an mtDNA variant [2].

A second shortcoming is that seizures, respectively, paroxysmal activity on EEG was not considered in the therapeutic management of SLEs. Since one of the hypotheses for the occurrence of SLEs is that seizures may trigger, maintain, or enhance a SLE [3], it is crucial that all patients experiencing a SLE undergo EEG recording and appropriate modification of their antiepileptic drug (AED) therapy or beginning of an AED therapy if indicated. It has been even proposed to supply all patients with a SLE with AEDs, irrespective of the presense of seizures or seizure activity on EEG [3]. Since seizures are a strong trigger or enhancer of SLEs, we should be informed in how many of the included patients SLEs were accompanied by seizures requiring modification of an established AED therapy or beginning of an AED treatment.

The concept of administering a vascular therapy in the absence of a primary vascular disease is contradictory and requires re-evaluation. Stroke-like lesions (SLLs), the morphological equivalent of an SLE, are per definition not confined to a vascular territory, suggesting that macroangiopathy does not play a major role in the development of a SLE. However, secondary to the territorial metabolic defect arteries located within the SLL may be affected by the metabolic defect. Such a secondary vasculopathy has been reported in patients with mitochondrial myopathy in which muscle biopsy may show succinate-dehydrogenase (SDH) hyper-reactive arterioles within muscle tissue [4]. Since nitric oxide (NO)-precursors generally have a dilative, anti-vasospasmic effect [5], contraction or stenosis of such arteries may resolve upon the administration of L-arginine [5]. To sufficiently assess if NO-precursors are effective, we should know about the results of the perfusion-weighted imaging (PWI) studies on MRI. SLE may go along with hyper- or hypoperfusion in the acute stage of a SLE [6].

Another shortcoming of the study is that it was uncontrolled. Thus it cannot be reliably assessed if L-arginine was superior to placebo. If the authors regard oral L-arginine as effective, why did those receiving L-arginine during an SLE not receive oral L-arginine interictally? Vice versa, why did those receiving oral L-arginine interictally, not receive L-arginine during the acute stage of a SLE?

A further shortcoming of the study is that drugs other than L-arginine or AEDs were not reported in the included patients. Since L-arginine and AEDs may interfere with various other drugs, it is crucial that regular medication of each included patient is reported. We also need to know kidney and liver function parameters.

The oral L-arginine trial lasted between 3/2009 and 6/2011. The intravenous L-arginine trial lasted between 12/2008 and 3/2011 [1]. How is it possible that five patients participated in both trials since both trials were carried out at the same time? This discrepancy needs to be addressed.

It is not comprehensible that 18, respectively, 20 patients were analysed for the efficacy and safety of L-arginine, although only 13, respectively, 12 finished the trial. This discrepancy needs to be solved. Furthermore, it is inappropriate

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to include 15 patients and to assess the effectivity of L-arginine only in 13 patients because 2 patients did not complete the 2-year clinical trial. It is crucial that the two excluded patients are included in the evaluation. Generally, the highly variable numbers of patients included, treated, and evaluated is rather confusing than convincing.

Overall, we do not agree that the study design is appropriate to demonstrate a beneficial effect of either oral or intravenous L-arginine. To unambiguously demonstrate a beneficial effect, it would be necessary to conduct a double-blind, placebo-controlled trial. In addition to the inappropriate study design, influences of heteroplasmy rates and of co-medication on the possible effect of L-arginine need to be considered. Following these lines of argumentation, we do not agree that there is currently sufficient evidence to conclude that L-arginine alone has a significant beneficial effect on SLEs in MELAS patients.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical standards The study was approved by the local ethics comittee.

Informed consent Informed written consent was obtained from all patients.

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