m.3243A>G carriers develop syndromic or non-syndromic multisystem phenotypes over time

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Received: 19 January 2021 / Accepted: 8 March 2021 / Published online: 18 March 2021
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Keywords MELAS · Heteroplasmy · m.3243A>G · Mitochondrial disorder · Respiratory chain · Myopathy

Letter to the Editor

With interest we read the article by Tanaka et al. about a 57-year-old male with maternally transmitted diabetes and deafness (MIDD) due to the variant m.3243A>G in *MT-TL1* (heteroplasmy rate 69.9%), in whom progressive renal involvement was regarded as initial manifestation [1]. It was concluded that mitochondrial dysfunction is mainly associated with progressive renal damage [1]. We have the following comments and concerns.

A first shortcoming of the study is that the multisystem nature of MIDD was not sufficiently considered. The m.3243A>G variant usually manifests phenotypically as a multisystem disease [2]. The multisystem nature of the phenotype may not be evident already at onset or the initial stages of the disease but may become increasingly evident with progression of the disease when more and more organs/systems become affected. Also the index patient did not only manifest in the ears, pancreas, and kidneys, but had a multisystem disease additionally affecting the pituitary gland (short stature) and the skeletal muscle (creatinine-kinase elevation, and myopathic muscle biopsy). Furthermore, half of the MIDD patients have cerebral involvement [3]. To further substantiate the multisystem nature of the phenotype it is thus warranted that the index patient and m.3243A>G carriers in general are prospectively investigated for multisystem disease. Of particular interest would be cerebral magnetic resonance imaging (MRI), electroencephalography (EEG),

echocardiography, electrocardiography (ECG), hormone levels, liver function parameters, and results of ocular investigations. Since the multisystem involvement may not necessarily manifest clinically, active search for it is required.

A second shortcoming is that renal involvement in mitochondrial disorders (MIDs) is more widespread than described and not only includes focal, segmental glomerulosclerosis (FSGS) or tubule–interstitial nephropathy but additionally nephrolithiasis, renal cysts, arterial hypertension, renal tubular acidosis, Bartter-like syndrome, Fanconi syndrome, nephrocalcinosis, and benign/malign neoplasms [4]. Renal involvement in m.3243A>G carriers is fairly common and includes FSGS, renal cancer, or renal cysts [5]. Since there is evidence that FSGS rather than diabetic nephropathy is responsible for chronic kidney disease (CKD) in MIDD patients [6], it is reasonable to conclude that MIDD itself plays an important role in the development of CKD.

Missing are the results of the genetic studies in first degree relatives. According to the family tree in figure 3, the mother of the index patient manifested with renal insufficiency and the brother of the index patient with renal insufficiency and deafness. To confirm MIDD, the maternal transmission of the disease needs to be documented. Thus, it is worthwhile to report if mother and brother also carried the m.3243A>G variant and its heteroplasmy rate. Since the mother of the index patient had died already, it is more informative with regard to maternal transmission to document if the brother of the index patient carried the mutation. It is particularly important that female patients with MIDD are referred for genetic work-up. We also should know if the mother, brother, or any other first-degree relative was prospectively investigated for subclinical or mildly manifesting multisystem involvement.

Concerning the muscle biopsy, we should know if biochemical investigation of the muscle homogenate showed deficiency of a single/multiple respiratory chain complexes.

Letter to the original article <https://doi.org/10.1007/s13730-020-00547-w>.

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According to figure 5 at least complex-IV-deficiency can be expected.

Overall, this interesting report has shortcomings, which should be accomplished before drawing conclusions as those presented. The spectrum of renal involvement in MIDs is broader than anticipated and renal involvement is a frequent manifestation of syndromic or non-syndromic MIDs. More important than classifying the mitochondrial syndrome is to confirm the diagnosis genetically, to investigate mutation carriers for multisystem involvement, and to start symptomatic and supportive treatment as early as possible.

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

Funding No funding was received.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The study was approved by the institutional review board.

Informed consent Informed consent was obtained.

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