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SHORT COMMUNICATION

Alternating Hemiplegia in a Child Misdiagnosed as Intractable Epilepsy Successfully Treated with Aripiprazole: A Case Report

Hémiplégie alternante diagnostiquée chez une enfant comme une épilepsie rebelle et traitée avec succès par l'Aripiprazole. A propos d'un cas

E. V. Badoe

ABSTRACT

BACKGROUND: **Alternating hemiplegia of children is a rare neurological disorder that in its characteristic form has few differential diagnosis. The diagnosis of intractable seizures is difficult to avoid for physicians not aware of the disease.**

OBJECTIVE: **To describe the clinical characteristics of Alternating Hemiplegia of Childhood (AHC), and response to various drugs**

METHODS: **A Ghanaian child with AHC was followed up for three years at the Neurology Clinic, Korle Bu Teaching Hospital, Accra. Her characteristics including EEG and MRI findings were documented. She was severely unsuccessfully treated as an epileptic. Further clinical re-evaluation provided clues to the diagnosis of aaalternating hemiplegia of childhood.**

RESULTS: **The child, a female patient, was seen within the first week of life. The initial complaints were abnormal eye movements, and subsequently recurrent hemiplegic episodes, that started at age two and lasted hours to days. Attacks occurred at a frequency of about three per month and lasted from several hours to three days. An established trigger was bathing with cold water. Sleep relieved symptoms. The child had evidence of global developmental delay and neurological abnormalities including ataxia. EEG and MRI were both reported as abnormal. She experienced recurrent seizures. Topiramate and several anti-convulsants were not helpful but aripiprazole reduced the frequency of attacks.**

CONCLUSION: **The case highlights the fact that AHC starts very early in life and is commonly misdiagnosed as epilepsy .It can coexist with epilepsy and abnormal MRI findings. Aripiprazole appears effective in its treatment. WAJM 2011; 30(2): 140–144.**

Keywords: **lternating hemiplegia of childhood (AHC), abnormal ocular movements, aripiprazole, epilepsy, misdiagnosed.**

RÉSUMÉ

CONTEXTE: l'hémiplégie alternante des enfants est une affection neurologique rare qui, dans sa forme caractéristique, a peu de diagnostic différentiel. Le diagnostic de crises épileptiques réfractaires est difficile à éviter pour les médecins qui méconnaissent la maladie.

OBJECTIF: Décrire les caractéristiques cliniques de l'hémiplégie alternante de l'enfance (HAE) et sa réponse à divers médicaments.

METHODES: Une enfant ghanéenne avec HAE a été suivie pendant trois ans à la clinique neurologique du Centre hospitalo-universitaire de Korle Bu à Accra. Les caractéristiques cliniques et paracliniques (EEG et IRM) de son HAE ont été documentées. Elle a été traitée sans succès comme un épileptique. Une re-évaluation clinique plus poussée a permis de poser le diagnostic d'une hémiplégie alternante de l'enfance.

RÉSULTATS: L'enfant, de sexe féminin, a été vu dans la première semaine de sa vie. Les premières plaintes étaient des mouvements oculaires anormaux. Par la suite des épisodes récurrents d'hémiplégie ont débuté à l'âge de deux ans et duraient de quelques heures à quelques jours. Les crises survenaient à une fréquence d'environ trois par mois et duraient de quelques heures à trois jours. Un facteur déclenchant connu était le bain à l'eau froide. Le sommeil allégeait les symptômes. L'enfant avait à l'évidence un retard global de développement et des anomalies neurologiques dont une ataxie. L'EEG et l'IRM étaient tous anormaux. Elle faisait des crises récurrentes. Plusieurs anti-convulsivants dont le Topiramate n'ont pas été efficaces. L'aripiprazole a réduit la fréquence des crises.

CONCLUSION: Ce cas illustre bien que l'HAE commence très tôt dans la vie et est souvent diagnostiquée à tort comme une épilepsie ; l'HAE peut coexister avec l'épilepsie et des anomalies à l'IRM. L'aripiprazole paraît efficace dans son traitement. **WAJM 2011; 30 (2): 140-144.**

Mots-Cles: Hémiplégie alternante de l'enfance (HAE), Mouvements oculaires anormaux, Aripiprazole, Epilepsie mal diagnostiquée.

Department of Child Health, University of Ghana Medical School, Ghana.

