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Original article

Early-onset encephalopathy with paroxysmal movement disorders and epileptic seizures without hemiplegic attacks: About three children with novel *ATP1A3* mutations

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Abstract

Objective: Heterozygous mutations in the *ATP1A3* gene are responsible for various neurological disorders, ranging from early-onset alternating hemiplegia of childhood to adult-onset dystonia-parkinsonism. Next generation sequencing allowed the description of other phenotypes, including early-onset epileptic encephalopathy in two patients. We report on three more patients carrying *ATP1A3* mutations with a close phenotype and discuss the relationship of this phenotype to alternating hemiplegia of childhood.

Methods: The patients' DNA underwent next generation sequencing. A retrospective analysis of clinical case records is reported.

Results: Each of the three patients had an unreported heterozygous *de novo* sequence variant in *ATP1A3*. These patients shared a similar phenotype characterized by early-onset attacks of movement disorders, some of which proved to be epileptic, and severe developmental delay. (Hemi)plegic attacks had not been considered before genetic testing.

Significance: Together with the two previously reported cases, our patients confirm that *ATP1A3* mutations are associated with a phenotype combining features of early-onset encephalopathy, epilepsy and dystonic fits, as in the most severe forms of alternating hemiplegia of childhood, but in which (hemi)plegic attacks are absent or only suspected retrospectively.

Keywords: *ATP1A3*; Encephalopathy; Movement disorder; Alternating hemiplegia of childhood

1. Introduction

ATP1A3 (OMIM 182350) encodes the α3-sub-unit of the Na+/K+-APTase pump which transports three molecules of Na+ out and two molecules of K+ into the cell to maintain the electrochemical gradient at the plasma membrane. It is expressed in heart and neuron cells, mostly in GABAergic neurons in all nuclei of the basal ganglia, which are a key circuitry in the control of fine movements [1].

Heterozygous mutations in *ATP1A3* are responsible for a wide range of neurological diseases. The three most frequent phenotypes identified to date are: Alternating Hemiplegia of Childhood (AHC; OMIM 614820) [2,3], Rapid onset Dystonia-Parkinsonism (RDP; OMIM 128235) and Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss syndrome (CAPOS; OMIM 601338). AHC is characterized by paroxysmal neurologic manifestations (epileptic and non-epileptic) before 18 months and alternating hemiplegia with onset usually by 8 months [4,5]. RDP is defined by a juvenile/abrupt onset (10–30 years) of dystonia and parkinsonism, with limited progression over weeks and little or no improvement thereafter [6]. First manifestations of CAPOS syndrome are recurrent episodes of cerebellar ataxia and altered consciousness during febrile illnesses in childhood, followed by the onset of neurological sequelae, optic atrophy and sensorineural hearing loss [7]. In addition, three rarer phenotypes were recently reported: i) Relapsing Encephalopathy with Cerebellar Ataxia (RECA) [8] ii) rapid-onset ataxia [9] iii) an early-onset epileptic encephalopathy with late hemiplegic attacks [10]. We report here three children with *de novo* *ATP1A3* mutations, early-onset encephalopathy and dystonic fits, but with no obvious (hemi)plegic attacks.

2. Patients

Patient #1 is a 16-year-old girl born full term after normal pregnancy with normal growth parameters. Episodes of paroxysmal movements started at 6 weeks of age and consisted in tonic spells or myoclonic jerks of upper limbs, behavioral arrest with staring and eye deviation or up-gaze, face flushing, cyanosis and irregular breathing. At the age of 10 months, a first ictal EEG recording during a complex partial seizure demonstrated left temporal epileptic seizure while the patient showed behavioral arrest, upper limb tremor and erratic myoclonic jerks lasting around 2–3 min (Fig. 1, Video 1). Similar focal seizures were further recorded at the age of 4 years. Several other EEG video recordings performed from 4 months to 5 years showed poor spatiotemporal organization in awake and sleep state with slowing of background activity and inconstant left frontotemporal slow waves with rare spikes. Several episodes of myoclonic jerks, eye movements, tonic or dystonic spells or staring showed no concomitant EEG modification (Fig. 2. Video 2). The patient also had episodes of apnea, dystonia, mouth movements, gaze deviation, and reduced responsiveness with no electrographic correlate (Videos 2 and 3). Thus, she had both epileptic and nonepileptic neurologic spells with similar clinical manifestations that were often difficult to differentiate. The epilepsy was pharmacoresistant and did not improve with a ketogenic diet introduced for three months at the age of three years. At the age of 16 years, the patient still had about five generalized seizures per

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