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Clinical Observations

Identical ATP1A3 Mutation Causes Alternating Hemiplegia of Childhood and Rapid-Onset Dystonia Parkinsonism Phenotypes

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ABSTRACT

BACKGROUND: Alternating hemiplegia of childhood and rapid-onset dystonia parkinsonism are two separate movement disorders with different dominant mutations in the same sodium-potassium transporter ATPase subunit gene, ATP1A3. **PATIENT:** We present a child with topiramate-responsive alternating hemiplegia of childhood who was tested for an ATP1A3 gene mutation. **RESULTS:** Gene sequencing revealed an identical ATP1A3 mutation as in three typical adult-onset rapid-onset dystonia parkinsonism cases but never previously described in an alternating hemiplegia of childhood case. **CONCLUSION:** The discordance of these phenotypes suggests that there are other undiscovered environmental, genetic, or epigenetic factors influencing the development of alternating hemiplegia of childhood or rapid-onset dystonia parkinsonism.

Keywords: ATP1A3, alternating hemiplegia of childhood, rapid-onset dystonia parkinsonism, movement disorder, genetics, topiramate

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Introduction

In 1971, Verret and Steele characterized alternating hemiplegia of childhood (AHC), a childhood-onset neurological disorder characterized by recurrent brief episodes, developing over minutes to hours, of alternating limb paralysis and/or dystonia with subsequent increasing developmental disability over many years.[1] In contrast, rapid-onset dystonia parkinsonism (RDP) is an adult-onset movement disorder with sustained dystonia and parkinsonism that develops over hours to weeks.[2]

These two movement disorders are related by way of discoveries in 2012 that AHC shares the same mutated protein as RDP, a sodium-potassium transporter ATPase subunit, ATP1A3, but each disorder prototypically has its own set of known mutations.[3] We present here a boy with AHC who was found to carry a mutation that has only been described previously in adult-onset RDP. This case demonstrates that an identical *ATP1A3* genotype can be related to either AHC or RDP.

Patient Description

At 2 years 6 months of age, this previously well, developmentally normal patient presented with a 12-hour period of waxing and waning abnormal eye movements, lethargy, slurred speech, drooling, and hypotonia/paralysis. He presented 10 weeks after a mild Influenza A (H1N1) upper respiratory tract infection and also 3 weeks after receiving an influenza vaccine, but had otherwise been well. Extensive investigations for infectious, inflammatory, metabolic, vascular, and neoplastic causes were unremarkable. A diagnosis of AHC was made over the subsequent months based on recurrent brief acute-onset transient episodes of paralysis or dystonia, provoked possibly by loud environments with excessive behavioral stimulation. These episodes were aborted by inducing sleep, including with lorazepam, and prevented with topiramate monotherapy started at 5 years of age but not by the initial flunarizine monotherapy started at 3 years of age. Formal neuropsychological assessment at 5 years 4 months of age described overall intellectual, language, and early academic skills within the lower end of the average range for his age with difficulties in articulation in expressive

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language and limited fine motor skills, particularly with dexterity, speed, and strength tasks. Further details of the neurological manifestations are summarized in Table. The child was of French Canadian and Spanish decent with no family history of consanguinity or other neurological disorders.

Before the discovery of *ATP1A3* mutations in AHC, the patient had clinical testing by sequencing of the *CACNA1A*, *ATP1A2*, and *SCN1A* genes, which had been associated with rare cases of AHC and familial hemiplegic migraine.[5] Additionally, sequencing was normal for the *MR1* gene associated with paroxysmal nonkinesigenic dyskinesia (OMIM #118800).

Sanger sequencing of the *ATP1A3* gene exons and exon-intron boundaries by a commercial clinical laboratory (Centogene AG, Rostock, Germany) revealed a missense mutation (c.829 G→A; p.E277 K). Parental carrier testing showed the mutation to be *de novo*. The patient and his parents consented to this report.

Discussion

The specific *ATP1A3* gene mutation identified in our patient with AHC has only been reported in RDP.[3] This finding demonstrates that the same mutation can result in either disorder, suggesting there must be other factors contributing to whether a patient will develop AHC or RDP.

