CASE REPORT

Alternating Hemiplegia of Childhood Caused by *ATP1A3* Mutations: A Report of Two Cases

Guange Yang*, Zhongli Zhao, Yang Yang, Li Lin,
Conglei Song, Xiaocui Wang, Bin Yang

Medical Department of Neurology, Anhui Provincial
Children's Hospital, Hefei 230053, China

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Abstract Alternating hemiplegia of childhood is a rare neurodevelopmental disorder. Most cases are reported as sporadic disorder due to *de novo* variants, and few with family members involved. Two boys were hospitalized due to epileptic seizures occurred initially at age of six to seven months. During the course of the disease, there were repeated episodes of paroxysmal weakness or paralysis affecting one side of the body. Genetic testing showed that both patients carried heterozygous missense mutations in the *ATP1A3* gene (OMIM: 614820): c.3025 (exon 22) A>G (p.K1009E) and c.2443 (exon 18) G>A (p.E815K). Flunarizine can significantly improve the paroxysmal motor symptoms of pediatric patients with alternating hemiplegia.

ALTERNATING hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder characterized by repeated episodes of muscle weakness or paralysis, often affecting one side of the body. Most cases are sporadic, and few cases have family history. In 1971, Verret and Steele^[1] first described the common characteristics of eight pediatric patients with AHC, such as onset age younger than three years, paroxysmal alternating unilateral paralysis, remission within 24 hours, intermittent headaches and epileptic seizures. Residual persistent neurological symptoms include mental retardation, choreoathetosis, unilateral dystonia, and ataxia but not persistent hemiplegia.

AHC has a prevalence of 1/1 000 000.^[2] Because of the epileptic seizures and developmental disorders in language, mental capacity, and motor skills, AHC is often misdiagnosed as cerebral palsy or epilepsy, and its clinical prevalence is thus underestimated. AHC has complex clinical manifestations and poor prognosis. Therefore, early diagnosis will help to reduce erroneous treatment and improve prognosis.

We reports two boys with AHC carrying *ATP1A3* mutation treated in our hospital. This study was approved by ethics committee of our hospital and written informed consents were given by their parents. Moreover, we searched publicly available databases for relevant articles from China and abroad and retrospectively summarized its clinical manifestations, genetic mutations, and treatment.

CASE DESCRIPTION

Case 1: A one-year-old boy was admitted

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*Corresponding author Tel: 86-551-62237720, E-mail: guangeyang@163.com

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because of recurrent seizures for six months. The first seizures occurred at six months of age, manifesting as generalized tonic-clonic seizures (GTCs) for 30 minutes. Remission was achieved after medication, with a return to normal after waking. A similar episode occurred at eight months of age and a third episode at 11 months. Remission was achieved after repeated intravenous injection of midazolam, and the mental condition between episodes was acceptable. Starting at eight months of age, paroxysmal muscle weakness on one side of the body occurred 3-4 times per month, and the weakness alternated from one side of the body to the other. The affected limbs were weak, but they improved on their own in 3-4 days. The boy had a normal birth history, and his developmental history was as follows. At seven months old, the boy could hold his neck straight, and could roll over at eight months. At one year of age, he could not sit up by himself for extended periods but could pronounce the sounds "ba" and "ma". There was no family history of paroxysmal disease. Significant positive signs included: languid, slow responses; head circumference of 44.5 cm; closed anterior fontanelle; two circular pupils of equal size (3.0 cm in diameter) and sensitive to light; inability to sit up by himself or speak; muscle strength grade IV, with low muscle tone; positive Babinski reflex. There were no abnormalities detected by routine blood tests, biochemical tests, or inherited metabolic disease (IMD) screening in blood and urine. Although his elec-

troencephalogram (EEG) at disease onset was normal, EEG at 4 months after onset showed generalized background slowing (4-5 Hz) and one focal seizure originated at the left temporal region while awake (**Fig. 1**). Cranial magnetic resonance imaging (MRI) revealed no abnormalities.

