Epileptic Disord 2020; 22 (1): 103-9

Epileptic encephalopathy with features of rapid-onset dystonia Parkinsonism and alternating hemiplegia of childhood: a novel combination phenotype associated with *ATP1A3* mutation

Linh Tran [1,a], Jason Richards [2,a], Marie McDonald [1], Allyn McConkie-Rosell [1], Nicholas Stong [3], Joan Jasien [1], Vandana Shashi [1], Mohamad A. Mikati [1,]

[1] Department of Pediatrics, Duke University Medical Center,
[2] Department of Neurology, Duke University Medical Center,
[3] Institute of Genomic Medicine, Columbia University, New York, NY, USA

[a] Authors contributed equally

Received August 09, 2019; Accepted December 04, 2019

ABSTRACT – Mutations in *ATP1A3* have been found to cause rapid-onset dystonia Parkinsonism, alternating hemiplegia of childhood, epileptic encephalopathy and other syndromes. We report a four-year, nine-month-old boy with episodes of frequent and recurrent status epilepticus, who first began having generalized tonic-clonic seizures at four months of age. Development was normal until the age of four months, and markedly slowed down after the onset of seizures. Between the age of seven months and two and a half years, the patient had recurrent attacks of unilateral and bilateral hemiplegia. At the age of 21 months, after a febrile illness with status epilepticus, he regressed and developed continuous severe dystonia and bradykinesia with superimposed intermittent painful dystonic spasms. Extensive neurological and genetic workup revealed a *de novo* p.V589F *ATP1A3* mutation (NM_152296.5:c.1765G>T, NC_000019.9:g.42482344C>A). This is a novel mutation associated with a novel phenotype that shares features with epileptic encephalopathy, alternating hemiplegia of childhood, and rapid-onset dystonia Parkinsonism.

Key words: *ATP1A3*, rapid-onset dystonia Parkinsonism, alternating hemiplegia of childhood, epileptic encephalopathy

Correspondence:
Mohamad A. Mikati
Division of Pediatric Neurology,
Vandana Shashi
Division of Genetics,
Department of Pediatrics,
Duke University
2301 Erwin Rd.
Durham, NC 27710, USA
<mohamad.mikati@duke.edu>
<vandana.shashi@duke.edu>

doi:10.1684/epd.2020.1127

Na+/K+-ATPases are membrane-bound transporters that establish the sodium/potassium ionic gradient across the plasma membrane (Heinzen *et al.*, 2014). Na+/K+-ATPases consist of α, β, and γ subunits. The α3 subunit, encoded by *ATP1A3*, is the predominant α subunit in neurons (Heinzen *et al.*, 2014). Pathogenic variants in *ATP1A3* have been found in rapid-onset dystonia parkinsonism (RDP), alternating hemiplegia of childhood (AHC), cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS) syndrome, relapsing encephalopathy with cerebellar ataxia (RECA) (previously called fever-induced paroxysmal weakness and encephalopathy [FIPWE]), epileptic encephalopathy (EE), childhood schizophrenia, autism and multiple intermediate syndromes (Heinzen *et al.*, 2014; Rosewich *et al.*, 2014; Panagiotakaki *et al.*, 2015; Termsarasab *et al.*, 2015; Masoud *et al.*, 2017a; Fernandes and Mikati, 2019; Sabouraud *et al.*, 2019). To our knowledge, a patient with the combined features of AHC, RDP and EE has not been previously reported. Here we report such a case.

Case study

The patient is a four-year, nine-month-old boy who first began having generalized tonic-clonic seizures at the age of four months. At the age of four months, prior to the onset of seizures, he had normal development and was visually alert, smiling interactively, tracking, and rolling over both ways. He also had a normal neurological exam. However, after the onset of the seizures and recurrent episodes of status epilepticus, development markedly slowed down. He subsequently developed generalized hypotonia, and he was only able to sit with support at one year of age and sit independently at 18 months of age.