Abbreviations: AHC, Alternating Hemiplegia of Childhood; **AOM,** Abnormal Ocular Movements; **EEG,** Electroencephalogram; **MRI,** Magnetic resonance image.

Correspondence: **Dr. Ebenezer V. Badoe,** Department of Child Health, University of Ghana Medical School, Ghana. E-mail: benbaboe@yahoo.co.uk Tel: 0244560828 (Mobile).

INTRODUCTION

Alternating hemiplegia of childhood (AHC) is a rare neurological disorder that goes undiagnosed in many cases. It has a prevalence of about one case per million.[1] It was first described by Vernot and Steele in 1971.[2] Within this diagnosis appreciable differences in clinical symptoms have been reported and it is common for diagnosis to be delayed or missed.[3] Although this patient had epilepsy, the condition appears to be distinct from epilepsy judging from the non response to anti epileptic drugs. The literature does not report abnormal MRI findings in this condition even though it is known to exist with true epilepsy.[4] This report suggests abnormal MRI findings are a possibility. This condition has a significant potential for long term disability and is unreported in the West African literature.

CASE REPORT

A five and a half-year-old female patient was first seen at the Paediatric Emergency Department Korle Bu Teaching Hospital at the tender age of 10 months. She was born the third child of a non- consanguineous marriage at term following an uneventful pregnancy. On the third day after delivery at a private clinic, she was noted to have episodes of eye deviation. She was admitted for over a week and treated with phenobarbitone. In the intervening period from the neonatal period to ten months, the mother had noticed episodes of lateral eye deviation (nystagmus). Prior to the first admission, she was noticed to be stiff in the limbs, accompanied by eye twitching intermittently over a week. She was started on phenobarbitone. Her head circumference was documented as 42.8cm (50^{th} centile). Her cranial CT scan and EEG were also normal. At 12 months of age, she was rushed in semi-conscious with .weakness affecting the right side of the body, excessive sweating and dystonic posturing. She was treated as a case of status epilepticus. Over a three year period there were several admissions for "status epilepticus". These were characterised by limb stiffening, tonic clonic seizures and very rarely with accompanying weakness. On three occasions malaria parasites were found. She also had three documented urinary tract infections due to E Coli over the period. On several other admissions, documented findings were mainly of weakness on one side, most commonly the right. This was very often accompanied by excessive sweating. Fundus examination was normal and neurological examinations after recovery was also normal. Blood pressure, echocardiogram, cerebrospinal fluid analysis, sickle cell screen, renal and liver function tests were all recorded as normal. Serum lipids and creatinine phosphokinase estimations were also normal.

A repeat EEG was done and this was normal. She took several medications including combinations of phenobarbitone, phenytoin sodium valproate, clonazepam, prednisolone and lamotrigine. These had no effect at all on her seizure frequency and several side effects were noted. Hair loss was attributed to sodium valproate and significant behavioural difficulties to clonazepam. Neurological examination in between admissions was normal except for delayed development. The poor response led to an MRI request and a repeat EEG. The EEG this time was abnormal showing epileptiform changes. There were well formed and symmetrical 8–9/sec alpha rhythms and a few scattered theta transients which transformed into bursts of generalised sharp slow waves during overbreathing. Photic stimulation was normal.

The MRI scan was done and films sent to the Department of radiology, Kings College Hospital, London. The report issued on the 24^{th} of September, 2009 noted that the right hippocampus was small and of high signal, most evident on the FLAIR images. Myelination in the anterior temporal lobe was correspondingly delayed in comparison to the left. The left hippocampus was said to be suspiciously small and bright on the T2 weighted and FLAIR images. The summary of the formal report suggested that there was evidence of right hippocampal sclerosis and a suggestion of left hippocampal sclerosis (Dr A. Baker, personal communication). On the basis of this report it was decided her diagnosis was epilepsy and she was started on Topiramate. She took this drug for several months without any beneficial effect.

In view of the poor response to all the conventional anti-epileptic drugs over two years the mother was invited to the neurology clinic for a special session to retake the history and document any subsequent clinical observations. She then revealed three key observations that led to the diagnosis of AHC. The first was noting that her child screamed a lot, as if in pain during attacks. She had noted weakness during attacks shifted from side to side alternately and very occasionally with whole body weakness of all four limbs.. This could last from hours to about three days. They occurred at a frequency of about 10–12 per month. Lastly in response to a direct question, she admitted that symptoms always disappeared on falling asleep. Attacks never occurred during sleep or for up to 30 minutes after awakening. She had noticed an advantage in feeding her at such times after sleeping when she appeared perfectly normal. Another interview a week later revealed that bathing her in cold water triggered attacks on some occasions and the mother was now using hot water only to bath her. There was no family history of migraine, epilepsy or history of a similar disease.

