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Tremor and Other Hyperkinetic Movements

Case Report

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

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

Discussion: Paroxysmal worsening of movement disorders should be suspected as part of the *ATP1A3* spectrum. Treatment outcome might be predicted based on the phenotype.

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

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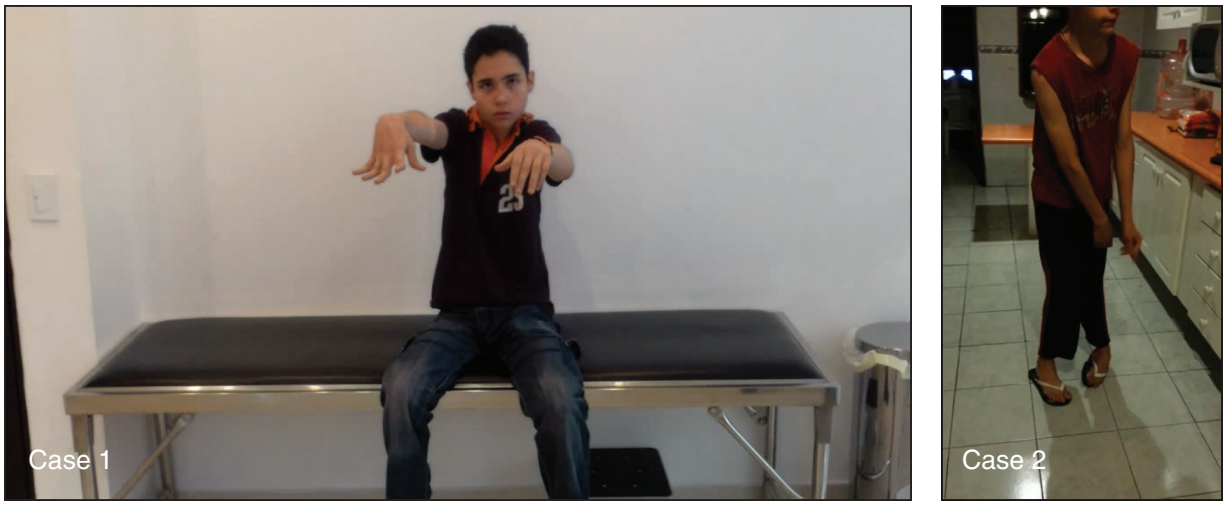
ATP1A3 mutations have been described all over the world. Classically, rapid-onset dystonia-parkinsonism (RDP); cerebellar ataxia, pes cavus, optic atrophy, and sensorineural hearing loss (CAOS/CAPOS) syndrome; and alternating hemiplegia of childhood (AHC) type 2 have been related to this gene mutation, 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).



Video **1. The Video Shows the Dystonic Posturing Seen in Case 1, while Minor Dystonia Was Noted in Case 2 during Interictal State.** The second segment of the video shows paroxysmal dystonic attacks in both cases.

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. *SCL2A1* (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 602066, locus MIM 600702), *KCNMA1* (phenotype MIM 609446, locus MIM 600150), *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), *ADCY5* (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).[1,2,3] 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.[1,2] 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.[1,2] 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*.[4] Nevertheless, there is still a possibility that the reported variant lacks pathogenicity among these subjects, mainly

Table **1.** **Results of Neuropsychological Assessment**

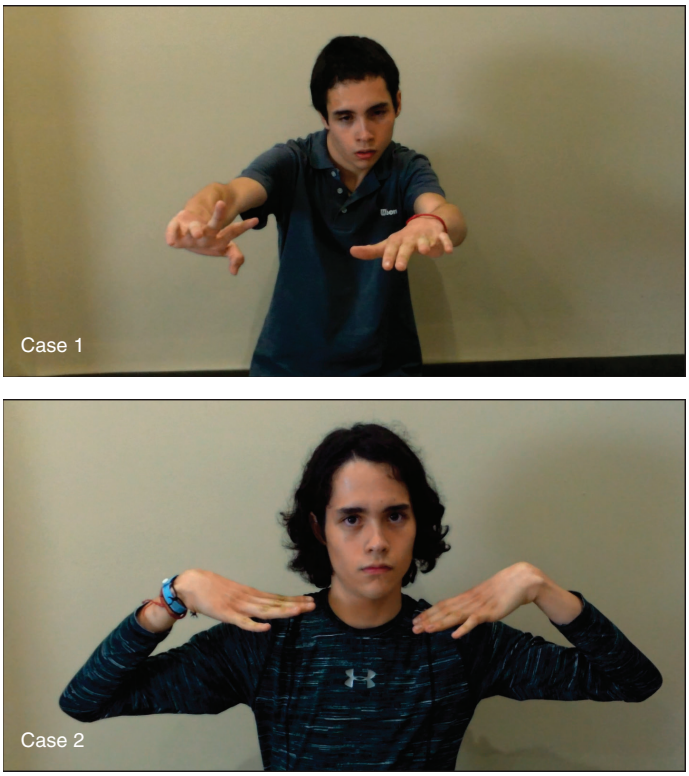
	CASE 1		CASE 2	
	Percentile Rank	**Qualitative Description**	**Percentile Rank**	**Qualitative Description**
Intelligence (WAIS-IV)				
Full-scale (intellectual quotient)	3	Borderline	5	Borderline
Verbal comprehension	14	Below average	16	Below average
Perceptual reasoning	2	Deficient	4	Borderline
Working 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
Memory				
CVLT word list learning	-	Below average	-	Deficient
CVLT word list recall	-	Average	-	Average
Test Batrcelona 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.