He was initially started on levetiracetam, but due to continued seizures, he sequentially received lacosamide, gabapentin, oxcarbazepine, clobazam, and topiramate. Despite this, he continued to have one generalized tonic-clonic seizure every one to two weeks, lasting several minutes in duration. By the age of 27 months, he had been admitted 11 times for recurrent episodes of generalized tonic-clonic status epilepticus. These episodes typically lasted between 30 minutes to several hours and resolved with one to four medications. These status epilepticus episodes were often followed by recurrence of several subsequent clinical generalized tonic-clonic seizures that usually recurred over the next one to two days. He also had subclinical seizures documented on video-EEG monitoring during these admissions. Seizures would subside with treatment but would recur in a few days or weeks. Interictal EEGs demonstrated generalized slowing with bilateral independent multifocal sharp waves. Captured seizures originated independently from different regions during different episodes, including the posterior quadrants, temporal lobes, and parasagittal areas with secondary generalization within a few seconds (example at age 13 months) (*figure 1A-C*). At the age of seven months, he developed recurrent episodes of unilateral and bilateral hemiplegia. These attacks occurred two to three times per week and lasted for one to two hours and were, when unilateral, either on the right or left side. They all resolved during sleep and were not preceded by any seizure activity. At the age of 21 months, he had a febrile illness with prolonged refractory generalized tonic-clonic status epilepticus requiring intravenous loading with lorazepam, phenytoin, and lacosamide, as well as intubation and midazolam drip. Examinations prior to this episode had shown that, despite some central and appendicular hypotonia, he had the ability to smile and play, sit on his own, reach for objects, take food by mouth, and attempted to walk. Deep tendon reflexes (DTRs) were 1+.

Following this episode of status epilepticus, he lost all these skills and unfortunately never regained them. He also required feeding by gastrostomy tube and at his last follow-up visit at the age of four years and nine months, he still was gastrostomy tube dependent. In addition, after this episode of status epilepticus, his examination revealed diffuse severely increased tone and bradykinesia with continuous rigidity of the trunk and all extremities. DTRs were more prominent than before and were 2+. He also had superimposed severe whole-body painful attacks of dystonic posturing, which typically lasted two to three minutes and occurred up to six times per day. EEG monitoring during these attacks confirmed that these were not seizures. He manifested intermittent episodes of diaphoresis, recurrent constipation, and fevers without obvious etiology, which were felt to be secondary to autonomic dysfunction. Furthermore, he had intermittent nystagmus with dysconjugate eye movements, which occurred with the dystonic spells or independently. Over the next six months following his episode of status epilepticus, his hemiplegia spells gradually decreased and then stopped. The last hemiplegia spell occurred at the age of two years and six months. At the time of the last follow-up visit at the age of four years and nine months, he had suffered no further episodes of hemiplegia but had continued to manifest the above-described bradykinesia, continuous dystonia, superimposed dystonic spasms, and episodes of status epilepticus.

Extensive neurological and genetic testing was performed. The patient had a normal male karyotype and microarray. Urine organic acids, acylcarnitine profile,

