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Contents

Semimonthly Volume 8 Number 1 January 6, 2020

REVIEW

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Observational Study

Prospective Study

CASE REPORT

LETTER TO THE EDITOR

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Volume 8 Number 1 January 6, 2020

Contents

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LETTER TO THE EDITOR

Cluster headache as a manifestation of a stroke-like episode in a carrier of the *MT-ND3* variant m.10158T>C

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Abstract

In a recent article Fu *et al* reported about a 52 years old female with a mitochondrial disorder due to the variant m.10158T>C in the mtDNA located gene *MT-ND3*. The study has a number of shortcomings. The study would particularly profit from providing more data about multisystem disease, from providing the current medication, the cerebro-spinal fluid findings, the detailed phenotypic presentation, and the genotype of first-degree relatives. Since the index patient had experienced recurrent seizures it is crucial to know the current and previous anti-seizure medication as it may strongly determine the outcome. Some of them are mitochondrion-toxic and particularly valproic acid may exhibit fatal side effects. The outcome may also depend on the degree of multisystem involvement why it is crucial to prospectively investigate the patient for subclinical involvement of organs not obviously affected. Additionally, the outcome of the stroke-like lesions on imaging would be interesting to see. Stroke-like lesions may completely disappear or may end up as white matter lesion, laminar cortical necrosis, focal atrophy, cyst, or as the so-called toenail sign. There is also a need of discussing more profoundly the imaging findings and their diagnostic significance and to investigate first degree relatives of the index patient clinically and genetically. Though highly interesting, the presentation of this case of a mitochondrial disorder lacks clinical and genetic data of the patient and his relatives. Outcome parameters, such as severity of disease, degree of progression, drugs, pathogenicity of the mutation, and multisystem involvement require a profound discussion.

Key words: Heteroplasmy; mtDNA; Oxidative phosphorylation; Stroke-like episode

Core tip: The recent report about a 52 years old female with a mitochondrial disorder due to the variant m.10158T>C in *MT-ND3* may profit from a more thorough investigation of the index case and his relatives. Outcome parameters, such as severity of disease, degree of progression, drugs, pathogenicity of the mutation, and multisystem involvement need to be assessed to guide treatment and genetic counselling.

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TO THE EDITOR

In a recent article, Fu *et al*[1] reported about a 52 years female with a mitochondrial disorder (MID) due to the variant m.10158T>C in *MT-ND3*. The patient manifested phenotypically with recurrent stroke-like episodes, cluster headache, and epilepsy. We have the following comments and concerns.

We do not agree with the statement that the m.10158T>C variant in *ND3* is a common mutation[1]. When searching PubMed for this particular mtDNA variant only five hits could be achieved. Thus, the variant m.101157T>C has to be classified as a rare variant.

Since the index patient had undergone a spinal tap, we should know if cerebrospinal fluid (CSF) lactate was elevated or not upon investigations of the CSF.

Since up to 75% of the mtDNA variants are transmitted *via* a maternal line of inheritance[2], we should know if the mother or any other first degree elative was clinically affected and if the mtDNA variant m.10158T>C was detected in any of the other first degree relatives.

Stroke-like lesions (SLLs) in the acute/expanding stage typically manifest with hyperperfusion on single-photon emission computed tomography or perfusion weighted imaging. Thus, we should know if perfusion weighted imaging was applied and if hyperperfusion could be detected. It is also crucial to demonstrate reduced oxygen extraction within the SLL by means of oxygen extraction fraction-MRI. Was this technique applied and was there reduced oxygen extraction?

Since SLLs may disappear without any remnants on MRI, or may end up as white matter lesion, laminar cortical necrosis, cysts, or the toenail-sign[3], we should know the outcome of the various SLLs in this patient. Which were the results of the long-term follow-up on MRI?

The index patient obviously did not only manifest in the cerebrum (SLLs, seizures, cognitive impairment) but also in the endocrine system (short stature), and the heart (atrial fibrillation). Since patients with a MID most frequently manifest with multisystem disease[4], we should know if the index patient was prospectively investigated for manifestations of the genotype in organs other than the brain and the endocrine organs. We also should be informed why the patient received oral anticoagulation with a vitamin-K antagonist. Was this due to atrial fibrillation, heart failure, or valve replacement therapy?

Missing is the current medication of the patient. Since the patient had experienced recurrent seizures, it is crucial to know the antiepileptic drug (AED) regimen. Since some of the AEDs are potentially mitochondrion-toxic[5] we should know if recurrence of seizures and SLLs could be attributed at least in part to the application of mitochondrion-toxic AEDs or to in-effectivity of the AEDs.

Cluster headache had been occasionally reported as a manifestation of a MID[6,7]. Did cluster headache in the index patient resolve upon application of widely agreed therapies for cluster headache?

Overall, this interesting case could be more meaningful by providing more data about multisystem disease, the current medication, the CSF findings, the phenotype and genotype of other first-degree relatives, outcome of the SLLs on imaging, and by discussing more profoundly the imaging findings and their significance.

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