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Case Report

Paediatrics Section

Frequent Fall: Seizure or Weakness? A Case Report of Alternating Hemiplegia of Childhood

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ABSTRACT

Alternating Hemiplegia of Childhood (AHC) is a complex disease which causes recurrent hemiplegic attacks. Although *ATP1A3* gene has been identified as the cause of this neurological entity, many variants are being reported nowadays, adding to the spectrum of *ATP1A3* gene-related disorders due to the advancement in genetic testing. Hereby, authors presents a case report of a 3-year-old male child who presented with a complaint of frequent falls while walking with gait abnormality and has been on treatment for seizure disorder since, 5 months of age. On assessing the history and evaluating the child, AHC was suspected and the same was confirmed using genetic tests.

Keywords: Ataxia, Gait abnormality, Genetic variants, Neurological disorder

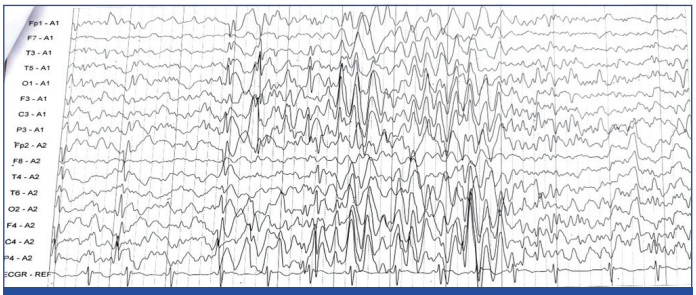
CASE REPORT

A 3-year-old male, first order child, born out of third-degree consanguineous marriage presented to the Department of Paediatrics, with complaints of frequent episodes of fall while walking and gait abnormality for the past 3 months. The child developed seizures, which was generalised tonic-clonic type, at 5 months of age. He was started on antiepileptic drug sodium valproate (20 mg/kg/day). Due to intermittent seizures Tab. Levetiracetam at 10 mg/kg/day was added following which there were no further seizures. The child was taken to the local practitioner one month back for the complaints of frequent falls while walking and gait abnormality following which the dose of levetiracetam was increased from 10 mg/kg/day to 20 mg/kg/day. As there was no improvement, he was presently brought to the Outpatient Department.

A detailed history was obtained from the mother. Following the falls, the child could not get up or move either of the limbs which would last for a few minutes to several hours. The longest duration observed was 6 hours, but the child would be completely normal in between the episodes of weakness. He would be normal after sleep, with no residual weakness. The child was developing such transient weakness, alternating both sides once every fortnight. Sometimes he also had multiple episodes per day. The child was conscious and aware of the surroundings during such episodes. He had excessive sweating associated with hemiparetic episodes. There was no associated fever, seizure, vomiting, visual disturbances, abnormal ocular movements, or headache during the episodes. The antenatal period was uneventful. The child was born at 39 weeks of gestation following normal vaginal delivery. There was no history suggestive of birth asphyxia. There was no family history of similar illness or seizure disorder in the family. Developmental milestones were normal for his age. The immunisation schedule was upto date.

On examination, higher mental functions were normal. Hearing and vision were normal. Head-to-toe examination revealed no dysmorphism. On examining, the central nervous system examination, tone, bulk, power, and reflexes were normal. The plantar response was flexor on both sides. Cranial nerve examination and fundus were normal. The child had an ataxic gait. During the episode of weakness, the child was brought to the emergency department and on examination, hypotonia with areflexia was documented on the affected side. The vital signs of the child were normal for that age.

Complete blood count, renal function test, liver function test, and serum electrolytes were normal. The previous Electroencephalogram (EEG) of the child, which was done at 5 months of age, was normal, but the subsequent EEG, which was done at 1 year, showed generalised epileptiform discharges [Table/Fig-1].



[Table/Fig-1]: EEG of the child at 1 year of age showing generalised epileptiform discharges.

Magnetic Resonance Imaging (MRI) brain was normal. As the clinical feature was suggestive of alternating hemiplegia of childhood, a blood sample was sent for genetic analysis. It revealed a missense mutation of *p.Asp801Asn* in *ATP1A3* gene. After analysis of the reports alternating hemiplegia of childhood was confirmed. Following the report, the child was started on flunarizine. He is on follow-up for the past 6 months. Before starting the treatment, the child used to experience 4 to 6 attacks per day, and now there has been a reduction in the number of attacks to 1 to 2 per day.