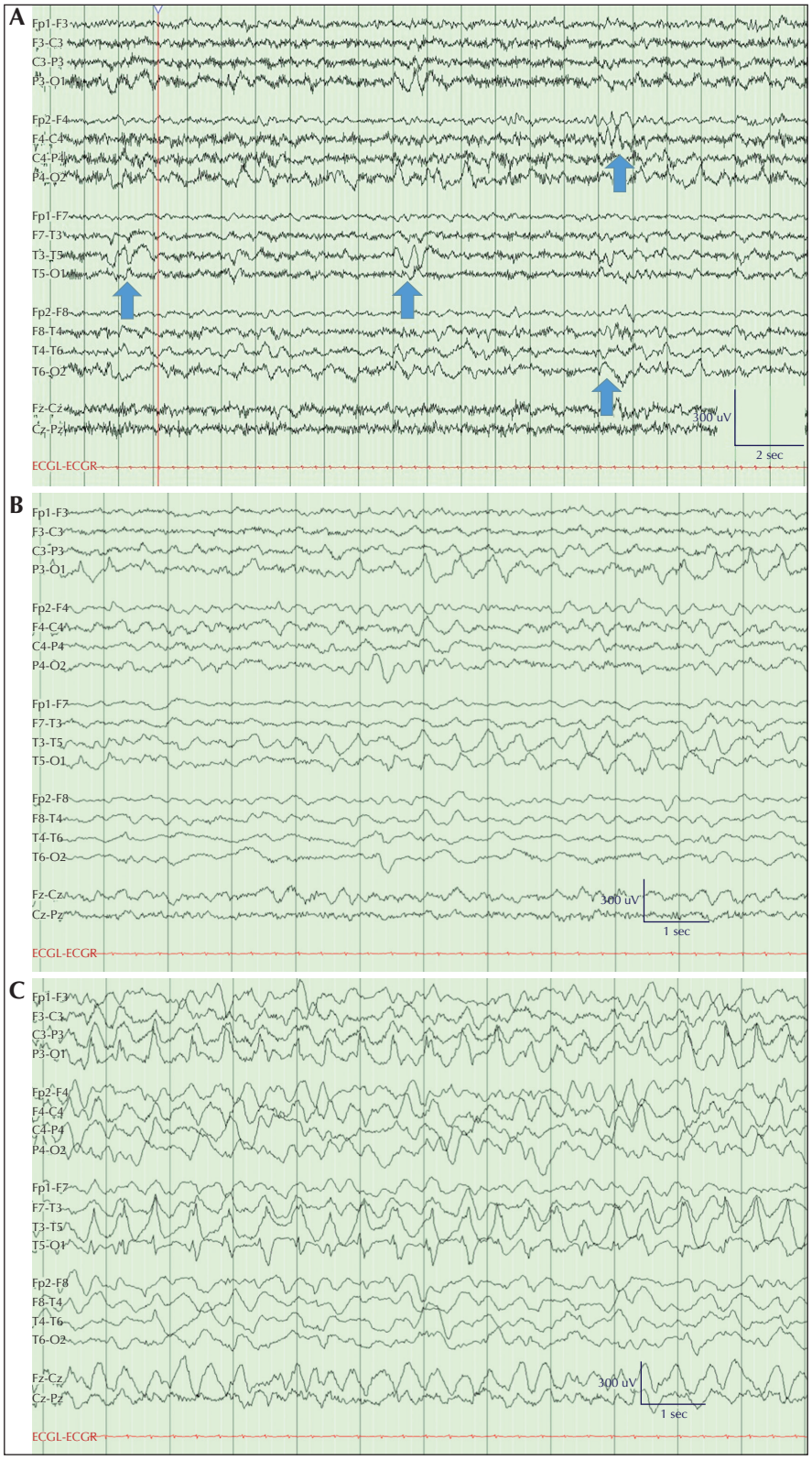

Figure 1. (A) Interictal EEG: generalized slowing and bilateral independent sharp waves (F4, T5, and T6; indicated by arrows). (B) Ictal EEG: seizure originating from the left posterior quadrant and consisting of rhythmic sharp delta activity, which is a relatively unusual pattern. (C) Ictal EEG: about five minutes later, the seizure has spread to other parts of the brain but is still maximal on the left, particularly in the left posterior temporal region.

