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*Case Report*

# Alternating Hemiplegia of Childhood: From Diagnosis to Treatment

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**Abstract** An 11-month-old girl presented to us with recurrent episodes of hemiplegia affecting either side of the body, which were associated with febrile illnesses. Extensive workup in efforts to rule out other causes including vascular, metabolic or neuromuscular causes were unremarkable. Clinical diagnosis of alternating hemiplegia of childhood (AHC) was made and was later confirmed with genetic analysis. This report aims to enlighten clinicians on the complex presentation of AHC and to highlight that epileptic seizure, although a different disease entity, may be common in the presentation of AHC.

**Key words** Alternating hemiplegia; *ATP1A3*; $Na^+/K^+$-ATPase; Sodium/potassium-transporting ATPase

## Case Report

Our case was born full term with uneventful antenatal and postnatal course. Her family history was unremarkable and her parents were non-consanguineous. She enjoyed good past health except known beta thalassemia trait.

She was initially known to us for onset of seizures at three months of age, presenting with loss of consciousness, staring eyes, increased four limb tone with no tonic-clonic convulsion. Seizure episodes lasted for a few minutes each with postictal drowsiness. She was started on phenobarbitone for seizure control and had one episode of breakthrough seizure at seven months of age.

Physical examination showed no dysmorphism or neurocutaneous stigmata. Her neurological exam was normal and development appropriate to her age at presentation. Wood's lamp showed no fluorescent skin lesions. Neuroimaging upon initial seizure presentation showed no abnormality. Electroencephalogram done at five months old was normal.

At nine months of age, she was admitted for two days of right-sided weakness associated with febrile illness. Her parents subsequently volunteered six months' history of alternating unilateral weakness lasting around two to three day and occurring once every one to two months. Muscle weakness was most prominent with fine motor movement, with gross motor function relatively spared. There was also associated involuntary eye deviation to the hemiplegic side but no alteration in sensorium or consciousness.

In view of the newly reported hemiplegic symptoms, evaluation to exclude other structural, vascular and metabolic disorders was performed. Magnetic resonance imaging of the brain with angiography was done to rule out structural lesions with no abnormality detected. Metabolic workup (including plasma lactate and

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ammonia; urine organic acids; plasma amino acids; serum free carnitine, acylcarnitine, transferrin isoforms, biotinidase and very long chain fatty acids) was unremarkable. Clinical diagnosis of alternating hemiplegia with recurrent episode of unilateral weakness was made. Genetic analysis for *ATP1A3* was performed by polymerase chain reaction followed by Sanger sequencing of genomic DNA extracted from EDTA blood samples of the proband and her parents, and confirmed a *de novo* heterozygous missense variant NM_152296.4(*ATP1A3*):c.2401G>A, p.(Asp801Asn) in the proband, which was a known pathogenic variant.[1] (Figure 1) The diagnosis of alternating hemiplegia of childhood (AHC) was confirmed and the patient was subsequently started on a trial of flunarizine at 2.5 mg daily dosing.

At 11 months of age, she was noted to have delayed development by about three months over the gross motor aspect. She was unable to pull to stand and had decreased ability to sit unsupported. She was referred for formal development assessment and training. Since then, her developmental milestone had shown gradual improvement especially over the gross motor aspect with no regression noted all along.

There were nine further episodes of hemiplegic attacks after presentation. Some of the episodes were associated with febrile illness and all had similar semiology of unilateral weakness with eye deviation to affected side, resolving spontaneously after two days. However, the attacks were reported to be milder in severity and duration. Flunarizine was stepped up to 5 mg daily to optimise control of the attacks.

In addition, there was an episode of breakthrough seizure at 17 months of age with increased tone over four limbs and starring gaze lasting a few minutes, features were different to those seen in her hemiplegic attacks. Phenobarbitone was gradually weaned off while anticonvulsant was being switched to sodium valproate at 13 months old. Later topiramate was added on for control of seizure and recurrent hemiplegic attack. Since the addition of topiramate there was no recurrence of hemiplegic episodes or breakthrough seizures. Her developmental milestone had caught up and was appropriate to age. The current management plan was to continue with flunarizine at 5 mg daily and step up topiramate as additional prophylaxis, while tailing off valproate gradually.

## Discussion

AHC is a rare early-onset neurological disorder with estimated incidence of 1 in 1,000,000 births.[2] The major pathognomonic features include paroxysmal attacks of hemiplegia or hemidystonia affecting either side of body, or generalised fluctuating dystonia, quadriplegia or quadriparesis with onset within six months of age. Other accompanying non-paroxysmal features may range from global developmental delay, variable intellectual disability, pyramidal tract signs, and epilepsy. Some patients may have atypical presentation including predominantly dystonic rather than hemiplegic paroxysmal episodes.[3] This disease was first characterised as a distinct syndrome in 1971, but the causative gene *ATP1A3* was identified only in 2012.[3,4]

*ATP1A3* encodes for the alpha-3 isoform of the catalytic subunit of the $Na^+/K^+$-ATPase transmembrane ion pump. This isoform is exclusively expressed in neurons and is crucial in maintaining the neuronal excitability.[1]

