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Letter to the Editor

NARP, Homoplasmic for M.8993T>G

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In a recent article, Claeys *et al.,* (2016) reported about a 30 years-old male with neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome due to the homoplasmic m.8993T>G mutation (Claeys, K. G. *et al.,* 2016). We have the following comments and concerns.

The patient had atypical absence epilepsy with generalised polyspikes and spike-slow waves complexes and was treated with valproic acid (VPA) and ethosuximide (ESM) (Claeys, K. G. *et al.,* 2016). Which was the dosage of these antiepileptic drugs (AEDs)? For how long were they taken? Which quality of seizure control could be achieved with these compounds? How were these AEDs tolerated? Is progression of the disease attributable to side effects of these drugs? From VPA it is well-known that it is mitochondrion-toxic (Finsterer, J., & Zarrouk Mahjoub, S. 2012). VPA inhibits complex I and IV of the respiratory chain, induces loss of cytochrome-c-oxidase, decreases O_2 rates and the mitochondrial potential$\Delta\psi$, depletes ATP levels, increases reactive oxygen species, and decreases the antioxidative capacity (Finsterer, J., & Zarrouk Mahjoub, S. 2012). From ESM it is known that it inhibits the mitochondrial Na, K-ATPase (Finsterer, J., & Zarrouk Mahjoub, S. 2012). Since VPA can lead to fatal hepatotoxicity, particularly in patients carrying POLG1 mutations, it should be avoided in patients with a mitochondrial disorder (MID) unless it is the only effective AED. Was the ketogenic diet, frequently effective in mitochondrial epilepsy, tried?

The patient had headaches (Claeys, K. G. *et al.,* 2016). Which types of headache did the patient develop? Headache types most frequently found in MID patients are tension headache, migraine-like headache, and cluster headache. Particularly migraine-like headache may be associated with stroke-like episodes (SLEs) (Tsujikawa, K. *et al.,* 2014). Did the patient ever experience a SLE? Did cerebral MRI show remnants of a stroke-like lesion, the morphological equivalent of a SLE?

Despite the prominent affection of peripheral nerves in NARP (Finsterer, J. 2011) muscle biopsy in the presented patient showed abnormal cristae formation in muscle mitochondria and paracristalline inclusions (Claeys, K. G. *et al.,* 2016). Did the patient present with clinical manifestations of myopathy? Did he undergo needle electromyography and did it show a myogenic pattern?

Serum lactate is frequently normal in MIDs but the lactate stress test (LST) may be abnormal and thus of diagnostic relevance. Frequently, lactate values during exercise increase but normalise during rest. Did the patient undergo a LST and which was the result? The LST is false positive in well-trained subjects. Which was the training status of the presented patient? How to explain that the cerebrospinal fluid (CSF) lactate was normal while MR-spectroscopy revealed a marked lactate peak?

To explain the absence of the mutation in the mother the authors assume germline mosaicism for the m.8993T>G mutation or a heteroplasmy rate <2% (Claeys, K. G. *et al.,* 2016). Is it conceivable that the mother was indeed not the biological mother or that the mutation in the index patient occurred spontaneously after fertilisation?

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Overall, this interesting study could be supplemented by information about epilepsy management and by performing a LST. Absence of a mtDNA mutation in the mother of an index case requires thorough explanation and may challenge genetic counselling of these patients.

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