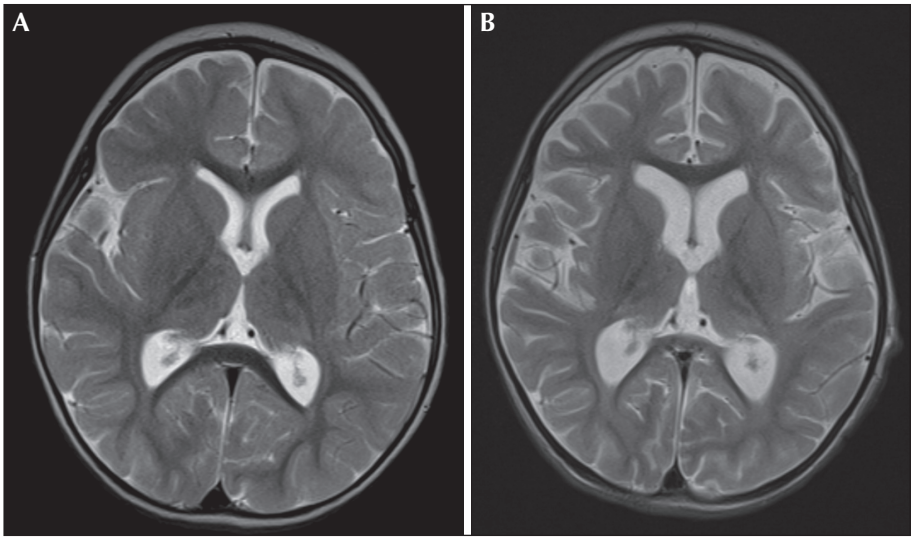

Figure 2. (A) Axial T2-weighed MR image performed at 20 months of age. (B) Axial T2-weighted MR image at age of 31 months showing volume loss.

plasma amino acids, urine purine panel, urine pyrimidine panel, urine creatine, urine sulfocystine, CSF amino acids, CSF alpha-aminoadipic semialdehyde, CSF 4-hydroxybutyric acid, CSF sialic acid, CSF 5-methyltetrahydrofolate, CSF neurotransmitters, CSF pyruvic acid, CSF tetrahydrobiopterin and neopterin were all within normal limits. Fragile X testing was negative. Whole-exome sequencing in a commercial laboratory revealed a novel, likely pathogenic variant in the *ATP1A3* gene (p. Val589Phe [NM_152296.5:c.1765G>T, NC_000019.9:g.42482344C>A]) in exon 13. This particular variant has not been previously reported as disease causing, but is absent in control databases (Lek *et al.,* 2016), is predicted to be damaging based on *in silico* analysis with high Polyphen (0.92 HVAR) and CADD scores (34), and is close to several other previously recognized pathogenic variants within the gene. *ATP1A3* is also an intolerant gene to damaging and missense variation (RVIS: 39% tile, Constraint Z-score: 6.4). We could not confirm that the variant was *de novo* as the father was unavailable (targeted testing of the unaffected mother and sibling was negative). The commercial laboratory classified the variant as being of uncertain significance, but had we been able to confirm *de novo* status of the variant, it would have been classified as pathogenic, using the American College of Medical Genetics criteria (Richards *et al.,* 2015). MRI of the brain at eight and 20 months of age were both normal, but MRI of the brain at 31 months of age, following this episode of status epilepticus, demonstrated global volume loss (*figures 2A, B*).

Discussion

ATP1A3 pathogenic variants have multiple presentations, including AHC, RDP, CAPOS, RECA, EE and intermediate phenotypes (Heinzen *et al*., 2014; Rosewich *et al*., 2014; Masoud *et al*., 2017a; Sabouraud *et al*., 2019; Fernandes and Mikati, 2019). AHC is diagnosed using the Aicardi criteria, consisting of onset prior to 18 months of age, recurrent attacks of hemiplegia and dystonia, paroxysmal attacks of oculomotor abnormalities, episodes of bilateral hemiplegia, resolution of symptoms with sleep, and permanent neurologic impairments, including motor abnormalities and neuropsychological impairments (Heinzen *et al*., 2014; Masoud *et al*., 2017b; Jasien *et al*., 2019). Approximately 75% of cases of AHC are caused by *ATP1A3* pathogenic variants (Heinzen *et al*., 2012; Panagiotakaki *et al*., 2015). Due to the multitude of presenting symptoms, AHC can be difficult to diagnose and manage. Flunarizine, a calcium channel blocker, may help reduce the duration and severity of the AHC attacks, but likely does not affect long-term cognitive outcomes (Mikati *et al*., 2000; Helseth *et al*., 2018). RDP consists of the abrupt onset of long-term dystonia and signs of Parkinsonism precipitated by an acute illness (Brashear *et al*., 1996). Patients are typically unresponsive to levodopa and most patients have the onset of motor symptoms in adolescence and early adulthood. *ATP1A3* is the only known RDP gene. Additionally, *ATP1A3* mutations can also present as EE, which has been described in two patients with *de novo ATP1A3* pathogenic variants with onset of repetitive seizures by six weeks of age (Paciorkowski *et al*., 2015).

