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Correspondence

Microvascular endothelial dysfunction in mitochondrial stroke-like episodes supports use of intravenous L-arginine

Dear Editor,

We appreciate the thoughtful Letter to the Editor by Drs. Finsterer and Zarrouk-Mahjoub [1] in response to our recent publication in *Molecular Genetics and Metabolism:* "8-year retrospective analysis of intravenous arginine therapy for acute metabolic strokes in pediatric mitochondrial disease [2]". While the underlying pathophysiology of acute stroke-like episodes (SLEs) in mitochondrial disease remains incompletely understood, vascular endothelial dysfunction due to altered nitric oxide metabolism is the cause for at least a subset [3–9]. However, mitochondrial disease SLEs are due to dysfunction of CNS microvasculature, not large arteries, explaining their absence of a vascular distribution [10]. Similarly, we agree that rather than large vessel vasospasm, a pathophysiologic mismatch occurs between metabolic activity and microvascular flow. This is mediated by abnormal nitric oxide metabolism and results in insufficient blood flow to support neuronal metabolic demand [11].

Mitochondrial disease SLEs are frequently followed by cytotoxic edema, a likely consequence of ischemia from microvascular spasm, as evidenced by diffusion restriction and decreased apparent diffusion coefficient (ADC). These findings may be proceeded by increased ADC, which is consistent with vasogenic edema and possibly represents abnormal autoregulation of the vascular endothelium due to mitochondrial dysfunction [12]. Thus, the occurrence of transient vasogenic edema is not inconsistent with the hypothesis that mitochondrial disease SLEs result from altered nitric oxide flux with vascular endothelial dysfunction.

Ultimately, we agree that a multi-center prospective trial is required to fully evaluate the efficacy of intravenous arginine therapy. We hope our retrospective report, which supports intravenous arginine as a low-risk and potentially beneficial intervention at the time of acute SLEs in diverse genetic etiologies of pediatric mitochondrial disease, encourages pursuit of prospective clinical trials. Until then, our analysis suggests that recent expert consensus practice guideline recommendations should be followed regarding consideration of intravenous arginine therapy for mitochondrial disease patients who experience acute SLEs [13].

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