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Brain Pathology in m.3243A>G Carriers

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LETTER TO THE EDITOR

We read with interest the article by Miyahara et al. who reported an autopsy study of six brains from patients carrying the mtDNA variant m.3243A>G in *MT-TL1* [Miyahara, H. *et al*., 2023]. Five of the six patients were classified as mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome [Miyahara, H. *et al*., 2023]. The sixth patient had a non-syndromic mitochondrial disorder (MID) [Miyahara, H. *et al*., 2023]. The researchers found swelling of smooth muscle cells in leptomeningeal vessels, with immunoreactivity against mitochondria antibodies, and decreased nuclear/cytoplasmic ratio of choroidal epithelial cells in all mutant cases [Miyahara, H. *et al*., 2023]. Common neuropathological findings such as cortical laminar necrosis and basal ganglia calcification were not observed in all mutant cases [Miyahara, H. *et al*., 2023]. Despite heterogeneous cortical lesions, high levels of heteroplasmy have been observed throughout the brain [Miyahara, H. *et al*., 2023]. It was concluded that an absence of a medial temporal lesion, mitochondrial vasculopathy in vessels at the leptomeninges, and increased cytoplasmic size of epithelial cells in the choroid plexus could be helpful neuropathological features in the diagnosis of MID [Miyahara, H. *et al*., 2023]. The study is excellent but raises concerns that should be discussed.

The main limitation of the study is that it does not take into account the dependence of cerebral neuropathological abnormalities in m.3243A>G carriers on the stage of the disease progression. Brains of m.3243A>G carriers are subject to permanent dynamic changes. Therefore, the knowledge gained must be interpreted in relation to the stage of the disease process. This is especially true for so-called stroke-lie lesions (SLLs), the morphological equivalent of stroke-like episodes (SLEs). Although the study did not include brains with acute SLLs, they may still be present in at least the five brains of patients who developed SLEs [Miyahara, H. *et al*., 2023]. SLEs do not always resolve but may result in white matter lesions, focal atrophy, cortical or subcortical cystic lesions, laminar cortical necrosis, or toenail sign [Finsterer, J. *et al*., 2020]. It is also known that a developing SLL can trigger the development of another SLL. Therefore, we should know whether or not SLLs in the five patients with SLEs had completely disappeared on imaging before death.

Surprisingly, only three of the six included patients had a family history positive for the disease [Miyahara, H. *et al*., 2023]. Since mtDNA variants are transmitted through the maternal line in 75% of cases [Poulton, J. *et al*., 2017], a higher familiarity rate would be expected. We should know whether all mothers and other first degree relative of the included patients were clinically and genetically examined. When heteroplasmy rates are low, phenotypic expressions may be mild or even subclinical and may not be recognised as an abnormality or disease by the affected individual.

Three of the six included patients had diabetes (patients M1, M3, M6) [Miyahara, H. *et al*., 2023]. Because poorly controlled diabetes can be complicated by diabetic encephalopathy, it is important to know whether diabetes was well or poorly controlled in the three patients with diabetes. In particular, we should know whether the last HbA1c values of these patients were elevated or in the normal range.

Regarding the three patients with epilepsy (patients M1, M3, M4) [Rai, A. *et al*., 2023], we should know whether the seizures were well controlled or whether the epilepsy in these three patients was intractable or poorly controlled. The quality of seizure control is critical as frequent seizures can be complicated by neuronal death and epileptic encephalopathy [Reimers, A. *et al*., 2023]. In addition, it is important to know which types of seizures originated from which locations in the three epilepsy patients. For example, neuropathological changes in temporal lobe

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epilepsy are found particularly in the mesial temporal lobe [Toscano, E.C. *et al*., 2023].

Another limitation is that the current medication was not related to the neuropathological findings. Since several drugs can be neurotoxic, it is important to know which drugs the six patients included were regularly taking at the time of their death.

Surprisingly, only one patient had cardiac involvement [Miyahara, H. *et al*., 2023]. Cardiac involvement is particularly common in MELAS patients [Finsterer, J. *et al*., 2000]. Were all six patients systematically and prospectively evaluated for cardiac disease?

Five of the six patients had SLEs [Miyahara, H. *et al*., 2023]. We should know the outcome of these SLEs and whether biopsies were taken from areas where the SLL was located.

Two patients received L-arginine, which is usually given to treat SLEs [Argudo, J.M. *et al*., 2022]. However, in the methods section it was mentioned that patients with SLEs were excluded from the study. This discrepancy should be clarified.

Patient M6 had a disease duration of 27y but not a single SLE. This is pretty unusual. We should know if it is possible that SLE were missed in this particular patient.

Patient M2 became ill at the age of 53 and died one year later, which is unusual. What was the cause of death in this particular patient? This patient had a brain weight of only 890g but no cognitive impairment. How does that fit?

In patient M6 with pulmonary fibrosis it is crucial to know if O2 saturation was within the normal range before the disease. Is it conceivable that the histopathological abnormalities found in this particular patient are partly due to cerebral hypoxia?

We disagree with a threshold of 60% according to the index study [Miyahara, H. *et al*., 2023]. Phenotype severity depends not only on heteroplasmy rates, but also on mtDNA copy number, haplotypes, and nuclear factors involved in mitochondrial morphology, metabolism and function [Chinnery, P.F. *et al*., 2000]. Low heteroplasmy rates may also be associated with disease.

Overall, the interesting study has some limitations and inconsistencies that call the results and their interpretation into question. Addressing these limitations would further strengthen and reinforce the statement of the study. To draw definite conclusions about histological abnormalities in m.3243A>G carriers and their usefulness for the diagnosis of MIDs, larger cohorts with similar disease stage need to be studies.

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