Oral administration of sodium valproate after the first seizures was ineffective. After diagnosis (1 year old), sodium valproate was stopped; flunarizine and topiramate were taken orally at doses of 2.5 mg BID and 25 mg BID, respectively. During follow-up, the boy at 2 years of age had poor mental capacity and severe fatigue under heat stress or physical exertion, but would return to normal the next day after rest. There were no seizures and no paroxysmal weakness on one side of the body. Signs of persistent developmental disorders in language and motor skills were present; food intake was low, and his weight was 10.5 kg. He was able to understand simple language, but was not an active speaker; he recognized his mother, had difficulty in standing and could hardly walk with assistance. There were no noticeable involuntary movements.

Case 2: A boy of eight months and four days old was admitted to our hospital on account of repeated seizures for more than twenty days. The manifestations of the first onset were as follows: sudden upward movements of the eyes while awake, loss of consciousness, perioral cyanosis, and tonic limb movements. The first episode lasted for more than 10 minutes, and

Figure 1. Electroencephalogram (EEG) changes of the two patients: A. Slow background in case 1. B. There is a focal episode in the wake-up phase, as characterized by binocular gaze and lip smacking, with a concomitant EEG in the left temporal region—high slow waves, mixed with sharp and spine waves in case 1. C. Discharge in the left temporal region involved the ipsilateral frontal region in case 1. D. Slow background in case 2. E, F. Asynchronous emission of slow and tip slow waves in bilateral occipital and posterior temporal regions during sleep in case 2.

he fell asleep after remission, without fever. Twenty days later, a similar episode occurred during nighttime sleep, lasting for approximately 3 minutes. In the previous two months, there were three episodes of recurrent paroxysmal paralysis on one side of the body. Each episode lasted for 0.5-4 days with spontaneous remission, and paralysis alternated from one side of the body to the other. The boy had a normal birth history, and his developmental history was as follows. At seven months of age, he could hold his neck straight. At eight months, he could not sit up by himself for extended periods, but could pronounce the sounds "ba" and "ma". There was no family history of paroxysmal disease. Significant positive signs were as follows: normal responses; head circumference of 44 cm; anterior fontanelle of 0.5 cm×0.5 cm, flat and soft; bilateral pupils were round and equal in size (3.0 cm in diameter) and sensitive to light; inability to sit up by himself or speak; muscle strength grade IV, with low muscle tone; negative Babinski reflex. There were no abnormalities in routine blood or cerebrospinal fluid tests, biochemical tests, or screening for IMD in blood and urine. Video EEG showed generalized background slowing (4-5 Hz) as well as asynchronous release of slow and sharp waves in the bilateral occipital and posterior temporal regions during sleep (**Fig. 1**). Cranial magnetic resonance revealed hyperintense patchy signals of the left parahippocampal gyrus on diffusion-weighted imaging (DWI) and apparent diffusion coefficient, but normal signals on T1 weighted imaging,

T2 weighted imaging and magnetic resonance angiography (**Fig. 2**).

One course of immunoglobulin therapy and oral administration of levetiracetam (symptomatic treatment) was not effective. Oral administration of sodium valproate was discontinued at the age of nine months and replaced with flunarizine and oxcarbazepine at doses of 5 mg QN and 0.0375 g BID, respectively. During follow-up at 2 years and 3 months, he still had seizures with the following manifestations: at the beginning of sleep (first several minutes), he screamed once because he was scared; his lips were cyanotic; the episode subsided after 1-2 minutes, and he then went back to sleep. There were 1-2 episodes monthly, with more episodes during hemiplegia. After taking flunarizine, the frequency and severity of paroxysmal hemiplegia episodes decreased from once a week to once a month. Paralysis that lasted 1-2 days before treatment, can relieved a few hours after treatment and significantly improved after sleep. Language development was delayed, and mental retardation was apparent. He could only pronounce the sounds "ba" and "ma" and only walk with assistance, but he had a normal weight.

Whole-exome sequencing

Whole-exome sequencing (WES) was performed for the patients' family members. For each family member (the patients and their parents), 2 ml of peripheral venous blood was collected for extraction of genomic

Figure 2. Cranial MRI of case 2 showing hyperintense patchy signals of the left parahippocampal gyrus on diffusion-weighted imaging (arrows, C, D) and apparent diffusion coefficient (E), but normal signals on T1 weighted imaging (A), T2 weighted imaging (B) and magnetic resonance angiography (F).

DNA using a Mini Blood Kit (Qiagen, Germany). The IDTxGen Exome Research Panel kit was used for exon capture and library construction. The Illumina Nova-Seq6000 platform was utilized to sequence exons in genome-wide coding regions. The captured target sequence was 51 Mb, and the overall sequencing coverage (20X and above) was 99%.

