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Case Report

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ATP1A3 Gene Mutation Causing Alternating Hemiplegia of Childhood: A Rare Case Report and Literature Review

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Abstract

Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder characterized by recurrent attacks of hemiplegia affecting either side of the body, oculomotor and autonomic disturbances, movement disorders, and progressive cognitive impairment. Herein we reported a case who presented with developmental delay, abnormal eye movement, dystonic attack, episodes of alternating hemiplegia, and multifocal seizures. Investigations performed including, MRA of the brain, EEG as well as metabolic evaluation, were normal. A genetic study revealed a mutation in the ATP1A3 gene (c.2878G>A) associated with AHC-2. Based on history, examination, and genetic study, a diagnosis of Alternating hemiplegia of childhood was ascertained. *[Journal of National Institute of Neurosciences Bangladesh, January 2024;10(1):70-74]*

Keywords: Alternating hemiplegia of childhood, dystonic spell, hemiplegia, ATP1A3 gene

Introduction

Alternating hemiplegia of childhood (AHC) is a severe neurological disorder with infantile-onset recurrent episodes of hemiplegia on either side of the body[1]. It was first described by Verret and Steele in 1971. Although its incidence is increasing gradually, often easily missed until the patient has been referred to a tertiary center[2]. The annual incidence is less than 1 in 100,000 newborns. In alternating hemiplegia of childhood, a complex phenotype combines paroxysmal non-epileptic episodes and epileptic seizures often triggered by contact with water, changes in temperature, and physical or psychological stress[3]. The clinical signs often follow a unique pattern and clinical progression tends to occur in sequential distinctive phases. Features of AHC are various and include developmental delay/intellectual disability (DD/ID), epilepsy, autonomic dysfunctions, abnormal eye involvement, movement disorders, ataxia, dystonia, and choreoathetosis[4]. Persistent neurologic disorders are common sequelae[3]. Specific diagnostic criteria for AHC, named "Aicardi criteria," were first proposed in 1993. Since then, the original criteria were periodically updated[5].

Case Presentation

A 4-year-5-month-old developmentally delayed girl presented with episodic hemidystonia and abnormal eye movement since 7 months of age. Thereafter she also developed recurrent attack of hemiparesis on each side of the body alternately or sequentially at an interval of 1 to 2 months. Dystonia was often associated with hemiparesis. Both disappeared with sleep and resumed 30 minutes after awakening. Initially, in between the attack, she remained completely well but over time both the duration and severity worsened. She also experienced focal to bilateral tonic-clonic convulsion at 2 years of age, which occurred one to two months interval and persisted for one to five minutes. There was no history of headache, visual impairment, diplopia, respiratory distress, unconsciousness, vomiting, hiccough, skin rash, or abnormal body odor. On examination, she had a borderline intellectual disability, dysarthric speech, spastic quadriparesis, and dystonia. MRI revealed a choroid fissure cyst (Figure I), and MRA (Figure II) was

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normal. The basic metabolic screening panel of blood and urine, serum and CSF lactate, CSF to blood glucose ratio and EEG findings were within normal limits. Genetic study revealed mutation in the ATP1A3 gene

