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CLINICAL CASE

Episodic Ataxia Type 2 in a Latin American Family

Ataxia episódica tipo 2 en una familia latinoamericana

Alonso Reyes-Fernández[a,b], Jorge Miles-Acuña[a,b], José Miguel González-del Valle[a,b], Daniela Ávila-Smirnow[a,b]

[a]Sección de Neurología, Departamento de Pediatría, Facultad de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.
[b]Unidad de Neurología, Departamento de Pediatría, Complejo Asistencial Dr. Sotero del Río. Santiago, Chile.

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What do we know about the subject matter of this study?

Episodic ataxia type 2 (EA2) is an inherited disease characterized by episodes of ataxia, dizziness, and nystagmus. There are about 100 cases described, but none from Latin America. Treatment with acetazolamide is effective in half of the cases.

What does this study contribute to what is already known?

We describe a Chilean family carrier of EA2, treated with a combination of acetazolamide and levetiracetam in low doses. Although levetiracetam has been used in exceptional cases in adult patients with EA2, the patients reported here are the first pediatric cases treated with this scheme.

Abstract

Episodic ataxia type 2 (EA2) is a rare and underdiagnosed autosomal dominant disorder caused by pathogenic variants of the *CACNA1A* gene. EA2 presents with episodes of ataxia lasting for hours and may be accompanied by dizziness and nystagmus. Acetazolamide is effective in half of the cases, and a combination of acetazolamide and levetiracetam has been used to treat some adult patients. **Objective:** To report 3 patients with EA2, successfully treated with a combination of acetazolamide and levetiracetam. **Clinical Case**: Three members of a family had recurrent episodes of gait instability, lasting minutes and occurring several times per week. Intrafamilial phenotypic heterogeneity was evident in clinical manifestations such as intellectual disability, migraine, epilepsy, and nystagmus. After an extensive study and a follow-up of more than five years, a new pathogenic variant in the *CACNA1A* gene, NM_001127221.1:c.1580T>G (p.Leu527*), associated with EA2, was identified. The three patients responded partially to treatment with acetazolamide; therefore, low-dose levetiracetam was added to two of them, which drastically reduced symptoms. **Conclusions**: A Chilean family with EA2 is reported. The genetic study allowed for obtaining an accurate diagnosis and initiating appropriate management with acetazolamide. As a second line, levetiracetam was effective. Further studies are needed to evaluate the efficacy of combining levetiracetam with acetazolamide in pediatric and adult patients, or the use of levetiracetam as monotherapy.

Keywords:
Ataxia;
Nystagmus;
Levetiracetam;
CACNA1;
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Correspondence:
Daniela Avila-Smirnow
davila@uc.cl

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Carolina Heresi Venegas

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Introduction

Episodic ataxia (EA) is a heterogeneous group of rare genetic disorders characterized by intermittent cerebellar dysfunction[1-3]. Its incidence is less than 1/100,000. The five genes implicated in EA are *KCNA1*, *CACNA1A*, *CACNB4*, *SLC1A3*, and *UBR4*[2].

EA type 2 (EA2) is the most common type of EA, however, only around 100 cases have been reported in the literature. It usually occurs in childhood[4] but is often diagnosed later in life[5,6]. EA2 is an autosomal dominant neurological disorder caused by mutations in the *CACNA1A* gene (chromosome 19p13), which encodes the alpha1A subunit of the P/Q-type calcium channel[7].

Episodes of ataxia in patients with EA2 usually last for hours and may present with intermittent vertigo, nystagmus, nausea, diplopia, dysarthria, and generalized weakness[8]. It has also been associated with other conditions of a recurrent nature such as epilepsy and hemiplegic migraine[9,10].

Symptomatic treatment with acetazolamide can reduce symptoms and improve quality of life[2,10], however, this therapy is effective in only 50% of cases and the impact may be only transitory[11]. Another drug that has shown effectiveness is dalfampridine in a trial involving only 10 patients[11]. The use of levetiracetam has been reported in three adult patients, from two families with this disease, showing a significant decrease in episodes. To the best of our knowledge, its use has not been reported in children[12-14].

The objective of this report is to present the case of a Latin American family with EA2, including two pediatric cases that responded to acetazolamide and levetiracetam.

Clinical Case

Case 1

Index patient. A girl born to an uneventful pregnancy who achieved independent walking at 14 months and understandable speech using sentences by the age of three. The patient showed no developmental abnormalities and appeared healthy until four years of age when she presented recurrent episodes of dizziness and gait instability, occurring up to five times a month, each lasting 30 minutes, triggered by physical exercise and anxiety.

