The Application of Clinical Genetics

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RESPONSE TO LETTER

Ketogenic diet attenuates cerebellar atrophy progression in a subject with a biallelic variant at the ATAD3A locus [Response to Letter]

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Dear editor

It is with great interest to read the comments of Dr. Josef Finsterer on our recent article, "Ketogenic diet attenuates cerebellar atrophy progression in a subject with a biallelic variant at the ATAD3A locus by Al Madhoun et al, 2019," which has received a substantial article-level metrics and respond to the queries raised single nucleotide polymorphisms and deletion mutations within ATAD3 are lethal at embryonic stage or postnatally and the few survivors are living with low quality of life.[1–3] Accordingly, ATAD3 genotyping enable prediction of genotype/phenotype relationship.

Desai et al (2017) associated ATAD3 function with cholesterol homeostasis and maintenance of the mitochondrial genome stability.[4] We thought that Ketogenic Diet (KD) may modulate mitochondrial biogenesis especially that it has proven efficacy in mitochondriopathies-mediated neurological disorders.[5,6] Thus, it is not unrealistic to include KD treatment in a disease that is caused by ATAD3 gene mutations.

The girl described in our paper is unique. She has been clinically evaluated extensively in Canada, but unfortunately, the family was not given a formal diagnosis. We diagnosed her with Harel-Yoon syndrome after discovering a novel pathogenic missense homozygous mutation in the ATAD3 gene (rs546711654 c.251C>T; p.Thr84Met). Globally, the variant allele frequency of rs546711654 is 0.0002 (https://www.ncbi.nlm.nih.gov/clinvar/variation/452865/). This information means that the disease is rare and therefore it is not possible to study other children harboring the same mutation.

In response to KD, we never claimed an increase in the relative sagittal length of the cerebellum. But rather, an obvious slowing of her cerebellar atrophy. The KD was applied between the 2nd and 3rd MRI examination at the age of 4 and 5.5 years old. It has been reported that KD lowers the blood pH, increases ATP by shifting from glucose- to ketone-based metabolism.[7] Although all body tissues are influenced by KD, the most prominent effect is on the nervous system activities.[8,9] Accordingly, we do not exclude a positive effect on the muscle function.

KD increases mitochondrial biogenesis.[10,11] We agree that a real-effect of KD can only be assessed reliably in double-blind randomized clinical trials, but this is

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obviously not possible in very rare cases such as ours. However, the parents were surprised with the improved quality of life of the child.

Science starts with an observation, which is then propagated through well-defined experimental procedures that address precise research questions. Our observation is a start and we look forward to learn how other children with cerebellar atrophy may benefit from our experience.

As we clearly mentioned in the manuscript, the patient suffered from frank ataxia and intentional tremor secondary to her cerebellar atrophy. However, clinically she had clear pill-rolling resting tremor. In our experience, children with parkinsonism do not necessarily present with classical Parkinson's disease symptoms. Neither DATScan test was performed nor L-DOPA was administered since compared to her other symptoms, particularly the severe osteoporosis, ataxia and intentional tremor, the parkinsonian tremor appeared minor. The functional neurological assessments included drawing, holding arms outstretched, gait and body posture and coordination.[12] The patient did not suffer from epilepsy.

No peripheral neuropathy was observed. Nerve conduct study revealed normal response at the peroneal and tibial terminal motor latency (1.95±0.24 ms), M-wave amplitudes were 3.6±0.2 mV and 8.5±1.1 mV, respectively, average duration 8.1±0.14 and the F-M wave latency was 20.7±0.6.

The patient, as expected, in Harel-Yoon syndrome had bilateral cataract and no optic hypoplasia was observed in the subject. In Harel et al study, optic atrophy was detected in some patients, but not all[1] other symptoms included congenital cataract, corneal cloudy and photophobia.[1,2,13] No functional retinal tests were performed.

It is important to note that the patient, during her long journey of diagnosis, has endured significant stress. Although we wish to perform many tests on her, we need to be diligent in our choices of tests. The family as mentioned above were disappointed with the lack of diagnosis after many years of laborious investigations, which culminated in more trauma, phycological and physical stress and were very rightly reluctant to undertake further tests. This is understandable. Moreover, mitochondria are present in every cell, while cerebellar atrophy appears to be the most likely presentation because of the high energy demand of neurons, one cannot exclude the possibility of pathologies in the muscle (myopathy), bone cells (osteoporosis), bone marrow, intestinal cells, etc. We are confident given our final diagnosis that the patients will have pathologies everywhere. Osteoporosis, bone fractures and osteomyelitis are now the major threat to the patient. When would one stop investigating?

Disclosure

The authors report no conflicts of interest in this communication.

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