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Letter to Editoe

Pathogenicity of the homozygous variant c.304G>A in *SDHB*, manifesting as Leigh syndrome, remains unproven

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LETTER TO THE EDITOR

In a recent article, Kaur *et al.*, 2020 reported an 18 months-old male with Leigh-syndrome manifesting clinically with developmental delay, cerebral and spinal white and grey matter lesions, seizures, optic atrophy, quadruspasticity, and lactic acidosis in the serum and cerebrospinal fluid (CSF) (Kaur, P. *et al.*, 2020). The phenotype was attributed to the homozygous point mutation c.304G>A in *SDHB* (Kaur, P. *et al.*, 2020). We have the following comments and concerns.

The main shortcoming of the study is that the pathogenicity of *SDHB* variant, remains unproven. Immune-histochemical, biochemical, and functional studies are required to confirm pathogenicity. Missing in this respect is the confirmation of reduced complex-II activity on immunohistochemistry or biochemical investigations.

We also should know how the authors explain the discrepancy between normal magnetic resonance-spectroscopy (MRS) and the elevated lactate levels on CSF investigations. Was this simply a false negative result or was the sample chosen for MRS not affected by lactic acidosis?

In the discussion the authors state that MRI of the brain and spinal cord "demonstrated white matter changes in cerebral hemispheres, corpus callosum, thalami, corticospinal tracts, pons, and spinal cord (Kaur, P. *et al.*, 2020)". It has to be noted that the thalami are not white matter.

Another discrepancy refers to the spinal cord involvement. The authors mention that the cortico-spinal tract was affected. However, in the description of the MRI they mention that the "central portion" of the spinal cord was affected. This may include the lateral portion of the corticospinal tract but not the medial portion. Furthermore, other structures of the spinal cord, such as the anterior and posterior horns the posterior columns, the reticular formation, may be additionally affected. Were there and indications for quadruparesis, or pallhypesthesia, or disturbed sense of position?

Since the patient had spinal cord involvement it would be interesting to know how the authors excluded LBSL (Alibas, H. et l 2014) or leucoencephalopathy with thalamus and brainstem involvement and lactic acidosis (LTBL) (Sellars, E. A. *et al.*, 2017)? Since the basal ganglia in the index patient were not affected, it cannot be excluded that the patient did not have Leigh-syndrome but rather another syndromic or non-syndromic mitochondrial disorder (MID). The thalamus is not a part of the basal ganglia.

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The patient had epilepsy. We should know if it was tractable or intractable and which anti-seizure drugs (ASDs) were applied. From some of the ASDs it is well-known that they are mitochondrion-toxic and may worsen the phenotype (Finsterer, J. 2017). Which was the long-term outcome of the patient?

We should also know if optic atrophy resulted in visual impairment and if visually evoked potentials, electroretinography, or optical coherence tomography revealed abnormal results.

Overall, this interesting case could be more meaningful if the discrepancies and shortcomings outlined above were addressed and solved. It is also crucial that the pathogenicity of the variant is confirmed by immune-histological, biochemical, and functional studies. As long as the pathogenicity of the variant is not confirmed, interpretation of the results has to be regarded with caution.

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