Stroke-like Episodes in MELAS are not Caused by Cerebral Vasculopathy

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Dear Editor

We reviewed the article by Goel et al. on a 19-year-old male with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) due to the m.3243A>G variant in MT-TL1, who presented with seizures (for 5 years), hypoacusis (for 4 years), basal ganglia calcification, cognitive decline, short stature, hypogonadism, and a stroke-like episode (SLE) with visual field defects, migraine-like headaches, and vomiting.[1] The antiepileptic drug was switched from valproic acid to levetiracetam, and a mitochondrial cocktail was added.[1] The study is interesting, but some points should be discussed.

The first point is that the tissue in which the m.3243A>G variant was detected was not mentioned.[1] It is crucial to know whether the MT-TL1 variant was found in the blood, oral mucosal cells, urinary epithelial cells, muscle cells, hair follicles, or skin fibroblasts, as some of these tissues may be clinically affected while others are clinically unaffected. There is also no information on heteroplasmy rates, mtDNA copy number, haplotype, mutations in nDNA, tissue distribution, and environmental factors, all of which strongly influence the phenotype. To establish a genotype–phenotype correlation, it is crucial to know these influencing factors.

The second point relates to the identification of a stroke-like lesion (SLL), the morphological equivalent of an SLE, in multimodal MRI.[1] SLLs can be hyperintense not only on T2/FLAIR, but also on diffusion-weighted images (DWI) and perfusion-weighted images (PWI).[2] They are hypointense on oxygen extraction fraction (OEF) MRI and hypometabolic on FDG positron emission tomography (PET).[1] SLLs are not confined to a vascular area and typically enlarge over several days until they reach a nadir, after which they regress and eventually end up as normal brain tissue, cyst, laminar cortical necrosis, focal atrophy, white matter lesion, or toenail sign.[1] Therefore, other critical MRI modalities should have been described, and long-term follow-up MRI results should have been provided.

The third point relates to the discrepancy between the high serum lactate levels (11.6 mmol/L) and the "unremarkable" muscle biopsy findings. Since lactate usually originates from muscles or blood cells,[3] it should be explained whether the high serum lactate originated from the brain, myocardium, or other tissue. It should also be explained why the patient had elevated creatine kinase levels but normal muscle biopsy findings.[1] Was the biopsy examined only by light microscopy or also by immunohistochemistry or electron microscopy?

The fourth point is that cerebrospinal fluid (CSF) findings were reported as normal, but it was not mentioned whether CSF lactate was measured or not. Since the magnetic resonance spectroscopy found an increased lactate peak, it is conceivable that the CSF lactate was also increased.

The fifth point is that we disagree with the notion that SLEs are due to cerebral vasculopathy.[1] Since SLLs are not confined to a vascular territory, they cannot originate from vasculopathy. More likely, SLLs are due to metabolic breakdown with consecutive spreading of the metabolic defect. Seizures are also unlikely to be the universal trigger of SLL, as there are SLEs in the absence of seizures.[4]

Finally, no reference limits were reported for the serum levels of parameters shown in the list of the case description. Without reference limits, it is difficult to interpret which of the parameters was increased, decreased, or normal. It is also not conceivable that the 19-year-old index patient could decline genetic testing of his siblings. Was the index patient the guardian of his siblings?

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