Published in final edited form as:
Dev Med Child Neurol. 2012 November ; 54(11): 1065–1067. doi:10.1111/j.1469-8749.2012.04421.x.

ATP1A3 mutations in infants: a new rapid-onset dystonia-Parkinsonism phenotype characterized by motor delay and ataxia

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Abstract

We report new clinical features of delayed motor development, hypotonia, and ataxia in two young children with mutations (R756H and D923N) in the *ATP1A3* gene. In adults, mutations in *ATP1A3* cause rapid-onset dystonia-Parkinsonism (RDP, DYT12) with abrupt onset of fixed dystonia. The parents and children were examined and videotaped, and samples were collected for mutation analysis. Case 1 presented with fluctuating spells of hypotonia, dysphagia, mutism, dystonia, and ataxia at 9 months. After three episodes of hypotonia, she developed ataxia, inability to speak or swallow, and eventual seizures. Case 2 presented with hypotonia at 14 months and pre-existing motor delay. At age 4 years, he had episodic slurred speech, followed by ataxia, drooling, and dysarthria. He remains mute. Both children had *ATP1A3* gene mutations. To our knowledge, these are the earliest presentations of RDP, both with fluctuating features. Both children were initially misdiagnosed. RDP should be considered in children with discoordinated gait, and speech and swallowing difficulties.

Mutations in *ATP1A3* typically present as rapid-onset dystonia-Parkinsonism (RDP), a disease characterized by abrupt-onset dystonia associated with bulbar symptoms and an age

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at onset ranging between 4 and 59 years.[1–7] First described as an autosomal dominant trait, recent reports have identified many patients with de novo mutations in *ATP1A3*.[8]Mutations in *ATP1A3* are not on the differential of delayed motor development and gait ataxia in young children. We report a novel phenotype associated with *ATP1A3* gene mutations in two unrelated children with onsets at age 9 months and 4 years respectively.[9] Case 2 had been reported previously but our team re-evaluated the patient in the field after case 1 presented.[7] Both had symptoms of motor delay from birth and periods of severe dystonic spasm before an episode leading to permanent motor disability. We suggest that *ATP1A3* mutations be considered in the differential diagnosis of motor delay in young children.

This study obtained Wake Forest University institutional review board approval for the use of human participants (ClinicalTrials.gov identifier NCT00682513). Parents signed an approved informed consent form and provided consent for disclosure of all videos and images. A standardized patient history questionnaire and neurological examination was completed for all participants. Videotapes of serial examinations were reviewed by a rater blinded to mutation status (JWM). DNA was obtained from all family members, and mutation analysis was performed as described previously.[9]

CASE REPORTS

Case 1

The child was healthy until 9 months of age, when she presented with lethargy. She had acute hypotonia and dysphagia but no fever, with complete recovery after 3 days. Her development proceeded normally until 11 months, when she became flaccid with a fever of 104°. Within 3 days she was drooling, unable to swallow, and limb spasms interfered with sitting. She had no ptosis, and eye movements and stretch reflexes were normal. She could not sit unsupported and was anarthric, with severe hypotonia and dysphagia. After 1 month she improved and could eat and participate in rehabilitation. At 18 months, after a fever, she abruptly worsened and could not swallow, talk, or lift her head from the prone position; she required a gastrostomy tube. She gradually improved and by 23 months could sit alone when placed, transition from sitting to a quadruped position, but could not crawl. At 2 years old she could point and vocalize with no words.

Her diagnostic workup after the second episode included an elevated creatine phosphokinase level of 1334ug/ml that later normalized. Studies included electromyogram and nerve conduction, ophthalmological examination, brain and spine magnetic resonance imaging (MRI), metabolic workup and muscle biopsy including uric acid, serum for amino acids, urine organic acids, acetylcholine receptor antibody, and free and acyl-carnitine levels; all were normal RDP was considered as a potential diagnosis after obtaining her father's history of several intermittent acute episodes of hypotonia at age 7 and 14 months. As an adult, he consented to DNA testing, but refused neurological examination.

The proband's mother reported onset of unprovoked seizures at age 4 years. Seizures were described as left upper extremity, jerking in sleep, and partial complex seizures emanating from bilateral parasagittal regions based on electroencephalography (EEG). MRI and EEG results were normal, and the seizures responded to levetiracetam. A fever at age 4 caused no neurological decline. At the most recent examination (age 5y), she was thin and unable to walk or stand unassisted. She crawled and sat unassisted. She demonstrated dystaxia on finger to nose bilaterally along with significant truncal ataxia, dysarthria with single-word answers, and severe dysphagia. Video SI (online supplementary material) demonstrates the child at ages 2 and 5 years.

Analysis of the *ATP1A3* gene identified a novel missense mutation, R756H, in both the father and the child. This change was not found in 500 Northern European control chromosomes nor was it present in any of the public variation databases (dbSNP135; EVS database [http://evs.gs.washington.edu/EVS/]).[10] Additionally, the R756 residue is highly conserved across species down through fungi as well as across paralogs. The mutation is two amino acids away from one of the first RDP mutations discovered, I758S,[4] and the same kind of mutation of the homologous residue in *ATP1A2*, R763H, causes familial hemiplegic migraine type 2 (FHM2),[11] emphasizing its functional importance.

