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Stroke-Like Lesions in NIID Patients Differ Morphologically and Pathophysiologically from MELAS

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LETTER TO THE EDITOR

We read with interest the article by Shi, *et al*., on the comparison of stroke-like episodes (SLEs) and stroke-like lesions (SLLs) between patients with neuronal intranuclear inclusion disease (NIID) (n=23) and patients with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (n=13) [Shi, Y. *et al*., 2024]. It was found that 11 of the 23 NIID patients had SLLs in the cortico-medullary junction [Shi, Y. *et al*., 2024]. NIID patients with SLE had more frequent headaches, seizures and sleep disturbances compared to patients without SLE [Shi, Y. *et al*., 2024]. Clinical manifestations, laboratory test results, neuroimaging and muscle biopsy findings overlapped between NIID and MELAS patients [Shi, Y. *et al*., 2024]. Older age at first SLE onset, movement disorders on admission, and hyperintensity in the corpus callosum were associated with NIID with SLE [Shi, Y. *et al*., 2024]. NIID patients were found to have phenotypic features of MELAS [Shi, Y. *et al*., 2024]. The study is impressive, but some points should be discussed.

The first point is that there is no definition of SLE or SLL [Shi, Y. *et al*., 2024]. SLEs in mitochondrial disorders (MIDs) are characterized by subacute onset hemiparesis, hemianopia, aphasia, headache, vomiting, seizures or hypoacusis [Alves, C. A. P. F. *et al*., 2023]. SLLs in MIDs are dynamic, i.e. they initially enlarge to a maximum value and then shrink again [Finsterer, J, 2023]. They may end up as a white matter lesion (WML), laminar cortical necrosis (LCN), cyst, toenail sign or normal brain tissue [Finsterer, J, 2023]. SLL show a characteristic pattern of hyperintensity on T2/FLAIR, diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) and hypointensity on OEF [Finsterer, J, 2023]. FDG-PET can show hypometabolism and magnetic resonance spectroscopy (MRS) can show a lactate peak [Finsterer, J, 2023]. Did all included MELAS patients fulfil these characteristics of SLL?

The second point is that MELAS is usually diagnosed according to the Japanese criteria or the Hirano criteria [Yatsuga, S. *et al*., 2012; Hirano, M. *et al*., 1992]. However, there was no mention in the methods section that the included MELAS patients met either of the two criteria.

The third point is that it is unclear whether all 13 MELAS patients tested positive for a pathogenic mtDNA variant [Shi, Y. *et al*., 2024]. Although whole-exome sequencing (WES) and long-range PCR for mtDNA deletions were performed in all SLE patients, it is not reported which point mutations or single mtDNA deletions were detected in the 13 MELAS patients. Were all 13 MELAS patients truly diagnosed genetically or were some diagnosed based on phenotype and muscle biopsy findings? In how many of the 23 NIID patients was a mtDNA point mutation or mtDNA rearrangement detected? Did any of the NIID patients have both disorders?

The fourth point is that only one of the 13 MELAS patients had DWI hyperintensity [Shi, Y. *et al*., 2024]. Since this SLL was located in the corpus callosum, it is conceivable that this particular lesion was merely misinterpreted as an SLL, as most SLLs originate in the cortex and spread either along the cortex or into the deep white matter.

The fifth point is that it is surprising that both NIID and MELAS patients had elevated serum lactate [Shi, Y. *et al*., 2024]. In how many MELAS and NIID patients was serum lactate truly elevated and was this accompanied by a lactate peak in the MRS?

In summary, it can be said that the index study has limitations that relativize the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the results of the study. Before comparing SLEs/SLLs in MELAS patients with those of NIID patients, the

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terms SLE and SLL need to be defined. In contrast to the conclusions of the index study, SLEs and SLLs are different in MELAS and NIID patients. In MELAS, not only the cortico-medullary junction but also the deep white matter and other regions may be affected.

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