

Alternating Hemiplegia of Childhood with ATP1A3 Gene Mutation- A Case Report

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Abstract

Alternating hemiplegia of childhood (AHC) is a rare neurological disorder manifested by transient repeated episodes of alternating hemiplegia associated with other neurological events. Though the exact etiology was largely unknown, recently the pathogenic mutation in the ATP1A3 gene encoding for the alpha3 catalytic subunit of Na⁺/K⁺ATPase was found to be the primary cause of AHC. We present the case of 8.5 year old girl with AHC who had a heterozygous de-novo p.Leu839Pro (c.2516T>C) pathogenic mutation of ATP1A3 gene on chromosome 19q13.

Keyword: Alternate Hemiplegia of childhood, ATP1A3, Mutation

Introduction

Alternating hemiplegia of childhood (AHC) is a complex neurological disorder characterized by paroxysmal hemiplegic attacks associated with other neurologic findings. Most cases of AHC are sporadic, but some may be transmitted by autosomal dominant inheritance. Diagnosis is mainly clinical according to criteria.¹ Specific diagnostic criteria for AHC, named "Aicardi criteria," were first proposed in 1993.² Presentation is highly variable. Besides the alternating hemiplegia, other neurological findings include developmental delay, epilepsy, movement disorders, behavioral and cognitive impairment, ocular abnormalities, autonomic involvement etc. In 2012, de novo heterozygous mutations in the ATP1A3 were identified as the cause of AHC.³ Though management is challenging as disease specific treatment does not exist, but several agents have been tried to reduce the severity and frequency of the paroxysms.

Case report

An 8.5 year old girl presented with history of early onset epilepsy, developmental delay and paroxysmal episodes of weakness occasionally associated with headache. The child had repeated episodes of sudden

onset paralysis of the body since her early infancy, more involving the right lower limb but occasionally bilateral from onset. She remained alert, able to talk, eat and walk with hemiplegic gait during the episodes. These episodes lasted for 20-30 min and then resolved completely with no residual effects. No bowel and bladder incontinence occurred. The frequency of the episodes was unpredictable, ranging from 2-3 days interval to several times a day. Occasionally both sides of the body were involved (quadriplegia). The episodes often precipitated by emotional stress, cold and infections. She occasionally developed bilateral band like headache with episodes of paralysis.

The child was born at term with history of perinatal asphyxia and neonatal seizure. She was diagnosed as a case of epilepsy since early infancy. She was initially treated with phenobarbitone followed by sodium valproate and levetiracetam with partial improvement. Oxcarbazepine was added at 2 years with significant improvement. Flunarizine was also given along with the antiepileptic medications. Her father had history of migraine.

She had global developmental delay, no dysmorphic features was observed, could follow simple commands. On neurological examination, she had normal muscle power, normal muscular tone and normal reflexes, her gait was ataxic. All other systems were unremarkable.

Electroencephalogram revealed focal epileptiform discharge, MRI and MRA of the brain showed normal findings. Genetic study: clinical exome sequencing was done which showed heterozygous de-novo p.Leu839Pro (c.2516T>C) pathogenic mutation in the exon 18 of ATP1A3 gene on chromosome 19q13.

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Discussion

AHC was first described by Verret and Steel in 1971 in 8 patients.⁴ The incidence is approximately 1 per 1,000,000 births.⁵ Neurological manifestations usually start before the age of 18 months. Alternating episodes of hemiplegia occur but sometimes weakness may extend to other side or may occur bilaterally from the very beginning.⁶ Reported patient also presented with neurological manifestation in early infancy and had typical alternating episodes of weakness and sometimes bilateral weakness. During the episodes of weakness consciousness usually remains normal and symptoms disappear upon sleep.⁶

Epilepsy is an important association which may be focal clonic, generalized tonic clonic or myoclonic.⁷ Nevsimalová et al.⁸ described that 87.5% of patient and Panagiotakaki et al. stated that, 52% of children of AHC may present with epilepsy.⁹ This patient also presented with early onset epilepsy. Headache was found in 56% patient with AHC.⁹ Initially it was thought to be a migrant variant due to some overlapping clinical features and often misdiagnosed as hemiplegic migraine. Familial Hemiplegic Migraine (FHM) is found to be caused by mutation in SCN1A, CACNA1A and ATP1A2 gene and have a strong family history of migraine in 1st degree relative.¹⁰ This reported patient also presented with headache and had a family history of migraine in her father.

Developmental delay is an important clinical feature of AHC. Panagiotakaki et al. also stated that 92% of patient with AHC may present with developmental delay.⁹ The patient also presented with global developmental delay. Dystonia may present within first month of life though this patient did not present with any movement disorder like dystonia or choreoathetosis, Mikati et al. stated that, dystonia may present in 95% of children with AHC.⁷ Most early clinical findings is oculomotor abnormalities including horizontal, vertical or rotatory nystagmus, gaze deviation, strabismus etc. Sweney et al. described, oculomotor abnormality may present in 93% of children.¹¹

Some authors described three stages of evolution of clinical manifestations including, stage 1: within 1st year of life presenting with oculomotor abnormalities, dystonic spells, autonomic manifestations, stage 2: from 1-5 years, present predominantly with paroxysmal episodes of hemiplegia, epilepsy, headache, movement disorders, ataxia etc. and lastly in stage 3, permanent

deficit may occur like, intellectual disability, permanent hemiparesis or quadriparesis, aphasia etc.⁶ Episodes may be triggered by some precipitating factors like, emotional stress, trauma, bright light, heat, cold, foods etc.⁶ This patient had some aggravating factor like cold, fever and stress.

Diagnosis is made mainly based on clinical criteria. Investigations are usually done to exclude other differentials.⁶ Neuroimaging including MRI and MRA of brain usually shows normal findings. Electroencephalography may be necessary to rule out epileptic vs. non-epileptic events as Todd's paresis. Confirmation is done by genetic test usually by next generation sequencing. In recent studies, de novo mutation of ATP1A3 gene is observed in about 74% patient.³ Another study involving 155 patients with AHC shows mutation in ATP1A3 gene in clusters most predominantly in p.Asp801Asn (43%), p.Glu815Lys (16%) and p.Gly947Arg (11%) regions.¹² This case showed heterozygous de-novo p.Leu839Pro (c.2516T>C) pathogenic mutation in the exon 18 of ATP1A3 gene on chromosome 19q13, which was not described previously. In the previous study p.Glu815Lys mutation was associated with a severe phenotype and more severe course, mutation in p.Asp801Asn was associated with a milder phenotypic expression, and p.Gly947Arg mutation showed most favorable prognosis.¹² Our case showed a novel mutation in p.Leu839Pro (c.2516T>C) region.

There is no specific treatment option, but several agents were administered in different small scale studies and case reports but not proven.¹³ Among them Flunarizine (5-20mg/day) is most commonly used which is a selective calcium channel blocker.^{1,12,14} Other agents including Topiramate,^{1,12} Aripiprazole,^{15,16} Betamethasone,¹⁷ Ketogenic diet^{18,19} were used in some case studies. Our patient was treated with flunarizine along with other anticonvulsant medications.

Conclusion

Due to highly variable clinical presentation, the diagnosis AHC may be delayed or missed. The recent advancement in the research field of AHC is the recognition of ATP1A3 gene pathogenic mutation which will not only help in early diagnosis may also aid in invention of newer therapeutic interventions.

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