A heterozygous missense mutation in the *ATP1A3* gene was detected in both cases (**Fig. 3**). Case 1 carried c.3025 (exon 22) A>G mutation, which has not been reported; Case 2 carried c.2443 (exon 18) G>A, which has been reported. Neither of them has been included in databases of the 1000 Genomes (1KG), the Exome Sequencing Project (ESP), and the Genome Aggregation Database (GnomAD). Two types of software that analyzed the conservation of nucleic acids (GERP,

phyloP) and two protein predictions (SIFT, PolyPhen) all indicated that the mutations are pathogenic (**Table 1**).

DISCUSSION

Clinical diagnostic criteria and gene detection in AHC

Bourgeois *et al.*^[3] formulated the clinical diagnostic criteria for AHC in 1993: (1) onset age less than 18 months; (2) paroxysmal symptoms including tonic limb movements or dystonia, abnormal eye movements (nystagmus), and autonomic nervous symptoms, with or without hemiplegia; (3) repeated hemiplegic attacks involving either side of the body; (4) diplegia or quadriplegia, with hemiplegic attacks starting from one side and alternating to the other side or starting from

Figure 3. DNA sequencing results of *ATP1A3* mutations in the two cases based on first-generation sequencing. A. Case 1, heterozygous missense mutation of *ATP1A3*, c.3025 (exon 22) A>G. B. Case 2, heterozygous missense mutation of *ATP1A3*, c.2443 (exon 18) G>A. No mutation was found at these sites in the parents.

Table 1. Mutations in the *ATP1A3* gene in two pediatric patients

No.	Mutation	Report	Amino acid change	Source of mutation	Rs number	1000 Genomes/GnomAD/ESP	SIFT/PolyPhen	GERP	ACMG guideline
Case 1	c.3025A>G	Not	p.K1009E(NM_001256214)	de novo	None	NA/NA/NA	Damaging (0.001)/possibly damaging (0.651)	D (3.32)	Likely pathogenic (PS2+PM1+PM2+PP3)
Case 2	c.2443G>A	Yes	p.E815K (NM_152296)	de novo	rs387907281	NA/NA/NA	Damaging (0.001)/probably damaging (1.0)	D (3.69)	Pathogenic (PS2+PS1+PM1+PM2+PM+PP5)

GnomAD: Genome Aggregation Database; ESP: Exome Sequencing Project; ACMG: American College of Medical Genetics and Genomics; NA: not available.

both sides; (5) all paroxysmal symptoms disappearing during sleep, possibly reappearing after waking; (6) signs of speech and language developmental delays and other neurological abnormalities, including dystonia, choreoathetosis, and ataxia; (7) exclusion of other diseases, such as treatable IMD and Moyamoya disease.

In 2012, Heinzen and Rosewich *et al.*^[4, 5] found that *ATP1A3* is the primary pathogenic gene for AHC; hence, this disease can be diagnosed through molecular genetics. The *ATP1A3* gene is located on chromosome 19q13.2 and encodes the A3 subunit of Na⁺/K⁺-ATPase. The A3 subunit is mainly expressed in neurons. The retrieved literature showed that most mutations in the *ATP1A3* gene are *de novo*, with few familial mutations.^[6] Three hotspot mutations in AHC patients are p.D801N, p.E815K, and p.G947R. Among them, p.D801N mutation is the most common; p.E815K mutation results in more epileptic seizures and the most severe clinical manifestations.^[7-9] The parents of the two children in this study carried the wild-type gene, and there was no history of similar diseases in the two families, which was consistent with reports in the literature.^[6]

In our study, both cases met the above clinical diagnostic criteria 1, 3, 4, 5, 6, and 7, and *ATP1A3* gene mutations were detected in both cases.