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,[5] epilepsy with early death and failure to thrive,[6] and relapsing encephalopathy with cerebellar ataxia,[7] among others. Other defects associated with less-specific phenotypes are seizures, dystonia, ataxia, and psychiatric conditions.[8]

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



Video 2. **The Video Shows Improvement of Dystonia in Case 1 after GPi DBS (Parameters on Each Side Were: −1 +3, 6.5 V, 60 Microseconds, 185 Hz) and Resolution of Dystonia in Case 2 after Oral Levodopa Was Started.** None of the cases showed dystonic paroxysms after treatment was initiated.

catalytic subunit of the Na^+/K^+ ATPase pump, and it is selectively expressed in neurons in the central nervous system. In those expressing α3 mutant alleles, reduced affinity of the Na^+/K^+ ATPase for intracellular Na^+ leads to elevated intracellular Na^+ concentrations, which in turn can result in an increased influx of Ca^{2+} ions in the cell, via the Na^+/Ca^{2+} exchange system, with toxic effects and possible liberation of excitatory amino acids. Moreover, since the neuronal uptake of some neurotransmitters relies on a correct Na^+ gradient, its reduction, due to increased intracellular Na^+, could functionally impair dopamine uptake, thus leading to dystonia and parkinsonism without degeneration of the nigrostriatal pathway.[9]

A clinical condition similar to PNKD has been described as part of the spectrum of *ATP1A3* mutations.[10] Pittock et al.[11] described an Irish family with RDP and one of the members (case II-9) showed "intermittent episodes of difficulty speaking, spasms of his arm and hand and unsteadiness in association with stress and anxiety." This case was catalogued by the authors as an atypical presentation of RDP. Three more subjects depicted mild dystonia in this family but were classified as part of the features of RDP.[11] Neither levodopa nor pallidotomy resulted in improvement of the symptoms featured in this family. Rosewich et al.[12] subsequently described 24 subjects with AHC, 23 of whom had dystonia as part of their clinical presentation, in most cases with onset during the first year of life. Choreoathetosis, dysarthria, hypotonia, intellectual disability, and ataxia were also observed in these subjects. Roubergue et al.[13] described six family members and three had paroxysmal exercise-induced dystonia. Lastly, in a review by Sweeney et al.[14] 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.[15,16] 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.[17] 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.[18–20] 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.[21] Our cases suggest that *ATP1A3* mutations should be considered in early onset generalized dystonia especially when combined with intellectual disability and paroxysmal movement disorders.

References

1. Erro R, Sheerin UM, Bhatia KP. Paroxysmal dyskinesias revisited: 500 genetically proven cases and a new classification. *Mov Disord* 2014;29(9):1108–1116. doi: 10.1002/mds.25933

2. Erro R, Bhatia KP, Espay AJ, Striano P. The epileptic and nonepileptic spectrum of paroxysmal dyskinesias: channelopathies, synaptopathies and transportopathies. *Mov Disord* 2017;32(3):310–318. doi: 10.1002/mds.26901

3. Erro R, Bhatia KP. Unravelling of the paroxysmal dyskinesias. *J Neurol Neurosurg Psychiatry* 2019;90(2):227–234. doi: 10.1136/jnnp-2018-318932

4. Hully M, Ropars J, Hubert L, Boddaert N, Rio M, Bernardelli M, et al. Mosaicismin ATP1A3-related disorders: not just a theoretical risk. *Neurogenetics* 2017;18(1):23–28. doi: 10.1007/s10048-016-0498-9

5. Yano ST, Silver K, Young R, DeBrosse SD, Ebel RS, Swoboda KJ, et al. Fever-induced paroxysmal weakness and encephalopathy, a new phenotype of ATP1A3 mutation. *Pediatr Neurol* 2017;73:101–105. doi: 10.1016/j.pediatrneurol.2017.04.022

