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**Letter to the Editor**

# The Phenotypic Spectrum of *NARS2* Variants is Still Expanding

**[1] Sounira Mehri, [2] Josef Finsterer**

[1] Biochemistry Laboratory, LR12ES05 "Nutrition-Functional Foods and Vascular Health", Faculty of Medicine, Monastir, Tunisia

[2] Neurology and Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

We read with interest the article by Cokyaman *et al*. about a 14 months-old female with a *NARS2*-related mitochondrial disorder (MID) manifesting with congenital hearing loss, developmental delay, myoclonic seizures, since age 4.5 months, generalised hypotonia, quadruspasticity, and mild lactic acidosis [1]. Cerebral magnetic resonance imaging (MRI) revealed generalised atrophy, and bilateral extensive subdural hematoma [1]. Electroencephalography (EEG) showed bilateral interspersed spikes and poly-spikes in a temporo-occipital distribution together with low amplitude cerebral bioelectrical activity [1]. The patient benefited from levetirazetam, clonazepam, nifedipine, tetracosactide, L-carnitine, coenzyme Q10, folinic acid, and vitamin C [1]. The study is appealing but carries limitations that raise concerns and should be discussed.

We disagree with the claim that the index patient is the first case of *NARS2* associated diabetes [1]. In August 2022 Yagasaki *et al*. reported two pediatric patients (patient-1: 3 years old female, patient-2: 1 years old male) with developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome [2]. Patient-1 developed diabetic ketoacidosis at age 3 months [2]. Patient-2 developed severe hyperglycemia requiring insulin therapy at age 3 days [2]. Both children presented with severe developmental delay, hearing loss and treatment-resistant epilepsy accompanied by progressive brain atrophy [2]. Whole exome sequencing revealed the compound heterozygous *NARS2* variants p.R159C and p.L217V, and the *GATA4* variant p.P407Q in both patients [2]. In addition to insulin, both patients received vitamin B1, L-carnitine, and coenzyme Q10 [2]. Patient-2 could be withdrawn from insulin therapy at age 6 months [2].

We should be informed about the cause and treatment of the subdural hematoma. In particular, we should know whether the history was positive for falls during epileptic seizures, whether the patient had coagulopathy due to hepatopathy, whether all coagulation parameters were within normal limits, or whether there was any indication for hypocoagulability. Did the patient undergo evacuation of the hematoma? Removal of the subdural hematoma is strongly recommended because it could be responsible for epileptic seizures.

A further limitation of the study is that the there is no mention whether the heterozygous parents manifested clinically or not. We should be informed whether the clinical exam or instrumental investigations of mother and father were indicative of *NARS2* manifestations.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Diabetes in *NARS2* carriers is not a novel phenotypic feature. Because only few cases with *NARS2*-related MID have been reported thus far, it is quite likely that the phenotypic spectrum will further expand in the future.

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