Expanding the Phenotypic Spectrum of ATP1A3-Related Disorders: Three Atypical Cases

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Introduction

Mutations in the ATP1A3 gene are linked to a broad spectrum of neurological disorders. Beyond the well-defined syndromes (Rapid-onset dystonia-parkinsonism-RDP, Alternating hemiplegia of childhood- AHC, CAPOS syndrome), atypical and overlapping phenotypes are increasingly recognized. These often include persistent neurological signs between attacks, challenging the traditional syndrome-based classification[1].

Case 1

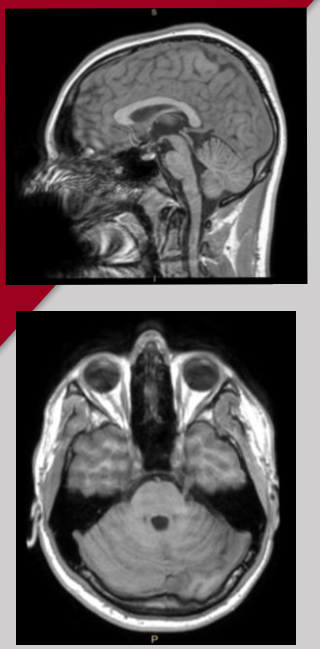
A 17-year-old Serbian male with intellectual disability had daily paroxysmal dystonic attacks since birth. Episodes (hemibody or generalized) were stimulus-triggered and ceased during sleep. Neurological examination revealed distal dystonia, myoclonus, dyskinesias of the upper limbs, and pyramidal signs. Brain MRI showed cerebellar hemispheric asymmetry and abnormal cortical gyration. Genetic testing identified a de novo *ATP1A3* variant (p.Asp801Asn). Flunarizine, topiramate, and clonazepam markedly reduced episodes.

Case 2

A 34-year-old woman developed dysarthria, dysphagia, dystonia with myoclonus, and gait disturbance following a febrile illness at the age of seven. Symptoms improved with rehabilitation but recurred transiently during fever. Investigations were normal, and a de novo *ATP1A3* mutation (p.Arg756His) was identified.

Case 3

The 10-year-old daughter of Case 2 presented at the age of four with ataxia, subcontinuous chorea, bulbar dysfunction, and oculomotor deficits during a febrile illness. EEG, MRI, and CSF analysis were unremarkable. Empiric immunotherapy (steroids and IVIG) was given for suspected autoimmune encephalitis, without benefits. Genetic testing confirmed the maternally inherited *ATP1A3* variant (p.Arg756His). Clinical stabilization was achieved through multidisciplinary rehabilitation.



Case 1, Brain MRI with T1-weighted sequences in sagittal and axial planes

Results

- Wide phenotypic heterogeneity, even within the same family.
- Onset often triggered by febrile illness, without seizures.
- Initial misdiagnoses and ineffective empirical treatment.

Take- home messages

- Recognition of atypical and non-classical features is mandatory for timely and accurate diagnosis.
- Early identification can guide appropriate management, avoiding unnecessary treatments[2,3].
- Importance of a flexible diagnostic approach and multidisciplinary care.
- ATP1A3-related disorders should be viewed as a neurodevelopmental spectrum rather than distinct syndromes[4].

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