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▶ To cite this version:

Josef Finsterer, Sinda Zarrouk-Mahjoub. ISCA2 mutations manifest differentially from DARS2 mutations. Metabolic Brain Disease, Springer Verlag, 2018, 33 (5), pp.1389-1390. 10.1007/s11011-018-0253-z . pasteur-02009056

HAL Id: pasteur-02009056
https://hal-riip.archives-ouvertes.fr/pasteur-02009056

Submitted on 6 Feb 2019

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Metabolic Brain Disease (2018) 33:1389–1390
https://doi.org/10.1007/s11011-018-0253-z

COMMENTARY

ISCA2 mutations manifest differentially from *DARS2* mutations

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Received: 3 May 2018 / Accepted: 17 May 2018 / Published online: 22 May 2018
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Letter to the Editor,

With interest we read the article by Toldo et al. about a 2-months-old girl with severe, progressive mitochondrial disorder (MID) due to a compound heterozygous *ISCA2* mutation, phenotypically manifesting as leucencephalopathy, muscle hypotonia, muscle weakness, paraspasticity, feeding difficulties, and nystagmus (Toldo et al. 2018). The patient died at age 3 months from respiratory failure. The article raises a number of comments and concerns.

Patients carrying *ISCA2* mutations have not only been reported by Toldo et al. and Al-Hassnan et al. 2015 (Al-Hassnan et al. 2015) as pretended but also by Alfadhel et al. 2018 (Alfadhel et al. 2018). Alfadhel et al. described 10 patients carrying *ISCA2* mutations other than the founder mutation c.229G > A (p.Gly77Ser) described by Al-Hassnan et al. (Alfadhel et al. 2018) or the mutation c.334A > G/(p.Ser112Gly) described by Toldo et al. (Toldo et al. 2018). In addition to neurodevelopmental regression, leucencephalopathy, lactic acidosis, and nystagmus, Alfadehl's patients presented with epilepsy ($n = 3$), elevated serum glycine (n = 3), elevated cerebral glycine ($n = 2$), and optic atrophy ($n = 10$) (Alfadhel et al. 2018). Did Toldo's case ever develop seizures, were there indications for optic atrophy on MRI or ophthalmologic investigations, or was serum/CSF glycine elevated?

Before establishing the molecular diagnoses, the patient was regarded to suffer from leucencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) and methylprednisolone was started. Which was the rationale for applying steroids? In none of the patients reported by Al-Hassnan or by Alfadhel were steroids applied. Furthermore, there are no reports about patients with LBSL who received steroids and who profited from their application. Use of steroids in MIDs may have a broad range of different effects (Finsterer and Frank 2015). Some patients may benefit from steroids whereas others may have a fatal outcome (Finsterer and Frank 2015). Is it conceivable that application of steroids contributed to the progressive course and the fatal outcome of the described patient? For how long were steroids administered?

The spinal cord may not only be involved in patients with LBSL or patients carrying a *ISAC2* mutation (Finsterer and Zarrouk-Mahjoub 2018). Among the specific MIDs spinal cord involvement has been additionally described in Leigh-syndrome, MERRF, KSS, IOSCA, MIRAS, PCH6, MELAS, CPEO, and LHON (Finsterer and Zarrouk-Mahjoub 2018). Additionally, non-specific MIDs due to mutations in *SURF1, tRNA(Glu),* or *POLG1,* may present with spinal cord involvement (Finsterer and Zarrouk-Mahjoub 2018).

MIDs are usually multisystem disorders either at onset or develop affection of multiple organs during the disease course. Particularly in the early stages multiorgan involvement may be subclinical or only mildly manifesting why these patients need to be prospectively investigated for involvement of the eyes, ears, endocrine organs, heart, intestines, kidneys, bone marrow, bones, or the skin. Was the presented patient prospectively investigated for multisystem MID (MIMODS)? Since biochemical investigations of the muscle biopsy revealed complex-II and complex-IV deficiency in Toldo's case, it is conceivable that their patient additionally had at least myopathy.

The authors state that there was restricted diffusion of white and grey matter (Toldo et al. 2018). Restricted diffusion means DWI hyperintesity and ADC hypointensity. However, no DWI sequences are presented.

In summary, this interesting report could be strengthened by discussing Alfadhel's cases and the variable phenotype, by investigating for multisystem affection, by discussing the

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application of steroids, and by specifying the type of spinal cord abnormalities detected.

Author's contribution JF: design, literature search, discussion, first draft, SZ-M: literature search, critical review.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

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