Pathogenicity of the variant m.12158A>G in ND5 in MELAS Remains Unsupported

Letter To The Editor

With interest we read the article by Lee et al., (2022) about a 23 years-old male with mitochondrial encephalopathy, lactic acidosis and stroke-like episode (MELAS) syndrome due to the variant m.12158A>G in ND5 with a heteroplasmy rate of 45.5% in blood lymphocytes. The study is appealing but raises the following comments and concerns. (Lee, H. et al., 2022).

The main limitation is that the pathogenicity of the variant remains unproven. The variant did not segregate with the phenotype within the patient’s family. No cybrid studies had been carried out. No biochemical investigations were performed, and no single fiber investigations were done. Applying the Yarham score, the patient reaches only a score of >6, which classifies the variant only as “neutral” (Finsterer, J. et al., 2018).

We are not convinced that the lesion presented in figure 1 is truly a stroke-like lesion (SLL), the morphological correlate of a stroke-like episode (SLE) (Lee, H. et al., 2022). Only T2-weighted images are shown. However, at least the results of other MRI modes should have been provided. SLLs typically show up as hyperintensity on diffusion weighted imaging, perfusion weighted imaging, as hypointensity on oxygen-extraction fraction MRI, and as hypometabolism on FDG-positron emission tomography (Finsterer, J., & Aliyev, R. 2020).

The patient also had a right-sided cerebellar lesion, which was not shown (Lee, H. et al., 2022). SLLs in the cerebellum are, if existing at all, rare (Taieb, G. et al., 2017). Applying the epileptogenic hypothesis as the pathophysiological mechanism of the cerebellar lesion, a seizure could not have triggered the lesions as cerebellar seizures have not been reported.

The unilateral lesion in the brain does not explain paraparesis of the lower limbs (Lee, H. et al., 2022). We should know if there was also a brainstem lesion, if the patient had myopathy, or if polynuropathy was diagnosed.

Overall, the interesting study has several limitations which should be met before drawing final conclusions. The pathogenicity of the variant remains unproven and the patient neither fulfils the Japanese or Hirano criteria for diagnosing MELAS.

REFERENCES