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

This article was published in the following Dove Press journal:
The Application of Clinical Genetics

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 1 711 657
Email ffigs1@yahoo.de

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.

References

1. Al Madhoun A, Alnaser F, Melhem M, Nizam R, Al-Dabbous T, Al-Mulla F. Ketogenic diet attenuates cerebellar atrophy progression in a subject with a biallelic variant at the ATAD3A locus. *Appl Clin Genet*. 2019;12:79–86. doi:10.2147/TACG.S194204
2. Bareš M, Husárová I, Lungu OV. Essential tremor, the cerebellum, and motor timing: towards integrating them into one complex entity. *Tremor Other Hyperkinet Mov (N Y)*. 2012;2:pii: tre-02-93-653-1.
3. Avanzino L, Bove M, Tacchino A, et al. Cerebellar involvement in timing accuracy of rhythmic finger movements in essential tremor. *Eur J Neurosci*. 2009;30:1971–1979. doi:10.1111/j.1460-9568.2009.06984.x
4. Harel T, Yoon WH, Garone C, et al. Baylor-Hopkins Center for Mendelian Genomics; University of Washington Center for Mendelian Genomics. Recurrent de novo and biallelic variation of ATAD3A, encoding a mitochondrial membrane protein, results in distinct neurological syndromes. *Am J Hum Genet*. 2016;99:831–845. doi:10.1016/j.ajhg.2016.08.007

Dove Medical Press encourages responsible, free and frank academic debate. The content of the The Application of Clinical Genetics 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the The Application of Clinical Genetics editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

The Application of Clinical Genetics

Dovepress

Publish your work in this journal

The Application of Clinical Genetics is an international, peer-reviewed open access journal that welcomes laboratory and clinical findings in the field of human genetics. Specific topics include: Population genetics; Functional genetics; Natural history of genetic disease; Management of genetic disease; Mechanisms of genetic disease;

Counselling and ethical issues; Animal models; Pharmacogenetics; Prenatal diagnosis; Dysmorphology. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/the-application-of-clinical-genetics-journal>