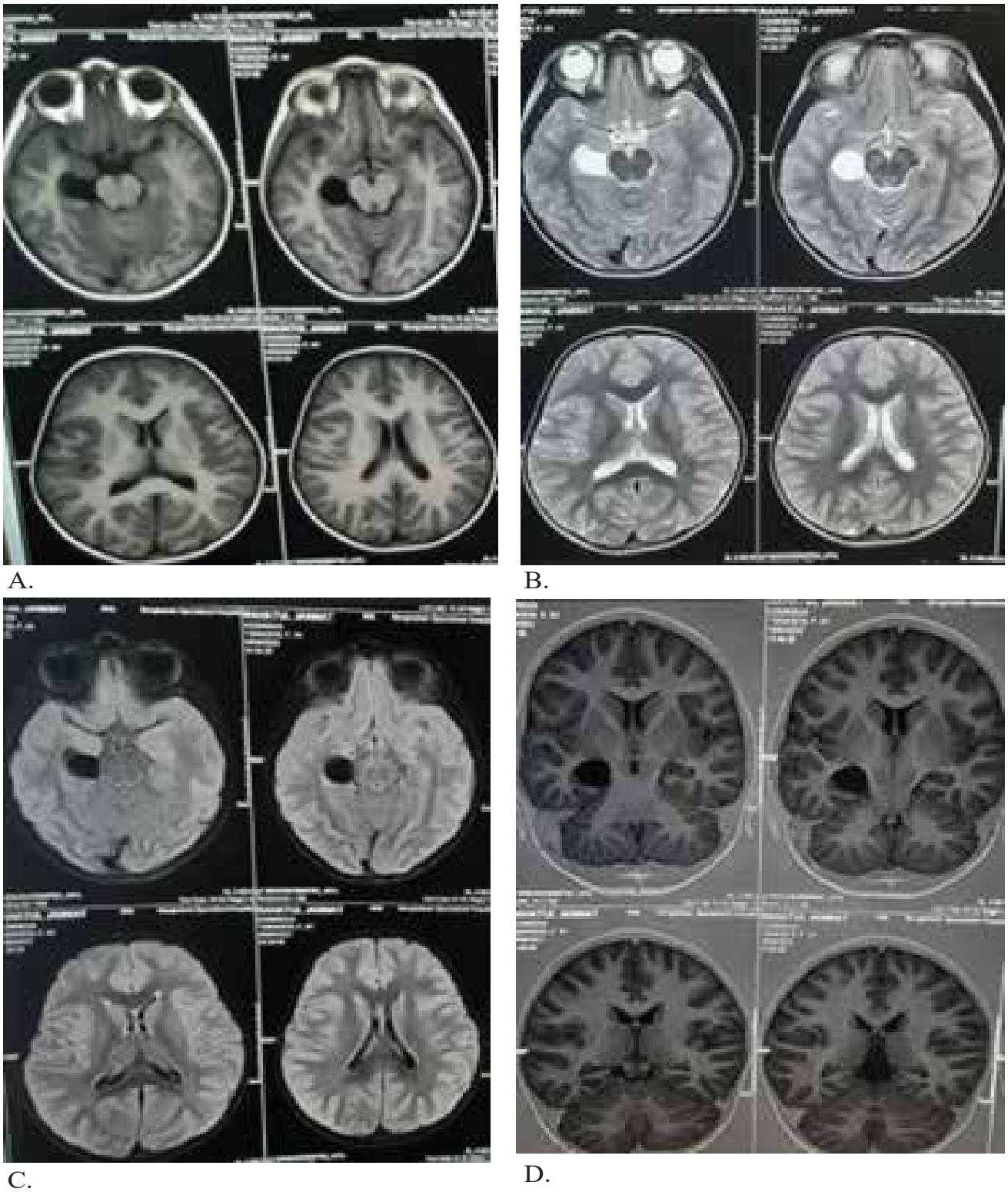

Figure I: Showing MRI of Brain A.T1 sequence showed hypointense cystic area in right media temporal region resembling choroid fissure cyst, B. T2 sequence showed hyperintense area in right medial temporal area, C and D showed FLAIR and Coronal section cystic lesion in same area.

(c-7828G>A) in exon 21. Based on history, clinical examination, and genetic study a diagnosis of Alternating hemiplegia of childhood was established. She was treated with flunarizine, clobazam, trihexyphenidyl, and anticonvulsant drugs. Her duration and severity of hemiplegic and dystonic spells were improved with these medications.

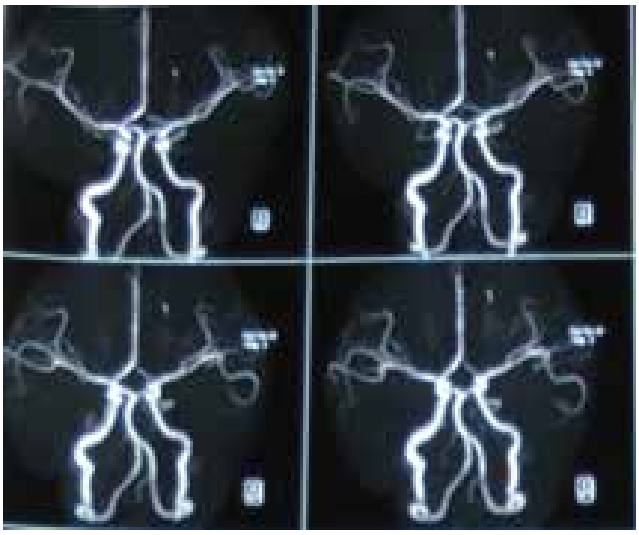

Figure II: Showing MRA of Brain Shows No Abnormality

Discussion

The reported case has the typical clinical features of alternating hemiplegia of childhood which fall within the diagnostic criteria for the disorder. The clinical course of patients with alternating hemiplegia of childhood is complex and evolves in three distinct phases. Phase one begins during the first few months of life and continues for 1 year. In this phase the most common features consist of unilateral nystagmus, ocular deviation, dystonic spells, and developmental delay. Phase two lasts from the age of one to five years, in which the hemiplegic spells become more typical, with a possible frequency of several times each month, and with a duration of several days or even weeks. In this phase, abnormal movements, dystonic attacks, and choreoathetosis are frequently observed. Phase three is represented by fixed neurologic deficits and obvious ID. In this phase, dystonic and hemiplegic episodes become less frequent and less severe[4]. Our patient developed abnormal eye movement and dystonia at 7 month and hemiplegic episodes at 10 months of age. In alternating hemiplegia of childhood, up to 50.0% of patients manifest generalized tonic-clonic seizures, and a subset of patients report generalized headaches that may or may not accompany episodes[6]. Our reported case has no headache but faced seizures at 2 years of age. We diagnose the reported case at phase three stage when she has already developed motor and cognitive deficit.

