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Letter to the Editor

EEG Changes Over Time in m.3243A>G Carriers may be Due not only to Disease Progression but also to Several Other Cofactors

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Letter to the Editor

We read with interest the article by Scarabella *et al*. on a retrospective analysis of longitudinal EEG changes in 16 m.3243A>G subjects in which delta-theta/alpha energy ratio (ER), Higuchi fractal dimension (HD) and paroxysmal activities (AR) were quantified [1]. ER increased over time in the parieto-temporal regions, and EEG traces shortly after a stroke-like episode (SLE) showed increased ER and decreased HD [1]. It was concluded that quantitative EEG metrics reveal progressive brain dysfunction and that SLEs are followed by a background slowing reduction in brain state complexity and recurrence of paroxysmal abnormalities [1]. The study is noteworthy, but several points should be discussed.

The first point is that the latency between the two or three EEGs varied widely, ranging from a minimum of 1 year to a maximum of 12 years [1]. Since the latency was not standardized, the results may also vary depending on the length of time between the two recordings. We should know whether a progression of the analysed EEG indices could also be documented in patients with a short latency between the two EEGs or whether the progression could only be observed in patients with a long latency between the EEGs.

The second point is that m.3243A>G carriers are usually multimorbid, either due to the underlying genetic defect or secondarily due to their lifestyle or comorbidities unrelated to lifestyle or the mtDNA defect [2]. These disorders may require treatment with medication, which in turn may affect EEG activity in addition to anti-seizure medication (ASM). Therefore, we should know how many of the 16 included patients were receiving regular medications that could have an impact on EEG recordings. Since ASMs or other medications may have changed over time, we should also know how many of the included patients' medications remained the same at the first and second recording and to what extent a change in medication between the first and second recording may have affected the results.

The third point is that no results of cerebral imaging were reported [1]. Since EEG 1 was recorded in three patients in temporal relation to an SLE and EEG 2 was recorded in two patients during an SLE, we should know what cerebral lesions were detected in these patients and how they evolved over time. Imaging should also have been performed in the other patients, as stroke-like lesions (SLLs), the morphologic equivalent of SLEs, do not always disappear completely, but can also end up as atrophy, cyst, white matter lesion, laminar cortical necrosis, or toenail sign [3]. The extent and quality of the cerebral lesion can strongly influence the morphology of the EEG traces.

The fourth point is that the family history was not reported [1]. Since mtDNA variants are passed on through the maternal line in 75% of cases [4], we should know in how many of the m.3243A>G carriers the mutation was inherited and in how many it occurred de novo. In how many of the included patients was the family history positive for epilepsy and in how many cases were first-degree relatives clinically affected by the mitochondrial disorder?

The fifth point is that the heteroplasmy rates were not correlated with the EEG indices [1]. Since heteroplasmy rates may be a determinant of phenotype [5], they should be correlated with EEG indices to assess whether a causal relationship exists.

The sixth point is that the m.3243A>G variant can also be associated with diabetes. Therefore, we should know how many of the 16 patients had diabetes and in how many of them the diabetes was poorly controlled and complicated by encephalopathy. Patients with diabetic encephalopathy should have been excluded. It is also conceivable that some patients had migraine, which is a common feature of m.3243A>G carriers. Migraine has been reported to be associated with EEG abnormalities. Those with migraine could also confound the results.

Some inconsistencies should also be resolved. In the methods, it was stated that persistent SLE was an exclusion criterion, but in the results section, two patients with persistent SLE during EEG recording were reported. This discrepancy should be

clarified and the two patients excluded from the analysis. It should also be explained why only 81% of patients received ASM. Did not all included patients have epilepsy, or were a number of patients seizure-free? It is also surprising that the pharmacological treatment did not differ between the two or three time points. Since the mean latency period between the first and second recordings was four years, it is quite unlikely that no changes in medication were made. In particular, ASMs and mitochondrial cocktails are often altered in their composition when clinical progression occurs.

Overall, EEG changes over time in m.3243A>G carriers may be related not only to disease progression, but also to changes in concomitant medication and the presence of comorbidities. To assess whether EEG changes over time in m.3243A>G subjects are truly due to progression of cerebral involvement, larger and more homogeneous cohorts should be analysed in terms of rate of progression, current state of disease, and the presence of comorbidities.

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