Pediatric Neurology 52 (2015) 56–64

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

The Expanding Spectrum of Neurological Phenotypes in Children With *ATP1A3* Mutations, Alternating Hemiplegia of Childhood, Rapid-onset Dystonia-Parkinsonism, CAPOS and Beyond

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ABSTRACT

BACKGROUND: *ATP1A3* mutations have now been recognized in infants and children presenting with a diverse group of neurological phenotypes, including Rapid-onset Dystonia-Parkinsonism (RDP), Alternating Hemiplegia of Childhood (AHC), and most recently, Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS) syndrome. **METHODS:** Existing literature on *ATP1A3*-related disorders in the pediatric population were reviewed, with attention to clinical features and associated genotypes among those with RDP, AHC, or CAPOS syndrome phenotypes. **RESULTS:** While classically defined phenotypes associated with AHC, RDP, and CAPOS syndromes are distinct, common elements among *ATP1A3*-related neurological disorders include characteristic episodic neurological symptoms and signs that vary in severity, duration, and frequency of occurrence. Affected children typically present in the context of an acute onset of paroxysmal, episodic neurological symptoms ranging from oculomotor abnormalities, hypotonia, paralysis, dystonia, ataxia, seizure-like episodes, or encephalopathy. Neurodevelopmental delays or persistence of dystonia, chorea, or ataxia after resolution of an initial episode are common, providing important clues for diagnosis. **CONCLUSIONS:** The phenotypic spectrum of *ATP1A3*-related neurological disorders continues to expand beyond the distinct yet overlapping phenotypes in patients with AHC, RDP, and CAPOS syndromes. *ATP1A3* mutation analysis is appropriate to consider in the diagnostic algorithm for any child presenting with episodic or fluctuating ataxia, weakness or dystonia whether they manifest persistence of neurological symptoms between episodes. Additional work is needed to better identify and classify affected patients and develop targeted treatment approaches.

Keywords: alternating hemiplegia of childhood, rapid-onset dystonia-Parkinsonism, CAPOS syndrome, ataxia, dystonia, hemiplegia, *ATP1A3*, sodium potassium ATPases

Pediatr Neurol 2015; 52: 56-64

Introduction

Na^+,K^+-adenosine triphosphatases (ATPases, sodium/potassium pumps) are P-type cation transport proteins that play a critical role in maintaining electrochemical gradients for Na^+ and K^+ across the plasma membrane. The energy for transporting ions is derived from hydrolysis of ATP, exchanging three molecules of Na^+ for every two molecules of K^+. The alpha subunit is the catalytic subunit, and three of the four alpha isoforms (alpha1, 2, and 3) are expressed in the nervous system.[1] Mutations of the alpha2 subunit (*ATP1A2*), expressed predominantly in astrocytes, are associated with familial hemiplegic migraine (FHM) type 2.[2] Mutations affecting the alpha3 subunit, *ATP1A3*, expressed in neurons, are associated with an expanding phenotypic spectrum of distinct yet overlapping neurological phenotypes, including rapid-onset dystonia Parkinsonism (RDP), alternating

Article History:
Received June 28, 2014; Accepted in final form September 23, 2014

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http://dx.doi.org/10.1016/j.pediatrneurol.2014.09.015

hemiplegia of childhood (AHC), and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndromes. The purpose of this review is to explore the recently expanding and diverse range of phenotypes associated with mutations in *ATP1A3*, to review phenotype-genotype associations, and to consider how new observations can help guide diagnostic and treatment approaches in the infant or child presenting with an acute onset of paroxysmal and fluctuating neurological symptoms and signs ranging from paralysis to ataxia to dystonia and beyond.

Dobyns et al.[3] provided the first evidence of a role for *ATP1A3* in human disease pathogenesis. They described a single large family with dominant transmission of a syndrome they called RDP.[4] Affected individuals manifested acute or subacute onset of rapidly evolving dystonia and Parkinsonism in adolescence or adulthood after a provocative stressor. Although acute progression of dystonia and bradykinesia were the initial manifestations of the disease, a more variable, slower decline in function was sometimes observed.[5] RDP was initially identified in its familial form, but sporadic cases have been increasingly identified.[6]

AHC is a unique and complex neurodevelopmental syndrome first described by Verret and Steele in 1971. It was initially thought to be a migraine variant because of the unique features of stimulus sensitivity-induced paroxysmal alternating hemiplegia in association with other paroxysmal neurological and autonomic symptoms.[7,8] The underlying pathophysiologic mechanism remained elusive until recently, when de novo mutations in *ATP1A3* proved causative in most cases.[9-12] After the discovery that mutations in *ATP1A3* were a frequent cause of AHC, and that AHC and RDP were in fact allelic disorders, an increasing number of patients with intermediate, nonclassic phenotypes have been described. However, AHC and RDP in their classic forms have, to date, almost exclusively nonoverlapping mutations in *ATP1A3*.

