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Letter to the Editor

Avoid valproate in patients with *IARS2* mutations

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We read with interest the article by Takezawa et al. about 2 siblings with Leigh syndrome and CAGSSS due to a mutation in the *IARS2* gene [1]. We have the following comments and concerns.

The main components of the basal ganglia are the striatum (caudate nucleus, putamen), the ventral striatum (nucleus accumbens, olfactory tubercle), the globus pallidus, the substantia nigra, and the subthalamic nucleus [2]. According to figure 1 of the study, the caudate nucleus and the putamen were predominantly affected in the presented patient showing up as symmetric T2-hyperintensity on MRI [1].

From valproic acid (VPA) it is well known that it is mitochondrion toxic [3] and thus may worsen the phenotype or may even result in death, particularly in association with *POLG1* mutations [4]. It is thus conceivable that the antiepileptic regimen with vitamin B6, ACTH, and VPA was ineffective due to the side effects of VPA. VPA may have contributed to the deterioration of epilepsy and the development of an untreatable condition. Did the authors ever discontinue VPA and did discontinuation improve epilepsy?

We do not agree with the statement that FGF21 and GDF15 are useful biomarkers of mitochondrial disorders (MIDs). Since these parameters may be elevated together with other conditions [5], specificity is low and thus these parameters are unsuitable for diagnosing MIDs.

Patient-2 was described as hypotonic [1]. Was hypotonia attributable to a central nervous system (CNS) lesion or to affection of the peripheral nerves or muscles? In case hypotonia was classified as central, which cerebral lesion can be made responsible for hypotonia?

In conclusion, the role of VPA in the deterioration of epilepsy needs to be specified. Furthermore, it needs to be mentioned that FGF21 and GDF15 currently have no role in the work-up of MIDs. The cause of generalised hypotonia should be discussed.

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Author contribution

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