The Application of Clinical Genetics

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LETTER

Ketogenic diet in *ATAD3A* mutation carriers may not improve cerebellar atrophy but some clinical features [Letter]

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Josef Finsterer

Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

Dear editor

With interest I read the article by Madhoun et al about a 4.5-year-old female with multisystem mitochondrial disorder (MID) due to the variant c.251T>C in the *ATAD3A* gene.[1] The patient was reported to have profited from the ketogenic diet (KD) by slowing the progression of cerebellar atrophy, and improving vitality, interaction, moaning, carrying, tremor, and weakness. I have the following comments and concerns.

It is quite unlikely that the cerebellar volume increased upon application of the KD. More likely is that the increase in the relative sagittal length of the cerebellum was due to variability of repeated measurements or simply due to the growing cerebellum in this developing child. Potential volumetric changes can be only confirmed by investigating a series of patients but not by assessing a single case.

The tremor in the patient was attributed to Parkinsonism most likely upon the phenotype as a hand pill rolling tremor. We should be informed about the DatScan results, if the tremor responded to L-DOPA, and if there were any other stigmata of Parkinsonism in this patient. More likely than Parkinson's tremor is a cerebellar tremor in the light of progressive cerebellar atrophy. A hand pill rolling tremor may also occur with a cerebellar syndrome.[2,3]

MRI in figure 1 suggests that there was also atrophy of the spinal cord.[1] It is conceivable that muscle weakness in the described patient was attributable to involvement of the anterior horn cells. Were there any indications for neuronopathy in the presented patient?

Though optic atrophy may be a feature of *ATAD3A* mutations,[4] it was not reported as a feature of the index case.[1] Optic atrophy may be subtle and not visible on ophthalmologic or imaging investigations but only on functional tests. Thus, we should be informed if latency and amplitude of visually evoked potentials were prolonged respectively reduced.

We should be informed if muscle weakness was attributed to affection of the central nervous system or due to myopathy. It should be mentioned if deep tendon reflexes were reduced or exaggerated. A normal needle EMG does not exclude myopathy.

Since seizures have been reported as a phenotypic feature of *ATAD3A* mutations,[4] we should be informed about the history in this regards and the EEG findings.

Correspondence: Josef Finsterer
Krankenanstalt Rudolfstiftung, Messerli Institute, Postfach 20, 1180 Vienna, Austria
Tel +43 1 711 657 2085
Fax +43 17 1165
Email fifigs1@yahoo.de

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Since it is not mentioned at which age the KD was started, it is difficult to correlate the potential effect with the time course of the clinical and MRI manifestations. Improvement of physical activities could be also attributed to a direct effect of the KD on the muscle or to the natural disease course.

Overall, this interesting case raises a number of concerns which need to be addressed before finally assessing a potential beneficial effect of the KD. The treatment effect of an intervention may be insufficiently assessed by evaluation of a single patient and requires more appropriate study designs.

Disclosure

The author reports no conflicts of interest in this communication.

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