Journal of Medical Case Reports and Reviews

Received 14 Feb 2021 | Revised 20 Feb 2021 | Accepted 22 Apr 2021 | Published Online 28 Apr 2021

JMCRR 04 (04), 851-852 (2021) ISSN (O) 2589-8655 | (P) 2589-8647

JMCRR

HOMOGENISATION OF M.3243A>G CARRIER SUBGROUPS IS A PREREQUISITE TO DELINEATE THEM UPON THE URINE METABOLOME

Finsterer J, MD, PhD [1]

[1] Klinik Landstrasse, Messerli Institute, Vienna, Austria

Key words: MELAS, heteroplasmy, m.3243A>G, mitochondrial disorder, respiratory chain, myopathy diabetes, renal insufficiency, metabolism

Corresponding author: **Finsterer J, MD, PhD**

Postfach 20 1180 Vienna, Austria,Tel. +43-1-71165-72085,Fax. +43-1-71165E-mail: fifigs1@yahoo.de

Letter to the Editor

With interest we read the article by Esterhuizen et al. about a study of 9 patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS), 30 patients with maternally inherited diabetes and deafness (MIDD), and 18 patients with mitochondrial myopathy (MM), all carrying the MT-TL1 variant m.3243A>G, for urine analysis by means of liquid chromatography tandem mass spectroscopy (LC-MS/MS), gas chromatography time-of-flight mass spectroscopy (GC-TOF-MS), and by NMR spectroscopy [1]. It was found that glucose metabolism is disturbed only in MIDD, that fatty acid metabolism is modified in MELAS, and that urine creatinine is elevated in MM [1]. The study is appealing but raises comments and concerns.

The first limitation of the study is that the phenotype, and thus the urine metabolomic profile, may not only depend on the syndromic classification, the HbA1c values, and the heteroplasmy rate, but on a number of other factors, including co-morbidities, co-medication, diet, hormone levels, environment, and physical activity. Thus, we should know if the four groups were homogeneous for these parameters or not. Of particular interest are renal function parameters, electrolyte levels, protein level, infection parameters to exclude renal or urinary infection, arterial gas analysis, hormone profiles, and other co-morbidities. According to table 1 gastro-intestinal compromise was significantly more prevalent in MELAS as compared to MIDD or MM patients [1]. Thus, it should be discussed to which degree metabolic disturbances due to gastro-intestinal compromise influenced the urine metabolome.

A second limitation is that the current medication the included patients were regularly taking was not discontinued prior to urine investigations, whereas it was stopped in healthy controls. The authors themselves mention in the discussion that e.g. the antioxidant glutathione can lower pyroglutamic acid [1]. Furthermore, angiotensin-converting enzyme inhibitors were more frequently taken by MIID as compared to MM or MELAS patients. Antiepileptic drugs (AEDs) were significantly more frequently taken by MELAS as compared to MM or MIDD patients. Insulin and sulfonyl-urea derivatives were more frequently taken by MIDD as compared to MELAS or MM patients [1]. Thus, it should be discussed to which degree the results were influenced by the variable current medication. How many patients were removed from the evaluation because of the current medication, as indicated in section 3.1.

A third limitation is that the phenotype may not only depend on the heteroplasmy rate but also on the mtDNA copy number and mtDNA polymorphisms. Additionally, the nuclear genetic background may further modify the urine metabolome. Anyhow, it appears that according to table 1 heteroplasmy rates in MELAS were significantly higher in MELAS patients as compared to MIDD and MM patients. Thus, it

is quite likely that differences in the urine metabolome are in fact attributable to variable heteroplasmy rates between the groups.

Since MELAS is associated with diabetes in some of the patients [2], we should know if the carbohydrate metabolism was disturbed in the same way in MELAS patients with diabetes as in MIDD patients.

According to the abstract, creatinine was elevated in the MM cohort but not in MELAS or MIDD. In the result section, on the contrary, it is mentioned that creatinine was "significantly affected" in MIDD patients [1]. This discrepancy requires clarification.

Overall, the study has limitations with regard to group homogeneity, which should be addressed before drawing conclusions as those presented. Urine metabolomics may be influenced by a number of factors which were not considered in the study, why it cannot be excluded that the differences found are not disease-specific but rather due to confounding factors such as renal function, other co-morbidities, co-medication, diet, or degree of physical activity. Delineation between MELAS, MIDD. and MM phenotypes upon the urine metabolome should be regarded with caution as long as factors possibly contributing to apparent differences were not excluded.

COI: The authors declare no conflicts of interest

Funding: No funding was received

Author contribution: JF: design, literature search, discussion, first draft, critical comments

Informed consent: was obtained

Ethics approval: The study was approved by the institutional review board

Data availability: not applicable

Consent to participate: not applicable

Consnet for publication: not applicable

References

1 Esterhuizen K, Lindeque JZ, Mason S, van der Westhuizen FH, Rodenburg RJ, de Laat P, Smeitink JAM, Janssen MCH, Louw R. One mutation, three phenotypes: novel metabolic insights on MELAS, MIDD and myopathy caused by the m.3243A > G mutation. Metabolomics. 2021 Jan 12;17(1):10. doi: 10.1007/s11306-020-01769-w.

2 El-Hattab AW, Almannai M, Scaglia F. MELAS. 2001 Feb 27 [updated 2018 Nov 29]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020.