6. Paciorkowski AR, McDaniel SS, Jansen LA, Tully H, Tuttle E, Ghoneim DH, et al. Novel mutations in ATP1A3 associated with catastrophic early life epilepsy, episodic prolonged apnea, and postnatal microcephaly. *Epilepsia* 2015;56(3):422–430. doi: 10.1111/epi.12914

7. Dard R, Mignot C, Durr A, Lesca G, Sanlaville D, Roze E, et al. Relapsing encephalopathy with cerebellar ataxia related to an ATP1A3 mutation *Dev Med Child Neurol* 2015;57:1183–1186. doi: 10.1111/dmcn.12927

8. Galaz-Montoya CI, Alcaraz-Estrada S, García-Montaño LA, Zenteno JC, Piña-Aguilar RE. A recurrent de novo mutation in ATP1A3 gene in a Mexican patient with alternating hemiplegia of childhood detected by massively parallel sequencing. *Bol Med Hosp Infant Mex* 2019;76(1):49–53. doi: 10.24875/BMHIME.M19000053

9. Carecchio M, Zorzi G, Ragona F, Zibordi F, Nardocci N. ATP1A3-related disorders: an update. *Eur J Paediatr Neurol* 2018;22(2):257–263. doi: 10.1016/j.ejpn.2017.12.009

10. Méneret A, Roze E. Paroxysmal movement disorders: an update. *Rev Neurol* (*Paris*) 2016;172(8–9):433–445. doi: 10.1016/j.neurol.2016.07.005

11. Pittock SJ, Joyce C, O'Keane V, Hugle B, Hardiman O, Brett F, et al. Rapid-onset dystonia-parkinsonism. A clinical and genetic analysis of a new kindred. *Neurology* 2000;55:991–995. doi: 10.1212/WNL.55.7.991

12. Rosewich H, Thiele H, Olhenbusch A, Maschke U, Altmüller J, Frommolt P, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. *Lancet Neurol* 2012;11:764–773. doi: 10.1016/S1474-4422(12)70182-5

13. Roubergue A, Roze E, Vuillaumier-Barrot S, Fontenille MJ, Méneret A, Vidailhet M, et al. The multiple faces of the ATP1A3-related dystonic movement disorder. *Mov Disord* 2013;28(10):1457–1459. doi: 10.1002/mds.25396

14. Sweeney MT, Newcomb TM, Swoboda KJ. The expanding spectrum of neurological phenotypes in children with ATP1A3 mutations, alternating hemiplegia of childhood, rapid-onset dystonia-parkinsonism, CAPOS and beyond. *Pediatr Neurol* 2015;52:56–64. doi: 10.1016/j.pediatrneurol.2014.09.015

15. Albanese A, Di Giovanni M, Amami P, Lalli S. Failure of pallidal deep brain stimulation in DYT12-ATP1A3 dystonia. *Parkinsonism Relat Disord* 2017;45:99–100. doi: 10.1016/j.parkreldis.2017.09.008

16. Brücke C, Horn A, Huppke P, Kupsch A, Schneider GH, Kühn AA. Failure of pallidal deep brain stimulation in a case of rapid-onset dystonia parkinsonism (DYT12). *Move Disord Clin Pract* 2015;2(1):76–78. doi: 10.1002/mdc3.12124

17. Van Coller R, Slabbert P, Vaidyanathan J, Schutte C. Successful treatment of disabling paroxysmal nonkinesigenic dyskinesia with deep brain stimulation of the globus pallidus internus. *Sterotact Funct Neurosurg* 2014;92:388–392. doi: 10.1159/000365226

18. Shetty AS, Bhatia KP, Lang AE. Dystonia and Parkinson's disease: what is the relationship? *Neurobiol Dis* 2019;132:104462. doi: 10.1016/j.nbd.2019.05.001

19. Luciano MS, Ozelius L, Sims K, Raymond D, Liu L, Saunders-Pullman R. Responsiveness to levodopa in epsilon-sarcoglycan deletions. *Mov Disord* 2009;24(3):425–428. doi: 10.1002/mds.22375

20. Randby H, Salvador CL, Oppebøen M, Skogseid IM, Koht J. Dopa-responsive dystonia. *Tidsskr Nor Laegeforen* 2018;138(19). doi: 10.4045/tidsskr.17.0595

21. Ruiz-Lopez M, Fasano A. Rethinking status dystonicus. *Mov Disord* 2017;32:1667–1676. doi: 10.1002/mds.27207