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Letter to the Editor

Single Large-Scale mtDNA Deletions can Manifest Phenotypically with Movement Disorders

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Letter to the Editor

We read with interest the article by Zhao *et al*. about a 25-year-old female patient with a mitochondrial disease (MID) due to the single mtDNA deletion m.8647-16082del [1]. Phenotypically, the disease manifested with mild cognitive impairment, hearing loss, head tremor, diabetes, mild lactic acidosis, and myopathy [1]. Despite a mitochondrial cocktail, the head tremor remained unchanged during the one-year follow-up [1]. The study warrants discussion.

First, mitochondrial diseases (MIDs) typically manifest as multisystem disorders, either at the onset of the disease or during its progression [2]. Therefore, MID patients should be prospectively screened for subclinical involvement of organs other than the brain, muscles, ears, or endocrine system. Of particular interest is the question of whether the heart is also affected, as this often determines the course of the disease.

The second point is that the family history was not provided [1]. To assess whether the mutation was inherited or arose de novo, it is essential to know if first-degree relatives were clinically affected or if the mother or another first-degree relative carried the mtDNA deletion of the index patient. Single mtDNA deletions are inherited maternally in 4% of cases [3]. Knowledge of the genetic background is crucial for assessing disease progression and providing genetic counseling.

The third point is that tremor, including head tremor, is not an uncommon phenotypic manifestation in MIDs. It has been previously described in MID patients [4]. In addition to tremor, MIDs can also be associated with other movement disorders such as Parkinson's disease, chorea, hemiballismus, dystonia, ataxia, myoclonus, choreoathetosis, restless legs syndrome, or Tourette syndrome [5].

The fourth point concerns the heteroplasmy rates in different tissues, which were not specified. To assess the tissue distribution of the variant, heteroplasmy rates in various clinically affected and unaffected tissues would be helpful. The mtDNA copy number, the tissue distribution, as well as nuclear variants that could have further influenced the phenotype, were also not mentioned.

Fifthly, we disagree with the classification of the head tremor as isolated. The index patient already exhibited multisystem involvement within the context of MID.

In summary, patients with pathogenic single mtDNA deletions require comprehensive diagnostic evaluation for multisystem disease, family screening to assess the heritability of the pathogenic variant, and identification of phenotype-determining factors.

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