A diagnosis of AHC was made at the age of four and half years on the basis of clinical episodes with complete recoveries and the characteristic features of alternating weakness and disappearance of all symptoms on falling asleep. An attempt was then made to procure flunarazine from Canada (only worldwide source) without success. Chloral hydrate and melatonin were prescribed to induce sleep during attacks but this was found not to be beneficial.

Aripiprazole was procured from the UK following a recent case report of its successful use in AHC by Haffejee S and Santosh P[5] who believed that an agent modulating both dopamine and histamine could be a good alternative to flunarazine. She started the drug in very small doses of 1.25mg a day at age five. The mother noticed a distinct decrease in frequency, and severity .of attacks. They now lasted for short periods when hemiplegic

Table 1: Clinical, Electrophysiological and Neuro-imaging Data in Patient

Characteristic	Remarks
Age at onset	First week of life
Initial presentation	Abnormal ocular movements, dystonic posturing, hypotonia
First hemiplegic attack	30 months. Alternating. Quadriparesis rarely with loss of consciousness
Trigger factors	Spontaneous, bathing in cold water
Epilepsy	Simultaneous attacks of status epilepticus with hemiplegic attacks very occasionally. Attacks appeared distinct
Duration of attacks	Hours to maximum 3 days
Learning disability	Moderate to severe
EEG	Initial EEG normal. Second abnormal. Generalised sharp slow waves during overbreathing
Neuro imaging	CT scan normal. MRI Abnormal report -suggested hippocampal sclerosis

EEG, Electroencephalogram; CT, Computerised tomography; MRI, Magnetic resonance image

Table 2: Accepted criteria for Alternating Hemiplegia of Childhood.[10]

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 generalization 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, mental retardation, neurological abnormalities, choreoathetosis, dystonia, or ataxia
7. Not attributable to another disorder

attacks occurred. She had apparently stopped all the anti convulsants on her own several months ago when she noted they were not beneficial except for phenobarbitone. The patient was now over five years old and had evidence of global developmental delay. She had just started to walk independently with an ataxic gait. Using the schedule of growing skills 2,[6] a developmental assessment toolkit to assess her developmental profile she demonstrated significant delays in her expressive/receptive language skills, fine motor skills, and gross motor skills functioning at the two year level for an age of five. Recent parental report confirmed abnormal ocular movements characterised by repetitive jerking of the left eye in an upward and sometimes lateral direction (rapid upbeat nystagmus) in response to taking her out into sunlight from a room. There was rapid blinking and the eyes appeared wide open. Hemiplegic attacks had become less severe (1–2 per month) and infrequent following aripiprazole therapy and she was much happier with her child who then played more. She made two to three word sentences and her speech was dysarthric. The clinical data are summarized in Table 1.

DISCUSSION

The diagnosis of AHC depends on the characteristic clinical features. The presence of epileptiform features initially was misleading in this patient. This case had an MRI report suggesting pathology associated with epilepsy. Epilepsy coexists in about 50% of AHC patients and these seizures are usually quite distinct from AHC attacks in their manifestations, although they may occur simultaneously. Neville *et al*[1] argue that if the phenotype is typical but there is an abnormal finding shown by MRI, they would still make a diagnosis of AHC. This patient had hippocampal sclerosis. Although not commonly found in children with intractable epilepsy younger than 10 years of age, identification of these abnormalities is a powerful indicator of the zone of epileptogenesis.[7] Whether hippocampal sclerosis is a cause or an effect of the repetition or prolongation of epileptic seizures is still debated.[8] The first phase of the clinical course was mainly abnormal eye movements and dystonic episodes starting soon after birth. Hemiplegic spells started after the first year of life and occurred with generalised convulsive status epilepticus very occasionally. There was no well defined aura in the history suggesting a cortical onset or seizures beginning with a focal onset. Examination findings in the post-ictal period were normal ruling out Todd Paresis or partial seizures with secondary generalisation. The main trigger factors identified here was bathing with cold water. The literature reports exposure to cold, emotional stress, fatigue, bathing, hypothermia and hyperthermia.[1] The child was globally delayed in development with abnormal ocular motility dysfunction. Abnormalities of the blink reflex suggest involvement of the brainstem.[9] As at last visit, there was global developmental delay and neurologic deficits. The seven accepted criteria for the diagnosis of Alternating Hemiplegia of Childhood are listed in Table 2.

