Int. j. adv. multidisc. res. stud. 2025; 5(6):1567-1568

Received: 07-12-2025
Accepted: 17-12-2025

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

The Factors Influencing Disease Burden in m.3243A>G Carriers are Diverse and Include Disease Severity and Rate of Disease Progression

Josef Finsterer
Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

DOI: https://doi.org/10.62225/2583049X.2025.5.6.5437
Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Stefanetti *et al*. on the identification of factors influencing disease burden by examining clinical, subjective, and objective parameters, with a particular focus on distinguishing between MELAS patients and non-MELAS m.3243A>G carriers [1]. Compared to non-MELAS patients, MELAS patients had a higher disease burden, reduced physical performance, and objectively measured lower physical activity, but patient-reported outcomes did not differ between the two groups [1]. While consistency between subjective and objective measurements was found in non-MELAS patients, MELAS patients showed weak or absent correlations, which were attributed to cognitive impairment, altered symptom perception, or disease-related adaptations [1]. The study is noteworthy, but some points require discussion.

The first point is that diagnosing MELAS based solely on a positive history of stroke-like episodes (SLEs) does not meet the diagnostic criteria [2, 3]. MELAS is usually diagnosed according to the Hirano or Japanese criteria [2, 3]. According to the Hirano criteria, MELAS is diagnosed when SLEs occur before the age of 40 and seizures or dementia, lactic acidosis or ragged red fibers, normal early development, recurrent headaches, or recurrent vomiting are present [2]. According to the Japanese criteria, MELAS is diagnosed when a corresponding phenotype and a causative mutation are present [3]. Did the six patients diagnosed with MELAS really meet the Hirano or Japanese criteria? Two patients suffered their SLE after the age of 40 and therefore do not meet the Hirano criteria. Was a muscle biopsy performed on all six patients and were ragged red fibers found in all of them?

The second point is that the 16 m.3243A>G carriers were not prospectively examined for subclinical or mild clinical multisystem diseases [1]. Since m.3243A>G carriers often manifest in the heart and since cardiac involvement is a strong outcome parameter, it would have been crucial to perform at least an echocardiography, long-term ECG recordings, and long-term blood pressure monitoring. Similarly, we should know how many of the m.3243A>G carriers had myopathy, which is also a common feature of the m.3243A>G genotype.

The third point is that three of the tests used to assess disease burden were based on subjective assessments (self-reported autonomic function, self-reported physical activity, patient-reported fatigue) [1]. Self-assessments are prone to bias, so these tests should be replaced with objective measurements or removed from the analysis.

The fourth point is that the phenotypes of m.3243A>G carriers depend not only on heteroplasmy rates, but also on mtDNA copy number, haplotype, tissue distribution of the m.3243A>G variant, and heteroplasmy at disease onset [4]. These factors can strongly influence the phenotype and thus also the disease burden.

The fifth point is that the disease burden can also depend heavily on the mental constitution of the patients included. Depressed patients have greater difficulty coping with the consequences of the disease than patients without mood disorders. Depressed patients who are successfully treated with antidepressants cope with their illness more easily than depressed patients who do not take mood enhancers. Therefore, we should know the current medications of the 16 patients included, especially how many regularly took mood stabilizers. In order to assess cognitive functions, behavior, and mood in detail, patients should have undergone comprehensive neuropsychological tests, specific behavioral tests, and mood tests (e.g., questionnaires on mood disorders).

The sixth point is that Timed Up and Go, acceleration measurement, and handgrip strength depend not only on brain function but also on whether a patient suffered from myopathy or neuropathy. Since no information was reported on the latter, the study results should be interpreted with caution.

The seventh point is that the disease burden depends heavily on the stage of the disease, but no long-term results were reported.

The disease burden may increase over time, which is why the tests performed should be repeated over the course of the disease.
The eighth point is that the number of patients is too small to draw general conclusions.
In summary, assessing the factors that influence the burden of disease in m.3243A>G carriers requires comprehensive objective testing that covers all possible symptoms and functional limitations in m.3243A>G carriers. Since m.3243A>G carriers develop a multisystem disease over time, the impairment of all organs should be tested, and due to the progression of the disease, long-term studies are more meaningful than cross-sectional studies.

Declarations
Ethical Approval: Not applicable.

Consent to Participation: Not applicable.

Consent for Publication: Not applicable.

Funding: None received.

Availability of Data and Material: All data are available from the corresponding author.

Completing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval. xx: contributed to literature search, discussion, correction, and final approval.

Keywords: MELAS, m.3243A>G, mtDNA, Disease Burden, Stroke-Like Episode

References
1. Stefanetti RJ, Charman SJ, Newman J, Hallsworth K, Blain AP, Ng YS, *et al*. Outcomes misaligned in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS): Implications for trial design. Brain Commun, Sep 9, 2025; 7(5):fcaf342. Doi: 10.1093/braincomms/fcaf342
2. Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, DeVivo DC, *et al*. Melas: An original case and clinical criteria for diagnosis. Neuromuscul Disord. 1992; 2(2):125-135. Doi: 10.1016/0960-8966(92)90045-8
3. Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, *et al*. Taro Matsuoka for MELAS Study Group in Japan. MELAS: A nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta, May 2012; 1820(5):619-624. Doi: 10.1016/j.bbagen.2011.03.015
4. Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, *et al*. Mitochondrial diseases. Nat Rev Dis Primers, Oct 20, 2016; 2:16080. Doi: 10.1038/nrdp.2016.80