A de novo missense pathogenic mutation c.2415C> G (p.Asp805Glu) in ATP1A3 gene in a patient with alternating hemiplegia of childhood with favorable response to biperiden hydrochloride

Gabriela Cabrera Garbuio[1], Jéssica Rezende Mio[1], Letícia Cassaro Feltrin[1], Marina Soccal da Silva[1], Zumira Aparecida Carneiro[1], Charles Marques Lourenço[1]

ABSTRACT

Alternating hemiplegia of childhood is a severe neurological disorder and a rare disease (1 in 100,000 newborns), characterized by repeated transient attacks of episodic hemiplegia or tetraplegia that can last minutes to hours, accompanied by other paroxysmal symptoms such as oculomotor and autonomic abnormalities, movement disorders such as ataxia, progressive cognitive impairment, seizures, dystonia, and chorea. Current treatments are largely symptomatic. In this case report, we present a female patient, 18 years old, who presented the first apparent episode of seizure with ocular version at ten months of age. The electroencephalogram and CT scan revealed no abnormalities, and several medications such as phenobarbital, carbamazepine, sodium valproate, topiramate, flunarizine dihydrochloride, clonazepam, cyproheptadine and pizotifen were administered, all without result. Due to the extrapyramidal symptoms, the patient started using biperidene, showing improvement in dystonia and the number of hemiplegic seizures. At age 13, she was diagnosed with Alternating hemiplegia of Childhood in the pathogenic missense de novo mutation c.2415C>G (p.Asp805Glu) in the ATP1A3 gene showing a good response to treatment with biperidene hydrochloride.

Keywords: Hemiplegia, Cognitive dysfunction, Seizures, Biperiden.

1. Faculdade de Medicina - Centro Universitário Estácio de Ribeirão Preto, Ribeirão Preto (SP), Brasil.

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INTRODUCTION

Alternating hemiplegia of childhood (AHC) is a severe and rare genetically determined neurological disorder, affecting about 1 in 100,000 newborns, resulting from heterozygous de novo mutations of *ATP1A3*[1–3].

The ATP1A3 gene belongs to a family of genes that are responsible for encoding the alpha-3 subunits of the sodium-potassium (Na+/K+) ATPase transporter protein, whose function is to regulate, by active transport, the concentration gradients of sodium and potassium, ions that are essential for controlling cellular osmolarity and action potentials of the excitable membrane[1,4].*ATP1A1*, *ATP1A2* and *ATP1A3* encode alpha subunits 1, 2 and 3, respectively, expressed mainly in interneurons and pyramidal cells, suggesting that they play important roles in the brain, although it is not yet fully understood how mutations in the *ATP1A3* gene lead to the clinical phenotype of recurrent hemiplegic seizures[4].

Mutations in the *ATP1A3* gene are associated with at least three distinct but overlapping neurological syndromes: the rapid onset parkinsonism-dystonia syndrome; the alternating hemiplegia syndrome of childhood; and CAPOS syndrome (***C****erebelar*, ***A****taxia*, *arreflexia,* ***P****es cavus,* ***O****ptic atrophy* ***S****ensorineural hearing loss*)[5,6].

AHC is characterized by repeated transient attacks of episodic hemiplegia or quadriplegia that may last minutes to hours, accompanied by other paroxysmal symptoms such as oculomotor and autonomic abnormalities, movement disorders such as ataxia, progressive cognitive impairment, seizures, dystonia, and chorea. AHC usually presents in childhood, with onset of manifestations and signs and symptoms usually before the age of 18 months[1,4].

AHC is predominantly seen in sporadic cases with no family history, although familial AHC with autosomal dominant inheritance has also been reported[4].

Current treatments are largely symptomatic and include sleep-inducing agents, such as benzodiazepines or chloral hydrate, to stop prolonged episodes of hemiplegia or dystonia[7].

Approximately 50% of children with AHC are also diagnosed with epilepsy, although the certainty of this diagnosis may remain unclear due to the similarity in clinical presentation between epileptic and non-epileptic paroxysmal events, such as dystonia, tremor or paresis[8].