The last updated Aicardi's criteria for AHC[3] are onset of paroxysmal events before 18 months of age, repeated bouts of hemiplegia involving the right and left sides of the body during some attacks, episodes of bilateral hemiplegia or quadriplegia starting either as a generalization of a hemiplegic episode or as bilateral from the start, other paroxysmal disturbances including tonic/dystonic attacks, nystagmus, strabismus, dyspnea, and other autonomic phenomena occurring during hemiplegic bouts or in isolation, immediate disappearance of all symptoms upon sleep, with probable recurrence of long-lasting bouts, 10 to 20 min after awakening and evidence of developmental delay, intellectual disability, neurological abnormalities, choreoathetosis, and dystonia or ataxia; and Not attributable to other disorders.

The pathophysiological mechanism of alternating hemiplegia of childhood remains unclear at present. The clinical signs and symptoms of the syndrome suggest that there is cortical involvement as manifested by developmental delay and basal ganglia involvement as well as evidenced by the extrapyramidal symptoms. Epileptic seizures may develop due to cortical pathology. Intermittent episodes of hemi-or quadriplegia may be due to intermittent exacerbations of a possible defect affecting several brain areas, such as the frontal lobe, basal ganglia, internal capsule, brainstem, and, at times, possibly the entire cerebral hemisphere[7].

High clinical suspicion is needed for early diagnosis. The diagnosis of alternating hemiplegia of childhood is mainly clinical but may be supported by molecular analysis. Neuroimaging often shows no abnormality. EEG findings may be normal or may show epileptiform discharges or focal slowing during attack[2]. MRI of brain of our patient has revealed a choroid fissure cyst which may not be related to the disease. MRA of brain and EEG have got no abnormality. We also exclude glut-1 deficiency syndrome, mitochondrial disorder, organic aciduria, homocystinuria, urea cycle disorder and vascular disorders. Thereafter we go for whole exome sequencing by which genetic diagnosis is made.

Although alternating hemiplegia of childhood is an autosomal dominant disorder, the majority of cases are sporadic or de novo mutations[6]. Relevant

etiopathogenetic role in AHC is linked to mutations in ATP1A2 (AHC-1; OMIM#104290) and in ATP1A3 genes (AHC-2; OMIM#614820), respectively which encode two different alpha subunits of the Na+ /K+ ATPase transmembrane ion pump. ATP1A3-related other neurologic disorders are rapid-onset dystonia-parkinsonism (RDP), cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS)[8], early infantile epilepsy with encephalopathy (EIEE) and the recurrent encephalopathy with cerebellar ataxia (RECA) phenotype[5]. ATP1A3 mutations account for more than 70.0% of cases of AHC[4]. In particular, three hotspot mutations account for about 60% of all cases. Specifically, the p.Asp801Asn variant has been found to cause 30.0% to 43.0% of all cases, p.Glu815Lys is responsible for 16.0% to 35.0% of cases and p. Gly947Arg accounts for 8.0% to 15.0%[4]. These three mutations are associated with different clinical phenotype in terms of symptoms, severity and prognosis. Our patient has revealed mutation in the ATP1A3 gene (c-7828G>A) in exon 21, phenotypically correlates to alternating hemiplegia of childhood-2. The location of ATP1A3 mutations along the coding sequence shows a genotype–phenotype correlation of the ATP1A3 clinical spectrum. Only specific mutation particularly near the transmembrane domains and consequently protein alterations result in alternating hemiplegia of childhood[9].

Acute management of the disease aims to avoid or minimize triggers to reduce symptoms during an attack, as well as facilitate relaxation and sleep, which can halt or shorten an attack. Buccal midazolam, chloral hydrate, and rectal diazepam are used during episodes to promote sleep and end the attacks. Flunarizine is a calcium channel blocker used in preventive therapy. It is a nonselective calcium channel blocker. Flunarizine can reduce the frequency, severity, and duration of dystonic and hemiplegic spells in alternating hemiplegia of childhood. Flunarizine dosing ranges from 5 to 20 mg/day. Whether flunarizine alters the long-term prognosis of the disease is unknown[1,10-11]. Antiepileptic drugs were mostly ineffective to treat symptoms other than seizures. Topiramate was the only drug able to influence the severity of alternating hemiplegia of childhood in some patients. We have administered Flunarizine, Trihexyphenidyl, Sodium valproate and clobazam. She is now seizure free for the last 2 months and the frequency and duration of hemiplegic and dystonic spells are decreased.

Conclusion

Alternating hemiplegia of childhood is a complex condition with diverse clinical pictures and understanding the natural course, prognosis and expectance is very crucial for patients' care, clinicians, and care-givers. The prognosis is significantly influenced by the age of onset, and especially early occurring hemiplegic spells. Its' diagnosis and management require a multidisciplinary team that addresses all aspects of complex disease and the needs of the patient and family. Active clinical and basic science research and collaboration among centers are needed to deepen the understanding of this disorder and to better treat it.

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Contribution to authors: Happy RA, Debnath B, Saha NC conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript.Happy RA, Debnath B involved in the manuscript review and editing. All authors read and approved the final manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Consent for publication: Informed consent was taken from a patient guardian. All methods were performed in accordance with the relevant guidelines and regulations.

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