Between the ages of 4 and 6, the episodes recurred with similar frequency, and she was evaluated in primary care. At six years of age, she was evaluated by neurology for the first time. Neurological examination showed normal anthropometry and head circumference, inattention, multidirectional nystagmus, and unstable tandem gait. Differential diagnoses were proposed including neurometabolic diseases (such as maple syrup urine disease, GLUT1 deficiency syndrome, mitochondrial diseases, and urea cycle disorder), epilepsy, migraine, benign paroxysmal positional vertigo, and CNS tumors.

A comprehensive study was conducted, including tests for ammonia, lactic acid, bilirubin, alkaline phosphatase, gamma-glutamyl transferase, blood urea nitrogen, creatinine, plasma electrolytes, venous blood gases, vitamin B12 levels, amino acid and acylcarnitine profiles, thyroid-stimulating hormone, thyronine, and brain MRI, all of which were normal. Electromyography with a long repeated exercise test was performed to evaluate signs of periodic paralysis, exploring the differential diagnosis of intermittent gait disorders, which was negative. An ophthalmological evaluation was performed, which showed normal visual acuity. The Wechsler Intelligence Scale for Children-V (WISC-V) revealed a full-scale IQ of 62.

The electroencephalogram revealed a single burst of generalized epileptiform activity, leading to the diagnostic suspicion of epilepsy. Therefore, levetiracetam 500 mg/12 hours was indicated. This treatment reduced the episodes of gait instability. However, the use of levetiracetam was associated with behavioral issues, which led to its discontinuation after 2 months of treatment.

At the age of eight, EA was suspected due to the association of gait instability, episodic dizziness with multidirectional nystagmus[15,16], and epilepsy, along with the absence of structural abnormalities on brain MRI and the abovementioned complementary tests. A genetic panel was requested, including two genes responsible for EA (*CACNA1A* and *SLC1A3*), which is commercially available for the study of familial hemiplegic migraine. This decision was made because our center did not have access to a panel specifically designed for the study of ataxias. Genetic panel analysis revealed a pathogenic variant in *CACNA1A*, NM_001127221.1:c.1580T > G (p.Leu527*). Acetazolamide 125 mg/12 hours (5 mg/kg/day) was initiated, and after 1 month of treatment, episodes were partially reduced to once a month. However, irritability and metabolic acidosis occurred (blood HCO3 = 16 mEq/L), which required treatment with oral bicarbonate at 1 g/day every 12 hours. No other adverse reactions to acetazolamide were observed.

At the age of nine years, the frequency and intensity of the episodes increased to twice a month; therefore, it was decided to add levetiracetam in progressive doses up to 250 mg/day (5mg/kg/day). The patient responded very well to this combined treatment with acetazolamide (5mg/kg/day) and levetiracetam (5mg/kg/day). After 2 weeks of combined treatment, a decrease in the

frequency and intensity of symptoms was observed, with only mild episodes of ataxia once every 6 months during the 12-month follow-up up to the present. With this low dose of levetiracetam, the patient had no behavioral changes or other adverse drug reactions. Given the good clinical response and in order to avoid the appearance of the symptoms previously observed in this patient with higher doses of levetiracetam, it was decided not to continue escalating the drug dose. During these 12 months, the same doses of both drugs were maintained, and no relapses were observed. A family segregation study revealed that the symptomatic brother and father of the index patient were carriers of the same pathogenic variant, while the asymptomatic mother and sister were not.

Case 2

Brother of the index patient. He had delayed language development, with his first words with clear meaning at three years old and two-word sentences at age five, requiring speech therapy. He was examined at age five due to hyperactivity and impulsivity. Neurological examination revealed attention difficulties and motor coordination issues, leading to a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). Treatment with methylphenidate was initiated and adjusted according to clinical response, showing improvement in the patient's behavior. However, learning difficulties persisted, thus he underwent a WISC-V test, which revealed a total IQ of 58.

At nine years of age, episodes of headaches associated with vertigo and sometimes vomiting were reported as often as five times per month. Episodes were triggered by exercise, crowded places, or road trips. At 11 years of age, horizontal nystagmus and bilateral Achilles tendon shortening which causes toe walking were observed. The sequencing of the *CACNA1* gene revealed the same pathogenic variant as that observed in his sister.

