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

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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 comprehensible 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...
wrong [1]. It must be 15:4. It should be explained why the syndrome occurred four times more frequently in males 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