



Received: 04-04-2023  
Accepted: 14-04-2023

ISSN: 2583-049X

Letter to the Editor

## **Diagnostic criteria for MELAS: In the cluster analysis, the entire spectrum of influencing variables must be taken into account**

**Josef Finsterer**

Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

We read with interest the article by Alves *et al.* on a retrospective, single-centre study of 35 patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome with the aim of rematching these patients using a hierarchical cluster analysis and accounting for 53 clinical, neuroimaging, laboratory, and genetic variables [1]. It was found that 19 patients had classical MELAS and 16 patients had atypical MELAS and that this distinction could allow clinical and research teams to better understand the natural history and prognosis of MELAS [1]. The study is compelling, but has limitations that should be discussed.

A limitation of the study is that no gold standard was used to diagnose MELAS. MELAS is usually diagnosed using the Hirano criteria or the Japanese criteria, which could be used as a gold standard. We should know how many of the 35 included MELAS patients met any of these criteria.

When selecting the variables, it was not taken into account that MELAS is a dynamic disease with episodes of progression and regression (e.g., after a stroke-like episode, after a seizure, or after an infection). Therefore, the clinical presentation is highly dependent on the stage of the disease. A MELAS patient with a disease course over several years can present itself completely differently at onset, for example with a first seizure, and with a multisystem phenotype at an advanced stage of the disease. Therefore, a patient may be classified as classic MELAS at one time point but as atypical MELAS at another time point. Because follow-up data were available, we should know how many patients had their classification changed over time.

In addition, the MELAS phenotype is highly dependent on heteroplasmy rates, mtDNA copy number, and haplotype. These influencing factors were not taken into account in the cluster analysis. Since these factors were not reported and included in the analysis, it cannot be ruled out that the cohort studied was genetically heterogeneous, which may have contributed to the classification of 19 patients as classical MELAS and 16 patients as atypical MELAS. Furthermore, it is unclear why a heteroplasmy cut-off of 30% was chosen. A heteroplasmy rate <30% in an unaffected tissue does not rule out a pronounced MELAS phenotype.

In addition, some clinical features of MELAS were not considered. These include short stature, dysmorphism, seizures between SLLs, arrhythmias, vomiting, lactic acidosis, respiratory chain complex dysfunction, and myopathy respectively muscle biopsy findings. We should know why these phenotypic traits were not included in the cluster analysis. Before performing a cluster analysis, all MELAS phenotypic traits that have ever been described should be collected and then a decision made as to which of these should be included in the cluster analysis. We should know the criteria used to select the 53 variables that went into the cluster analysis. It is not clear why “Leigh syndrome spectrum” was included and what the difference is between “cortical visual impairment” and “vision loss at SLL onset”.

MELAS can also be due to *POLG1* variants [2soulis]. In particular, *POLG1* variants have been reported to cause MELAS/SANDO overlap syndrome [3hansen]. Patients with *POLG1* variants causing MELAS were excluded with the argument that the pathophysiology of stroke-like lesions (SLLs) might differ from that in mtDNA variants [1]. However, there is currently no evidence that the pathophysiology of SLLs differs between mutation types. Most likely, SLLs develop in the cortex to spread to subcortical regions triggered by oxidative stress. SLLs should be considered not only as a cortical pathology but also as a subcortical pathology.

It is unclear whether maternal inheritance was documented in each of the 35 cases. We should know if MELAS was truly hereditary or sporadic in some cases.

There is no mention of oxygen-extraction fraction MRI, perfusion weighted images, and of positron emission tomography, which may contribute to the characterisation of SLLs.

Overall, the interesting study has limitations that call the results and their interpretation into question. Addressing these issues would strengthen the conclusions and could improve the status of the study. For reasons of management of patients with a mitochondrial disorder, it may not be necessary to assign these patients to a specific syndrome, but to identify the underlying genetic defect and treat them symptomatically as early as possible. Lumpers have the advantage over splitters that they can begin treatment without knowing whether or not a particular phenotype fits the criteria of a particular syndrome.

### Acknowledgements

**Data availability statement:** Data that support the findings of the study are available from the corresponding author.

**Funding:** No funding was received

**Author contribution:** JF: design, literature search, discussion, first draft, critical comments, final approval.

**Disclosures:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**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.

**Keywords:** MELAS, mtDNA, MT-TL1, Respiratory Chain, Stroke-Like Episode

---

### References

1. Alves CAPF, Zandifar A, Peterson JT, Tara SZ, Ganetzky R, Viaene AN, *et al.* MELAS: Phenotype Classification into Classic-versus-Atypical Presentations. *AJNR Am J Neuroradiol*, 2023. Doi: 10.3174/ajnr.A7837.
2. Tzoulis C, Bindoff LA. Melas associated with mutations in the polg1 gene. *Neurology*. 2008; 70(13):1054; author reply 1054-5. Doi: 10.1212/01.wnl.0000307661.98694.c3
3. Hansen N, Zwarg T, Wanke I, Zierz S, Kastrup O, Deschauer M. MELAS/SANDO overlap syndrome associated with POLG1 mutations. *Neurol Sci*. 2012; 33(1):209-212. Doi: 10.1007/s10072-011-0631-3