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Phenotypic manifestations of the m.616T>C variant in MT-TF may be more diverse than anticipated

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ABSTRACT

Patients carrying the m.616T>C variant in MT-TF may not only manifest with cerebral disease and mitochondrial tubule-interstitial kidney disease (MITKD), but also with phenotypic manifestation sin other organs if systematically looked for. Focal epilepsy in MITKD may be a clinical manifestation of a stroke-like lesion (SLL). If anti-seizures drugs (ASDs) fail to stop seizure activity in these patient, the ketogenic diet should be tried. Patients with a mitochondrial disorder affecting the respiratory chain may profit from the additional application of antioxidants and cofactors.

Key words: mtDNA–heteroplasmy–renal failure–MT-TF

1 INTRODUCTION

With interest we read the article by Lorenz et al. about a 5yo female with mitochondrial tubule-interstitial kidney disease (MITKD), developmental delay, and epilepsy being attributed to the homoplasmic variant m.616T>C in *MT-TF* [1]. It was concluded that kidneys and brain are predominantly affected because these tissues are rich in mitochondria and require high amount of tRNA(Val), which cannot be replaced by tRNA(Phe) [1]. We have the following comments and concerns.

We do not agree with the explanation for the predominant affection of the brain and the kidneys in carriers of homoplasmic m.616T>C variants. The number of mitochondria is also high in the heart or the retina but these organs were clinically not affected. Thus, it cannot be the high number of mitochondria, which explains the tissue selection. More likely is that the variant m.616T>C influences tissue segregation such that mutated mitochondria are predominantly allocated to the two tissues affected in MITKD.

A further shortcoming is that the patient was not systematically investigated for mild or subclinical affection of organs other than the brain and the kidneys. Mitochondrial disorders (MIDs) are multisystem diseases in the majority of the cases [2]. This is the case either already at onset of the disease or becomes evident during progression of the disease, with successively increasing affection of more and more tissues.

A frequent manifestation of MIDs is lactic acidosis, particularly when the skeletal muscles are affected. Since the presented patient had metabolic acidosis [1], we should know if acidosis was attributable to elevated serum lactate levels or due to renal acidosis. Since lactate is also frequently elevated in the brain, we should know if lactate was elevated in the cerebrospinal fluid (CSF) or on magnetic resonance spectroscopy (MRS).

Blood pressure may not only be elevated due to chronic renal failure but also due to hyperthyroidism, hyperaldosteronism, elevated serum cortisol levels, stenosis of the renal arteries, elevated catecholamines, increased sympathetic tone, or due to cardiac causes. Arterial hypertension has been even reported as primary manifestation of a MID [3]. Thus, we should know if explanations other than renal failure were excluded as causes of arterial hypertension in the presented patient.

Since particularly mtDNA-related MIDs are characterised by broad intra-familial phenotypic heterogeneity, it is not sufficient to investigate first-degree relative for kidney and cerebral disease. When describing the family history any medical abnormality should be reprted. [4, 5]

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