

Letter to the Editor

Morphological Diversity of Stroke-Like Lesions May Depend on Heteroplasmy Rates and Haplotypes

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Josef Finsterer, MD, PhD**Keywords:** mtDNA, stroke-like episode, stroke-like lesion, mitochondrial disorder, oxidative phosphorylation.

With interest we read the article by Hongo *et al.* about a retrospective study of 13 patients with MELAS due to the variant m.3243A>G who altogether experienced 44 stroke-like episodes (SLEs) associated with 29 classical stroke-like lesions (SLLs) and 15 non-classical SLLs (Hongo, Y. *et al.*, 2019). Non-classical SLLs developed more frequently in early-onset mitochondrial disorder (MID) (Hongo, Y. *et al.*, 2019). In 2 adult-onset MIDs stroke-like episodes (SLEs) began as subacute encephalopathy (Hongo, Y. *et al.*, 2019). The other SLEs occurred acutely. We have the following comments and concerns.

A shortcoming of the study is that heteroplasmy rates (amount of mutated mtDNA in a cell) of the m.3243A>G variant were not provided (Hongo, Y. *et al.*, 2019). Knowing heteroplasmy rates in affected and not affected tissues is crucial, as the severity of the phenotype may increase with the heteroplasmy rate (Majamaa-Voltti, K. A. M. *et al.*, 2006). It is conceivable that heteroplasmy rates differed between the classical SLLs and the non-classical SLLs. Since there are indications that heteroplasmy rates can increase with disease duration (Majamaa-Voltti, K. A. M. *et al.*, 2006), it is also conceivable that disseminated SLLs were associated with short disease duration and the classical type of a SLL with long disease duration. Morphological appearance of a SLL may also depend on the haplotype why we should know if the 13 included patients belonged to the same haplogroup or not.

Since SLLs are frequently associated with epileptogenic activity (Finsterer, J. 2018), we should know if there was a difference between classical SLLs and the atypical SLLs with regard to associated epileptogenic activity on EEG. It would be also interesting to know if there was a difference between the classical and atypical SLLs with regard to response to treatment. Since only scarce information was provided about the applied treatment, we should know which type of individual treatment was applied and if the response to treatment was different between the two groups.

Though multimodal MRI was applied, no ADC maps were evaluated. Assessment of ADC maps is crucial as the differentiation between ischemic and vasogenic lesion on MRI is only possible by application of DWI and ADC maps together. Application of ADC is necessary as classical SLLs may occasionally present with ischemic areas within the lesion.

A further shortcoming is that the family history was not provided. Knowing the family history is crucial as three quarters of the patients may have inherited the mutation from their mother (Poulton, J. *et al.*, 2017) and that affected patients potentially transmit the variant to their offspring (Poulton, J. *et al.*, 2017). Thus, for adequate genetic counselling it is crucial to provide a family tree with at least three generations to guide the consultant sufficiently through all open questions.

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Though SLLs, the morphological correlate of SLEs, predominantly occur in MELAS, they may also occur in other specific mitochondrial syndromes, such as MERRF, Leigh syndrome, LHON, and CPEO (El-Hattab, A.W. *et al.*, 1993-2019). Additionally, SLLs may not only occur supra-tentorially, but also infra-tentorially, including the brain stem.

Treatment of SLEs not only includes NO-precursors but also antioxidants, steroids, antiepileptic drugs (AEDs), and the ketogenic diet. We should be informed which treatment was applied to each individual patient, which dosages were applied, and if the applied therapy had a beneficial effect with or without side effects. Knowing the therapeutic effect of anti-SLL measures is crucial as this effect may strongly influence the outcome.

Overall, this interesting study has a number of shortcomings which need to be addressed before re-interpreting the results. Morphological diversity of SLLs encountered in the present study should be related to the genetic background implying that treatment options need to be invented which are more specific depending on the morphological expression of a SLLs should not only be expected in MELAS.

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