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Considerations on the management of pyruvate dehydrogenase deficiency

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With interest we read the review article by Ebertowska et al. [1] about the causes, pathogenesis, clinical presentation, diagnosis, and treatment of pyruvat-dehydrogenase (PDH) deficiency. The authors concluded that phenylbutyrate could be a beneficial compound in the treatment of PDH-deficiency [1]. We have the following comments.

Elevation of serum and cerebrospinal fluid (CSF) lactate is a common finding in PDH deficiency [2]. Since the degree of lactic acidosis is crucial for the course and outcome of the disease it should not only be determined in the serum but also in the CSF, either by direct measurement in the CSF or by determination with magnetic resonance spectroscopy (MRS). MRS may show a typical lactate peaks [3].

The ketogenic diet (KD) may not only be beneficial for refractory epilepsy in patients with a mitochondrial disorders (MID) [4], but also in patients with migraine [5], autism spectrum disorder [6], obesity [7], and other mitochondrial and non-mitochondrial diseases.

Rarely, PDH deficiency may be complicated by stroke-like episodes (SLEs) [8]. Since SLEs may manifest with seizures, visual impairment, confusion, and muscle weakness and favourably respond to L-arginine, it is crucial to consider SLEs in case of appropriate manifestations not only in mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) patient but also in patients with PDH deficiency.

We disagree with the notion that dichloroacetate (DCA) should be given for lowering lactate levels in PDH patients [1]. In a study of 30 patients with MELAS due to the variant m.3243A>G, application DCA during a period of 24 months resulted in onset or worsening of peripheral neuropathy in 17 of 19 patients receiving the study drug. In some of the patients neuropathy was irreversible [9].

Concerning the recommendation of phenylbutyrate as a treatment option for PDH deficiency, we want to remind that the compound is not free of side effects. Adverse reactions reported in association with phenylbutyrat6e treatment include impairment of liver regeneration [10], induction of bipolar disorder [11], or reduction of branched-chain amino acids in acute hepatic injury [12].

Seizures occur in about half of the patients with pyruvate dehydrogenase deficiency [13]. Since some of the antiepileptic drugs (AEDs) are potentially mitochondrion-toxic [14], it is recommended not

use mitochondrion-toxic AEDs as first line treatment of epilepsy in PDH-patients. Alternative option for epilepsy treatment not only include the KD but also AEDs with low mitochondrion-toxic potential [14].

Overall, this informative and comprehensive review has some limitations and shortcomings, which should be addressed and discussed to further increase the reliability of the conclusions.

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