Another unique disorder recently associated with a mutation in *ATP1A3* is CAPOS syndrome (OMIM #601338). In 1996, Nicolaides et al.[13] described a mother and two children with relapsing, early onset cerebellar ataxia in association with areflexia, pes cavus deformity, optic atrophy, and sensorineural hearing loss, features for which the syndrome was ultimately named. However, they also observed an abrupt onset of neurological symptoms, predominantly hypotonia and ataxia, in association with a stressor such as a febrile illness, with onset of first episodes ranging from 9 to 16 months. Recently, three additional families were described with a single, identical *ATP1A3* missense mutation.[14]

In the following, we review the classical clinical presentations and neurological features of each disorder and relevant data on genotype-phenotype correlations. We compare and contrast onset and evolution (including nonmotor features), pathophysiologic mechanisms, differential diagnostic considerations, and current therapeutic approaches.

Clinical features

Alternating hemiplegia of childhood

Verret and Steele initially described a series of eight children with onset of intermittent episodes of alternating hemiplegia in association with a variety of other characteristic but more variable neurological features including developmental delay, choreoathetosis, and dystonia.[7] Diagnostic criteria were subsequently refined[8,15] and are listed in the following. Table 1 compares and contrasts key features of classically defined AHC and RDP.

Classic diagnostic criteria:

1. Onset of symptoms before 18 months of age
2. Paroxysmal disturbances including tonic or dystonic spells, oculomotor abnormalities, and autonomic phenomena during hemiplegic episodes or in isolation
3. Repeated attacks of hemiplegia involving either side of the body
4. Episodes of bilateral hemiplegia or quadriplegia as generalization of a hemiplegic episode or bilateral from the beginning
5. Immediate disappearance of symptoms upon sleeping, which later may resume after waking
6. Evidence of developmental delay and neurological abnormalities including choreoathetosis, dystonia, or ataxia

In reports summarizing series of patients with AHC diagnosed using classic criteria,[16-18] age of onset for both dystonic and hemiplegic episodes occurred in the majority in the first year of life. The frequency, duration, and severity of episodes are highly variable, occurring from multiple times per day to every few days and lasting from minutes to days or even weeks with a waxing and waning course.[16] Abnormal eye movements, including monocular nystagmus,[19] frequently occur in association with other types of episodes or in isolation and in some instances may be the first manifestations of the disease.[16]

A hallmark of the disorder, aside from the pathognomonic, often migratory, uni- and bi-lateral plegic episodes, is a pronounced sensitivity to environmental and physiologic triggers. Provocative factors have included physical activity, specific foods, light sensitivity, water exposure, and medications.[16] Cessation, or significant improvement, of paroxysmal neurological deficits occurs with sleep, although at times only transiently.[17] Anecdotally, this feature often serves as the only window during which families can provide food, water, and medications for affected children, because bulbar and respiratory function can be impaired during episodes, making oral intake unsafe. Additional persistent neurological comorbidities are frequently present and are increasingly penetrant with age, including gross and fine motor delay, cognitive and intellectual deficits, dysarthria, ataxia, chorea, and dysautonomia.[16,17,20]

Before the identification of mutations in *ATP1A3*, diagnostic studies performed to identify a specific biomarker or metabolic abnormality in AHC proved unrevealing or inconsistent.[21-25] Neuroimaging studies are usually normal, at least early in the course of the disease, although nonspecific cortical atrophy, mesial temporal sclerosis, or cerebellar atrophy are present in some patients, and the presence of such abnormalities may depend on age and phenotypic severity. Single-photon emission computed tomography or fludeoxyglucose positron emission tomography scans performed during a hemiplegic episode have demonstrated hypometabolism in the contralateral