

Cognitive impairment in children with CACNA1A mutations.

Humbertclaude V., Riant F., Krams B., Zimmermann V., Nagot N., Annequin D., Echenne, B., Tournier-Lasserre E., Roubertie A. *Developmental Medicine & Child Neurology*. 2020 (62):330-337.

Variants: p.Q2064X, c.3412delC, c.2042delA,146dupA, p.Q736X, p.Q1154X; p.Y1706_11709del (deletion where amino acids 1706-1709 are missing), p.G677R, p.T666M, p.R1352Q, c.3825+1G>A(splice site variant), T1458M, C1417X, 1063dupG (extra single G nucleotide).

Diagnosis/symptoms: Episodic ataxia, hemiplegic migraines, BPT (benign paroxysmal torticollis), BPV (benign paroxysmal vertigo), BTU (benign tonic upward gaze), nystagmus, hypotonia, cognitive impairment, cerebellar atrophy, motor and speech delay.

This paper summarizes clinical and radiological data collected on 18 patients with various *CACNA1A* variants. The population included 9 males and 9 females between the ages of 3 years to 17 years. Fourteen variants were identified through sequencing: 8 nonsense variants (those with a premature STOP codon), 1 splice site variant, and 5 missense variants, 2 of which were brand new. The authors set out to systematically study these patients to look for a correlation between *CACNA1A* variants, neurological conditions, and cognitive impairment.

Episodic events

The authors used the following as their criteria for episodic events in patients: episodic ataxia, hemiplegic migraines, BPT, BPV, and BTU. Some patients showed only one episodic event, but over half showed a combination. Fifteen out of 18 patients had episodic ataxia or hemiplegic migraines, with 5 of those showing BTU, BPV, or BPT as infants. Overall, episodic ataxia was the predominant episodic event seen (11 out of the 18), followed by hemiplegic migraines (5 out of 18), BTU (4 out of 18), BPT (3 out of 18), and BVP (1 out of 18). Two patients also experienced seizures and another had myoclonus (twitching muscles).

On average, the first manifestation of an episodic event occurred at 24 months. BTU, BVP, and BPT were the very first events seen in 8 patients before age 4. Six of them first exhibited these events prior to age 1. The frequency of these episodes varied widely but had notably disappeared in all 8 patients prior to being recruited for the current study.

Episodic ataxia manifested first in 6 out of 18 patients, and was followed by another type of episodic event in 5 of those patients. The frequency of the ataxia varied from a few per year to 600 for one patient.

Hemiplegic migraines were the first episodic event seen in 4 out of 18 patients, with an average onset age of 9. Migraine frequency was less than or equal to 12 per year.

The authors also collected data regarding drug treatment for episodic episodes for 10 patients. Acetazolamide was effective for a small number of patients with episodic ataxia or hemiplegic migraines. Lamotrigine had no positive impacts and actually worsened symptoms for episodic ataxia.

Neuropsychological assessments

For neurological functions, the authors found that half of the patients exhibited a motor or speech delay. Nystagmus was observed in 7 of the 9 patients, 3 of them in combination with some sort of cerebellar syndrome (imbalance, unsteadiness). Two other patients showed hypotonia (low muscle tone), while 3 others showed what seemed like non-progressive congenital ataxia.

When the authors looked at academic performance as a neurological output, 15 out of 18 patients reported learning difficulties. Nine out of the 18 patients attended a special school. The other 9 attended regular school but 4 of those patients had some type of learning assistance. Overall, 13 out of 18 patients received support services of some sort, including speech and/or occupational therapy, or fine-motor rehabilitation therapy.

The authors also looked at IQ as a readout for neurological function. Assessment was completed and reported for 12 of the 18 patients. Moderate intellectual disability (IQ<50) was reported in 5 patients. Mild intellectual disability (IQ = 50-69) was reported in 2 patients. Four patients were borderlined with IQs ranging between 70-79. Two other patients showed IQs in the average range (80-119). MRI data was also studied in all 18 patients. Five of them exhibited cerebellar atrophy. Out of those 5 patients, 3 had episodic ataxia, 2 had hemiplegic migraines, and 4 had abnormal neurological exams including nystagmus. Four of the five with the cerebellar atrophy also showed a decrease in IQ.

When family history was studied in all 18 patients, 6 of them showed random episodic manifestations. Two patients had *de novo* (new, non-inherited) variants, thus symptoms had not been present in their families. Another variant had been inherited from an asymptomatic father with the same variant. The remaining 8 patients all had family members who showed the same or similar symptoms (ataxia, migraines, cognitive impairment, BTU, and BPT).

After assessing the data, the authors identified that there was a correlation between cerebellar atrophy and cognitive impairment. Furthermore, the atrophy patients also exhibited more motor delays than those without atrophy. The authors also noted that patients with nonsense mutations only accounted for 1 out of the 5 cases of cerebellar atrophy, but did not comment any further on any of these correlations. They also emphasized that their study does not advance any epilepsy or ASD (autism spectrum disorder) correlations with *CACNA1A* as only 2 patients exhibited seizures and no autism symptoms were observed.

The authors concluded that their study confirms the diversity of episodic events and varying degrees of severity seen in patients with *CACNA1A* variants. Furthermore, these episodic events often occurred in combination with each other. The authors also stated that early onset symptoms, such as BTU or BPT, could be used as biomarkers for ataxia or migraines later in life as nearly half of the patients exhibited them. They also emphasized the 50% prevalence of cognitive impairment found in the *CACNA1A* patients, ranging from average to moderate intellectual disability. This suggests that *CACNA1A*-related disorders may present as a neurodevelopmental disorder outside of the ataxia and hemiplegic migraines normally associated with *CACNA1A*. Furthermore, early intervention in skills required in academics (speech, fine motor skills, cognitive development, etc) would greatly benefit *CACNA1A* patients later in life.