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Letter to the Editor

Assessing Genotype-phenotype Correlations in Mitochondrial Disorders Requires Genetic and Prospective Clinical Studies

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We read with interest the article by Ozlu *et al*. about a retrospective, single-centre observational study of 50 patients diagnosed with a mitochondrial disorder (MID) collected over a 10-year period [1]. A pathogenic nDNA mutation was identified in 27 patients, a pathogenic mtDNA mutation in 17 patients, and no causative mutation in 6 patients. The phenotypes of these patients were very different and the age of onset ranged from 9 to 36 months [1]. The study is impressive, but some points require further discussion.

The first point is the retrospective design [1]. A retrospective design has the disadvantage that data can be missing, the accuracy of the data cannot be easily checked, desired missing or new data can no longer be generated, and clues for specific investigations are often not comprehensible. A retrospective design also does not allow for follow-up studies. We should know whether all patients were prospectively evaluated for multisystem involvement, how much data of the cohort was missing, and the extent to which this affected the results. How many patients were excluded due to missing data and incorrectly coded by ICD codes and therefore not included? It is also unclear whether only inpatients, outpatients, or both were included in the study. Prevalence rates of phenotypic traits are unreliable unless they are systemically screened for in all patients.

The second point is that the diagnosis was not genetically confirmed in six patients. Since histological, immune-histological, and biochemical examinations of the muscle can also be abnormal secondarily in non-MID patients [2], a diagnosis of MID is only possible if a pathogenic variant has been documented in either the mtDNA or nDNA. Therefore, the 6 patients without a genetically confirmed MID should be excluded from the study.

The third point is that there is a discrepancy between the abstract, which states that 50 patients with genetically confirmed MID were included and the methods and results section, which states that 6 patients did not have a genetic diagnosis. This discrepancy should be resolved.

The fourth point is that ICD codes from non-MIDs (e.g. Friedreich ataxia) were included in the search. What was the reason for including this ICD code when a few lines later Friedreich ataxia was excluded from further evaluation?

A fifth point is that it is unclear why patients <6 years of age were excluded from the analysis. What was the reason for excluding these patients?

A sixth point is that stroke-lesions (SLLs) have been reported in subcortical regions such as the basal ganglia, thalamus, midbrain, pons, cerebellum, and medulla [1]. Since SLLs are thought to have a cortical origin, it is quite unlikely that they occur in the regions described. Did these subcortical lesions meet the diagnostic criteria of SLL [3]? Were these lesions hyperintense on T2/FLAIR, DWI, and PWI and hypointense on OEF? Did these subcortical lesions demonstrate hypometabolism on FDG-PET? Were they confined to one vascular territory or not? Did they show a lactate peak and a reduced NAA peak on MR-spectroscopy? Did all patients with SLL also have seizures, which are considered one of the most common triggers of SLLs?

A seventh point is that MERRF and Kearns-Sayre syndromes should not be classified as common MIDs [1]. The prevalence of MERRF is estimated at 0-1.5/100000 [4, 5] and that of KSS at <1.6/100000 [6].

Since data collection ended in December 2022, it can be assumed that some patients suffered from SARS-CoV-2 infection (SC2I) or received a SARS-CoV-2 vaccination (SC2V). Did SC2I or SC2V affect the phenotype in any patient?

In summary, MIDs should be diagnosed based on clinical, histological, biochemical, and genetic examinations. SLLs should only be diagnosed if imaging criteria are met.

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