Case Report

Generalized Dystonia and Paroxysmal Dystonic Attacks due to a Novel ATP1A3 Variant

Carlos Zúñiga-Ramírez1,2,3, Mirelle Kramis-Hollands1, Rodrigo Mercado-Pimentel1,3, Héctor Alberto González-Usigli1,4, Michel Sáenz-Farret1,2, Alberto Soto-Escageda1,2, & Alfonso Fasano1,6

1Movement Disorders and Neuropathological Diseases Unit (UMANO), Guadalajara, MX, 2Hospital Civil de Guadalajara “Fray Antonio Alcalde,” Guadalajara, MX, 3Department of Genetics, Hospital Español, Mexico City, MX, 4Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, MX, 5Edmond J. Safra Program in Parkinson’s Disease and Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital and Division of Neurology, UHN, Division of Neurology, University of Toronto, Toronto, CA, 6Krembil Brain Institute, Toronto, Ontario, CA

Abstract

Background: Paroxysmal movement disorders are a heterogeneous group of neurological diseases, better understood in recent years thanks to widely available genetic testing.

Case report: A pair of monozygotic twins with dystonia and paroxysmal attacks, resembling paroxysmal non-kinesigenic dyskinesias, due to a novel ATP1A3 variant are reported. The complete resolution of their paroxysms was achieved using levodopa and deep brain stimulation of the internal globus pallidus.

Discussion: Improvement of interictal dystonia was also achieved with this therapy.

Keywords: ATP1A3, paroxysmal dyskinesia, dystonia, status dystonicus, AHC-2, rapid-onset parkinsonism-dystonia

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ATP1A3 mutations have been described all over the world. Classically, rapid-onset dystonia-parkinsonism (RDP); cerebellar ataxia, pes cavus, optic atrophy, and sensorineural hearing loss (CAOS/CAPOS) syndrome; and alternating hemiplegia of childhood (AHC) type 2 have been related to this gene mutation, although mixed phenotypes have been increasingly reported. Paroxysmal dyskinesias include a wide spectrum of diseases that are characterized by movement disorders, epilepsy, and neurological deficits.1,2 Herein, we report a pair of monozygotic twins carrying an ATP1A3 variant who developed paroxysmal dystonic spells resembling non-kinesigenic dyskinesia (PNKD) and more severe episodes similar to status dystonicus.

Twenty-year-old monozygotic twins (case 1 and 2) presented during the first months of life with paroxysms of hyperkinetic movements characterized by painful abnormal postures lasting from minutes to hours, presenting up to 20 times per week. These movements were triggered by weather changes, mood swings, caffeine intake, exercise, fever, and infections, among others. Later on, they were also characterized by speech arrest. Both parents and two more siblings (21 and 11 years old) did not show any neurological disease. The 67-year-old paternal grandfather developed a dystonic head tremor at 65 years of age.

Neurologic examination of case 1 showed interictal generalized dystonic postures mainly affecting the axial muscles and both upper extremities (particularly distally and more severe on the right) as well as both legs, also causing scissoring gait. Case 2 presented a similar distribution but with an overall milder phenotype. Dystonic spells involved the whole body in both cases, in some cases reaching the severity of status dystonicus. Speech arrest was a feature that was also observed during these spells (Video 1).
Blood and cerebrospinal fluid (CSF) testing as well as electroencephalography and brain magnetic resonance imaging (MRI) were unremarkable. Neuropsychological assessment revealed borderline intelligence in both cases (case 1: IQ 72; case 2, IQ 75) with an advantage in verbal comprehension scale, deficiencies in focal, selective, and sustained attention; limitation of working memory which compromises execution of mathematical and reading comprehension, with deficits in codification memory process in verbal tasks and recall memory process in visual tasks. Processing speed, visuospatial, constructional, and executive functions (abstract thinking) were also impaired; case 1 also showed self-monitoring and inhibitory control deficiencies with motor perseveration (Table 1).

