The Expanding Phenotypic Spectrum of ATP1A3 Gene Mutations

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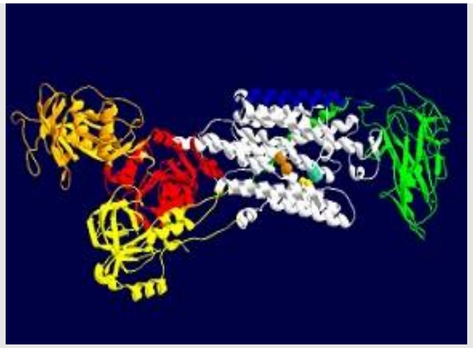

Figure 1 illustration of a ribbon diagram of Na,K-ATPase.

INTRODUCTION

ATP1A3 mutations have been recognized in infants and children presenting with a diverse group of neurological phenotypes, including Rapid-onset Dystonia Parkinsonism (RDP), Alternating Hemiplegia of Childhood (AHC), and Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS). A phenotype of fever-induced paroxysmal muscle weakness and encephalopathy (FIPWE) in patients with ATP1A3 mutations at c.2267G>A has been described recently in few cases. We hereby describe 3 cases of ATP1A3 mutations with different phenotypic presentations with their management.

METHODS

Case series.

RESULTS

Patient 1: an 18-month-old male; presented with fever induced episodes of encephalopathy, hypotonia, developmental regression, and seizures. His work up ruling out central nervous system infections and metabolic causes was repeatedly negative. A trial of oxcarbazepine was attempted, but he showed a limited response to Oxcarbazepine, therefore it was stopped. The episodes were less severe with aggressive fever management. He is now developmentally delayed with hypotonia at the age of 4 years.

Patient 2: at the age of 3 years; this boy presented with recurrent episodes of right-sided body hemiplegia involving the face and the body with slurred speech. A gradual spontaneous recovery occurred within a maximum of 3 days with no residual deficits. He had a history of neonatal seizures and delayed motor development. He was commenced on oxcarbazepine.

Since then, all his episodes stopped completely and there had been a remarkable improvement in speech and cognitive development. He continued to have a steady development with no delay.

Patient 3: A girl presented at the age of 14 months with episodes of alternating hemiplegia and abnormal eye movements. Additionally, she also had focal seizures, hypotonia and developmental delay. A trial of oxcarbazepine was started but she showed a minimal response to it. Following that, she was started on flunarizine, which fully controlled her hemiplegia and seizures. She is currently 4 years old and is attaining a slow developmental progress, but she remains to be delayed.

Discussion

Patients with ATP1A3-related disorders demonstrate a wide phenotypic spectrum presenting with impairments in cognition, language, mood, behavior, gross motor, and fine motor functions [1]

As with several channelopathies genes, the phenotypic spectrum of ATP1A3 is expanding with non-classic presentations now described.

Fever-induced paroxysmal muscle weakness and encephalopathy (FIPWE) in patients with a novel mutation of ATP1A3 at c.2267G>A p residue 756H is a recently described phenotype [2].

These patients present with fever-induced encephalopathy as a key differentiating feature [2].

Another well described phenotype seen in our first and third patient is alternating hemiplegia of childhood (AHC). AHC is a rare neuro-developmental disorder characterized by repeated episodes of transient alternating hemiplegia and/or tetraplegia.

In terms of treatment, flunarizine is used in cases with AHC [3]. The ATP1A3 gene encodes the alpha-3 subunit of the Na+/K+ ATPase pump which maintains the electrochemical gradients of sodium and potassium ions across the plasma membrane. It is possible that oxcarbazepine plays a positive role in this mechanism, but our patient didn't seem to benefit from it

REFERENCES

1. Research conference summary from the 2014 International Task Force on ATP1A3-related disorders. Rosewich H, Sweney MT, DeBrosse S, et al. Neurol Genet. 2017;3

2. Fever-induced paroxysmal weakness and encephalopathy, a new phenotype of ATP1A3 mutation. Yano ST, Silver K, Young R, DeBrosse SD, Ebel RS, Swoboda KJ, Acsadi G. Pediatr Neurol. 2017;73:101–105.

3. Paroxysmal features responding to flunarizine in a child with rapid-onset dystonia-parkinsonism. Fornarino S, Stagnaro M, Rinelli M, et al. Neurology. 2014;82:2037–2038.