CASE REPORT

A 19-year-old female patient, daughter of young, non-consanguineous parents, with no family history of neurological disease, was referred for evaluating "difficult to control seizures".

The patient was born at term (38 weeks and 5 days), normal delivery, 47 cm long, weighing 3,180g, head circumference (HC) 35cm, gestation without clinical complications. She presented Apgar scores of 8 and 9 (first and fifth minutes, respectively). She walked at two years and two months, sat up at one and a half years, and began speaking at three years. She had no other health problems until she was ten months old when she had her first apparent seizure episode with ocular version, requiring evaluation with a neurologist.

Electroencephalogram and CT scan were ordered, which revealed no abnormalities. The patient was diagnosed with focal convulsive seizures and started on phenobarbital up to its maximum dose of 4 mg/kg/day.

At the age of one year and ten months, the patient presented with hemiplegia in both upper limbs lasting from five to 30 minutes, sometimes for hours, and with a frequency of two to three seizures per week. The mother reports that, until then, this had never occurred. She also reports that sometimes, together with the loss of movement, the patient presented fixed gaze and loss of speech.

Two months after the previous episode, the patient was referred by her parents to the emergency unit for having seizures for two consecutive days. Sodium valproate was administered at its maximum dose of 60 mg/kg/day and was gradually replaced by carbamazepine. With the use of carbamazepine in the maximum dose of 1200 mg/day, however, the patient continued with hemiplegia, now only of the right upper limb, and loss of speech maintaining a duration of five to 30 minutes in some moments lasting hours and the frequency of two to three seizures per week.

At two years and eight months the patient remained with hemiplegia of the upper limbs and speech loss with a variable frequency, usually maintaining two to three seizures per week.

When she was six years old, the patient used the following medications: phenobarbital, pizotifen, flunarizine dihydrochloride all in maximum dose and lamotrigine (500 mg/day) was added. After three months, pizotifen was withdrawn. There was no improvement in the hemiplegic episodes nor the ocular alteration seizures. Examination of magnetic resonance imaging of the brain was compatible with normality.

At ten years of age the patient presented a more significant seizure episode and clonazepam 20 mg/day was added together with topiramate (1600mg/day). The patient, however, evolved, at 11 years of age, with regression of speech, with genitor referring sporadic episodes of dysphagia and in use of a locomotion chair due to instability of ambulation, unbalance and front falls.

From ten months to 13 years of age, the patient used various therapeutic regimens such as carbamazepine 1200 mg/day, sodium valproate 60 mg/kg/day, flunarizine dihydrochloride 10 mg/day, topiramate 1600 mg/day, cyproheptadine 16 mg/day, pizotifen 1.5 mg/day, lamotrigine 500 mg/day and clonazepam 20 mg/day.

At the age of 13, after evaluation with a geneticist, sequencing of the ATP1A3 gene was requested, with the presence of a de novo pathogenic missense mutation c.2415C>G (p.Asp805Glu) in exon 17, confirming the diagnosis of childhood alternating hemiplegia. This mutation had been previously described in the literature in other patients with this disease.

Currently, the patient takes clonazepam, risperidone, and biperidene hydrochloride (initially introduced to treat the patient's dystonic syndrome). After introducing the last drug, she had no more seizures, revealing an improvement in her quality of life and a slowing in the evolution of the disease. Regarding her neuro-psychomotor development, she cannot read or write, speaks with difficulty, presents comprehension, walks independently, performs daily activities, attends regular school in a special room, and undergoes multiple rehabilitation therapies, such as speech therapy, psychopedagogy, and physical therapy.

On current physical examination, the patient presents symmetrical facies, hypomimic, no alterations in eye movement, preserved muscle strength in the upper and lower limbs, reflexes alive globally, decreased tonus in the lower limbs, dysmetria, dysdiadochokinesia, dystonia in the hands, preserved sensitivity and gait with slightly widened base.

