Molecular Genetics and Metabolism Reports 21 (2019) 100538

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Correspondence

MLASA1 is a poly-phenic but not a di-phenic condition

ARTICLE INFO

Keywords:
Mitochondrial
MELAS
Heteroplasmy
Ketogenic diet
Muscle strength

With interest we read the article by Woods et al. about two brothers aged 37y and 35y with MLASA due to the novel variant c.302A > G in *PUS1*.[1] The two patients presented, in addition to myopathy and anemia, with affection of the brain, the endocrine organs, the heart, and the bones.[1] The study has several shortcomings.

We do not agree that MLASA due to *PUS1* variants (MLASA1) affects only the skeletal muscle and the bone marrow.[1] As with most of the mitochondrial disorders (MIDs), MLASA1 is also a multisystem disease affectin,g in addition to the muscle and the bone marrow, the brain (mental retardation, generalised hypotonia, microcephaly, failure to thrive),[2,3,4] the endocrine system (hypopituitarism, diabetes, hypoglycaemia, hypothyroidism, short stature, osteoporosis, hypopituitarism),[1,2,3,4] the intestines (hepatopathy, chronic diarrhoea),[3,5] the bones (dysmorphism such as pseudoepicanthus or hypertelorism),[4] and the heart (cardiomoypathy).[1,3]. Not only MLASA1 but also MLASA2 and MLASA3 are multisystemic.[6].

Given the multisystem nature of MLASA1 we should know if the index patient was prospectively investigated for multisystem disease and if there were any subclinical or mildly manifesting comorbidities, which may determine the outcome of the patient.

Missing in this report is a thorough family history and a thorough clinical, instrumental and genetic investigation of first-degree relatives, particularly the father and mother of the index case. We should know if either parent was clinically affected or carried the culprit variant in *PUS1*. Knowing the genetic status of the parents is crucial for assessing the trait of inheritance, providing proper genetic counselling, and to assess the intra-familial phenotypic heterogeneity.

Overall, this interesting study may profit from providing a thorough family history and genetic investigations of the parents, from prospective investigations for multisystem disease in the index patient and his brother, and from classifying MLASA1 as a multisystem disease not only affecting two organs.

Funding

No funding was received.

Author contribution

JF: design, literature search, discussion, first draft,

Declaration of Competing Interest

There are no conflicts of interest.

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https://doi.org/10.1016/j.ymgmr.2019.100538
Received 27 October 2019; Accepted 28 October 2019
Available online 09 November 2019

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Josef Finsterer*
Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria
E-mail address: fifigs1@yahoo.de.

* Corresponding author at: Postfach 20, Vienna 1180, Austria