SYNGAP1-related intellectual disability with ataxia and late onset of epileptic seizures

N. Gogatishvili, T. Tkemaladze, V. Skrahina, S. Kasradze, A. Rolfs (Tbilisi, Georgia)

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Objective: To characterize seizures in a patient with *SYNGAP1* mutation and the efficacy of antiepileptic drugs (AEDs).

Background: *SYNGAP1*-related intellectual disability is characterized by developmental delay (DD) or intellectual disability (ID), autism spectrum disorder (ASD) and epilepsy. According to the literature, generalized epileptic seizures usually begin at the age of about 3.5 years and so far there is no evidence regarding choice of any specific AED.

Method: Case report.

Results: We report the case of a 14-y old girl with severe ID, ASD, epilepsy and ataxia. She was born from non-consanguineous parents with birth weight 3000 gr. The patient presented with hypotonia, delayed psychomotor development, unstable ataxic gait and autistic behavior (hand flapping, obsessions with objects). She was able to walk at the age of 2 years and had first words at 5 years. She developed epilepsy at 8 years and presented with recurrent eyelid twitching, accompanied by loss of consciousness.
Standard EEG demonstrated multiple bursts of 2,5-3,5 Hz generalized spike-wave discharges, High amplitude 2-2,5 Hz generalized slow-sharp-wave discharges, with predominance in fronto-central regions. Brain MRI was without any structural abnormalities. AED treatment was started with Lamotrigine with decrease in seizure frequency but not complete remission; Valproic acid was added in AED treatment. Now she is seizures free on a combination of Valproic acid and Lamotrigine for 3 years.
Clinical exome sequencing (WES) was performed and a novel frameshift c.542_543del p.(His181Leufs) variant was identified in *SYNGAP1* gene. The variant creates a shift in the reading frame starting at codon 181. The new reading frame ends in a stop codon 2 positions downstream. *In silico* tools predict the change disrupts normal protein function. Parental testing confirmed de novo status of the variant.

Conclusion: *SYNGAP1* gene should be considered in individuals with GDD, ID, ASD, epilepsy, especially with combination of eyelid myoclonia with absences and myoclonic-atonic seizures. Clinical WES represents first-line diagnostic test in individuals with neurodevelopmental problems. Our case provides further support for the efficacy of Valproic acid in patients with SYNGAP1 mutation-related epilepsy.

References: Genetic analysis was performed at Centogene AG within the clinical study: “BioCDS – Biomarkers for Creatine Deficiency Syndromes”.

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