Prevalence Figures about Phenotypic Features of tRNA (LYS) Variants Should Derive from Prospective but Not Retrospective Investigations

Abstract:

Keywords: mtDNA, mitochondrial, central nervous system, myopathy, prevalence, multisystem.

LETTER TO THE EDITOR

With interest we read the article by Ji, K. et al., 2020 about a retrospective study of 23 Chinese patients carrying a pathogenic tRNA(Lys) variant, of whom 13 patients were classified as symptomatic (Ji, K. et al., 2020). The authors concluded that tRNA(Lys) variants are commonly associated with myo-neuropathy necessitating the investigations for tRNA(Lys) mutations in patients with pure myo-neuropathy (Ji, K. et al., 2020). We have the following comments and concerns.

It is contradictory to state in the method section that all 23 patients underwent needle electromyography (EMG), nerve conduction studies (NCS), electrocardiography (ECG), echocardiography, magnetic resonance imaging (MRI) of the brain and electroencephalography (EEG) and to state in the results that only 11 patients underwent needle EMG and only 9 patients underwent muscle biopsy. Furthermore, cerebral MRI and EEG findings are not mentioned or discussed at all. In this respect we should know why asymptomatic patients underwent EMG, EEG, MRI, and NCS.

The conclusions are highly questionable for several reasons. The study had a retrospective design implying that not all included patients underwent the same investigations. Only 11 patients underwent needle EMG and only 9 patients underwent muscle biopsy. Cerebral MRI was not reported for any patient at all. If not all patients were investigated according the same protocol, it is conceivable that a number of phenotypic manifestations, either in symptomatic or asymptomatic patients, were missed consequently reducing corresponding prevalence figures of central nervous system (CNS) or muscle manifestations.

The study had a retrospective design implying that not all included patients underwent the same investigations. Only 11 patients underwent needle EMG and only 9 patients underwent muscle biopsy. Cerebral MRI was not reported for any patient at all. If not all patients were investigated according the same protocol, it is conceivable that a number of phenotypic manifestations, either in symptomatic or asymptomatic patients, were missed consequently reducing corresponding prevalence figures of central nervous system (CNS) or muscle manifestations.

Particularly missing are imaging studies of the CNS. Knowing the results of cerebral imaging studies is crucial, as tRNA (Lys) variants may manifest on imaging without a concomitant clinical phenomenon. Thus, CNS involvement can be asymptomatic but present on cerebral computed tomography (CCT) or cerebral magnetic resonance imaging (MRI). CCT scans respectively MRI may show asymptomatic focal or diffuse atrophy, white matter lesions, grey matter lesions, cysts, aneurysm formation, ectasia of arteries, pituitary adenoma, basal ganglia calcification, the toenail sign, or optic atrophy. Prevalence of CNS involvement is only reliable if truly all patients underwent cerebral MRI and if these findings were included in the evaluation. Additionally, magnetic resonance spectroscopy (MRS) needs to be included in the evaluation, as it may show a reduced N-acetyl-aspartate (NAA) peak and an increased lactate peak. Thus, the conclusion that one third of the included patients did not have CNS involvement is not comprehensible given the potential presence of subclinical abnormalities on cerebral MRI.
Inherent to the retrospective design is also that the 9 asymptomatic patients were not prospectively investigated for subclinical CNS involvement. Thus, there is a strong need to prospectively investigate the 9 asymptomatic mutation carriers for CNS involvement. Classifying 9 patients as asymptomatic without considering MRI findings, is not justified.

A further shortcoming of the study is that the size of the investigated group is small. The authors draw conclusions from only 13 symptomatic patients carrying a tRNA (Lys) variant without including cerebral MRI or EEG. The small number of patients does not allow drawing reliable conclusions.

Furthermore, the prevalence of various phenotypic features was calculated for Chinese patients, thus for a certain haplotype. Since haplotype determines the phenotypic expression, it is crucial that the evaluation is repeated for patients carrying other haplotypes. Caucasian patients may present with completely different phenotypes. In this respect we should know the tuna copy number which also determines the phenotype.

Missing are also repeated EEG recordings, since a single EEG may not be meaningful.

Finally, if 23% of the m.8344A>C carriers present with MERRF, one cannot speak of a rare manifestation.

Overall, the interesting study by Ji et al., has a number of shortcomings, which should be addressed before drawing general conclusions. A prospective design should be applied, patients should be prospectively investigated for subclinical involvement of various organs, mtDNA copy number, and the haplotype should be included in the evaluation.

REFERENCES