

Alternating Hemiplegia of Childhood-A Case Report and Literature Review

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Abstract

Case Report

Alternating hemiplegia of childhood is a rare condition that affects approximately 1 in 1 million people is a severe disorder affecting the neurological system of children usually before 18 months of age, The paralysis may affect different parts of the body at different times and may be brief or last for several days .here we present a case report of 17 months baby boy presented with history of abnormal movement in form of twitching of mouth to right side and tonic movement of right arm for 3 days at age of 3 months then sudden onset of paralysis in right side of body at age of 17 months lasting for 3 days. Genetic testing confirmed diagnosis of Alternating hemiplegia of childhood

Keywords: Alternative, hemiplagia, seizure, nystagmus, ATP1A3.

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INTRODUCTION

Alternating hemiplegia of childhood is a rare condition that affects approximately 1 in 1 million people is a severe disorder affecting the neurological system of children usually before 18 months of age; the paralysis may affect different parts of the body at different times and may be brief or last for several days.

Alternating hemiplegia of childhood also causes mild to severe cognitive problems, almost all affected individuals have some level of developmental delay and intellectual disability, their cognitive functioning typically declines over time.

CASE REPORT

The Patient is 17 months old Saudi boy product of full term normal delivery presented to emergency at age of 3 months with history of abnormal movement in form of twitching of mouth to right side and tonic movement of right arm which was repeated for 3 days.

At age of 17 months he developed sudden onset of paralysis in right side lasting for 24 to 72 hr associated with difficult swallowing then patient return to normal.

Regarding his gross motor development he can sit with support and he started to support his head .had mild pincer grasb .he can recognize his family and he

can say mama, dad, was no concern about hearing or vision.

Family history reveled his parent were first degree cousins, his mother known case of migraine and there is positive history of febril convulsion in the family.

On examination

Patient was conscious, alert, attentive ,not in respiratory distress or pain ,well hydrated, not dysmorphic, vitally stable, the growth parameter his head circumference 45 cm just below 3rd centil, height 80 cm on 25th centil and weight 8.4kg below 3rd centil.

ENT examination: clear, no lymphadenopathy, CNS: patient was conscious alert with central hypotonia , power 3 to 3+ and reflexes +2, chest examination :equal bilateral air entry with no added sounds, CVS examination: audible first and second heart sounds no murmur, GIT examination: soft and lax abdomen no organomegally, no hernia ,normal back normal male genitalia both testes down.

Full investigation done for him and his lab work include complete blood count, renal, liver and bone profile all were unremarkable. vit D3 level, metabolic screening all were within normal, MRI brain (figure 1) done and reported as Prominence of the lateral ventricles and frontotemporal subarachnoid spaces, can be transient physiological hydrocephalus,

Otherwise unremarkable MRI of the brain., EEG done

and was consistent with partial seizure disorder



Fig-1: Prominence of the lateral ventricles and frontotemporal subarachnoid spaces

Genetic study for our patient showed gene mutation (ATP1A3) which is consistent with diagnosis of Alternating hemiplegia of childhood

DISCUSSION

Classic AHC causes recurrent episodes of paralysis (hemiplegia) that involve one or both sides of the body, multiple limbs, or a single limb. The paralysis may affect different parts of the body at different times and may be brief or last for several days.

It is a severe disorder affecting the neurological system of children, usually before 18 months of age with association of tonic or dystonic attacks, nystagmus, and sometimes autonomic phenomena with cognitive impairment and developmental delay and choreoathetotic movement disorder. Interestingly, the attacks of hemiplegia were relieved by sleeping [1].

There are some atypical cases which might present after the age of 18 months. With the same characteristic, but with moderate developmental delay [2].

AHC is considered an AD condition. Most cases of AHC result from new mutations in the gene and occur in people with no history of the disorder in their family. However, the condition can also run in families and for unknown reasons, the signs and symptoms are typically milder when the condition is found in multiple family members than when a single individual is affected, the etiology of this condition remains unclear, but it is likely a symptom complex with multiple causes. Neurophysiologic recordings during an attack have shown impaired brainstem circuits. The attacks occurring in AHC and familial

hemiplegic migraine (FHM) are clinically similar raising the question of AHC caused by mutation in ATP1A3 and rarely by mutation in ATP1A2. The clinical presentation is characteristic and the diagnosis can be confirmed by mutation analysis.

AHC is distinguished from Familial hemiplegic migraine by infantile onset. Although some authors found that both diseases may share the same gene mutation [3].

Two gene mutations have been identified for this disease (ATP1A2) and (ATP1A3)

Our patient has been found to have the more rare form of gene mutation (ATP1A3) (4) – FIG.2

A diagnosis of AHC is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of specialized tests. Specific diagnostic criteria have been proposed for AHC

The seven criteria are

- Onset of symptoms before 18 months.
- Repeated episodes of hemiplegia that sometimes involve both sides of the body.
- Quadriplegia that occurs as an isolated incident or as part of a hemiplegic attack.
- Relief from symptoms upon sleeping.
- Additional paroxysmal attacks such as dystonia, tonic episodes, abnormal eye movements or autonomic dysfunction.
- Evidence of developmental delay or neurological abnormalities such as
- Choreoathetosis, ataxia or cognitive disability.