Treatment started with acetazolamide at 125mg/12h (5mg/kg/day). After 2 weeks of treatment, the episodes decreased in frequency, but the treatment produced metabolic acidosis (blood HCO3 = 21 mEq/L), therefore, oral bicarbonate 1g/day every 12h was started. No other adverse reactions to acetazolamide were observed. At 12 years of age, after 1 year of treatment, an increase in the intensity and duration of ataxia episodes was observed, coinciding with environmental changes such as greater school demands and increased physical activity. Therefore, levetiracetam at 250mg/12h (10mg/kg/day) was added, which after 1 month led to a reduction in the number of ataxic episodes to twice per month. Treatment with levetiracetam was associated with mild irritability. However, it was decided to continue with this treatment because the decrease in ataxic episodes correlated with a significant improvement in quality of life. With this scheme, the patient stabilized and has completed 1 year of treatment, combined with acetazolamide (5mg/kg/day) and levetiracetam (10mg/kg/day).

Case 3

Father of patients 1 and 2. Patient with a history of language and learning difficulties, without previous neuropsychological evaluation. Since the age of 10 years, he presented episodes of dizziness associated with gait instability and recurrent headaches. These episodes were triggered by vehicle travel, crowded places, sports, or anxiety. Although the patient consulted for this condition during his childhood, no specific diagnosis or treatment was obtained. Symptoms diminished over the years and at age 33, he was first evaluated by our team after a recent diagnosis of EA2 in his children. At that time, he presented with ataxia episodes once a day. On examination, a slight horizontal nystagmus in lateral gaze was observed and genetic testing revealed the same pathogenic variant as previously described for the *CACNA1* gene. He was treated with acetazolamide 250mg/12h but later discontinued his check-ups, making it impossible to demonstrate the efficacy of the treatment, any adverse reactions, or to complete a standardized cognitive evaluation.

In this report, all procedures were performed according to the current regulations and have been approved by the corresponding institutional committee. The Ethics Committee of the Southeast Metropolitan Health Service approved this study.

Discussion

We present three members of a Chilean family, including two pediatric patients with EA2 related to the new pathogenic variant *CACNA1A*, NM_001127221.1:c.1580T > G (p.Leu527*), which was successfully treated with low doses of acetazolamide and levetiracetam, as previously reported in adult patients[13]. After a review in PubMed, Scielo, and Scopus databases, only one possible case of EA2 has been published in a Latin American patient and no genetic testing was performed, so this would be the first report in a journal indexed in the mentioned databases[17].

Before the ataxia episodes onset, language delay and ADHD were observed in two family members. Subsequently, the intellectual deficit was evidenced in them. Language delay, ADHD, and intellectual disability have been frequently described in EA2, in 5%, 11%, and 14% of individuals, respectively (table 1, figure 1)[18-26]. Epilepsy and febrile seizures have also been frequently observed in 9% and 7% of patients, respectively, as in the proband of this family.

Table 1. Demographic data, comorbidity and triggers of ataxia in 97 patients published in the literature

Total	Age, years	Age at onset, years	Sex F/M	Origin	Comorbidities					Triggering factors					
					Epilepsy	ADHD	Language Disorders	ID	Febrile seizures	Anxiety	Physical activity	Alcohol	Fatigue	Fever	Ref.
4	20.5	6.7	2/2	China	0	0	0	0	0	4	0	0	3	3	1
17	38.6	17.8	7/10	South Korea	0	0	0	0	0	1	0	0	1	0	2
3	38.3	9.3	2/1	South Korea	0	0	0	0	0	0	0	0	0	0	13
4	51.25	15.25	3/1	Italy	2	0	0	0	0	0	0	0	0	0	20
1	17	11	0/1	China	0	0	0	0	0	1	1	0	0	0	22
4	43.7	25.6	2/2	Germany	0	0	0	0	0	2	0	0	0	0	11
4	7	6.5	SD	Italy	0	0	1	1	0	0	1	0	0	0	9
1	27	13	0/1	SD	0	0	0	0	0	0	1	1	0	0	23
1	31	28	0/1	SD	0	0	0	0	0	0	1	1	0	0	8
1	34	4	0/1	SD	0	0	1	1	1	1	0	0	0	0	16
2	36	9,5	1/1	Slovakia	0	0	0	0	0	1	1	0	0	0	19
4	25.7	17.2	2/2	South Korea	2	0	0	0	0	0	4	0	0	0	23
16	24.2	8.1	6/10	ND	4	11	3	12	6	5	6	0	5	2	24
1	46	46	SD	ND	0	0	0	0	0	1	0	0	1	0	6
1	27	17	SD	Italy	0	0	0	0	0	1	1	0	0	0	25
1	46	46	SD	ND	0	0	0	0	0	0	0	0	0	0	21
8	56.2	19.4	4/4	Austria	0	0	0	0	0	4	4	1	0	0	22
3	32.3	12	2/1	Suiza	0	0	0	0	0	1	1	1	0	0	17
1			SD	Canada	0	0	0	0	0	1	1	1	0	0	3
11	34.3	11.4	5/6	China	1	0	0	0	0	2	4	0	1	0	13
6	37.6	20	4/2	South Korea	0	0	0	0	0	6	6	0	0	0	5
2	40		0/2	ND	0	0	0	0	0	0	0	0	0	0	12
1	23	23	1/0	ND	0	0	0	0	0	0	0	0	0	0	4
Number, 97			40/48		9	11	5	14	7	31	32	5	11	5	
Percentage					9%	11%	5%	14%	7%	32%	33%	5%	11%	5%	
Mean	35	13													

