Phenotypic variability of MTO1-deficiency

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We read with interest the article by O'Byrne et al. about the presentation of 2 and review of 35 patients with MTO1-deficiency [1]. We have the following comments and concerns.

Patient-1 had febrile seizures since age 2.5y and absence seizures since age 3.5y [1]. Which antiepileptic drugs (AEDs) were administered during the course? This issue is crucial since some AEDs, such as valproic acid, carbamazepine, phenytoin, or phenobarbital may exhibit mitochondrion-toxic effects, and may worsen the phenotype [2]. Particularly valproic acid may exhibit severe side effects in patients with a mitochondrial disorder (MID) and may even cause death, particularly in patients carrying *POLG1* mutations [3]. Seizures were refractory to treatment at age 11y [1]. Was refractoriness attributable to the mitochondrion-toxic effect of the applied AEDs?

At age 11y patient-1 developed multiple, transient T2-hyperintensities within the peduncles, basal ganglia, and the cortex [1]. Were these imaging abnormalities stroke-like lesions, the morphological equivalent of stroke-like episodes (SLEs)? Did the phenotype deteriorate during this episode? Were these lesions hyperintense on DWI and ADC, thus indicative of a vasogenic edema, typical for a stroke-like lesion? Did the patient receive L-arginine during this episode, which is frequently recommended as acute treatment of SLEs [4]. Were other causes of the transient T2-hyperintensities, such as ADEM or an epiphenomenon of the seizure activity, considered?

One of the dominant phenotypic features seems to be hypertrophic cardiomyopathy and arrhythmias (Table 1) [1]. How many of the analysed patients developed heart failure or systolic dysfunction and required cardiac therapy? Was non-compaction, frequently associated with MIDs [5], detected in any patient?

Overall, this interesting study could be more meaningful by providing more details about the AED treatment and its influence on the phenotype, about the cerebral imaging findings, about the cardiac involvement in the disease, and about the family history.

Conflicts of interest

There are no conflicts of interest.

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Author contribution

JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments

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Table 1
Phenotypic features in 35 patients carrying MTO1 mutations.

Feature	Number of patients
Brain	
Intellectual disability	26
Muscle hypotonia	22
Failure to thrive	15
Abnormal cerebral imaging	15
Seizures	12
Optic atrophy	9
Ataxia	7
Developmental delay	6
Dystonia	1
Eyes	
Cataract	1
Pigmentary retinopathy	1
Heart	
Hypertrophic cardiomyopathy	27
Cardiac arrhythmias	8
Dilated cardiomyopathy	1
Muscle	
Lactic acidosis	20
Myopathy	7
Respiratory insufficiency	5
Endocrine abnormalities	
Hypoglycemia	2
Short stature	1
Gastrointestinal	
Feeding difficulties	15
Hepatopathy	3
Renal	
Hypocalcemia	1
Tubulopathy	1
Others	
Dysmorphism	1
Microcephaly	1
Hyper-ammonemia	1

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