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LETTER TO THE EDITOR

Early-age *Ndufs4* knockout mice are an inappropriate animal model of Leigh syndrome

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Letter to the Editor

With interest, we read the article by Saito et al. about a study applying chemical exchange saturation transfer (CEST) and magnetic resonance spectroscopy (MRS) using 7T magnetic resonance imaging (MRI) in *Ndufs4* knockout (KO) mice, which supposedly represented an animal model of Leigh syndrome, to detect lactate elevation prior to the presence of cerebral morphological abnormalities [1]. The authors reported increased magnetization transfer ratio (MTR) asymmetry maps at offset frequencies of 0.5, 1.0, and 2.0 ppm, but not at 3.0 or 3.5 ppm [1]. Additionally, lactate was elevated in all KO mice on MRS. T2-weighted MRI was normal in KO mice. We have the following comments and concerns.

A shortcoming of the study is that the *Ndufs4* KO mice investigated in the present study do not represent an animal model of Leigh syndrome. Leigh syndrome is characterized by symmetrical necrotic lesions in the basal ganglia, brain stem, cerebellum, or spinal cord [2]. Additionally, clinical features such as failure to thrive, generalized hypotonia, developmental delay, central respiratory compromise, ataxia, and epilepsy should be present [2]. However, none of the investigated mice showed structural cerebral lesions and it was not reported if they were clinically affected. Thus, it is crucial that the KO mice investigated at 5 weeks of age are reinvestigated at an age when they have developed morphological or clinical features of Leigh syndrome.

Furthermore, we do not agree with the notion that non-invasive imaging of cerebral lactate using CEST and MRS is useful for diagnosing mitochondrial disorders (MIDs) in general. Although a number of MIDs manifest in the brain, there are many more MIDs that do not manifest in the cerebrum, such as in patients with chronic progressive external ophthalmoplegia, primary mitochondrial cardiomyopathy, Leber's hereditary optic neuropathy, maternally inherited deafness and diabetes syndrome, neuropathy, ataxia, and retinitis pigmentosa syndrome. Only exceptionally will patients with such disorders ever develop cerebral involvement. There are also MIDs with structural abnormalities on imaging (e.g., basal ganglia calcification, atrophy), but without elevation of cerebral lactate [3]. In such cases, CEST and MRS may not be supportive for diagnosing MIDs.

The authors claim that the increase in cerebral lactate on MRS reflects an early stage of the disease before morphological abnormalities on T2-weighted MRI can be found. Thus, it would be interesting to determine whether the investigated KO mice were followed up and whether 7T MRI truly detected bilateral lesions in the basal ganglia in the later course, as would be expected in humans harboring *NDUFS4* variants [4].

Concerning the elevated cerebrospinal fluid (CSF) lactate in KO mice on MRS that reflected as increased CEST signals at 0.5, 1.0, and 2.0 ppm, we should be informed whether CSF lactate was measured directly from the CSF as well to confirm whether cerebral lactate was truly elevated in this putative mouse model of Leigh syndrome. It should also be discussed why diffusely elevated cerebral lactate is associated with focal and usually symmetric lesions in the further course of animal and human Leigh syndrome. It would also be interesting to determine if lactate concentrations varied at different cerebral sample locations.

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It should be discussed why MTR asymmetry maps at offset frequencies of 0.5, 1.0, and 2.0 ppm were increased in *Ndufs4* KO mice, but not at offset frequencies of 3.0 or 3.5 ppm. Since these results may be temperature-dependent [5], we should be informed if all MRI investigations were carried out at the same temperature.

Overall, this interesting study could be more meaningful if true animal models of Leigh syndrome were investigated, if the clinical presentation was provided, if cerebral lactate was measured in the CSF, and if some inconsistencies were discussed.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethical standards International ethical standards were met.

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