Movement Disorders
CLINICAL PRACTICE
LETTER: GENOTYPE AND PHENOTYPE

Pediatric Onset of Generalized Dystonia, Cognitive Impairment, and Dysmorphic Features in a Patient Carrying Compound Heterozygous GNAL Mutations

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Variants in *GNAL* have been mostly associated to adult-onset focal dystonia, involving laryngeal and craniocervical regions with superimposed tremor, being inherited in an autosomal dominant manner with reduced penetrance.[1] To date, biallelic variants in *GNAL* have been described only in one family.[2]

We report a 15-year-old boy who presented with abrupt onset of neck flexion, which occurred a few weeks before without fever, infections, or bulbar signs. Initially, this abnormal posture was not fixed, presented diurnal fluctuations, without clear circadian rhythm; in the following weeks it became sustained. Local pain, dyspepsia, and epigastric pain were absent.

During childhood, he presented a delayed language development (first words at the age of 2), a tendency to keep the mouth gaping, and walk on tiptoe. At 5 years a neurological evaluation showed a cranial circumference of 52 cm (75th percentile), truncal hypotonia, and dystonia (anteflexion), more evident when walking, which started ~1 year before. A moderate intellectual disability (ID) was also diagnosed (total Griffith scale score 59). His family history was unremarkable and no consanguinity was reported.

Neurological examination revealed mild axial dystonia with left laterodeviation of the trunk, a marked cervical dystonia (anterocollis and laterocollis) with superimposed spasmodic movements, dystonic dysarthria, and whispering dysphonia. There was also dystonic posture of the left harm with a dystonic tremor. A mild bilateral upper limb bradykinesia was also present. He displayed dysmorphic features such as hypertelorism, broad nasal tip, and prognathism (Video 1).

A levodopa trial was started (until 300 mg/day) without benefit. The brain magnetic resonance imaging was unremarkable, and brainstem auditory evoked potentials revealed sensorineural hearing loss. Treatment with Trihexyphenidyl (12 mg/day) and botulinum toxin in the cervical region determined a moderate benefit, whereas dysarthria worsened over the years. Because of his ID, he presented difficulties in attending school and did not take the secondary school degree.

A comparative genomic hybridization array revealed a 166 kb deletion on chromosome 10 (10q11.21: 44,256,337–44,422,255 × 1) also detected in the unaffected mother. Fragile X syndrome was excluded. Whole exome sequencing displayed two compound heterozygous variants in *GNAL* (NM_182978.4): c.1163-1G>A and c.899A>T (p.Gln300Leu), each one inherited from one healthy parent. Despite that both variants are still classified as variants of unknown significance according to the latest American College of Medical Genetics and Genomics criteria, they are absent from population databases and there is evidence in favor of their pathogenic role. The first one is a canonical splice site variant predicted to generate a truncated protein (without nonsense mediated decay), whereas the missense variant one is predicted as deleterious by several in silico tools (e.g. Combined Annotation Dependent Depletion - score 25).[3]

This is a complex case featuring generalized dystonia, sensorineural hearing loss, facial dysmorphic features, and intellectual disability, likely as a consequence of biallelic *GNAL* variants. *GNAL* monoallelic variants have been associated with adult-onset craniocervical dystonia, whereas childhood-onset patients have been rarely reported.[4–8] In these cases, carrying monoallelic variants, dystonia had a heterogeneous body distribution, ranging from focal to generalized, but none reported an abrupt onset.

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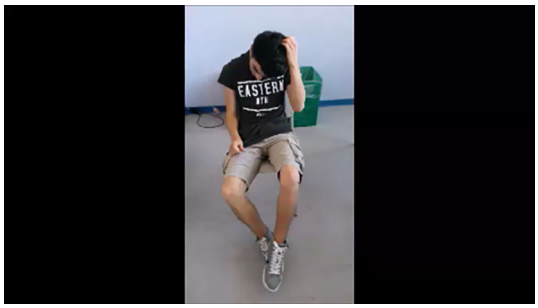

Video 1. Neurological examination of the patient at the beginning of the symptomatology and after botulinum toxin injection on the cervical region.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14124

The sub-acute onset, as in our case, appears to be unique in this genetic dystonia. To date, only two siblings carrying biallelic homozygous *GNAL* mutations have been reported.[2] These children were born to consanguineous Turkish parents, presented exaggerated muscle tone at the age of one, and developed generalized dystonia, respectively, at 15 and 11 years in the context of ID.

This is the first Caucasian patient harboring biallelic *GNAL* variants, and further evidence is needed to unequivocally confirm the causative role of the identified variants. The presence of clinically unaffected parents could be explained by incomplete variants penetrance, as already described.[1] Accordingly, from a biological point of view, fully haploinsufficient variants are sufficient on their own to cause the disease in heterozygous state (even if with reduced penetrance), whereas "recessive" variants are likely resulting in proteins, which retain at least in part their function.[2] As for *GNAL*, few other dystonia-genes with both dominant and recessive patterns were reported: *GCH1* (DYT5a), *THAP1* (DYT6), *ADCY5*, and *SPR* present a more frequent dominant inheritance, although rare bi-allelic variants carriers have been described.[9]

Another atypical aspect relies on the body distribution of dystonia. The here-presented prominent craniocervical focal involvement, without severe generalization, is more in line with the typical adult-onset forms of *GNAL*-related dystonia and differs from other childhood-onset genetic dystonia (*DYT1, DYT6 KMT2B*).[9]

Our case suggests that biallelic *GNAL* variants can underlie a complex phenotype where dystonia (mostly generalized) may coexist with dysmorphic features, sensorineural hearing loss and intellectual disability. Notably, no similar cases in *GNAL* variants carriers have been reported. Dystonia may indeed be part of the clinical spectrum of neurodevelopmental diseases where it may coexist with other neurological and systemic symptoms.[9]

Clinicians should be aware of these rare presentations, and *GNAL* genetic screening should be included in the workout of these complex pediatric patients given the good response to globus pallidus internus-deep brain stimuation.[10]

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

L.M.: 1A, 3A, 3B
E.C.: 3B
P.B.: 1C
F.C.: 1C
M.C.: 3B
S.D.A.: 1C, 3B
L.C.: 1C, 3B

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