M: male, F: feminine, ADHD: attention deficit with hyperactivity disorder, ID: intellectual disability, Ref: reference, ND: no data.

Table 2. Characteristics of ataxia episodes in 97 patients reported in literature

Total	Ataxia	Dizziness/ Vertigo	Nystagmus	Headache	Vomiting	Weakness	Diplopia	Tinnitus	Dysarthria	Dysmetria	Tremor	Hypertonia	Ref.
4	0	4	1	0	3	2	0	0		0	0	0	1
17	13	17	0	3	0	0	1	1	10	0	0	0	2
3	2	3	3	1	3	0	1	0	3	0	0	0	13
4	4	4	2	1	0	0	0	0	1	1	0	3	20
1	1	1	0	1	1	1	0	0	0	0	0	0	22
4	3	2	2	2	0	1	0	0	0	1	0	0	11
4	1	1	1	1	1	1	0	0	0	0	0	0	9
1	1	1	0	0	1	0	1	0	1	1	0	0	23
1	1	1	1	0	0	1	0	0	1	1	1	0	8
1	1	1	1	0	1	0	0	0	0	0	0	0	16
2	2	1	1	1	1	0	0	0	1	0	0	0	19
4	1	4	0	3	4	0	0	0	1	0	0	0	23
16	13	5	15	4	3	0	0	0	2	0	0	0	24
1	1	0	0	1	0	0	0	0	1	0	0	0	6
1	1	0	0	0	1	0	0	0	0	0	0	0	25
1	1	0	0	1	0	0	1	1	0	0	0	0	21
8	0	8	5	3	0	0	2	0	5	0	0	0	22
3	2	1	1	1	0	0	1	0	1	0	0	0	17
1	1	1	1	0	1	0	1	0	1	0	0	0	3
11	7	5	2	5	6	0	6	3	8	0	1	0	13
6	0	6	4	0	0	0	6	0	0	0	0	0	5
2	2	0	2	0	0	0	0	0	0	0	0	0	12
1	1	0	1	1	1	0	0	0	0	0	0	0	4
Number, 97	59	66	43	29	27	6	20	5	36	4	2	3	
Percentage	61%	68%	44%	30%	28%	6%	21%	5%	37%	4%	2%	3%	

Ref: reference.

