ATP1A3 mutations

What is the phenotype?

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Rapid-onset dystonia-parkinsonism (RDP) occurs in children older than 18 months of age, teens, and adults, and alternating hemiplegia of childhood (AHC) occurs in children younger than 18 months. They appear to be different diseases, but both are caused by mutations in *ATP1A3*.[1–4] *ATP1A3* encodes the α subunit of the Na^+/K^+-ATPase that is partially responsible for maintaining the electrical gradient in neurons. Motor symptoms, particularly dystonia, are obvious in both RDP and AHC, but RDP is predominantly fixed and AHC is known for its episodic and fluctuating course. There is now a broader phenotypic spectrum of RDP than originally described in 1993,[5,6] including psychosis,[7] new phenotypes in children,[8] and late onset.[9] The nonmotor phenotypes of both RDP (cognitive and psychiatric) and AHC (developmental delay, cognitive, and behavioral)[10,11] suggest that *ATP1A3* mutations may play a role in other neurologic and psychiatric disorders. Mutations causing RDP or AHC cause symptoms such as dystonia, parkinsonism, epilepsy (including status epilepticus), hemiplegic episodes, abnormal ocular movements, developmental delay, psychosis, depression, anxiety, and gait disorders in ages ranging from newborns to 87 years. It is likely that there will be a broad continuum of patients found, and even a role for the gene in polygenic disorders.

There are at least 40 different mutations in *ATP1A3* that cause either RDP or AHC, and the question arises whether there is a genotype–phenotype correlation. The article by Sasaki et al.[12] in this issue of *Neurology*® investigates this by examining the clinical course of 33 patients diagnosed with AHC with mutations in the *ATP1A3* gene. Two recurrent mutations, E815K and D801N, were identified in two-thirds of the patients. The E815K mutation group had more severe symptoms than the others, with earlier neonatal nystagmus, significantly worse gross motor level, more status epilepticus episodes, and respiratory paralysis compared with the other mutation-positive AHC cases. The D801N mutation in this cohort resulted in a moderate form of AHC. A patient with D923N had the mildest course, compatible with prior reports of the same mutation in childhood-onset RDP with symptoms overlapping AHC[8] and with the diagnoses of RDP and AHC in the same family.[4] While the numbers of patients in the study are small, this raises the question of whether the type of mutation is responsible for the severity of the symptoms. At the molecular level, RDP and AHC phenotypes may differ partly based on how different mutations affect protein function, with AHC mutations (onset in infancy) being more severe. Given the expanding knowledge of *ATP1A3* mutations, it is likely that there will be other individuals with mutations in *ATP1A3* with intermediate or altogether different phenotypes. However, in families with RDP, the symptoms within one family range from wheelchair-bound and requiring feeding tubes to asymptomatic elderly gene carriers—all with the same *ATP1A3* mutation. This suggests that triggers, or the presence of variants in other genes that modify symptom severity, may influence severity or age at onset.

Stress brings on abrupt onset of an irreversible cluster of disabling symptoms in patients with RDP,[6] and even mild stress triggers paroxysmal symptoms in AHC.[10] The article by Sasaki et al. documents stepwise deterioration in AHC. A number of patients experienced abrupt worsening episodes associated with fever (also a trigger in RDP), status epilepticus, or following discontinuation of flunarizine. These changes were irreversible. Patients with RDP also sometimes have second events of worsening. A better understanding of the interaction of physiologic stress and genetic predisposition may help us understand the wide phenotype spectrum associated with *ATP1A3* mutations. More important, since there are no cures for AHC and RDP, an informed response to physiologic triggers could lead to an effective prevention strategy.

Flunarizine, a relatively nonspecific channel blocker, appears to reduce episodic symptoms for many patients with AHC,[10] and few other medications have been found to be as helpful. Sasaki et al. note that 7 of the 8 patients who had severe abrupt or stepwise motor

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deterioration did so after discontinuing flunarizine. Because of catastrophic deterioration events, they also "recommend that all patients with AHC, regardless of genotype, should not discontinue flunarizine administration even if this does not show any obvious short-term effectiveness against recurrent hemiplegic attacks." There are no randomized trials in the use of this drug in patients with AHC, it has not been studied in RDP, and it is not available for prescription in the United States or Japan. This longitudinal analysis of its use, however, is a promising way to synergize clinical and genetic findings.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. de Carvalho AP, Sweadner K, Penniston J, et al. Mutations in the Na+/K+-ATPase alpha3 gene *ATP1A3* are associated with rapid-onset dystonia parkinsonism. Neuron 2004;43:169–175.
2. Heinzen EL, Swoboda KJ, Hitomi Y, et al. De novo mutations in *ATP1A3* cause alternating hemiplegia of childhood. Nat Genet 2012;44:1030–1034.
3. Rosewich H, Thiele H, Ohlenbusch A, 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.
4. Roubergue A, Roze E, Vuillaumier-Barrot S, et al. The multiple faces of the *ATP1A3*-related dystonic movement disorder. Mov Disord 2013;28:1457–1459.
5. Dobyns WB, Ozelius LJ, Kramer PL, et al. Rapid-onset dystonia-parkinsonism. Neurology 1993;43:2596–2602.
6. Brashear A, Dobyns WB, de Carvalho AP, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the *ATP1A3* gene. Brain 2007;130:828–835.
7. Brashear A, Cook JF, Hill DF, et al. Psychiatric disorders in rapid-onset dystonia-parkinsonism. Neurology 2012;79:1168–1173.
8. Brashear A, Mink JW, Hill DF, et al. *ATP1A3* mutations in infants: a new rapid-onset dystonia-parkinsonism phenotype characterized by motor delay and ataxia. Dev Med Child Neurol 2012;54:1065–1067.
9. Barbano RL, Hill DF, Snively BM, et al. New triggers and non-motor findings in a family with rapid-onset dystonia-parkinsonism. Parkinsonism Relat Disord 2012;18:737–741.
10. Sweney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. Pediatrics 2009;123:e534–e541.
11. Panagiotakaki E, Gobbi G, Neville B, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. Brain 2010;133:3598–3610.
12. Sasaki M, Ishii A, Saito Y, et al. Genotype–phenotype correlations in alternating hemiplegia of childhood. Neurology 2014;82:XX–XX.