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Letter to the Editor

When Assessing the Cognitive Functions of MELAS Patients, Confounding Factors should be Taken into Account

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Letter to the Editor

We read with interest the article by Winqist *et al*. on cognitive impairment, defined as impairment in at least five of seven cognitive domains, in 45 patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) [1]. Cognitive impairment was found in 16 of the patients, six of whom had severe cognitive impairment [1]. Cognitive impairment included impaired abstract thinking, memory problems, motor dysfunction, and executive problems [1]. Executive functions were most severely affected, verbal memory least severely affected, and cognitive dysfunction correlated positively with heteroplasmy rates [1]. The study is impressive, but some points should be discussed.

The first point is that the neuropsychological findings did not correlate with the results of cerebral imaging [1]. Cognitive deficits in MELAS depend heavily on the location of stroke-like lesions and their residues in the brain. Depending on the location of the lesions, patients may exhibit cognitive deficits in different domains [2]. The six main areas of cognitive function, including complex attention, executive functions, learning and memory, language, perceptual-motor functions, and social cognition, are assigned to different areas of the brain [2]. In general, the frontal lobe is associated with executive functions such as planning and decision-making, the temporal lobe with memory and language, the parietal lobe with sensory integration, and the occipital lobe with visual processing [3]. Therefore, we should be aware of the results of cerebral MRI at the time of cognitive testing. How many of the included patients had lesions in the frontal, temporal, and parietal lobes, or a combination thereof?

The second point is that cognitive impairments in MELAS can also depend on the duration of the disease [4]. The longer the duration of the disease, the more likely it is that a MELAS patient will develop cognitive impairments.

The third point is that cognitive impairments may also depend on the type and frequency of seizures. Since one of the phenotypic characteristics of MELAS is epilepsy [5] and since stroke-like episodes with seizures occur, among other things, it would have been useful to include the frequency and type of seizures in the analysis. Patients who frequently suffer from status epilepticus or poorly controlled epilepsy may be more likely to develop cognitive impairments than patients with well-controlled epilepsy.

The fourth point is that patients were not tested for comorbid depression [1]. Since depression can mimic cognitive dysfunction, it would have been helpful to rule out depression as a factor contributing to the neuropsychological findings.

Finally, it should be noted that the phenotypic expression of mtDNA variants depends not only on the heteroplasmy rate, but also on several other determining factors. It should also be taken into account that heteroplasmy was determined using cells from the oral mucosa, a tissue that is not usually clinically affected in MELAS.

Overall, the study could benefit from the inclusion of various confounding variables that influence the cognitive performance of MELAS patients.

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