Throughout his infancy, our patient's predominant and overwhelming clinical presentation was seizures and recurrent refractory status epilepticus with accompanying marked slowing of his previously normal development. The International League Against Epilepsy definition of epileptic encephalopathy is defined as "where the epileptic activity itself contributes to severe cognitive and behavioral impairments" and this has been taken to include both EEG electrical seizure activity as well as recurrent severe seizure activity (Berg *et al*., 2010; Stafstrom and Kossoff, 2016; Scheffer *et al*., 2017). This strongly supports the designation of epileptic encephalopathy for our patient. In addition, although the patient fit the clinical criteria for AHC, his hemiplegias were much less remarkable than his recurrent seizures and episodes of status epilepticus. His hemiplegias stopped after the age of two and a half years, and since then, his clinical picture has been dominated by severe bradykinesia, dystonia, and persistent seizures. We, from our center, recently reported that patients with AHC could present initially with seizures before they have hemiplegias (Uchitel *et al*., 2019). However, of the nearly 100 AHC patients we have observed in our center, none had an initial presentation similar to this patient's presentation. In addition, our review of the literature did not reveal any patients with a clinical picture similar to that of our patient. Our case is, therefore, unique in that the initial presentation was that of an epileptic encephalopathy with subsequent AHC and then RDP symptomatology. This type of clinical presentation should therefore be recognized as one that can be followed by other manifestations of *ATP1A3*-related disease, including AHC and RDP.

Although most patients with AHC do have dystonia, their tone in between dystonic attacks is, as a rule, decreased (Sasaki *et al*., 2014a). This is also observed to be the case in patients that regress after status epilepticus (Sasaki *et al*., 2017). However, what is unique about our patient is that he had an unusual clinical picture after regression, with sustained severe dystonic tone rather than hypotonia or spasticity. This feature is common in RDP and not in AHC. In addition, the fact that it occurred after a febrile illness is another feature in common with RDP. This favors our classification of this patient as a case of a combined phenotype that includes RDP features rather than just a case of severe AHC.

There are a few case reports of patients with *ATP1A3* pathogenic variants with intermediate phenotypes, manifesting some features in common with AHC and RDP. One eight-year-old boy has been reported to have attacks of flaccid paralysis and unilateral body dystonia. These attacks began at two years of age. Brain MRI and EEG were normal. This child was found to have an *ATP1A3* pathogenic variant (c.2767G>A, p.D923N). Due to the attacks of hemiplegia and dystonia, it was thought he had an intermediate phenotype between AHC and RDP (Sasaki *et al.,* 2014b). A 17-year-old girl has also been reported to have an intermediate RDP and AHC phenotype. She began having seizures at three months of age, but unlike our patient, did not have recurrent status epilepticus. She subsequently developed paroxysmal episodes consisting of generalized weakness, tonic gaze deviation, or right-sided hypotonia. She then developed bradykinesia and dystonia at 12 years of age. MRI and EEG were unremarkable and metabolic testing of the blood and CSF studies were unrevealing. *ATP1A3* gene sequencing revealed a p.D583Y variant (c.1747G>T), which was predicted to be damaging based on *in silico* analysis (Nicita *et al.,* 2016). Like our patient, both of these reported cases had episodes of paroxysmal dystonia or paroxysmal hemiplegia. Our patient and the reported 17-year-old girl both had seizures and dystonic posturing. However, our patient had the added feature of severe epileptic encephalopathy with recurrent status epilepticus (*table 1*). Our patient satisfied the clinical criteria for AHC and had the added feature of onset of severe continuous dystonia and superimposed dystonic spasm after an acute illness, similar to RDP patients. Unlike RDP patients, his onset of severe dystonia occurred at the age of two years rather than in adolescence or early adulthood. Finally, his EE was characterized by severe recurrent episodes of generalized tonic-clonic seizures and status epilepticus rather than other EE syndromes such as West or Lennox-Gastaut.