Case 2

Case 2 was previously reported by Anselm et al.[7] but recently examined by our group after the unique presentation described in case 1. This report contains only the content of that re-evaluation and was developed solely from our personal assessment of the child and from discussion with his mother. This patient did not walk until age 14 months, and he was diagnosed with hypotonia and delayed motor development at age 3 years. At age 4, before the onset previously reported, he had an episode of lethargy accompanied by a fever of 104°F. Two weeks after this episode, motor skills returned to baseline, but he remained socially withdrawn. At 2 and 3 weeks after fever, his mother noted transiently slurred speech. Six weeks later the patient again had minutes of slurred speech. That day, coinciding with the previous report,[7] he fell and hit his head with no injury, but remained irritable and did not want to walk. Within an hour, his mother reported he was withdrawn, with a `scissoring' gait and uncoordinated feeding, and within hours his eyes `crossed'. He was admitted to the intensive care unit with intermittent spasms in his arms and legs. His last spoken word was 2 days after hitting his head.

This patient underwent multiple metabolic tests, skin and muscle biopsies, and brain MRIs, all of which were unrevealing. One month after initial onset, ^{18}F-flurodeoxyglucose (FDG)-PET scanning demonstrated moderate hypermetabolism in the striatum.[7] Further delineation of testing was previously described.[7]

Over 10 years he has become able to walk with braces, but remains very unbalanced. He cannot talk, and continues to have profound drooling and dysphagia. At age 15 years, he demonstrated marked tongue apraxia and could not stand unsupported without braces, preferring to crawl and sit on the floor. Dystonic postures were noted in both hands, worse in the left. Remaining movements were slow and uncoordinated, with significant dystonic posturing in arms and ataxic gait. Video SII (online supplementary material) shows the patient at ages 4 and 15 years. He had a de novo D923N mutation.[7] This mutation has been reported in another case of sporadic RDP, with onset at age 20 years after physical exertion.[6]

DISCUSSION

The onset and progression of symptoms in young children with RDP appears to be notably different from adolescents and adults, where muscle cramps in the extremities is the most common antecedent feature.[9] The history is unusual in case 1, with three episodes of intermittent flaccidity preceded by illness with and without fever. Case 2 had a baseline history of hypotonia with superimposed spells of flaccidity and bulbar symptoms before sudden onset of dystonia. Ultimately, however, both patients displayed a feature most characteristic of adult-onset RDP: bulbar symptoms including severe dysarthria and dysphagia. Together, these cases suggest a novel infant-variant of RDP with an initially episodic course, which could be characterized as hypotonia evolving to dystonia with ataxia.

In both cases, RDP was not suspected initially because the presentation in infancy mimicked more common diseases such as acute inflammatory demyelinating polyneuropathy,

myasthenia gravis, inborn errors of metabolism, or mitochondrial disorders. On blinded review of the videotapes without any case history, the reviewer (JWM) did not consider forms of dystonia in the differential diagnosis. Table I demonstrates the unique features of these cases.

The family history in case 1 was not readily apparent, as the father's residual neurological symptoms were minor and he refused neurological assessment. However, his phenotype as an infant/small child was similar to his child's, and as a child he had a tentative diagnosis of muscular dystrophy.

Before the report from Anselm et al., the youngest reported child with RDP was a 4-year-old female with onset after head trauma.[7] These cases are important because of the fluctuating presentation and the very young age at onset. In both cases, significant motor delays were noted as well as high fever before onset of dystonic symptoms. Although case 2 has been previously reported, with onset subsequent to patient falling and hitting his head at age 4 years, fever and lethargy were noted 6 weeks before this event with resulting slurred speech and social withdrawal. His presentation is, therefore, distinct from what has been previously reported. Both cases presented together suggest a novel infant-variant phenotype for RDP in very young children.

Our presentation of these two cases suggests that mutations in *ATP1A3* may present and manifest differently among young children and infants compared with typical cases of RDP. In addition, one of these cases resulted from a de novo mutation, highlighting the need to consider this diagnosis even without a family history. *ATP1A3* mutation analysis should be considered in children with discoordinated gait and speech, and swallowing difficulties, in whom the cause is not clear.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the National Institute of Neurological Disorders and Stroke 5R01NS058949-05 (to AB). We thank Dr William B Dobyns for his initial description of RDP. We also thank the National Heart, Lung, and Blood Institute GO Exome Sequencing Project[10] and its ongoing studies, which produced and provided exome variant calls for comparison: the Lung GO Sequencing Project (HL-102923), the WHI Sequencing Project (HL-102924), the Broad GO Sequencing Project (HL-102925), the Seattle GO Sequencing Project (HL-102926), and the Heart GO Sequencing Project (HL-103010).

ABBREVIATION

RDP Rapid-onset dystonia-Parkinsonism

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What this paper adds

- Rapid-onset dystonia-Parkinsonism (RDP) is described in children under age 4 years for the first time.
- RDP in young children fluctuates and presents with broader ranges of symptoms than in older children and adults.
- RDP can be mistaken for developmental motor delay.

Table I

Descriptive characteristics of patients with infantile rapid-onset dystonia–Parkinsonism

Case	Age at onset of dystonia	Triggers	Baseline motor delay?	Number of episodes	Seizure?	Ataxia on blinded video review?	Familial?
1	11mo	Fever	Yes	Three, then fixed	Yes	Yes	Yes
2	4y	Fever	Yes	One, then fixed	No	Yes	No