NEXT GENERATION SEQUENCING -- WHOLE EXOME ANALYSIS

TEST(S) REQUESTED: Whole Exome Sequencing (WES)

CLINICAL INDICATION(S): Gross motor delay, Seizures

RESULTS

A heterozygous variant of *ATP1A3* (*ATP1A3:NM_001256213:exon9:c.1198G>A;p.E400K*) was identified in this patient. According to ACMG guidelines it should be classified as a **VOUS (variant of uncertain significance)**. Missense variants of *ATP1A3* are frequently the cause of Alternating hemiplegia of childhood 2, 614820 (3), Autosomal dominant; CAPOS syndrome, 601338 (3), Autosomal dominant; Dystonia-12, 128235 (3), Autosomal dominant. Parental screening to determine the *de novo* status or otherwise of the variant is strongly recommended and may support a causative role of this variant in this instance.

The following **Known Saudi Mutation(s)** should, according to ACMG guidelines, be classified as **pathogenic**. This individual is a **CARRIER** of the mutation(s).

Fig-2: whole exome analysis for our patient

Molecular Genetics

Gene function

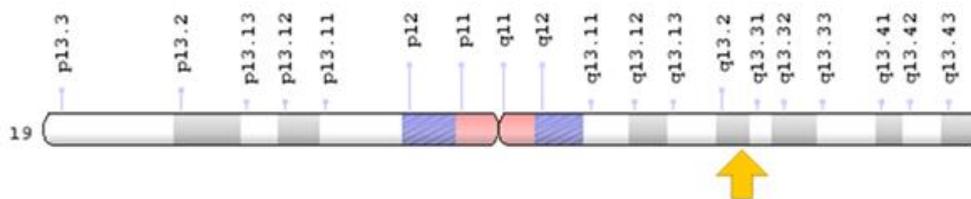
The *ATP1A3* gene provides instructions for making one part (the alpha-3 subunit) of a protein known as Na⁺/K⁺ ATPase or the sodium pump. This protein uses energy from a molecule called adenosine triphosphate (ATP) to transport charged atoms (ions) into and out of cells. Specifically, it pumps sodium ions (Na⁺) out of cells and potassium ions (K⁺) into cells.

Na⁺/K⁺ ATPase that include the alpha-3 subunit are primarily found in nerve cells (neurons) in the brain and are critical for their normal function. The movement of sodium and potassium ions helps regulate the electrical activity of these cells and plays an important role in the signaling process that controls muscle movement. The activity of Na⁺/K⁺ ATPase also helps regulate cell size (volume)[6].

Additionally, Na⁺/K⁺ ATPase helps regulate a process called neurotransmitter reuptake. Neurotransmitters are chemicals that transmit signals from one neuron to another. After a neurotransmitter has had its effect, it must be removed quickly from the space between the neurons. The reuptake of neurotransmitters is carefully controlled to ensure that signals are sent and received accurately throughout the nervous system [8].

Cytogenetic Location: 19q13.2, which is the long (q) arm of chromosome 19 at position 13.2

Molecular Location: base pairs 41,966,582 to 41,994,276 on chromosome 19 (Homo sapiens Annotation Release 109, GRCh38.p12. [7].



Locus heterogeneity in AHC is strongly suggested by the identification of infants and children with a phenotype meeting the classic clinical criteria for AHC but in whom no apparent pathogenic variant involving *ATP1A3* or its locus have been identified [8].

In several large studies of individuals with features of AHC 82%-85% had pathogenic variants in *ATP1A3*, suggesting a different (unknown) genetic cause for disease [10].

Whole-exome sequencing showed heterozygous *de novo* missense variant involving *ATP1A3*

(*ATP1A3:NM_001256213:exon9:c.1198G>A;p.E400K*) was identified in this patient.

Missense variants of *ATP1A3* are frequently the cause of alternating hemiplegia of childhood 2, Autosomal dominant;

This variant has been confirmed by Sanger sequencing. It is classified as likely pathogenic (class 2)

according to the recommendations of Centogene and ACMG guidelines [9].

In 82 of 105 patients with alternating hemiplegia of childhood identified 19 different heterozygous mutations in the ATP1A3 gene.

The first mutations were identified through exome sequencing of affected individuals. Thirteen of the 18 mutations observed in sporadic cases were confirmed to occur de novo in multiple cases [11].

Treatment of AHC is divided into acute management of attacks and episode prophylaxis, IN Acute management some authors have advocated the use of buccal midazolam or rectal diazepam to provide rapid sedation and for Episode prophylaxis should consist of avoiding known triggers as i.e. cold, emotional stress, fatigue, bathing in hot water, hot or cold weather with different degree of This has been reported to decrease the frequency and severity of attacks but not to stop them completely.

Although the prognosis of the disease is poor, some medications have been suggested to reduce the attacks and the severity of the disease of which, Flunarizine at a dose of 5–20 mg/day.

It is unclear if pharmacologic intervention helps to improve learning, but lessening the severity and frequency of attacks may lead to an improved quality of life.

So the prognosis it depend how sever is the disease and when they start the medication. Some studies showed that the use of amantidne shows promising result. But more research about it needs to be done [5].

CONCLUSION

Alternating hemiplegia of childhood which is rare neurological disease can present initially with seizures then the attacks of hemiplagia like our patient. High index of suspicion, early diagnosis and management is important to counsel the family and follow the patient.

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