Clinical features and treatment of AHC

The initial symptoms of AHC are mostly eye movement disorders, alternating hemiplegia, and epileptic seizures.^[7] Uchitel *et al.*^[10] reported 32 cases of AHC with epileptic-like seizures. Among them, 25.0% cases had epilepsy as the initial symptom, and 59.4% cases had drug-resistant epilepsy; successful vagus nerve stimulation therapy was performed in 5 of 6 cases. Video-EEG monitoring showed that stretches of nonepileptic loss of consciousness (with or without epilepsy) frequently occurred in patients. Brain MRI results of AHC patients at early stages are mostly normal, but they can change with age and are closely related to the severity of the disease. Patients with severe irreversible motor and mental deterioration often present progressive frontal lobe atrophy, diffuse cerebellar cortical atrophy, and severe hippocampal atrophy.^[11] Some AHC patients have significant autonomic dysfunction. In these patients, Q-T interval is shortened on electrocardiogram, and incidence of intraventricular conduction delay or incomplete right bundle branch block is significantly increased. Moreover, an abnormal

heart rhythm often occurs independently of epilepsy and hemiplegia.^[12]

There are very few atypical AHC cases, including onset age older than 18 months,^[7] early-onset epileptic encephalopathy with dystonia (no hemiplegia),^[13] paroxysmal hemiplegia accompanied by autism,^[14] obvious mental health symptoms with or without paroxysmal hemiplegia,^[15, 16] and catastrophic early life epilepsy in the newborn.^[17, 18] In general, vascular mechanisms are involved in the pathogenesis of AHC.^[19]

Regarding treatment plan for the acute phase, during hemiplegia attack, a child with mild symptoms should be kept in a quiet room, with reduced stimulation and awaiting spontaneous relief. If spontaneous relief is not possible, it is best to give oral midazolam, chloral hydrate or diazepam *via rectum* under pulse oxygen monitoring to promote sleep and end the attack. If child's condition is progressive or there're complications, child should be sent to a medical institute for observation or hospitalization. When epileptic seizures continue for more than 5 minutes, the same plan as above should be implemented.^[2]

To prevent attacks, flunarizine, a nonselective, voltage-dependent calcium channel blocker, can block sodium currents, thereby preventing high-frequency discharge by cortical neurons and reducing hyperexcitability of cortex. Flunarizine is used to improve hemiplegic pediatric patients with AHC. The efficacy of flunarizine in treatment of AHC patient carrying different genotypes does not show significantly different. The effective dose of flunarizine ranges from 5 to 20 mg/d, though it is unclear whether flunarizine can alter long-term prognosis of AHC. For coexisting epilepsy, drugs should be chosen according to type of clinical seizure.^[2] As it has been reported that topiramate has a good effect on epileptic seizures, migraine and hemiplegia in children with AHC, it can be used as the first choice or for children who do not respond to flunarizine treatment.^[20]

Based on basic researches, *ATP1A3* could give rise to multiple levels of pathophysiological changes, which could serve as target of AHC treatment. Mutations in *ATP1A3* can reduce ATPase function and pump function of Na⁺ and K⁺ exchange, thus increasing excitability of neurons. The effect of ATP therapy can act against the ATP_{ase} function reduction, and restore excitability of neurons. Inactivation of Na⁺/K⁺ ATPase pump can open N-type voltage-gated calcium channels and lead to increased intracellular calcium. Flunarizine

can act on Na^+/K^+ ATP_{ase} pump to reduce calcium influx into neurons. In addition, because inhibiting K_{ATP} channel of Na^+/K^+ ATP_{ase} pump on neurons can induce hyperexcitability of cells, ketone bodies, activators of K_{ATP} channel, may be beneficial to *ATP1A3* associated AHC. Moreover, multiple signal transduction pathways have been found to be modulated by Na^+/K^+ ATP_{ase} , but no drug is clinically available up to now. *ATP1A3* mutations induced excitatory/inhibitory imbalance in signal transduction network may increase excitability of neurons, which, therefore, consequently may result in seizures or a predisposition to spreading depression. Benzodiazepines might have the ability to restore the balance. There are ongoing open-label clinical trials and one controlled study of triheptanoin for AHC therapy.^[21]

Other drugs have also proven to be effective, such as aripiprazole, chloral hydrate, niaprazine, acetazolamide, melatonin, olanzapine, 5-hydroxytryptophan, amitriptyline, and mirtazapine, but the mechanisms remain unknown.^[8, 22, 23]

In this study, episodic hemiplegia improved significantly after application of flunarizine. For the two patients, Case 1 was treated with topiramate and flunarizine, and no hemiplegia or epileptic seizures were observed; Case 2 received flunarizine treatment without topiramate, and hemiplegia was alleviated, but epileptic seizures were not controlled. Therefore, it is speculated that topiramate combined with flunarizine may be helpful for children with AHC. The difference in therapeutic effect of the two cases may be attributable to difference in *ATP1A3* mutation sites.