DISCUSSION

AHC is a genetic disease mostly caused by mutations in the ATP1A3 gene (responsible for 74% of AHC cases)[9]. It is worth noting that AHC is a heterogeneous entity from the genetic point of view, because mutations in other genes have already been identified as responsible for this clinical picture. Among them, mutations in genes CACNA1A, SLC2A1, SLC1A3 and ATP1A2 have been identified in a small portion of patients with AHC, but generally these patients present the hemiplegia episodes associated with a more atypical clinical picture. In general, in most of the published articles, the ATP1A3 gene is the major responsible for AHC cases[9].

In the case of the ATP1A3 gene, it is a gene whose function is to encode the alpha 3 subunits (isoform) of the sodium - potassium (Na + / K +) ATPase transporter protein, responsible for the establishment and maintenance of electrochemical gradients of sodium and potassium ions across the plasma membrane of neurons (Figure 1), ions essential for the control of cellular osmolarity and action potentials of the excitable membrane[10].

In addition to AHC, other diseases associated with heterozygous mutations of the ATP1A3 gene have been reported, such as rapid onset parkinsonism-dystonia syndrome (PDS) and CAPOS syndrome (cerebellar ataxia, alexia, clubfoot, optic atrophy and sensorineural hearing loss.[9] These diseases are clinically different from AHC, but have some elements in common, such as extrapyramidal symptoms (cerebellar ataxia, dystonia), which reveals the wide range of phenotypic expression of mutations in this gene.

The first symptoms of AHC occur before 18 months of age as observed with our patient whose symptoms appeared around ten months of age. They are characterized by hemiplegia lasting minutes to days occurring on alternate sides of the body: sometimes it may start unilaterally but later evolve to bilateral hemiplegia or transfer to the opposite side of the body during an attack. Usually, hemiplegia ceases during sleep and reappears on awakening, but not immediately.