The child presented here is consistent with those described in the largest published AHC cohorts, varying only in the age of onset at 2 years 6 months versus younger than 18 months but this is still within the published age ranges.[6] His findings are certainly distinct from those of RDP, which typically present in the second or third decade of life with more sustained dystonia and Parkinsonism.[2]

The E277 K mutation we report has only been described in three individuals with adult-onset RDP: (case 1: references 2, 6; case 2: reference 6; case 3: reference 7).[7] The neurological manifestations in these three RDP patients are summarized in Table in comparison to our AHC case. Experiments have shown the deleterious biological effect of this E277 K mutation.[4]

Only one other *ATP1A3* mutation, D923N, has clearly been observed in both AHC and RDP. Roubergue et al. recently described a family with five affected members with AHC across four generations who carried this inherited mutation.[8,9] Their family study highlighted that the family shares the D923N mutation with an unrelated individual with adult-onset RDP. The RDP patient developed generalized dystonia with prominent bulbar involvement that plateaued over weeks starting at age 20 years. He had no history of brief or transient hemiplegic or dystonic episodes typical of AHC.

Even before Roubergue et al.'s work though, an early phenotype-genotype study of a family with multiple members with RDP described an *ATP1A3* genotype presenting with both an AHC and a RDP phenotype but the AHC phenotype was not identified as such by the authors.[10] Pittock et al. described an affected male member of the family whose only symptoms were transient acute-onset episodes since 4 years of age of mostly left-sided hemidystonia and dysarthria (patient II-9). This case was labeled RDP, because it belongs to an RDP family, but actually represents a mild AHC case or an intermediate presentation between AHC and RDP, much closer to AHC than RDP. A T613 M mutation was later found in all of the affected family members of this family (and in almost 40% of all RDP cases), but has not been found in other cases of AHC, again suggesting presence of certain unknown modifying factors at play, with major phenotypic influences.[2,3]

Alternate amino acid substitutions at the same amino acid position have been observed to produce differing phenotypes: D801 E and D801 N (both AHC) compared with D801Y (RDP), and I274 N (AHC) compared with I274 T (RDP).[3,11] However, in these cases, unlike in ours, the change is not identical and the alternate substitution may easily

TABLE.
Characteristics of our Patient with AHC Compared with Published cases with RDP with Identical *ATP1A3* p.E277 K Mutations

Characteristics	Current AHC Case	RDP Case 1 [2, 6]	RDP Case 2 [6]	RDP Case 3 [7]
Gender; age at last follow-up	Male; 6.5 y	Male (not available)	Male (not available)	Female; 30 y
Age of onset of paralysis/dystonia (time to plateau)	2.5 y (min)	20 y (1 wk)	22 y (abrupt onset, gradually worsening)	26 y (uncertain/months)
Duration	Minutes to hours	No improvement	Improvement	No improvement
Frequency	Multiphasic (every 1-4 mo)	Monophasic	Biphasic	Triphasic
Localization of paralysis/dystonia	Bulbar, mono/hemi/all limb (arm > leg) paralysis or dystonia; rare abnormal eye movements	Bulbar, limb (arm and leg) dystonia	Bulbar, limb (arm > leg) dystonia	Bulbar, hemidystonia (arm and leg)
Triggers (alleviating factors)	Stress, loud environment, illness (rest, sleep, benzodiazepine)	Fever, head trauma	None	Upper respiratory "symptoms" (unspecified)
Permanent neurological deficits	Mild dysarthria Decreased fine motor skills	Unable to walk; dystonia; parkinsonism	Walks with assistance; dystonia; parkinsonism	Wide-based gait; dystonia; parkinsonism
Other paroxysmal episodes	1 generalized seizure (2.5 y, brief with propofol)	Seizure (adulthood)	None	None
Medication response	Flunarizine: minimal to no response Topiramate: 75% reduction in episodes	(Not available)	(Not available)	Carbidopa-levodopa: no response Trihexyphenidyl: some response

Abbreviations:
AHC = Alternating hemiplegia of childhood
RDP = Rapid-onset dystonia parkinsonism