Prior work indicates that pathogenic variants presenting as RDP are evenly distributed throughout the *ATP1A3* gene, whereas variants presenting with AHC are clustered within certain regions of that gene. Typically, AHC occurs in variants with an amino acid position at less than 400 or above 800 (Heinzen *et al.,* 2014). In addition, the p.E815K pathogenic variant in patients with AHC tends to be associated with a higher risk of status epilepticus and regression (Sasaki *et al*., 2014b; Panagiotakaki *et al*., 2015). The 17-year-old girl's gene variant (p.D583Y, c.1747G>T) and our patient's variant (p.V589F, c. 1765G>T) lie outside of the typical position for AHC mutations. Interestingly, these gene variants are relatively close together in position and are associated with similar clinical presentations, suggesting a possible phenotypic link between variants in this area of the *ATP1A3* gene. Pathogenic variants in *ATP1A3* cause increased excitability in pyramidal cells and reduced firing of fast spiking parvalbumin positive GABAergic interneurons (Hunanyan *et al.,* 2015, 2018). This could potentially lead to increased predisposition to excitotoxicity, which can be associated with regression of neurological status and development of additional neurological manifestations.

Table 1. Comparison of clinical features between AHC, RDP, two previously reported intermediate phenotype cases and our case.

Feature	Our patient	AHC	RDP	8 year old boy	17 year old girl
Continuous dystonic posture	Present	Rarely	Present	Absent	Present
Paroxysmal dystonia	Present	Present	Present	Present	Present
Postural instability without tremor	Present	Absent	Present	Absent	Not specified
Paroxysmal episodes of hemplegia	Present	Present	Absent	Present	Present
Abnormal eye movements	Present	Present	Absent	Not specified	Not specified
Episodes of bilateral hemiplegia or quadriplegia	Present	Present	Absent	Not specified	Present
Seizures	Present	Present	Rarely	Absent	Present
Recurrent status epilepticus	Present	Not specified	Absent	Absent	Not specified
Improvement with sleep	Present	Not specified	Not specified	Not specified	Not specified

In conclusion, our patient manifested a novel phenotype, which differs from the intermediate phenotype cases mentioned above, by manifesting the combined features of AHC, RDP and EE manifestations. Our case also revealed a novel *ATP1A3* variant with strong bioinformatics signatures. Given the heterogeneity of phenotypes associated with *ATP1A3* mutation, additional work is needed to more fully predict phenotype based on genotype in patients with such variants in the *ATP1A3* gene. □

Acknowledgements and disclosures.
This work was supported by Duke University funds and by a donation from the CureAHC foundation (MAM) as well as by the National Institutes of Health (NIH) Common Fund 1U01HG007672-01 (VSh).

References

Berg AT, Berkovic SF, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51(4): 676-85.

Brashear A, Farlow MR, Butler IJ, Kasarskis EJ, Dobyns WB. Variable phenotype of rapid-onset dystonia-parkinsonism. *Mov Disord* 1996; 11(2): 151-6.

Fernandes C, Mikati MA. The expanding spectrum of ATP1A3 related disease. *Eur J Paediatr Neurol* 2019; 23(3): 345-6.

Heinzen EL, Swoboda KJ, Hitomi Y, *et al*. *De novo* mutations in *ATP1A3* cause alternating hemiplegia of childhood. *Nat Genet* 2012; 44(9): 1030-4.

Heinzen EL, Arzimanoglou A, Brashear A, *et al*. Distinct neurological disorders with *ATP1A3* mutations. *Lancet Neurol* 2014; 13(5): 503-14.

Helseth AR, Hunanyan AS, Adil S, *et al*. Novel E815K knock-in mouse model of alternating hemiplegia of childhood. *Neurobiol Dis* 2018; 119: 100-12.

Hunanyan AS, Fainberg NA, Linabarger M, *et al*. Knock-in mouse model of alternating hemiplegia of childhood: behavioral and electrophysiologic characterization. *Epilepsia* 2015; 56(1): 82-93.

