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Letter to the Editor

Reply to: Avoid valproate in patients with *IARS2* mutations

We express our gratitude to Josef Finsterer et al. for writing a letter about our article on the clinical concerns. We understand their concern and would like to respond as follows.

First, valproic acid was induced as initial treatment for West syndrome, as explained in our report [1], followed by gradually discontinuing it over a few months as adrenocorticotropic hormone (ACTH) injection therapy starts to show effectiveness. Hence, we do not think that valproic acid could play the central role in worsening the phenotype of our patients. Second, as a clinical test for mitochondrial diseases, fibroblast growth factor 21 (FGF-21) and growth differentiation factor 15 (GDF-15) have some inherent limitations, as mentioned by you [2]; however, this concern also applies to lactate/pyruvate examination [3]. At present, no clinical test has adequate power to diagnose mitochondrial diseases by itself. Thus, for the comprehensive diagnosis of mitochondrial diseases, we cannot help but consider such biomarkers, including FGF-21, GDF-15, and lactate/pyruvate, as useful despite several limitations.

Finally, concerning the etiology of hypotonia presented in both of our patients, we conducted muscle biopsy in patient II-1 and detected no abnormality [1]. Then, we assumed that myogenic hypotonia might be contradictory. Conversely, as we did not perform nerve conduction study, we cannot confirm whether it was because of the peripheral nerve or the central nervous system (CNS). Nevertheless, we attribute their hypotonia to the CNS because other reported IARS2-related disorders without Leigh syndrome did not exhibit severe hypotonia, and some patients with Leigh syndrome reportedly presented hypotonia [4]. However, the mechanism of central hypotonia remains unclear [5].

We hope that these responses addressed your concerns adequately.

Disclosure

The authors have no conflicts of interest to declare.

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