DISCUSSION

Alternating hemiplegia of childhood is a neurological disorder, first reported in 1971 by Verret S and Steele JC [1]. It is characterised by recurrent and alternating episodes of hemiplegia which may last from a few minutes to several hours or even days. The neurological dysfunction can be associated with oculomotor abnormalities, autonomic dysfunction, headaches, developmental delay, movement disorders, and speech abnormalities [2]. Although Alternating Hemiplegia of Childhood (AHC) has been stated as a rare disease in the literature, with a reported incidence of 1 in 1,000,000 children, it is often a misdiagnosed or underdiagnosed disease with the incidence being underestimated [3]. This disorder is often misdiagnosed as seizure disorder or migraine due to its broad spectrum of manifestations. It is also diagnosed late because of

its variability in clinical presentation and lack of knowledge about the clinical entity.

The pathophysiology of AHC has been attributed to mutations in the *ATP1A3* gene which encodes a α-subunit (the α3-isoform) of the sodium-potassium pump (Na+ K+-ATPase) pump, primarily found in the nervous system. The *ATP1A3* genetic mutation in AHC cases was first identified in 2012 by two research groups [4,5]. The heterozygous mutation of ATP1A3 gene have also been associated with rapid-onset dystonia parkinsonism [6]. CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) [7,8], episodic Cerebellar ataxia, Areflexia, Optic atrophy, and Sensorineural hearing loss (CAOS) syndrome [9], the Early Infantile Epilepsy with Encephalopathy (EIEE) [10,11] and the Recurrent Encephalopathy with Cerebellar Ataxia (RECA) phenotype [12,13]. The other genes which have been reported to be associated with AHC cases are the *ATP1A2* gene, *GLUT-1* gene, and *CACNA1A* gene [14]. *ATP1A3* mutations affect the whole coding sequence causing many pathogenic variants, which are more frequently found in exons 17 and 18 [15]. The *ATP1A3* clinical spectrum depends on the location of *ATP1A3* mutations and various studies like Capuano A et al., [16], Viollet L et al., [17], Panagiotakaki E et al., [18], Yang X et al., [19] have reported the correlation between genotype and phenotype.

Rosewich H et al., stated that mutations, particularly near the transmembrane domains which consequently cause protein alterations, result in AHC [20]. In a study by Panagiotakaki E et al., most common mutations were identified p.Asp801Asn, p.Glu815Lys and p.Gly947Arg of *ATP1A3* in AHC cases, however, they have also reported cases gene who have fulfilled the clinical diagnostic criteria with no genetic mutation [18]. The pGlu815Lys mutation was associated with a more severe phenotype with less favourable prognosis, early onset plegic attacks, epilepsy, paroxysmal manifestation, and severe psychomotor delay. The pAsp801Asn mutation presented with a milder phenotype, intermediate onset, less frequent plegic attacks and ataxia. The p.Gly947Arg mutation has a positive prognosis, late onset plegic attacks, less frequent epilepsy, and rarely movement disorders [18]. The present case had pAsp801Asn missense mutation of ATP1A3 gene with hemiplegic attacks and ataxia. The child was only 3 years of age but there was an early onset of seizure at 5 month of age, and he had no developmental delay which was different from the phenotype described by Panagiotakaki E et al., [18].

The clinical course of AHC has been described in three phases by Mikati MA et al., [21]:

1. Phase 1 is seen during the early infancy lasting up to 1 year which are characterised by hemiplegic spells, eye movement abnormalities, and dystonic episodes. Ocular abnormalities like nystagmus, up rolling of eyes, deviation of eyes predominates in this phase when compared to hemiplegic spells.
2. Phase 2 begins at 1 year and lasts till 5 years of age. This phase is characterised by increased cluster of hemiplegic episodes often associated with the regression of development, which the patient slowly gains after the episode subsides. Seizures may appear during this phase.
3. Phase 3 begins after 6 years of age, characterised by persistent attacks of dystonia, less frequency of hemiplegic attacks, developmental delay, fixed neurological deficits, and epilepsy.

Although all these three phases may not be seen in all cases of AHC, it occurs in many [21]. The present patient was in phase 2, with an increased frequency of hemiplegic attacks but the child started having seizures early by 5 months of age, which is unusual in phase 1.

The clinical features of AHC can be categorised as paroxysmal features and non paroxysmal features. Paroxysmal features include recurrent hemiplegic episodes alternating in laterality, tonic or dystonic attacks, oculomotor abnormalities like monocular and binocular nystagmus, strabismus, disconjugate gaze, ocular bobbing, ocular flutter, and dysautonomic phenomenon accompanying the paroxysmal neurological episodes. Hemiplegic attacks can get progressed to become a quadriplegic attack. Non paroxysmal features include developmental delay, behaviour problems, intellectual disability, epilepsy, dysarthria, movement disorders, ataxia, dystonia, and choreoathetosis. The prevalence of neurological abnormalities or deterioration may increase with age [22-26].

