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Editorial

The expanding spectrum of ATP1A3 related disease

The spectrum of manifestations secondary to ATP1A3 mutations is expanding given the current increasing availability of gene panel and whole exome sequencing testing and the increasing awareness of the phenotypes caused by such mutations.

The article "*Relapsing encephalopathy with cerebellar ataxia (RECA) are caused by variants involving p.Arg756 in ATP1A3*"[1] describes the case series of 8 patients with RECA (previously called fever-induced paroxysmal weakness and encephalopathy-FIPWE). As described in two previous single case reports, these eight patients had symptoms of fluctuating ataxia, epilepsy and encephalopathy, occurring with febrile illnesses. This article adds value to the recognition of RECA as a distinct and, likely, currently underdiagnosed entity with emphasis on its trigger, fever, and on the variability of its severity and manifestations. Unlike RECA, other ATP1A3 related syndromes often decompensate secondary to varied triggers. These include physical or emotional stress and excitement in Alternating Hemiplegia of Childhood (AHC) and alcohol binges or overheating in Rapid Onset Dystonia-Parkinsonism (RDP).

Currently physicians are faced with diagnostic challenges in recognizing ATPA13 related disease due to the protean, expanding and overlapping number of symptoms caused by ATP1A3 mutations.[2] Table 1 lists the currently known syndrome entities and corresponding symptoms. The presence of

Table 1

SYMPTOMS	SYNDROMES							
	COS	ASD	EE	CAPOS/CAOS	CROA	RDP	AHC	RECA
CHILDHOOD SCHIZOPHRENIA								
ENCEPHALOPATHY								
EPILEPSY								
AREFLEXIA								
DEAFNESS								
OPTIC ATROPHY								
ATAXIA								
CATASTROPHIC REGRESSION								
DYSPHAGIA								
DYSTONIA								
COGNITIVE IMPAIRMENT								
FLUCTUATING SYMPTOMS								
RECURRENT HEMIPLEGIA								
NYSTAGMUS								
AUTISM Sx								
MECHANISMS STUDIED				E818K **Ion Pump Dysfunction:** CAPOS mutation causes a weaker voltage dependence of the pumping rate and stronger inhibition by cytoplasmic K+ and reduced Na+ affinity of the cytoplasmic facing sites preventing proper pump function[87]		D801Y **Ion pump dysfunction:** Impairs pump mediated Na+ / K+ exchange [88] **Network Abnormality:** Causes irregular firing of purkinje fibers and deep cerebellar nuclei leading to dystonia (mutation also causes AHC in humans) [146] D923N **Ion Pump Dysfunction:** Selective reduction of the affinity of the Na+/K+ ATPase for cytoplasmic Na+, hampering the phosphorylation of ATP.[36] F780L **Ion Pump Dysfunction** No disturbance of K+ binding[89]	D801N **Ion Pump dysfunction:** Repulsion phenomenon which affects K+ transport across Na+/K+ ATPase channel[90] **Network abnormality:** Decreased firing of fast spiking parvalbumin positive interneurons, increased pyramidal cell excitability and increased firing, predisposing to spreading depression [147] E815K **Ion pump dysfunction:** Prevents the H+ current across the Na+/K+ ATPase channel[90] **Network abnormality:** Reduced threshold for flurothyl induced seizures and for amygdala kindling [151] 1810N **Ion Pump Dysfunction** Reduced Na+ K+ ATPase activity[90] **Network Abnormality** Increased pyramidal cell excitability [90]	

Table 1. Spectrum of distinct syndromes and corresponding symptoms of related to ATP1A3 mutations. Please note due to the phenotypic variability in ATP1A3 related syndromes the following points: 1) The symptoms indicated to occur in specific syndromes often do not occur in all patients but are common enough to be mentioned as part of the syndrome. 2) Some symptoms not indicated to be present in some of the syndromes may occur in a minority of patients with that syndrome but were not included as they are not very common. The references below indicate articles reporting the features in ATP1A3 disease. *Abbreviations:* COS, childhood onset schizophrenia; EE[81], epileptic encephalopathy; CAPOS[9,11], Cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss; CAOS[81] Cerebellar ataxia, areflexia, optic atrophy and sensorineural hearing loss; CROA[5], childhood rapid onset ataxia; RDP[5,11], rapid onset dystonia parkinsonism; RECA[1], relapsing encephalopathy with cerebellar ataxia; AHC, alternating hemiplegia of childhood.[8,11,121] ; ASD Autism Spectrum disorder[13,14]; Sx: symptoms

several of such symptoms, whether they fit a specific syndrome or not, should raise suspicion of ATP1A3 related disease and should lead to genetic testing for ATP1A3 mutations as there are patients who do not necessarily fit in any one syndrome. This is quiet akin to the various, albeit different, symptoms that occur in mitochondrial disease. Symptoms that raise the suspicion of mitochondrial disorders often segregate as separate syndromes and at other times present in a spectrum of intermediate phenotypes. ATP1A3 related disease is emerging as another, albeit distinct, class of diseases with a spectrum of distinct and at times overlapping and intermediate phenotypes.

The Na+/K + -ATPase pumps which regulate the neuronal sodium-potassium gradient are structurally formed by α, β, and γ subunits[2,3] ATP1A3 encodes for the neuronal α3 subunit, which maintains the sodium-potassium gradient predominantly during rapid neuronal firing. Neurons with ATP1A3 mutations have impaired Na–K-ATPase enzyme and pump functions that alter neuronal firing. The pathophysiological effects of such mutations are summarized in Table 1.[3–14]

Currently therapy is focused on symptomatic treatments. However, with our increasing understanding of the underlying pathophysiology we anticipate development of novel effective therapies. Research for effective treatments is focusing on precision therapies targeting either the pump function itself, for example by small molecules or gene therapy, or targeting specific signal transduction pathways and maladaptive downstream effects.

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