

Letter to the Editor

Assessment of Dietary Effects in M.3243A>G Carriers Requires Homogenous Study Populations

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With interest we read the article by Zweers *et al.*, about a study of 20 patients carrying the mtDNA variant m.3243A>G who received an individually tailored diet and were assessed with regard to personal goals, indirect calorimetry, physical activity levels, nutritional intake, anthropometry, body composition (BC), fatigue, gastrointestinal complaints, quality of life, and handgrip strength (HGS) (Zweers, H., *et al.*, 2019). It was concluded that personalised diet improves BC, HGS, and gastrointestinal compromise (Zweers, H., *et al.*, 2019). We have the following comments and concerns.

Since patients received an individually tailored diet, the study group was inhomogeneous (Zweers, H., *et al.*, 2019). The comparison with the control group, which was homogenous, is thus inappropriate with regard to the outcome parameters. The study population was also inhomogeneous for the phenotype. One patient had MELAS, 10 MIDD, and 9 myopathy. Concerning the comparability between controls and the intervention group the marked difference in the heteroplasmy rate for the mutation is apparent, suggesting that the difference was statistically significant. However, no statistical figures were presented. We should know for all parameters of table 1 if there was a significant difference between study group and controls, in particular for the amount of calories and HGS. It appears that the calorie intake was different between the groups after having applied the diet.

Patients carrying the m.3243A>G variant frequently develop migraine or migraine-like headache (Smeitink, J., *et al.*, 2019), which has been shown responsive to the ketogenic diet (KD) (Barbanti, P., *et al.*, 2017). We should know how many of the 20 patients had migraine and how many profited from the diet with regard to headache.

Since mitochondrial disorders (MIDs) occasionally respond favourably to vitamins, co-factors, or antioxidants (Sproule, D.M., *et al.*, 2008), it is crucial to know the current medication of each included patient. Particularly, we should know how many of the patients were taking coenzyme-Q, riboflavin, vitamin-C, L-arginine, L-carnitine etc. Additionally, other drugs patients and controls were regularly taking should be provided to exclude any interactions between the diet and the medication.

Insufficient food intake by MIDs may be also due to gastrointestinal involvement. Particularly in m.3243A>G carriers gastrointestinal involvement has been reported (Pickett, S.J.,). We should know how many of the 20 patients had gastrointestinal involvement.

Since inappetance and vomiting may be triggered by lactic acidosis we should know in how many of the 20 patients was serum or CSF lactate elevated and how many had vomiting or reduced appetite due to lactic acidosis.

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Surprisingly, HGS increased after the first three months of observation in controls without any therapy. This phenomenon requires a plausible explanation.

Isolated myopathy is an uncommon presentation of the m.3243A>G variant (Nesbitt, V., *et al.*, 2013). A plausible explanation for this finding should be provided. It is also of interest if heteroplasmy rates were different between patients with MELAS, MIDD, and isolated myopathy.

Overall, this interesting study lacks a sufficient explanation for the high frequency of isolated myopathy and for the spontaneous improvement of HGS in controls. Data should be reevaluated after homogenisation of the study group for diet and of controls and study patients with regard to heteroplasmy, and phenotype. We need to know the current medication of each patient to assess any beneficial effect of the applied diet.

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