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Letter to the Editor

Mitochondrial Epilepsy in *LIPT1* Carriers

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In a recent article, Stowe *et al.,* (2018) reported about a 2 months-old male with Leigh syndrome manifesting as irritability, epilepsy, elevated proline, beta-alanine, 4-guanidino-butanoate, and lactate in the serum, as elevated succinate, fumarate, and 2-hydroxy-glutarate in the urine, and as pyruvate-dehydrogenase complex (PDHC) deficiency, due to a mutation in the *LIPT1* gene (Stowe, R. C. *et al.*, 2018). The study raises a number of comments and concerns.

The patient was described to have been treated for epilepsy and continuous electrical seizures on EEG with levetiracetam and phenobarbital without effect (Stowe, R. C. *et al.*, 2018). Even after adding phenytoin, seizure activity continued. Seizure frequency, the maximal daily dosage of these compounds, and duration of treatment was not provided (Stowe, R. C. *et al.*, 2018). From phenobarbital and phenytoin it is well known that both are mitochondrion-toxic (2 Finsterer, J. 2017). Obviously, this antiepileptic regimen was kept after a short interplay with a beneficial ketogenic diet. Were these two antiepileptic drugs the reason why epilepsy became difficult to treat or even intractable? Were ever combinations of other antiepileptic drugs than these three tried? A current medication with "multiple antiepileptic medications" has been described but was not detailed. Was lamotrigine ever applied, which can be highly beneficial in mitochondrial epilepsy (Kai, T. *et al.*, 2013)?

Symmetrical cytotoxic edema on cerebral imaging is unusual (Stowe, R. C. *et al.*, 2018). Did these lesions persist during follow-up or was there a dynamic change over time? Were these lesions interpreted as stroke-like lesions or as cytotoxic edema and thus ischemic stroke? Did the patient carry any cardiovascular risk factors for ischemic stroke? Were NO-precursors, such as L-arginine or L-citrulline applied? NO-precursors are frequently given to mitochondrial disorder (MID) patients experiencing stroke-like episodes and are reported to be potentially beneficial in this indication (Ganetzky, R. D., & Falk, M. J. 2018). Did the patient benefit from these compounds? In a study of 9 patients with a MID experiencing 17 stroke-like episodes, L-arginine had a marked beneficial effect in the acute stage of a stroke-like episode but also as a prophylaxis in most of these patients (Ganetzky, R. D., & Falk, M. J. 2018).

Though the family history was described as non-contributory, it would be of value to know if first degree relatives other than the parents carried either of the *LIPT1* variants of the index case and if they were seen by a neurologist to be investigated for clinical or subclinical manifestations of the *LIPT1* variants. Did the LIPT1 defect secondarily affect the respiratory chain? Was activity of respiratory chain complexes reduced in fibroblasts or muscle homogenate from the index case?

The authors described the variant c.539T>C in the mother as a variant of unknown significance but damaging on SIFT analysis (Stowe, R. C. *et al.*, 2018). Compound heterozygosity in the index case was made responsible for the phenotype and PDHC deficiency described as secondary (Stowe, R. C. *et al.*, 2018). Were mutations in genes other than *LIPT1* excluded as primary causes of PDHC deficiency?

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The patient was described as "grunting, tachycardic, and mottled". Was tachycardia due to involvement of the heart? Did the patient undergo cardiologic work-up?

In summary, this interesting report has several limitations in terms of the antiepileptic regimen, the pathogenicity of the *LIPT1* variant, and the work-up for multisystem involvement, which should be addressed in future publications.

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