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Letter to the Editor

A new variant in *UNC50*, which manifests phenotypically as congenital myasthenic syndrome, requires extensive clinical, electrophysiological, and biochemical investigations

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Letter to the Editor

We read with interest the article by Shravya *et al*. on five patients with congenital myasthenic syndrome (CMS) from two unrelated families (family A, family B) caused by the biallelic variant c.644-13_644-9del in UNC50 [1]. Two patients (patient-1, patient-2) from family A were stillborn and the third patient (patient-3) lived one day [1]. One patient from family B (patient-4) lived 54 days and the other patient (patient-5) lived 18 days [1]. The study is remarkable, but several points should be discussed.

The first point is that congenital myasthenic syndrome (CMS) is usually a multisystem disorder that affects not only the skeletal muscles, but also the brain (e.g., seizures, encephalopathy, cognitive impairment, atrophy), bones (e.g., microcephaly, dysmorphia, dysmorphism), and the brain. microcephaly, dysmorphism, deformities (retrognathia, clinodactyly, club feet, rocker bottom feet)), connective tissue (e.g. joint deformities), heart (e.g. reduced heart rate variability), ears (e.g. hypoacusis), eyes (e.g. myopia) and kidneys (e.g. renal failure) [2, 3]. Which organs or tissues other than the brain, muscles and joints were affected in the five index patients? Knowledge of the overall phenotypic expression is crucial not only for disease prognosis but also for genetic counseling.

The second point is that no autopsy was performed on any of the five index patients. To assess the phenotypic spectrum of UNC50 variants, it would have been useful to document any previously unreported phenotypic abnormalities. An autopsy could also be helpful to determine the cause of death. Did the five patients die of respiratory failure, cardiac failure, sudden unexplained death in epilepsy (SUDEP) or a homeostatic abnormality?

The third point is that neither patient 4 nor patient 5, who lived only a short time, had undergone low or high frequency repetitive nerve stimulation (RNS) [1]. RNS may have documented a decremental or incremental response. To assess whether neuromuscular transmission was impaired by the UNC50 variant, single fiber electromyography would also have been useful. Immunohistochemical examination of the motor endplate would also have been useful to assess the extent to which the UNC50 variant impairs the formation, structure and function of postsynaptic acetylcholine receptors.

The fourth point is that no treatment for CMS was reported in either of the two patients who survived for a short time [1]. At least some patients with CMS may benefit from acetylcholinesterase inhibitors, 3,4-diamino-pyridine, salbutamol, fluoxetine, ephedrine or quinidine [4].

The fifth point is that only T1 and T2 images of cerebral MRI were provided [1]. To assess whether this patient had cerebral abnormalities other than generalized atrophy, it would have been helpful to also see DWI, ADC, PWI, and SWI images. Was there evidence of hypo-myelination, hypoxia, or cytotoxic or vasogenic edema?

In conclusion, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. All open questions need to be clarified before readers uncritically accept the conclusions of the study. A new UNC50 variant phenotypically manifesting as CMS requires a comprehensive clinical, electrophysiologic, and biochemical investigation to determine the correlation between genotype and phenotype.

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