The clinical findings in 30 personal cases of Aicardi are listed in Table 3[11] (reproduced with permission).

Aetiology and Genetics

The pathophysiology of AHC is currently unknown and it has been considered to be a migraine variant, a movement disorder, or a form of epilepsy.[12] More recently, suggested aetiologies have included channelopathy, mitochondrial dysfunction, and cerebrovascular dysfunction.[13,14] The paroxysmal nature of hemiplegic attacks suggests that it could be a channelopathy which are typically unpredictable events and often precipitated by external conditions.[15] Genetic studies are still ongoing and new hypothesis being tested.[16]

Treatment Options

Therapies for this condition come mainly from case reports and only one study has been a randomized control design.[17]

Flunarazine: This condition is commonly treated with flunarazine, a calcium channel blocker. Flunarazine reduced the duration, severity, and frequency of

Table 3: Clinical Findings in 30 Cases of Alternating Hemiplegia of Childhood

Characteristic	Finding
Sex	17 Girls, 13 Boys
Age of onset of attacks	3 days -13 months
Onset with tonic attacks	11
Paroxysmal Features	
*Onset with tonic attacks	14
Onset with bouts of hemiplegia	5
*Hemiplegic episodes:	30 (shifting bilateral involvement in 25)
*Tonic attacks	27(unilateral in all cases; bilateral attacks in 9)
*Paroxysmal nystagmus	23(unilateral in 17)
Paroxysmal strabismus	11
*Screaming, apparent pain	28
*Vasomotor disturbances	23 (pallor, flushing, coldness, sometimes unilateral)
*Disappearance with sleep	30
Paroxysmal respiratory disturbances	14 (dyspnoea, cyanosis, may be life threatening)
Nonparoxysmal Features	
*Mental retardation (learning difficulties)	25
Neurological signs	
Choreoathetosis	29
*Ataxia	27
Pyramidal tract signs	9

*** Key areas:** *The patient described showed all the clinical features in Table 2 and in key areas for Table 3 listed with an asterisk. The presence of all these diagnostic criteria is not necessary to make the diagnosis in an otherwise typical case.*

hemiplegic episodes in 78% of the 27 patients treated with flunarazine in a cohort of 44 patients.[18] This drug could not be obtained for our patient as only one single pharmacy was licensed to sell the drug in Canada.

Topiramate: Topiramate has been found effective in a few children.[19] This drug was taken for several months and stopped by the mother on account of inefficacy and side effects. A peculiar side effect of excessive fear of ants was noted and the same phenomenon has been seen in three other patients treated by the author for epilepsy.

Other Drugs: Prednisolone (a course of six weeks), chloral hydrate and melatonin were not effective. Lamotri-gine, phenytoin, sodium valproate and clonazepam were not effective. Phenobarbitone appeared useful for clinical seizures.

Aripiprazole: Aripiprazole is a novel atypical antipsychotic with partial dopamine agonist activity. It is a dopamine system stabilizer acting as an agonist where levels are low and an antagonist where levels are high. It acts as a partial agonist at dopamine D2 and serotonin 5 HT 1A receptors and is an antagonist at 5HT2a, 5HT2c, alpha adrenergic and H1 receptors [20].side effects in the paediatric population include sleepiness, weight gain, extra pyramidal disorder, and headache.[21] This patient has made a significant response to aripiprazole and its use in AHC is worth exploring in future research.

Conclusion

The characteristics exhibited by the patient suggests that AHC starts early dominated by abnormal eye movements and the second phase by hemiplegic spells and developmental delay and later by fixed neurological deficits. This girl had coexistent epilepsy with an abnormal MRI consistent with focal epilepsy. This has not been previously reported as a finding in AHC but this case showed that if coexistent with epilepsy MRI could be abnormal. Anticonvulsants were not effective. Aripiprazole was modestly effective. There is a lack of awareness of this condition and this report should make it easier for physicians not familiar with the disease to make a diagnosis.

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