

Infantile-onset Leigh-like syndrome due to homozygous *SLC19A3* variants

Josef Finsterer^{1*} and Marlies Frank²

1 Krankenanstalt Rudolfstiftung, Vienna, Austria

2 First Medical Department, Krankenanstalt Rudolfstiftung, Vienna, Austria

Received: June 06, 2018; Accepted: July 02, 2018; Published: July 10, 2018

Letter to the Editor

A recent article by Alfadhel et al. described a male neonate with a non-specific mitochondrial multiorgan disorder syndrome (MIMODS) due to a *SLC19A3* variant [1]. Despite immediate treatment with biotin and thiamine, the patient deceased four months after birth [1]. We have the following comments and concerns.

Since mitochondrial disorders frequently present as MIMODS, the patient should have been prospectively investigated for involvement of organs other than the brain. Leigh- and Leigh-like syndrome frequently not only manifest in the central nervous system, but also in other organs, such as the heart, gastrointestinal tract, ears, pancreas and kidneys with inter-individual heterogeneity [2-5]. Results of autopsy should be provided.

Though echocardiography was reported as normal it would be interesting to know if the authors have particularly looked for left ventricular hyper trabeculation/noncompaction (LVHT), which is particularly prevalent in MIMODS and which is frequently missed if the apex is not visualized and if it is not particularly looked for [6].

The parents were consanguineous [1]. Though they were described as "healthy" it would be interesting to know if they were prospectively investigated for clinical or subclinical manifestations of MIMODS and which organs were investigated. We should also be informed about the family history, particularly if the mother's or father's first-degree relatives were clinically affected and if family members other than the parents were genetically investigated. The patient had nystagmus. It should be determined if nystagmus could be attributed to a brainstem or a cerebellar lesion, a labyrinth lesion, or to the medication. Interestingly, the ophthalmologic investigation was described as normal [1]. Had nystagmus resolved already at the time of the ophthalmologic investigation?

It should be described which types of seizures the patient developed in addition to focal seizures. Since phenobarbital is known to be mitochondrion-toxic, it is not comprehensive why this antiepileptic drug was chosen [7]. It is thus conceivable

that deterioration of the patient's condition, requiring mechanical ventilation, was attributable to the administration of phenobarbital.

Which was the reason why the patient required antibiotics and which type of antibiotic was administered? Was the antibiotic one that potentially enhanced epilepsy, such as penicillin, cephalosporins, fluoroquinolones, or carbapenems [8]?

Subdural effusions were reported but it is not mentioned if it was blood, cerebrospinal fluid, or other tissue fluid [1]. It is not reported if the patient had a history of subdural hematoma from a fall because of epilepsy or his muscle weakness, or if he had experienced another head trauma.

Concerning **Table 1** by Alfadhel et al. it would be interesting to know the causes of death among those patients who died during follow-up [1]. It should be mentioned how many died from epilepsy, ventricular arrhythmias, heart failure, respiratory insufficiency, sepsis, renal failure, metabolic disturbances, due to brainstem involvement, or due to affection of the respiratory muscles, or the innervating nerves.

The male:female ratio provided by Alfadhel et al. in **Table 1** is

*Corresponding author:

Josef Finsterer

✉ fipaps@yahoo.de

Krankenanstalt Rudolfstiftung, P.O. Box 20, 1180 Vienna, Austria.

Tel: +43-1-71165-92085

Citation: Finsterer J, Frank M (2018) Infantile-onset Leigh-like syndromes due to homozygous *SLC19A3* variants. J Biol Med Res. Vol.2 No.2:16

wrong [1]. It must be 15:4. It should be explained why the syndrome occurred four times more frequently in males as compared to females. It is conceivable that females more frequently die during early development than males. Were serum hormone levels within the normal range?

Though *SLC19A3*-related Leigh-like syndrome is regarded as completely reversible, most of the patients in **Table 1** by Alfadhel et al. died [1]. Was the latency between diagnosis and beginning of thiamine substitution too long? Did the patient undergo lumbar puncture and were thiamine levels reduced also in the cerebro-spinal fluid (CSF)?

Table 1 by Alfadhel et al. does not contain two recently published

cases from India with a *SLC19A3* variant [9]. Also, the two children reported by Whitford et al. and the patient reported by Aljabri in 2016 have not been included in **Table 1** by Alfadhel et al. [10,11].

Overall, this interesting case could be more meaningful if more clinical and instrumental data about the index case and his first-degree relatives would have been provided. A more extensive discussion of the previous literature is warranted. Several errors need to be corrected.

Author Contributions

JF: Design, literature search, discussion, first draft.

SZM: Literature search, discussion, critical comments.

References

- 1 Alfadhel M (2017) Early infantile leigh-like *SLC19A3* gene defects have a poor prognosis: Report and review. *J Central Nerv Syst Dis* 9:1179573517737521.
- 2 Davison JE, Rahman S (2017) Recognition, investigation and management of mitochondrial disease. *Arch Dis Child* 102: 1082-1090.
- 3 Duff RM, Shearwood AM, Ermer J, Rossetti G, Gooding R, et al. (2015) A mutation in MT-TW causes a tRNA processing defect and reduced mitochondrial function in a family with Leigh syndrome. *Mitochondrion* 25: 113-119.
- 4 Dermaut B, Seneca S, Dom L, Smets K, Ceulemans L, et al. (2010) Progressive myoclonic epilepsy as an adult-onset manifestation of Leigh syndrome due to m.14487T>C. *J Neurol Neurosurg Psychiatry* 81: 90-93.
- 5 Distelmaier F, Haack TB, Catarino CB, Gallenmüller C, Rodenburg RJ (2015). MRPL44 mutations cause a slowly progressive multisystem disease with childhood-onset hypertrophic cardiomyopathy. *Neurogenetics* 16: 319-323.
- 6 Finsterer J, Stöllberger C, Towbin JA (2017) Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors. *Nat Rev Cardiol* 14: 224-237.
- 7 Finsterer J (2017) Toxicity of antiepileptic drugs to mitochondria. *Handb Exp Pharmacol* 240: 473-488.
- 8 Czapińska-Ciepiela E (2017) The risk of epileptic seizures during antibiotic therapy. *Wiad Lek* 70: 820-826.
- 9 Gowda VK, Srinivasan VM, Bhat M, Benakappa N (2017) Biotin thiamin responsive basal ganglia disease in sibs. *Indian J Pediatr* 85: 155-157.
- 10 Whitford W, Hawkins I, Glamuzina E, Wilson F, Marshall A, et al. (2017) Compound heterozygous *SLC19A3* mutations further refine the critical promoter region for biotin-thiamine-responsive basal ganglia disease. *Cold Spring Harb Mol Case Stud* 3: pii a001909.
- 11 Aljabri MF, Kamal NM, Arif M, Al-Qaedi AM, Santali EY (2016) A case report of biotin-thiamine-responsive basal ganglia disease in a Saudi child: Is extended genetic family study recommended? *Medicine (Baltimore)* 95: e4819.