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Letter to Editor

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Pathogenicity of AIFM1 Variants and Beneficial Effect of Riboflavin Need to Be Appropriately Confirmed

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Introduction

We read with interest the article by Heimer et al. about two pediatric patients with X-linked cerebellar ataxia due to two different mutations in the *AIFM1* gene [1]. We have the following comments and concerns.

We do not agree that the mutation c.422C>T is truly pathogenic. Pathognicity was claimed after in-silico prediction and after protein modelling [1]. No other family member carried the mutation, thus there was no segregation, and no biochemical or functional investigations were carried out. Location of the variant in a region where pathogenic mutation cluster not necessarily implies that the variant c.422T>C is also pathogenic.

Patient 2 was initially diagnosed with epilepsia partialis continua and three antiepileptic drugs (AEDs), benzodiazepines, valproic acid, and levetirazetam, were tried, but without effect [1]. Why were only 3 AEDs given and no further AEDs tried? Were they given in monotherapy or in combination? Why was valproic acid chosen from which it is well known that it is mitochondrion-toxic [2] and can even cause fatalities in some mitochondrial disorders (MIDs) [3]. Did the authors try pirazetam or was the patient ever put on a ketogenic diet?

The description of the phenotype in patient 1 is confusing. On the one hand the patient is described with "decreased deep tendon reflexes in lower limbs" and on the other hand he had "areflexia" [1]. Was areflexia present on the upper limbs? A further discrepancy refers to muscle biopsy in patient 2 [1]. In the description of patient 2 muscle biopsy is described as normal but it is mentioned that muscle biopsy was not available. Since AIFM1 functions as a NADH oxidoreductase, it would be interesting to know if there was complex-I deficiency on biochemical investigations of the muscle homogenate.

How can the authors be sure that improvement of ataxia was due to a therapeutic effect of riboflavin and not due to the natural course of the disease? From a number of MIDs it is known that they may improve spontaneously with progression of the disease, such as in LHON [4] or other MIDs [5]. Thus, the presumed beneficial effect of riboflavin may be incidental and not causal. A suspected therapeutic effect of riboflavin on the phenotype in *AIFM1* mutation carriers needs to be confirmed by a prospective cohort study.

Patient 2 manifested with cardiomyopathy [1]. Which type of cardiomyopathy was diagnosed? Hypertrophic, dilated, restrictive, or histiocytoid cardiomyopathy, Takotsubo syndrome, or noncompaction? Mild systolic dysfunction was diagnosed [1]. Did the patient receive neurohumoral treatment and did it experience a beneficial effect? Was improvement of cardiac function truly attributable to riboflavin or rather due to the beneficial effect of cardiac therapy? Was the family history positive for cardiac disease?

Overall, this interesting report could be more meaningful if more clinical data about the antiepileptic treatment and cardiomyopathy would be provided, if biochemical and functional tests would be carried out to confirm the pathogenicity of the variants, and if the presumed beneficial effect of riboflavin would be confirmed in a larger series of patients.

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