Heteroplasmy of the m.3243A>G Mutation May Influence Phenotypic Heterogeneity

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Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9056-17
Intern Med 56: 3123, 2017
http://internmed.jp

【 LETTERS TO THE EDITOR 】

Heteroplasmy of the m.3243A>G Mutation May Influence Phenotypic Heterogeneity

Key words: mitochondrial, tRNAs, myopathy, cardiac involvement, heart failure, central nervous system

(Intern Med 56: 3123, 2017)
(DOI: 10.2169/internalmedicine.9056-17)

To the Editor We read with interest the article by Tashiro et al. about a 49-year-old man carrying the m.3243A>G mutation, which manifested as hypertrophic cardiomyopathy, intellectual decline, basal-ganglia-calcification, cerebellar atrophy, elevated cerebrospinal fluid (CSF)-lactate, exophoria, and diabetes (1). We have several comments and concerns regarding this study.

The previously unreported mismatch between ^{99m}Tc-methoxyisobutylisonitrile (MIBI) and 123I-BMIBB scans may be attributed to different heteroplasmy rates in the present and previous cases. Each patient carrying a m.3243A>G mutation is unique, since heteroplasmy rates differ between various tissues in each individual. Was the heteroplasmy rate determined in the myocardium and compared with that in hair follicles, buccal cells, fibroblasts, or urine epithelial-cells, as well as with the findings described in previous publications?

If we attribute the low uptake of 123I-BMIBB to myocardial fibrosis rather than to energy production from beta-oxidation, then a reduced uptake of ^{99m}Tc-MIBI should also be expected, since it is a marker for myocardial perfusion and is reduced in fibrous tissue. This is also the case if we assume that late gadolinium-enhancement (LGE) represents viable cardiomyocytes surrounded by fibrocytes.

Since myocardial affection in mitochondrial disorders (MIDs) is usually progressive, it would be interesting to know if follow-up investigations of the ^{99m}Tc-MIBI and 123I-BMIBB scans were carried out and if the pattern was reproducible or if it changed over time.

The family history of the patient is also missing. Was the mutation inherited or *de novo*? Was the mother investigated for the presence of the mutation? If she was found to be carrying the mutation, did she also present with cardiomyopathy and the same pattern on ^{99m}Tc-MIBI and 123I-BMIBB scans?

Figure 3c suggests that the patient presented with non-compaction left ventricular hypertrabeculation (LVHT) (1). Were cardiac MRI and echocardiography evaluated for LVHT, which is frequently found in MID patients (2)? LGE is also often associated with LVHT (3) and thus represents a further argument for the presence of noncompaction.

In the majority of the cases, m.3243A>G mutation carriers manifest with mitochondrial multiorgan disorder syndrome (MIMODS) (4). Was the presented patient systematically investigated for MIMODS? If so, which organs other than the cerebrum, extraocular muscles, pancreas, and myocardium were found to be additionally affected? Was there any involvement of the eyes, ears, the gastrointestinal tract, the kidneys, the lungs, the bone marrow, or the skin?

Overall, this interesting case requires explanation of a number of unresolved issues concerning the clinical manifestations and the patient's genetic background. Unique organ manifestations and phenotypic heterogeneity between family members and other families can be attributed to the tissue distribution of heteroplasmy rates, the influence of the haplotype, or variable progression rates of heteroplasmy rates during the disease course.

The authors state that they have no Conflict of Interest (COI).

Josef Finsterer and Sinda Zarrouk-Mahjoub contributed equally to this work.

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Received: February 23, 2017; Accepted: March 30, 2017; Advance Publication by J-STAGE: October 11, 2017
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