Mikati MA et al., analysed 44 cases of AHC. They reported abnormal ocular movements in all patients, whereas in the present case abnormal ocular movements were not recorded, neither during the hemiplegic episodes nor as the presenting sign. They also reported that developmental delay was greater in patients who had AHC episodes onset at a young age and in their study 91 % of the patients showed developmental delay. Developmental milestones were normal for the present case [21].

Aicardi J et al., proposed the first diagnostic criteria in 1993 named “Aicardi criteria”. It includes, (1) onset before 18 months of age; (2) repeated episodes of hemiplegia involving the right or left side of the body, at least in some episodes; (3) episodes of bilateral hemiplegia or quadriplegia, starting either as generalisation of a hemiplegic episode or bilaterally; (4) other paroxysmal disturbances including tonic/dystonic attacks, nystagmus, strabismus, dyspnoea, and other autonomic phenomena occurring during hemiplegic attacks or in isolation; (5) immediate disappearance of all symptoms on going to sleep, with recurrence 10 to 20 minutes after awakening in long-lasting attacks; (6) evidence of developmental delay, learning disability, neurological abnormalities, choreoathetosis, dystonia, or ataxia; and (7) not attributable to another disorder [27].

In the present case, although the criteria 1 was not satisfied as the child started developing hemiparetic episodes at 3 years of age, the child had other features supporting the diagnosis of AHC, viz, repeated episodes of hemiplegia involving either left or right side associated with autonomic phenomena (excessive sweating) with disappearance of episodes after sleeping . Other disorders attributing to weakness were excluded by investigating for other causes.

Children with AHC often have coexisting seizures which may occur either along with the hemiplegic attacks or occur distinctly from the attacks [28]. Epileptic seizures can be focal or generalised or status epilepticus with a varied presentation, frequency, drug resistance depending on the various genetic mutations [29]. The index patient had first episode of generalised tonic clonic seizure at 5 months of age followed by intermittent seizures even after starting sodium valproate.

The clinical features of alternating hemiplegia of childhood mimics various other diseases which presents as acute neurological deficit. Hence, diagnosing the disease clinically amidst various diseases presenting as acute focal weakness is quite challenging. These diseases which manifest as acute neurological paralysis or paresis are stroke caused by vasculitis, autoimmune disorders, vasculopathy (sickle cell disease), hypercoagulable states, Moyamoya syndrome, and metabolic disorders like homocystinuria, neuromuscular disorders like compression neuropathy, seizure with post ictal paralysis, familial hemiplegic migraine, head trauma, AHC [30].

Mikati MA et al., reported that 78% of the patients had some provoking factors like excitement, emotional stress, fatigue, trauma, temperature changes, loud noise, bright light, menstruation, and illness preceding their hemiplegic attacks [21]. Sweney MT et al., reported the trigger factors in to five major groups like environmental stress (75%), water exposure (61%), specific physical activities (50%), lighting (47%) and foods (10%). No such provoking factors were noticed by the mother in the present case [31]. Although AHC can be diagnosed clinically, it has become very essential now to confirm the diagnosis with genetic testing as it helps in early diagnosis and prognosticating the disease. It is often misdiagnosed as epilepsy or other disorders which mimics AHC like glucose transporter, glutamate transporter, neurotransmitter disorders, mitochondrial disease like Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and hemiplegic migraine [32]. AHC is a heterogenous disorder with various phenotypes which can be correlated with the genetic mutations affecting the various neuronal networks leading to dysfunctions of the nervous system with paroxysmal and non paroxysmal features.

Management of AHC cases includes treating the acute episodes and preventive therapy for reducing the severity, frequency, and duration of each episode along with multidisciplinary care for disabilities. Treatment of acute attacks involves removing the trigger factors and sleep stimulation. Neville BG and Ninan M, have stated the use of melatonin for early sleep induction but further experimental studies should be conducted to study the safety and efficacy of the drug in children [28]. Various treatment options like flunarizine, ketogenic diet, topiramate, methysergide, amantadine, aripiprazole, haloperidol, triheptanoin steroid, oral adenosine triphosphate, coenzyme Q, acetazolamide have been reported in the literature with the various success rates [33]. The most widely used drug option among these is flunarizine which is reported to be effective in 78% of patients [21]. The index patient also had good improvement with a reduction in frequency and severity of attacks after starting flunarizine.

CONCLUSION(S)

Alternating hemiplegia of childhood is primarily a neurological disorder with hemiplegic episodes occurring as a predominant feature associated with autonomic nervous system dysfunction, musculoskeletal disorders, cognitive dysfunction and several other features. Though, it can be diagnosed clinically, genetic test plays a major role in confirming the disease early, especially in AHC disorders presenting with atypical features or unusual presentation. Also, better knowledge of genetic studies provides a platform for exploring newer therapeutic options. Thus, genetic testing not only helps in early diagnosis, but also helps in prognosticating the disease and also better understanding of the spectrum of disorders associated with different gene mutations.

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