Genetic testing for PKND mutations was negative. SLC2A1 (solute carrier family 2 member 1, also known as GLUT-1) mutations were not sought since both CSF glucose and lactate levels were normal, and patients did not show improvement on following a ketogenic diet. Whole exome sequencing showed a novel heterozygous missense variant of the ATP1A3 gene [Chr19(GRCh37): g.42474553A>C NM_001256214.1: c.2444T>G p.(Leu815Arg)] classified as probably pathogenic based on the recommendations of the American College of Medical Genetics (ACMG), and Human Gene Mutation Database (HGMD) number CM145544. Also, in silico analysis (SIFT (sorting intolerant from tolerant)) establishes it as deleterious and the mutation tester establishes it as pathogenic. CADD score of 28.4 and REVEL score of 0.972 were obtained. However, we were unable to calculate MetaLR. This finding was also replicated in the affected sibling. Genetic testing for this specific ATP1A3 variant was negative among their parents, siblings, and paternal grandfather.

Levodopa/carbidopa titrated up to 1 gram daily was tried in both twins, with complete resolution of paroxysms and marked improvement of interictal dystonia in case 2. Case 1 instead required bilateral internal globus pallidus deep brain stimulation (GPi DBS), which resulted in a remission of paroxysms and improvement of interictal dystonia (total UDRS pre-GPi DBS: 50/120, 4 months post-GPi DBS: 28/120) (Video 2).

**Discussion**

Currently, the known genes underlying the pathogenesis of paroxysmal dyskinesias are PRRT2 (phenotype MIM 128200, locus MIM 614386), PNKD (phenotype MIM 118800, locus MIM 609023), SLC2A1/GLUT-1 (phenotype MIM 601042, locus MIM 138140), SCN8A (phenotype MIM 609446, locus MIM 600150), KCNMA1 (phenotype MIM 602066, locus MIM 600702), ECHS1 (phenotype MIM 616277, locus MIM 602292), PDHA1 (phenotype MIM 312170, locus MIM 300502), PDHX (phenotype MIM 245349, locus MIM 608769), DLAT (phenotype MIM 245348, locus MIM 608770), ADCT3 (phenotype MIM 606703, locus MIM 600293), CACNA1A (phenotype MIM 108500 and 141500, locus MIM 601011), GCH1 (phenotype MIM 128230, locus MIM 600225), and SLC16A2 (phenotype MIM 300523, locus MIM 300095). In our cases, the ATP1A3 variant produces a phenotype similar to PNKD, particularly the wide range of duration and frequency, the lack of sudden movement or exercise as precipitant, and the presence of aggravating factors such as stress and fatigue. However, in contrast to PNKD, our patients also presented with interictal mild dystonia, speech arrest, and intellectual disability. Nevertheless, interictal neurological deficits and a wide clinical overlap have been described among subjects with paroxysmal dyskinesias. Although a de novo mutation is suspected in our cases, the paternal grandfather who started with late-onset dystonic tremor, tested negative for ATP1A3. The reason for this remains unknown but germinal mosaicism has been recently reported as a mechanism of inheritance in ATP1A3. Nevertheless, there is still a possibility that the reported variant lacks pathogenicity among these subjects, mainly...
explained by its absence in their grandfather and responsiveness to the aforementioned treatment.

The large variety of phenotypes due to mutations in the *ATP1A3* coupled with clinical features shared with other diseases presents a diagnostic challenge. *ATP1A3*-related disorders, such as AHC, RDP, and CAPOS syndrome, are just some of the overlapping entities that share common features: abrupt-onset, asymmetric anatomical distribution, and association with triggering factors. However, recent descriptions of diseases with different mutations at the *ATP1A3* have shown some similarities to those already known: fever-induced paroxysmal weakness and encephalopathy, epilepsy with early death and failure to thrive, and relapsing encephalopathy with cerebellar ataxia, among others. Other defects associated with less-specific phenotypes are seizures, dystonia, ataxia, and psychiatric conditions.