Hunanyan AS, Helseth AR, Abdelnour E, *et al*. Mechanisms of increased hippocampal excitability in the Mashl(+/-) mouse model of Na(+) /K(+) –ATPase dysfunction. *Epilepsia* 2018; 59(7): 1455-68.

Jasien JM, Bonner M, D'alli R, *et al*. Cognitive, adaptive, and behavioral profiles and management of alternating hemiplegia of childhood. *Dev Med Child Neurol* 2019; 61(5): 547-54.

Lek M, Karczewski KJ, Minikel EV, *et al*. Exome Aggregation Consortium. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016; 536(7616): 285-91.

Masoud M, Prange L, Wuchich J, Hunanyan A, Mikati MA. Diagnosis and treatment of alternating hemiplegia of childhood. *Curr Treat Options Neurol* 2017a; 19(2): 8.

Masoud M, Gordon K, Hall A, *et al*. Motor function domains in alternating hemiplegia of childhood. *Dev Med Child Neurol* 2017b; 59(8): 822-8.

Mikati MA, Kramer U, Zupanc ML, Shanahan RJ. Alternating hemiplegia of childhood: clinical manifestations and long-term outcome. *Pediatr Neurol* 2000; 23(2): 134-41.

Nicita F, Travaglini L, Sabatini S, *et al*. Childhood-onset ATP1A3-related conditions: report of two new cases of phenotypic spectrum. *Parkinsonism Relat Disord* 2016; 30: 81-2.

Paciorkowski AR, McDaniel SS, Jansen LA, *et al*. Novel mutations in *ATP1A3* associated with catastrophic early life epilepsy, episodic prolonged apnea, and postnatal microcephaly. *Epilepsia* 2015; 56(3): 422-30.

Panagiotakaki E, De Grandis E, Stagnaro M, *et al*. Clinical profile of patients with *ATP1A3* mutations in alternating hemiplegia of childhood-a study of 155 patients. *Orphanet J Rare Dis* 2015; 10: 123.

Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17(5): 405-24.

Rosewich H, Baethmann M, Ohlenbusch A, Gärtner J, Brockmann K. A novel *ATP1A3* mutation with unique clinical presentation. *J Neurol Sci* 2014; 341(1-2): 133-5.

Sabouraud P, Riquet A, Spitz MA, *et al*. Relapsing encephalopathy with cerebellar ataxia are caused by variants involving p.Arg756 in ATP1A3. *Eur J Paediatr Neurol* 2019; 23(3): 448-55.

Sasaki M, Ishii A, Saito Y, *et al*. Genotype-phenotype correlations in alternating hemiplegia of childhood. *Neurology* 2014a; 82(6): 482-90.

Sasaki M, Ishii A, Saito Y, Hirose S. Intermediate form between alternating hemiplegia of childhood and rapid-onset dystonia-parkinsonism. *Mov Disord* 2014b; 29(1): 153-4.

Sasaki M, Ishii A, Saito Y, Hirose S. Progressive brain atrophy in alternating hemplegia of childhood. *Mov Disord Clin Pract* 2017; 4(3): 406-11.

Scheffer IE, Berkovic S, Capovilla G, *et al*. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58(4): 512-21.

Stafstrom CE, Kossoff EM. Epileptic encephalopathy in infants and children. *Epilepsy Curr* 2016; 16(4): 273-9.

Termsarasab P, Yang AC, Frucht SJ. Intermediate phenotypes of ATP1A3 mutations: phenotype-genotype correlations. *Tremor Other Hyperkinet Mov (NY)* 2015; 5: 336.

Uchitel J, Helseth A, Prange L, *et al*. The epileptology of alternating hemiplegia of childhood. *Neurology* 2019; 93(13): e1248-59.

TEST YOURSELF

(1) What syndromes have been associated with *ATP1A3* mutations?

(2) What are the clinical criteria required to diagnose alternating hemiplegia of childhood?

(3) What does the *ATP1A3* gene code for?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".