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Letter to the Editor

Quantitative EEG Analysis in m.3243A>G Carriers Requires Correlation with Clinical, Genetic, and Imaging Characteristics

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Letter to the Editor

We reviewed the article by Scarabello *et al*. on a retrospective study of the ability of quantitative EEG to detect disturbances in physiological brain activity in carriers of m.3243A>G without stroke-like episodes (SLEs) and the behavior of delta bursts and epileptiform discharges in association with or without SLEs in 16 patients with mitochondrial encephalopathy, lactate acidosis, and a stroke-like episode (MELAS syndrome) or MELAS spectrum syndrome (MSS) with interest [1]. It was found that the delta-theta energy ratio (ER) increased over time in the temporal-parieto-occipital regions and that EEG curves recorded shortly after SLEs showed a higher ER, lower Higuchi fractal dimension (HD), and an increasing trend in paroxysmal activity (AR) [1]. It was concluded that quantitative EEG can reveal a disturbance of posterior background rhythms in both MELAS and MSS and that the early stages of SLE are characterized by a slowing of background activity, a reduction in the complexity of brain states, and a recurrence of paroxysmal abnormalities [1]. The study is noteworthy, but some points should be discussed.

The first point is that the study was retrospective in design, which has several disadvantages [2]. Retrospective studies carry a high risk of memory and selection bias, as researchers rely on existing, potentially inconsistent data that may have been collected for other purposes [2]. Retrospective designs may have low internal validity, making it difficult to establish a causal relationship, and may lack external validity due to differences in patient populations [2]. Data is also often missing because medical records were not created for research purposes, and confounding variables may not be measured, leading to inaccurate conclusions [2].

The second point is that the results of EEG recordings in m.3243A>G carriers depend not only on age, sex, disease duration, and antiepileptic drugs (ASMs), but also on comorbidities, disease stage, medications other than ASMs, mtDNA copy number, haplotype, presence of lactic acidosis, and mutations in nuclear mtDNA-related genes. Unless these confounding variables are included in the analysis, the results may be biased and misleading.

The third point is that no cerebral imaging results were reported [1]. Since MELAS is characterized by the occurrence of so-called stroke-like lesions (SLLs), the morphological equivalent of SLEs, it would have been essential to indicate how many of the 16 patients had a history of SLEs and in how many the SLLs had not completely disappeared after the end of the SLE. SLLs follow a typical dynamic pattern on MRI and either end up as permanent structural brain lesions (laminar cortical necrosis, white matter lesion, gray matter lesion, cyst, atrophy, toenail sign) or disappear completely without leaving any structural abnormalities in the brain tissue [3].

The fourth point is that the results of magnetic resonance spectroscopy (MRS) were not reported [1]. MRS can be used to determine whether the lactate level in the brain is elevated or normal. It is known from lactic acidosis in the brain that acidotoxicity depolarizes neuronal membranes and may thus be responsible for the hyperexcitability of neurons and the triggering of epileptiform discharges [4].

The fifth point is that the criteria used to distinguish MELAS from MSS were not specified [1]. Nor were the criteria used to diagnose MELAS specified [1]. MELAS is usually diagnosed according to the Hirano or Japanese criteria. Knowledge of the diagnostic criteria used is crucial in order to assess whether MELAS and MSS patients have been correctly classified.

The sixth point is that ER, HD, and AR were not correlated with the heteroplasmy rate, disease duration, or other clinical features of the syndrome.

Finally, it is not clear why the inclusion criteria only required at least two EEG recordings within a period of 12 years [1].

MELAS is a progressive disease characterized in the majority of patients by seizures that are either associated with or independent of SLEs. Therefore, it is imperative to monitor EEGs much more closely, unless the included patients were unexpectedly stable in their clinical course over many years.

In summary, quantitative EEG analysis of normal cortical activity to assess the progression of brain involvement in carriers of the m.3243A>T variant over time requires a prospective design, regular EEG recordings at fixed intervals, regular cerebral imaging, and measurement of lactate acidosis in serum and cerebrospinal fluid.

Declarations

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