**GARS-1 variants may not only cause CMT2D but also epilepsy**

**Article History**

Received: 25.06.2020  
Accepted: 22.07.2020  
Revision: 27.07.2020  
Published: 01.08.2020

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**How to Cite the Article:**

Josef Finsterer (2020); GARS-1 variants may not only cause CMT2D but also epilepsy. *IAR J Med Sci.*, 1(3):134-135.

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**Abstract:**

Keywords: GARS-1, hereditary neuropathy, nerve conduction, epilepsy, axonal.

**LETTER TO THE EDITOR**

With interest we read the article by Yalcouye et al. about two siblings (IV-4, IV-6) from consanguineous parents (II-3, II-4), who carried the heterozygous, missense variant c.794G>A in GARS1 [1]. Clinically, the two patients manifested with axonal Charcot-Marie-Tooth disease 2D (CMT2D) and epilepsy [1]. We have the following comments and concerns.

We do not agree with the classification of pure CMT2D [2]. Though the two clinically manifesting patients IV-4 and IV-6 obviously had predominantly sensorimotor neuropathy, they and proband V-1 also had seizures, suggesting that at least the brain was affected in addition to the peripheral nerves. Since GARS1 mutations may not only manifest in the peripheral nerves [3], it cannot be excluded that in the two affected patients and the asymptomatic mother (III-7) and proband V-1 other organs were subclinically affected or that they manifested with subtle clinical manifestations. We should be informed if the three mutation carriers and proband V-1 were prospectively investigated for multisystem disease, which may remain unrecognised particularly in its early stage if not specifically looked for. The phenotype should be rather classified as CMT2D plus than CMT2D.

We should also know if the autonomic nervous system (ANS) was involved in the two patients manifesting with increased sensitivity to light, dry skin or hyperhidrosis, orthostasis, bradycardia, bladder dysfunction, or sexual dysfunction.

Since both siblings had epilepsy only around 12y [1] we should know why epilepsy had occurred only for such a small period of time, if both siblings required anti-seizure drugs (ASDs), which types of ASDs were applied, and if ASDs were effective. From several ASDs it is known that they are potentially toxic, why we should know if the applied ASDs were well tolerated or associated with side effects or even worsened the phenotype. We should also know if V-1, who also had epilepsy, carried the GARS1 variant of his father. When did epilepsy start in proband V-1? Since the cause of epilepsy was not reported, it can be speculated that it was due to the underlying GARS1 mutation as well. However, no GARS1 mutation carriers with epilepsy have been reported thus far. Thus, a second genetic trouble in this family should be excluded. Result of cerebral MRI should be presented.

It was reported that the two Bambura siblings inherited the variant from their mother who also carried the culprit variant [1]. It should be discussed why the two siblings manifested phenotypically but not the mother or other first degree family members carrying the mutation [1]. Which was the reason for the reduced penetrance in this family?

There is a discrepancy between the description of the onset manifestations in the text and table 1. In the text clinical onset was in the upper limbs in both patients. According to table 1, however, onset in the two patients was obviously dissimilar in both. Whereas neuropathy in the male patient IV-4 started in the upper limbs, neuropathy in patient IV-6 started in the lower limbs. It should be clarified which is the correct description.
Since foot deformities are a frequent manifestation of hereditary neuropathies [4], we should be informed if the two patients, the mother, the son of the male patient, or other family members alive were systematically investigated for dysmorphic feet and if those with foot deformities also had neuropathy.

A short coming of the study is that the mother, the son of the male patient, and other first degree family members did not undergo nerve conduction studies. Nerve conduction studies may be abnormal prior to clinical manifestations of neuropathy.

In summary, this interesting case series could be more meaningful if other first degree relatives than the mother were systematically investigated for neuropathy and manifestations in other organs, if results of blood chemical tests were provided, if nerve conduction studies were carried out in seemingly unaffected family members, and if epilepsy in both affected siblings was better characterised and the treatment type and effect reported.

REFERENCES