Pathophysiological mechanisms involved in the development of *ATP1A3*-related disorders are largely unknown. *ATP1A3* encodes the α3

### Table 1. Results of Neuropsychological Assessment

|                              | CASE 1          | Qualitative Description | CASE 2          | Qualitative Description |
|------------------------------|-----------------|-------------------------|-----------------|-------------------------|
| **Intelligence (WAIS-IV)**    |                 |                         |                 |                         |
| Full-scale (intellectual quotient) | 3               | Borderline              | 5               | Borderline              |
| Verbal comprehension         | 14              | Below average           | 16              | Below average           |
| Perceptual reasoning         | 2               | Deficient               | 4               | Borderline              |
| Working memory               | 1               | Deficient               | 1               | Deficient               |
| Processing speed             | 1               | Deficient               | 6               | Borderline              |
| **Attention**                |                 |                         |                 |                         |
| Stroop interference index    | 5               | Borderline              | 1               | Deficient               |
| **Language**                 |                 |                         |                 |                         |
| Test Barcelona fluency and grammar | -           | Average                 | -               | Average                 |
| Semantic verbal fluency      | 5               | Borderline              | 15              | Below average           |
| Test Barcelona verbal repetition | -           | Average                 | -               | Average                 |
| Test Barcelona complex verbal comprehension | 10      | Below average           | 10              | Below average           |
| Test Barcelona Text reading  | -               | Slow with additions and substitutions | - | Slow with additions and substitutions |
| **Memory**                   |                 |                         |                 |                         |
| CVLT word list learning      | -               | Below average           | -               | Deficient               |
| CVLT word list recall        | -               | Average                 | -               | Average                 |
| Test Barcelona texts memory  | 10              | Below average           | 40              | Average                 |
| Test Barcelona visual memory | 1               | Deficient               | 1               | Deficient               |
| Rey–Osterrieth complex figure recall | 1        | Deficient               | 2               | Deficient               |
| **Visuospatial skills**      |                 |                         |                 |                         |
| Rey–Osterrieth complex figure copy | 1           | Deficient               | 10              | Below average           |
| Test Barcelona constructional praxis | 1     | Deficient               | 10              | Below average           |
| **Executive functions**      |                 |                         |                 |                         |
| ToL total moves              | 74              | Average                 | 74              | Average                 |
| ToL rule violations          | 1               | Deficient               | 21              | Below Average           |
| ToL initiation time          | 82              | Above average           | 72              | Average                 |
| ToL execution time           | 5               | Borderline              | 13              | Below Average           |

Abbreviations: CVLT, California Verbal Learning Test; ToL: Tower of London Drexel University; WAIS-IV: Wechsler Adult Intelligence Scale.
dystonia as part of their clinical presentation, in most cases with onset during the first year of life. Chorea, athetosis, dystonia, hypotonia, intellectual disability, and ataxia were also observed in these subjects. Roussignol et al. described six family members and three had paroxysmal exercise-induced dystonia. Lastly, in a review by Sweeney et al., in 2015, “dystonic spells” are described as part of the clinical criteria for AHC but no mention of paroxysmal dyskinesias is made.

Treatment remains symptomatic. Interestingly, case 2 responded to levodopa while case 1 had an excellent response to GPi DBS. Neither levodopa nor GPi DBS have been previously reported to successfully treat subjects with ATP1A3 mutations. Nevertheless, resolution of paroxysmal episodes in our case is in line with the reports of significant and sustained improvement in subjects with PNKD after undergoing bilateral GPi DBS. The reason for improvement through levodopa being limited to one of the two cases remains unclear; however, levodopa has been shown to improve different entities where dystonia coexists: Parkinson’s disease dystonic features, myoclonus dystonia, and dopa-responsive dystonia, among others. A milder phenotype in one of the cases could be the reason for responsiveness to levodopa. It seems that a reduced activity at the nigrostriatal dopaminergic system would be responsible for the emergence of dystonia as the causative mechanism.

In conclusion, this is the first description of an ATP1A3 variant causing paroxysmal worsening of dystonia resembling PNKD and status dystonicus in more severe episodes. Our cases suggest that ATP1A3 mutations should be considered in early onset generalized dystonia especially when combined with intellectual disability and paroxysmal movement disorders.

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