Molecular Genetics and Metabolism Reports 14 (2018) 41–42

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

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

Correspondence

Phenotypic spectrum of FARS2-deficiency

ARTICLE INFO

Keywords:
Mitochondrial
FARS2
Phenotype
Genotype
Encephalopathy
Lactic acidosis

Letter to the Editor,

We read with interest the article by Vantroys et al. about two unrelated pediatric patients with FARS2-deficiency [1]. We have the following comments and concerns.

Insomnia is a rare manifestation of a mitochondrial disorder(MID). Only in a study of 20 CPEO patients, 75% reported sleep dysfunction [2]. Did patient-2 take drugs that could explain sleeplessness? What were the results on polysomnography? Was insomnia due to a respiratory problem with nocturnal O2-desaturations, restless-legs, or due to nocturnal seizures? Which were the EEG results? Did patient-2 also carry a mutation in the prion-protein? Did she take antiretroviral compounds? Was insomnia due to a withdrawal reaction from carbamazepine? [3].

Cryptorchism is only occasionally associated with MIDs [4]. In a study of 25 *TMEM70*-associated MIDs, 67% had cryptorchism [4]. In patient-1 cryptorchism was diagnosed at age 13 y but usually it is congenital [5]. Did cryptorchism remain undetected before age 13 y or did it truly developed during puberty? Was puberty delayed in patient-1?

Patient-1 had developed convulsive seizures [1]. Were they focal or generalised? From carbamazepine it is well-known that it is mitochondrion-toxic [6]. Did the general condition of the patient deteriorate upon application of carbamazepine?

If onset of clinical manifestations is $>$ 1 y after birth, the phenotype is less severe than with onset $<$ 1 y after birth [1]. Patients with onset $>$ 1 y hardly have seizures and have a normal MRI, whereas patients with onset $<$ 1 y have epilepsy and non-specific white matter lesions on MRI [1]. What is the reason for the phenotypic variability?

Patient-1 not only manifested in the brain but also in the gastrointestinal tract and muscles. Which other organs were affected?

Were the parents investigated for the FARS2 mutations? Were they heterozygous for the mutations? Were the parents clinically affected?

Overall, we suggest to explain manifestations unusual for the FRAS2 phenotype, to investigate the parents genetically, and to stress the multiorgan nature of FARS2-deficiency.

Conflict of interest

There are no conflicts of interest.

Both authors contributed equally.

No funding was received.

Author contribution

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

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Received 17 November 2017; Received in revised form 18 November 2017; Accepted 18 November 2017

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