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Letter to the Editor

Assessing the Phenotype of the M.13094T>C Variant Requires A Prospective Design and Long-Term Follow-Up

Josef Finsterer^{1*}, Sinda Zarrouk-Mahjoub²

¹Krankenanstalt Rudolfstiftung and the Messerli Institute, Veterinary University of Vienna, Vienna, Austria

²University of Tunis El Manar and Genomics Platform, Pasteur Institute of Tunis, Tunisia

***Corresponding author:** Josef Finsterer, Krankenanstalt Rudolfstiftung, Vienna, Austria. Tel: +43171165; Email: fifigs1@yahoo.de

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We refer to a recently published article by Ng et al. about 24 patients pretended carrying the *ND5* variant m.13094T>C who manifested clinically with broad phenotypic heterogeneity [1]. We have the following comments and concerns.

The main disadvantage of this study is its retrospective design. Multisystem involvement can be reliably assessed only by a prospective approach. Thus, multisystem involvement reported by Ng and colleagues is not representative for the phenotype. A number of organs may be mildly or only subclinically affected and may go thus undetected with a retrospective design. To unambiguously assess, which organs or tissues are affected or become affected during the course, each patient needs to be investigated by a standardised protocol and repeatedly during a long-term follow-up.

It is also not comprehensible why patient 2.2 was included although no mutation was identified. This also the case for patient 2.3 in whom the mutation was not found either. Thus, the study should have included only 22 instead of 24 patients.

We do not agree with the statement that LHON is a single organ disorder. It is well appreciated that LHON may not only manifest in the retinal ganglion cells but also in the brain (myoclonic epilepsy, temporal lobe epilepsy, leukoencephalopathy, psychomotor regression[†], posterior reversible encephalopathy syndrome, migraine, chorea, ataxia, or dementia), the ears (hypoacusis), endocrine organs (diabetes, hypothyroidism, pituitary adenoma), myocardium (dilated cardiomyopathy, noncompaction,

arrhythmias, angina chest pain, exertional dyspnoea, sudden cardiac death), arteries (aortic stiffness), kidneys (renal failure), bone marrow (anemia, fibrous dysplasia), or the peripheral nervous system (skeletal muscle) [2,3].

Interestingly, one patient not carrying the mutation, had ischemic stroke [1]. Was the stroke confirmed by multimodal cerebral MRI? Which were the cardiovascular risk factors in this patient? Hypertension, diabetes, hyperlipidaemia, smoking, or atrial fibrillation, or was the stroke classified as embolic stroke of unknown significance (ESUS)? Since one of the family members had a stroke-like episode, it is conceivable that a stroke-like lesion was mis-interpreted as ischemic. Which were the clinical manifestations of the stroke?

Heteroplasmy rates in blood lymphocytes decreased with age, which was attributed to negative selection of the mtDNA variant-containing blood stem cells in the bone marrow [1]. Since heteroplasmy rates were determined also in muscle and urine and in three patients in various other tissues post-mortem, it should be mentioned if the negative correlation between heteroplasmy rate and age was also found in tissues other than lymphocytes.

How to explain that among 10 patients undergoing biochemical investigations, 6 did not have a complex-I defect? Were heteroplasmy rates in these 6 patients too low to result in reduced complex-I activity? Was there another cause than the *ND5* variant which could explain the phenotype?

The authors reported 8/24 patients with refractory epilepsy [1]. Which was the cause of refractoriness? Were these patients non-compliant or did they receive mitochondrial-toxic antiepileptic drugs, such as valproic acid, phenytoin, carbamazepine, or phenobarbital [4]? Particularly from valproic acid it is well-known

that it may worsen mitochondrial epilepsy and can be even fatal in mitochondrial patients with hepatopathy [5].

Two patients had a tracheostoma [1]. Which was the reason for this measure and did they require mechanical ventilation? Did they manifest with muscular respiratory failure, or did they have a pulmonary problem, or was respiratory insufficiency attributable to a brainstem lesion?

Since 10/24 patients had died, we should be informed about the causes of death. Did they decease from cardiac, pulmonary, cerebral, gastrointestinal, renal, infectious causes or from malignancy?

In summary, this interesting study could be more meaningful if a prospective design would have been applied and if long-term follow-up data would have been included.

Declarations

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