Other clinical phenotypes correlating with *ATP1A3* gene

In addition to AHC, clinical phenotypes associated with *ATP1A3* mutations are rapid-onset dystonia-Parkinsonism (RDP),^[24-28] cerebellar ataxia, areflexia, optic atrophy and sensorineural hearing loss syndrome (CAPOS),^[29, 30] and recurrent encephalopathy and cerebellar ataxia syndrome (RECA),^[31-35] there are many atypical cases with overlapping phenotypes.^[36-39] Therefore, it is believed that phenotypes of nervous system dysfunction caused by *ATP1A3* mutations are associated with a wide spectrum of diseases.

Conclusions

This study reports two pediatric boys with AHC, as confirmed by genetic testing. Case 1 carried a pre-

viously unreported mutation, c.3025 (exon 22) A>G (p.K1009E), which enriches the reported profile of *ATP1A3* mutations. The patient had seizures at age of 6 months and repeated hemiplegic attacks at 8 months. Case 2 carried a c.2443 (exon 18) G>A (p.E815K) mutation, which confirmed the mutation hotspot in this gene. The patient had onset of hemiplegia at the age of 6 months and epilepsy at 7 months. Both patients had developmental delays in cognition and motor skills. In addition to prominent paroxysmal hemiplegia, epilepsy and general developmental retardation, we should pay attention to some paroxysmal symptoms, such as abnormal eye movements (nystagmus), involuntary movements, unexplained paroxysmal abnormalities, and nonepileptic loss of consciousness.

Conflicts of Interest Statement

The authors declare no conflict of interest.

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中文摘要

骨质疏松性骨折风险评估的潜在生物分子：一项综述回顾

刘婕妤^{1,2,3 #}, 王嘉祥^{1,2,3 #}, 许力^{1,2}, 邓飞艳^{1,2*}

¹ 苏州大学医学部公共卫生学院遗传流行病学与基因组学, ³ 流行病学与生物统计学教研室,
江苏, 苏州 215123

² 苏州大学医学部, 江苏省老年病预防与转化医学重点实验室, 江苏, 苏州 215123

摘要

骨质疏松症是一种系统性的慢性骨骼疾病, 其特征为骨矿密度低、骨质疏松性骨折风险升高。骨质疏松症好发于中老年人群, 尤其是绝经后妇女。伴随着人口老龄化, 骨质疏松症已成为全球范围内严重的公共卫生问题。尽早识别高危人群、及时有效的干预和治疗对于预防骨质疏松性骨折至关重要。鉴于骨质疏松症的遗传率较高且发病机制复杂, 有必要综合考虑重要的生物分子、从而对骨质疏松性骨折进行准确的风险评估。为此, 我们总结回顾了可用于骨质疏松性骨折风险评估的潜在生物分子及其最新研究进展。未来对于这些生物分子的系统评估有助于研发新的方法和检测策略, 比如开发生物芯片, 以应用于骨质疏松症的早期识别和骨质疏松性骨折的预防。

关键词: 骨质疏松性骨折; 分子; 预测; 诊断

中文摘要

ATP1A3 基因突变致儿童交替性偏瘫：2 例病例报道

杨广娥, 赵忠礼, 杨阳, 林丽, 宋丛磊, 汪晓翠, 杨斌

安徽省儿童医院神经内科, 合肥 230053

摘要

儿童交替性偏瘫是一种罕见的神经发育性异常, 绝大多数为散发病例, 极少数有家族史。我院收治 2 例男性患儿, 6~7 月龄时开始癫痫发作, 表现为反复发作性全身无力或一侧肢体偏瘫。基因检测显示两患儿均携带 *ATP1A3* 基因杂合缺失突变 (OMIM:614820): c.3025 (exon 22) A>G (p.K1009E) 和 c.2443 (exon 18) G>A (p.E815K)。氟桂利嗪可以显著改善交替性偏瘫患儿的发作性运动症状。

关键词: *ATP1A3* 基因; 儿童交替性偏瘫; 癫痫