East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online)
Published By East African Scholars Publisher, Kenya

Volume-2 | Issue-4 | Apr-2020 | DOI: 10.36349/EASJMS.2020.v02i04.022

OPEN ACCESS

Letter to Editoe

There are different Leigh syndromes

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Article History
Received: 28.02.2020
Accepted: 15.04.2020
Published: 19.04.2020

Journal homepage:
http://www.easpublisher.com/easms/

Quick Response Code

Abstract:

Keywords: mitochondrial, mtDNA, ophthalmoplegia, heteroplasmy, cognition, brain

LETTER TO THE EDITOR

With interest we read the article by Bolea *et al.,* 2019 about a comprehensive study of three different mouse models of Leigh syndrome (LS), resulting from deactivation of the ND1 protein ndufs4 in glutamin-ergic, GABA-ergic and cholin-ergic neurons (Vglu2:Ndufs4cKO mice, Gad2:Ndufs4cKO mice, and ChAT:Ndufs4cKO mice) (Bolea, I. *et al.,* 2019) We have the following comments and concerns.

The main shortcoming of the study is that NDUFS4 is only one of numerous proteins mutated in LS. LS is genetically extremely heterogeneous due to mutations in >75 genes (Lake, N. J. *et al.,* 2016). Patients carrying NDUFS4 mutation represent only a small portion of the LS patients. Thus, pathomechanisms leading to LS in these mouse models are different depending on the underlying mutation. Accordingly, the conclusions drawn from the presented data cannot be applied to all LS patients. Additionally, LS may be rarely also due to mutations in mtDNA located genes (Lee, S. *et al.,* 2019). In mtDNA-related LS patients phenotype may strongly depend heteroplasmy rates, i.e. the ration between mutated and wild-type mtDNA.

It is quite unlikely that no functional abnormalities were detected in ChAT:ndufs2cKO mice (Bolea, I. *et al.,* 2019). We should be informed about the reasons why this strain did not manifest phenotypically whereas the two other strains nonetheless developed significant abnormalities.

We do not agree that the symmetric brain lesions in LS represent neuro-inflammation. Strong arguments against any inflammatory processes are that application of gadolinium does not result in any enhancement and that inflammatory markers are usually negative in LS patients. Additionally, neuropathologic studies have rather detected degeneration than inflammation.

Another shortcoming of the study is that the levels of cerebro-spinal fluid (CSF) lactate were not considered as modifiers of the phenotype. CSF lactate may strongly determine the inspiratory and expiratory drive and may also influence muscle tone (Willems, J. L. *et al.,* 1977). Thus, it is crucial to know the CSF levels in all three strains of LS-imitating mice. Thus we should know if CSF lactate levels differed between Vglut2:ndufs4cKO and Gad2:ndufs4cKO mice. If there is indeed a neuro-inflammatory reaction it is conceivable that it is due to secondary effect on neuronal death or a reaction to increased reactive oxygen species (ROS) production.

Reduced ventilatory performance in Vglu2:ndufs4cKO mice could be also attributed to tiredness or involvement of the peripheral nerves or the skeletal muscles. Thus, we should know if peripheral nerves or muscles were primarily involved in Vglut2:ndufscKO mice and if lactic acidosis was more

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frequent in Gad2:ndufs4cKO mice as compared to wt-mice. Were Vglu2:ndufs4cKO mice more severely affected because of more pronounced astrocyte involvement in the disease process?

Furthermore, we do not agree that myoclonic epilepsy is a hallmark of MIDs. The most frequent type of seizures in MIDs is still generalised tonic clonic seizures. Myoclonic seizures are a hallmark of MERRF syndrome, which is a rare, syndromic subtype of MIDs.

Body temperature in Vglu:ndufs4cKO mice may simply decrease with progression of the disease. Reduced body temperature could be also explained with reduced body weight and thus fat. Reduced subcutaneous fat may be prone to loss of body temperature,

The difference in the electrophyiologic results could be due to inconsistent electrophysiological recordings.

Concerning the definition of LS, not only lesions in the basal ganglia and brainstem may manifest as LS but also lesions in the cerebellum (Chourasia, N. *et al.*, 2017).

We appreciated to read the interesting study by Bolea *et al.,*. but before final assessment of the results some shortcomings need to be solved and some open questions need answers.

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