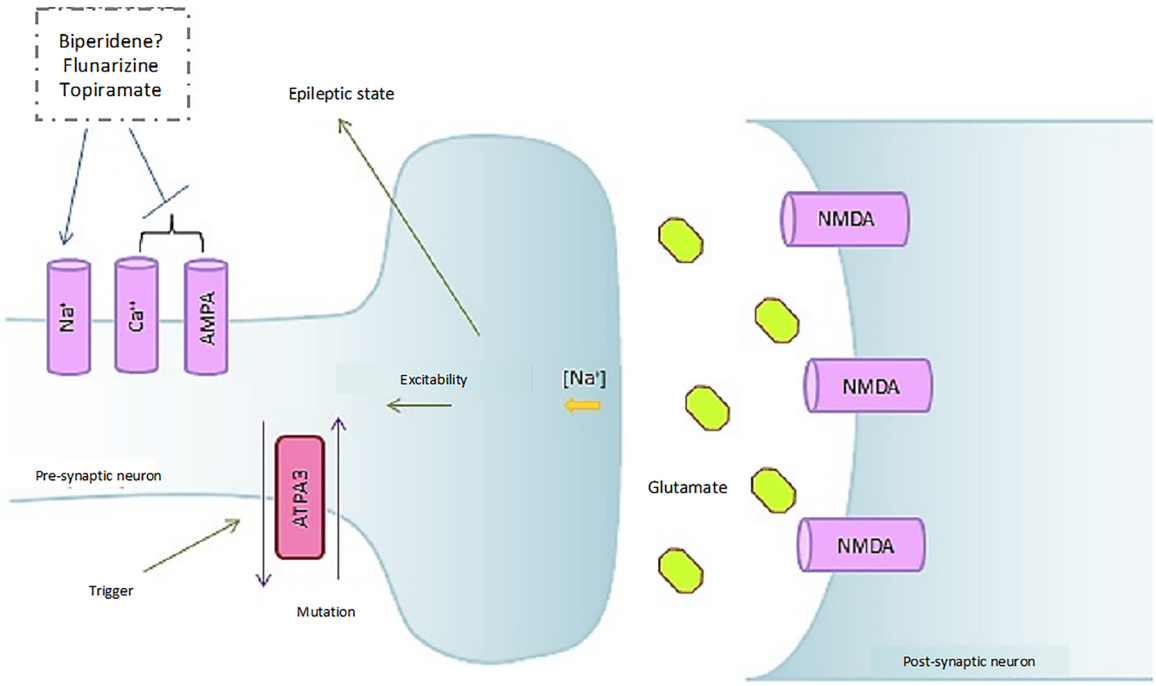

Figure 1: Adapted from Algahtani H. et. Al. Schematic representation showing dysfunctional Na + / K + -ATPase pump activity due to mutation of ATP1A3 in neurons affecting the activity of the glutamatergic system. Mutation in ATP1A3 causes a decrease in Na + / K + -ATPase pump activity and an increase in intracellular Na +, which results in hyperexcitability that affects neuronal function. Flunarizine and topiramate are shown as treatment options for hemiplegic seizures caused by mutations in this gene. In the case of the patient of this report, perhaps biperidene has the same modulatory effect on neuronal hyperexcitability through the Na+/K+ pump, similar to that observed with flunarizine and topiramate10.

Source: The authors (2019).

Cognitive deterioration has not been associated with episodes of hemiplegia[2]. Some authors suggest that AHC evolves following three distinct phases with relatively specific clinical features for each one[11]**.** (Figure 2)

Sudden and unexpected onset of hemiplegia has also been observed in some patients, but always with the patient being awake with hyperventilation or autonomic dysfunction. Triggering factors can lead to episodes of hemiplegia, such as excitement, stress, fatigue, trauma, bright light, heat, cold, or bathing[12,13].

Involuntary movements, including facial dyskinesia, dystonia, and choreoathetosis were associated with hemiplegic seizures or occurred independently, even in the absence of hemiplegic episodes, as in the case of the patient in the report who had signs of chronic dystonia[2].

In cases of AHC that manifest themselves during the first days of life, eye movement disorders (such as involuntary eye version movements, strabismus, nystagmus) are usually the first to be observed[2,10]. Involuntary eye movements are characterized as intermittent eye deviation, nystagmus, and non-conjugate eye movement, lasting from one to three minutes. The abnormal eye movements are most commonly unilateral and ipsilateral to the hemiplegia[14].

Prodromal signs before paroxysmal phenomena were reported by 41% of patients. The premonitory phase consists of a change in mental status with shouting, irritability, or behavioral changes[2].

Headaches may occur at the onset of an attack, but not after it (they were reported by 58% of children with AHC, although migraine with aura was diagnosed in 16%). Extrapyramidal involuntary movements (such as choreoathetosis) may also be a feature exacerbated by the headache condition[2,10].

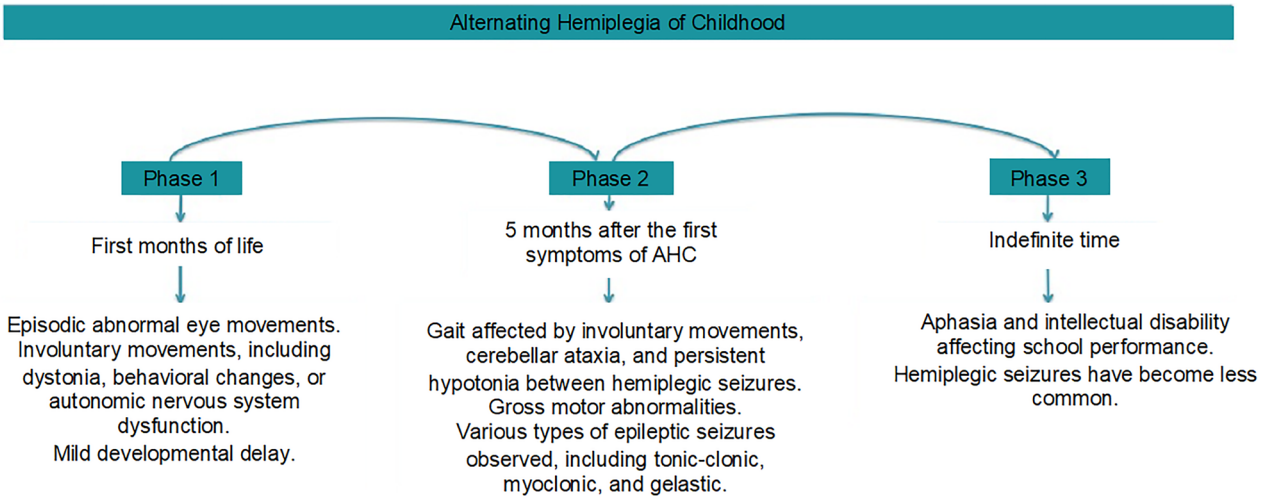

Figure 02: The three stages of symptom evolution in patients with AHC11

Source: The authors (2019).