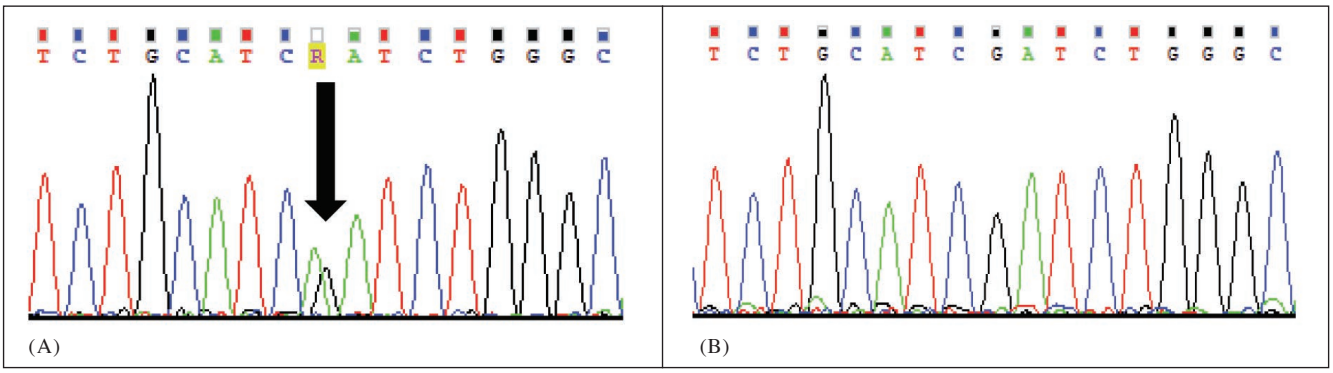


**Figure 1** Electropherogram of (A) heterozygous pathogenic *ATP1A*3 variant, c.2401 G>A p.(Asp801Asn), detected in the proband and (B) wildtype sequence detected in the parents. The affected nucleotide is marked by an arrow.

Pathogenic variants in *ATP1A3* may account for up to 74% of patients with sporadic, typical AHC.[4] To date, at least 34 unique variants in *ATP1A3* clustering near the transmembrane domains have been identified, including two recurrent variants p.Asp801Asn and p.Glu815Lys. Functional studies showed the p.Asp801Asn variant, which was found in the proband, had decreased binding to potassium ions and reduced ATPase catalytic activity.[5] The variant was found to be associated with a milder phenotypic expression.[6]

Apart from AHC, the spectrum of *ATP1A3*-related disorders encompasses two other clinical phenotypes: rapid-onset dystonia-parkinsonism (RDP) and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS). Presence of atypical phenotypes and the findings of different phenotypes among patients carrying the same pathogenic variant suggest that the three phenotypes may represent a continuum of neurological disorder.[7] Before the discovery of the causative gene in 2012, the diagnosis of AHC was based on expert-consensus clinical criteria (Table 1).[8] A new diagnostic approach that advocates referral for *ATP1A3* molecular analysis based on neurologic symptoms or signs broadly supporting an association with *ATP1A3*-related disease instead of specific syndromes has been proposed at the 2014 International Task Force meeting on *ATP1A3*-related disorders.[9] With this case-finding approach, there may be expansion of the phenotypic spectrum and improved understanding of the pathophysiology behind these disorders.

Due to the disease's complexity and variability in phenotypes, its diagnosis and subsequent multidisciplinary management is often difficult and delayed.[2] Most children with AHC will have some degree of long term disability and other medical problems, with majority of them having developmental delay and 50% of them having epilepsy.[3] The prognosis of patients with AHC are often poor due to associated developmental delay and stepwise deterioration after severe attacks.

The mainstay of treatment is by prophylactic medication and acute management of hemiplegic attacks. Lifestyle measures such as avoidance of precipitating factors including psychological stress, fatigue and early induction of sleep is recommended as part of the management strategy. Early recognition of febrile illnesses and vaccinations are also recommended to patients with AHC. There is no curative treatment but various medications including steroids, coenzyme Q10, acetazolamide have been recommended. However, current evidence for the above medications is inconclusive with their clinical efficacy evaluated mostly in case reports or case series. A case report in our locality achieved remission while being treated with corticosteroids, possibly through direct induction of the $Na^+/K^+$-ATPase activity.[10] Topiramate, an anticonvulsant, may improve the frequency and severity of non-epileptic paroxysmal symptoms and seizure-like episodes.[11,12] However, patients treated with topiramate are at risk of anhidrosis and hyperthermia, thus care-takers should be educated to monitor these side effects and avoid overheating. Increasing evidence has shown flunarizine, a calcium channel blocker to be effective in reducing the frequency and severity of the hemiplegic attacks.[3,13,14] The efficacy of flunarizine is based on its use in hundreds of patients, albeit in open-label experience, whereas reports for the other agents were either single case reports or case series of a small number of patients.[15] As in our case, the combination of the above drugs including flunarizine and topiramate had led to improved outcome in terms of the hemiplegic attack and seizure control.

In summary, *ATP1A3* is the major pathogenic gene of AHC patients and is associated with multiple neurological phenotypes. Lower threshold for genetic analysis of the *ATP1A3* gene is recommended, once clinical symptoms fulfil the diagnostic criteria and also

**Table 1** Aicardi criteria for the diagnosis of alternating hemiplegia of childhood

| Diagnostic criteria for alternating hemiplegia of childhood |
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| 1. Symptoms onset before age 18 months |
| 2. Repeated episodes of hemiplegia, alternating between two sides of the body |
| 3. Quadriplegia that occurs as an isolated incident or as part of a hemiplegic attack |
| 4. Relief from symptoms upon sleeping, which may later recur after waking up from sleep |
| 5. Additional paroxysmal attacks such as dystonia, tonic episodes, abnormal eye movements, or autonomic dysfunction |
| 6. Evidence of developmental delay or neurological abnormalities such as choreoathetosis, ataxia, or cognitive disability |

for those with atypical presentation. Correct and timely diagnosis can help to avoid delayed management and unnecessary treatments while more evidence is needed in evaluating the effectiveness of different treatment modalities.

## Declaration of Interest

The authors declare that there is no conflict of interest.

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