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Letter to the Editor

Cerebral Imaging Abnormalities in Single mtDNA Deletion Carriers are more Diverse than Expected

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Letter to the Editor

We read with interest the article by Sobeh *et al*. on a retrospective study to characterize the clinical and neuroradiological manifestations in 11 patients with single mtDNA deletions that manifested clinically as Kearns-Sayre syndrome (KSS), Pearson syndrome, and chronic progressive external ophthalmoplegia [1]. Cerebral magnetic resonance imaging (MRI) was abnormal in only seven patients and showed symmetrical T2/FLAIR hyperintensities with/without diffusion changes involving the dorsal brainstem in 7/7, the cerebellum in 6/7 and the globi pallidi in 6/7 [1]. MR spectroscopy (MRS) of the basal ganglia showed an increased lactate peak in 3/7 patients [1]. Subcortical and deep white matter abnormalities were noted in 3 patients [1], imaging progression was observed in four patients [1]. The study is noteworthy, but several points should be discussed.

The first point is that cerebral imaging results are highly dependent on disease stage. Since mitochondrial disorders (MIDs) are usually progressive diseases, the type and intensity of imaging increases with the duration of the disease, as shown in four patients. Therefore, it should be indicated when the disease started and how long it has lasted.

The second point is that the heteroplasmy rate (ratio between mutant and wild-type mtDNA) was not included in the analysis. Heteroplasmy rate is a recognized determinant of phenotypic expression, so it must be included in the analysis. Determinants that should be considered responsible for the phenotype also include mtDNA copy number, haplotype and nuclear DNA influences.

The third point is that this was a retrospective design [1]. Retrospective designs have several disadvantages [2]. Since they are based on the review of medical records that were not originally intended for research purposes, the data may be incomplete. Selection and recall errors also affect the results, and the reasons for treatment differences between patients and those lost to follow-up cannot be determined, which can lead to bias [2]. The retrospective design has the disadvantage that necessary examinations were not systematically performed on every patient. This is one reason why the MRS was only performed in seven patients. Missing data can lead to misinterpretation of the available data.

The fourth point is that no angiographic data were reported. MIDs, including those due to single mtDNA deletions, can manifest not only in the parenchyma but also in the cerebral vasculature [3]. Abnormalities of the cerebral vasculature in MIDs include the formation of aneurysms, dissections, ruptures or vasospasms [3]. Therefore, digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA) data of the included patients should also be reported.

The fifth point is that no results of nDNA were reported [1]. Mutations in certain nuclear genes can cause not only multiple mtDNA deletions or mtDNA depletion (reduction in the number of mtDNA), but also single mtDNA deletions [4]. Therefore, it would have been useful to also perform whole-exome sequencing (WES) to determine whether any of the reported mtDNA deletions are due to a nDNA mutation.

The sixth point is that the family history was not reported in detail [1]. Since single mtDNA deletions are inherited through the maternal line in 4% of cases [5], we should also know in how many patients the family history was positive for the disease.

Various other information is also missing. Regarding cerebral lactic acidosis, we should know in how many patients a CSF examination including a lactate determination was performed and how many of the patients with a lactate peak in the MRS also had increased lactate in the CSF. Since individual mtDNA deletions can also manifest with optic atrophy [6], we should know in how many of the 11 patients optic atrophy could be detected on MRI. It is also not mentioned in how many of them the pituitary gland was involved in the disease. A pituitary adenoma is a rare manifestation in KSS, but is a major determinant of the severity and course of the disease.

Overall, the phenotypic spectrum, including cerebral imaging, is broader in mtDNA deletion carriers than discussed in the index study. To assess the nature, frequency, and rate of progression of cerebral imaging abnormalities in individual mtDNA deletion carriers, prospective studies are warranted, including MRI, MRA. MRS, MRV fMRI and FDG-PET.

Declarations

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