The prognosis is greatly influenced by the age of onset and especially by the early occurrence of hemiplegic seizures in infancy. Children with neonatal onset manifestations usually suffer from severe developmental delay. Recurrent seizures can also lead to deterioration in psychomotor development. In some children, the motor dysfunction caused by the disease has necessitated the use of a wheelchair, but others have been able to lead independent lives in adulthood. As patients age, hemiplegic seizures and abnormal eye movements become less common and hypotonia less severe[2].

The treatment of AHC is based on the control of acute episodes and their prophylaxis[15]. In the acute phase, the focus is on removing known triggers and facilitating early sleep. The use of oral midazolam or rectal diazepam has been advocated by some authors as providing rapid sedation[15]. Prophylaxis, on the other hand, is based on avoiding triggering factors (such as sleep deprivation, for example) and long-term use of medications to decrease the frequency of seizures. Several drugs have been proposed for the treatment of AHC, but calcium channel blockers are the most effective. The most commonly used is flunarizine, which is considered the drug of choice, reducing the frequency and severity of attacks but not stopping them completely[15].

Other proposed treatments include beta-blockers, anticonvulsants, methysergide, amantadine, aripiprazole, and haloperidol[3,16]. Antiepileptic drugs are effective in treating seizures only. Topiramate has positively influenced the clinical response in some patients with AHC, attenuating the symptoms of AHC seizures[10]. Recently, the use of oral adenosine-5'-triphosphate was described in patients with AHC who were followed for two years, showing promising and successful results[17].

In addition, some reports have suggested the possible beneficial effect of the ketogenic diet in patients with AHC[18,19]. The long-term outcome of patients with AHC is generally poor, due to the associated developmental delay and gradual deterioration after more severe attacks.

In the case studied, biperidene hydrochloride was administered to reduce the dystonia and ended up ceasing the patient's seizures, besides revealing a significant impact on the evolution of the disease. Despite not being the most indicated medication in this treatment, a significant improvement in the patient's quality of life was observed, including the abandonment of the locomotion chair.

Biperidene has muscarinic anticholinergic action, exhibits diltiazem-like action of enhancing [3H]nitrendipine binding, overcomes the inhibition caused by 2.5 μM thiapamil, increasing [3H]

nitrendipine binding from 10% to 80%. It exhibits biphasic effects like diltiazem, causing inhibition of [3H]nitrendipine binding at higher concentrations[19].

Biperidene also acts by inhibiting Ca2+-dependent contractions of the ileal muscle. It can be considered that biperidene has an effect on modulating neuronal membrane hyperexcitability, similarly to flunarizine and topiramate (Figure 1), which would explain the clinical response observed in the patient of the report. Even so, it would be important to observe whether this clinical effect of biperidene occurs in other patients with AHC whose control of hemiplegic episodes is still not being done optimally (even with the use of flunarizine and topiramate).

The mutation observed in the patient has been previously described in the literature in patients with the classic AHC phenotype, with difficult-to-control hemiplegic episodes[1,8]. In none of these patients, however, was the use of biperidene reported.

In summary, AHC is a serious disease that is becoming increasingly recognized along with its associated comorbidities. Its diagnosis and management require a multidisciplinary team that addresses all aspects of this complex disease and the needs of the patient and family. Targeted clinical research and collaboration among centers dedicated to this disease have made it possible to deepen the understanding and improve the therapeutic management of this rare disease[3].

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Corresponding author:
Charles Marques Lourenço
charlesgenetica@gmail.com

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