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Letter to the editor

Consider Non-Syndromic Mitochondrial Disorders as Part of the Pediatric Phenotypic Spectrum

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With interest we read the article by Ardissone et al. about a retrospective, single-center study of 150 pediatric patients with a genetically confirmed mitochondrial disorder (MID) due to a pathogenic mtDNA variant (mtDNA point mutation or single mtDNA deletion) [1]. The study is excellent but has limitations that are cause of concerns and should be discussed.

A limitation of the study is that only syndromic MIDs were included [1]. Since MIDs often do not fit into any of the syndromic phenotypes, we should know whether these patients were deliberately excluded or did not appear at the study center at all. We should know whether the entire group of 902 patients also included patients with non-syndromic MIDs.

Another limitation is that heteroplasmy rates were only determined by estimating the densitometric ratio between wild-type and mutant mtDNA [1]. Heteroplasmy is usually determined by a number of quantitative methods, such as Sanger sequencing, high performance liquid chromatography, pyrosequencing, Snapshot, high resolution melt profiling (HRM), temporal temperature gradient gel electrophoresis (TTGE), invader assay, amplification refractory mutation system (ARMS), endonuclease method using Surveyor nuclease, and next generation sequencing (NGS) [2]. These techniques usually provide more accurate results than semi-quantitative estimation.

There is a discrepancy between the statement in the method section ("only few data were not available from all patients") and the results section ("CSF data were available from only 17 %, follow-up data only from 47%, and biochemical data only from 58 % of patients") [1]. This discrepancy should be clarified.

Another limitation is that the total observation time up to the last follow-up was not given [1]. Knowing this latency is important to assess the speed of disease progression and estimate the outcome.

There is also a discrepancy between the statement in the result section that "outcome data were evaluated from 70 patients" and the detailed description in the results section, which included 71 patients. Which number is correct?

Surprisingly, the biochemical examination was normal in almost a quarter of the patients with Leigh syndrome. We should know if these results are from studies of just muscle or fibroblasts, or if other tissues have been studied as well If only muscle or

fibroblasts were examined, we should know whether or not these tissues were clinically affected in the one quarter of the Leigh patients.

Surprisingly, only two thirds of the MELAS patients presented with stroke-like episodes (SLEs), which are pathognomonic for MELAS. We should know if this was due to the short observation or follow-up time in these patients. According to what criteria were these patients without SLE classified as MELAS? Were the Hirano or Japanese criteria applied? We should also know how "MELAS-like" was defined.

There is no mention of the underlying mutations in the PEO patients. It would be interesting to know if these patients all carried a single mtDNA deletion, a nuclear DNA-located variant, or an mtDNA point mutation.

Overall, the interesting study has limitations that call the results and their interpretation into question. With a prospective design and extensive and long-term follow-up, the study goals could be better achieved.

Keywords: mtDNA, mitochondrial, respiratory chain, melas, stroke-like episode

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Statement of Ethics: a) The study was approved by the institutional review board (responsible: Finsterer J.) at the 4th November 2022. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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