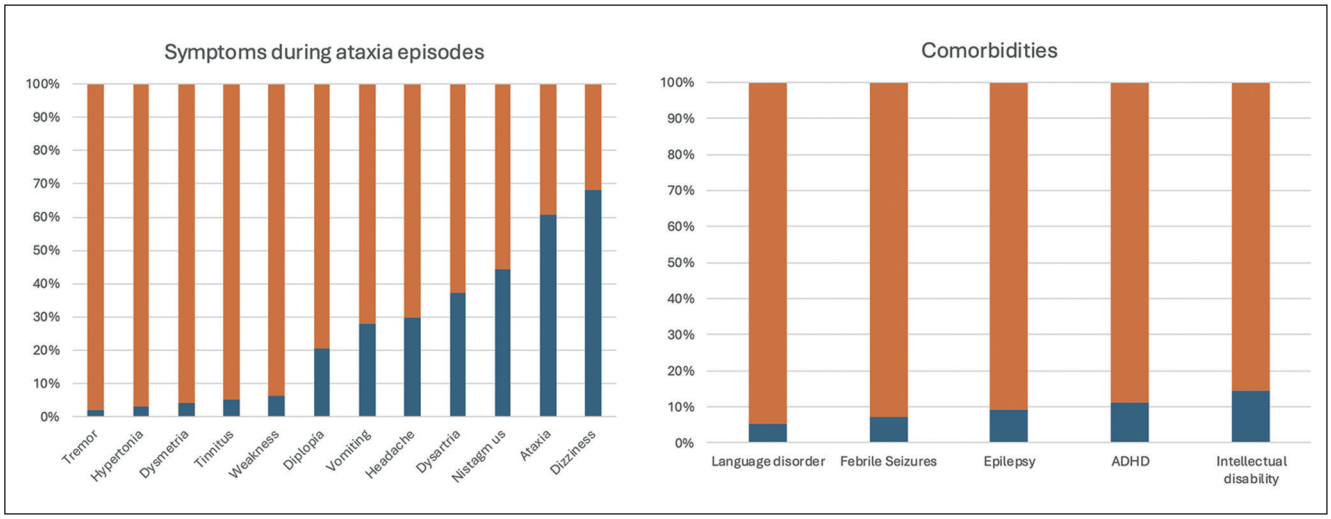

Figure 1. Comorbidities and characteristics of ataxia episodes in patients with EA2 reported in literature (N=97 patients). **A.** Frequently described comorbidities: intellectual disability (14%), attention deficit with hyperactivity disorder (ADHD) (11%), epilepsy (9%), and language impairment (5%). **B.** Signs and symptoms included dizziness (68%), ataxia (61%), nystagmus (44%), dysarthria (37%), and headache (30%). Refer to Tables 1 and 2 for references.

Multidirectional nystagmus was a key diagnostic feature in the proband. Unlike the father and brother, who had horizontal nystagmus in lateral gaze, which can be mistaken for physiologic nystagmus, the proband had multidirectional nystagmus, which pointed to cerebellar involvement[26]. Different types of nystagmus are described in EA2, mainly horizontal nystagmus, with intrafamilial variability[15,16].

The age of presentation of EA in this family occurred at the end of the first decade (4 to 10 years), with associated symptoms such as dizziness and headache; all patients had permanent nystagmus. Similar to this family, in the literature, EA in patients with EA2 was typically observed at an average age of 13 years, and the most frequently reported symptoms were dizziness (68%), ataxia (61%), nystagmus (44%), dysarthria (37%), and headache (30%) (table 2).

Sporadic cases of successful treatment with a combination of acetazolamide and levetiracetam have been reported in adults. However, we found no references for this treatment in children. Acetazolamide is the most commonly used drug for the treatment of EA2 in 50% of the reported cases, and its mechanism of action is presumed to be related to the sensitivity of voltage-gated calcium channels to changes in blood pH. States of alkalemia (e.g., respiratory alkalosis induced by intense exercise) favor symptomatic episodes in some patients; therefore, the ability of acetazolamide to lower arterial pH may be responsible for the striking symptomatic improvement observed in these patients. In contrast, levetiracetam has been used much less frequently and we found only three adult cases treated with this regimen. Levetiracetam inhibits presynaptic calcium channels in the CNS, which reduces intra-neuronal calcium release, which is related to the pathophysiology of EA2 based on voltage-gated calcium channels[14].

The three patients reported, belonging to two families, were carriers of the pathogenic variants c.5035C >T/p., Arg1679Cys and c.3855C > G/p. Tyr2319*, the latter being a truncating variant similar to that reported in this Chilean family. The literature reports a variable decrease in the frequency of episodes after the use of levetiracetam, from around 2 per week to 1 per month on average.

In the family reported here, the father had a diagnostic delay of two decades and the daughter had a delay of five years due to overlap and coexistence of symptoms with the aforementioned comorbidities (table 1, figure 1)). Because the treatment of EA2 differs from that of the above conditions and can produce significant symptomatic relief, early diagnosis is important.

The limitation of this study is its small number of patients, all from the same family, which highlights the need to advance our knowledge of genetic diseases in Latin America and the therapies available for the treatment of EA2 through multicenter randomized controlled clinical trials.

Conclusion

To our knowledge, this is the first report of a Latin American family with EA2, including two children who responded adequately to treatment with low doses of acetazolamide and levetiracetam. This suggests

its effectiveness in children with a poor response to acetazolamide monotherapy, especially in those with truncating variants in the *CACNA1A* gene, as has been reported in the literature in an adult family.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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