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REVIEW

Therapy of episodic ataxias: case report and review of the literature

Daniele Orsucci MD, Laura Maria Raglione MD, Monica Mazzoni MD, Marco Vista MD

Unit of Neurology, San Luca Hospital, Lucca, Italy

Abstract
Episodic ataxias (EAs) are characterized by recurrent, discrete episodes of vertigo and ataxia. EA1 and EA2 are the two most common forms. In the interictal interval, myokymia is typically present in EA1, whereas EA2 patients present with interictal nystagmus. Specific pharmacological therapies are available for EA1 and especially EA2. We briefly discuss the case of an Italian young man with EA2, with a novel de novo CACNA1A mutation, who in our opinion is particularly illustrative for introducing the therapeutic approach. Acetazolamide could fully suppress EA episodes in our patient. We also provide a perspective review of the topic. 4-Aminopyridine is another valid treatment option. For EA1 (and for rarer EAs), the therapeutic possibilities are more limited. Carbamazepine is probably the treatment of choice for EA1, but the optimal treatment plan is unknown. A better understanding of the molecular processes involved in the mediation of EAs will lead to more specific and efficacious therapies for this still elusive group of disorders.

Keywords: acetazolamide, ataxia, CACNA1A, episodic ataxia, episodic ataxia type 1, episodic ataxia type 2.

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Introduction
The term ‘cerebellar ataxias’ comprises a wide spectrum of neurological diseases with ataxia as the pivotal feature. Ataxia is characterized by imbalance (e.g. truncal ataxia, gait ataxia) or incoordination of a limb while executing a task (dysmetria). Ataxia is usually caused by dysfunction of the cerebellum or its connections. However, patients can also have ataxia from peripheral sensory involvement. Neurological examination allows a correct distinction of the two conditions. Furthermore, cerebellar ataxia is frequently associated with other signs of cerebellar dysfunction, including abnormal eye movements (e.g. nystagmus, saccadic pursuits, hypermetric or hypometric saccades), kinetic tremor, dysmetria, dysarthria, and/or dysphagia.

Once acquired conditions leading to cerebellar ataxia have been ruled out, making a correct etiological diagnosis of ataxia may be a challenge, considering the overlap in phenotypes and the different presentations of cerebellar ataxias.

Genetic ataxias are commonly progressive, chronic conditions. Few rare genetic ataxias are episodic. In this paper, we present an illustrative case report followed by a perspective review. We focused our attention on the two most common genetic forms of episodic ataxia (EA). We searched PubMed in October 2018 for all articles about ‘episodic ataxia’, and we reviewed the abstracts to identify relevant publications on treatment of EAs. Furthermore, we briefly discuss the case of an Italian young man with EA, who in our opinion is particularly illustrative for introducing the therapeutic approach.

Episodic ataxias
EAs are characterized by recurrent episodes of ataxia and/or dizziness. These diseases can be progressive or not. Most EA genes code for ion channels. Intermittent neurological phenotypes are typical of most channelopathies. The differential diagnosis includes paroxysmal dyskinesias and other paroxysmal motor disorders.

EA type 1 (EA1) is clinically defined by brief episodes of ataxia. It is due to mutations in the KCNA1 gene. In EA type 2 (EA2), attacks tend to last longer and there is usually ataxia on neurological examination; the causative gene is CACNA1A. In the interictal period, myokymia is present in hand muscles when analyzed by EMG in EA1, whereas EA2 patients present with interictal nystagmus (downbeat nystagmus, gaze-evoked nystagmus, and/or rebound nystagmus) (Table 1).
There are other few rare forms. Many other different genes have been associated with an EA phenotype, including CACNB4 (EA4), SLC1A3 (EA6), SCN2A42, SLC2A14, and FGFR43. With the exception of CACNA1A and KCNA1, leading to EA1 and EA2, the rest have been found mutated in only one or few patients and will not be discussed here. Next generation sequencing (NGS) tools will allow a better understanding of the complexity and genetic heterogeneity of EA phenotypes.

### Episodic ataxia type 1

EA1 is caused by mutations in the potassium channel gene KCNA1, which encodes the Shaker-related channel Kv1.1. These channels have a major role in action potential repolarization at cerebellar basket cell terminals. The mutant channels show accelerated decay of outward potassium current during prolonged depolarization of the membrane potential, leading to a reduction in Kv1.1 current amplitude in basket cells. Interestingly, mutations underlying EA1 may also antagonize Kv1.1 RNA editing.

EA1 is an autosomal dominant channelopathy characterized by persistent myokymia (with muscle twitching or intermittent cramps) and episodes of ataxia. Neurological spells can include unsteady and wide-based gait, incoordination, dizziness/vertigo, dysarthria, and other manifestations (i.e. nausea and vomiting, headache, muscular weakness, and/or stiffness). Myokymia may be misinterpreted as peri-ocular, peri-oral, or finger tremor. Typical attack duration is in minutes though events may persist for hours. Episode frequency varies widely, and typical triggers include physical exertion, emotional stress, and environmental temperature extremes. Neuroimaging is typically normal, though cerebellar atrophy has been reported. The finding of deafness in some individuals raises the possibility of a link between Kv1.1 dysfunction and hearing impairment, but further studies are needed. Interestingly, it has been reported that about 20% of EA1 patients accumulate persistent cerebellar symptoms and signs, contrary to the perceived course of this condition. The first episode of ataxia occurs before age 20 in nearly all patients, and quality-of-life score correlates negatively with attack frequency. EA1 patients may improve on a modest dose of carbamazepine, which is probably the treatment of choice (even if valproic acid and acetazolamide may also be effective in some instances).

### Episodic ataxia type 2

The CACNA1A gene codifies a calcium-dependent voltage channel, expressed in neurons. Mutations in this gene lead to a broad clinical spectrum including EA2, spinocerebellar ataxia type 6, familial hemiplegic migraine, and more recently epileptic encephalopathy. Even if different mutations tend to associate with different phenotypes, some families show a wide variability of the neurological manifestations associated with the same variant. The calcium channels that are altered in EA2 are highly expressed in the central nervous system and are particularly present in cerebellar Purkinje cells and in axon terminals. Cav2.1 dysfunction in episodic ataxia type 2 also has negative effects on axon excitability.

Most EA2-associated variants in the CACNA1A gene cause loss of function of the channel. Missense variants leading to decreased channel currents have also been reported, as well as deletions in CACNA1A.

EA2 is characterized by recurrent spells of ataxia, lasting for several hours (sometimes days), which may be induced by stress or exercise. Neurological findings between attacks include signs of central ocular motor and vestibular dysfunction, such as downbeat nystagmus. Acetazolamide frequently leads to significant improvement.

### Case report

We present the case of a 20-year-old man presented because of increasingly frequent spells of gait instability, dizziness, and dysarthria. The patient’s identity may not be ascertainment from this report.

These attacks began at age 10 and typically lasted 3–6 hours. He was having 2–4 episodes per month, mostly evoked by physical exertion (typically after amateur five-a-side football matches). He was empirically treated with valproic acid and subsequently levetiracetam with no improvement. Family history was unremarkable.

Intercital neurological examination was normal except for a congenital gaze-evoked downbeat nystagmus, impaired smooth pursuit, and for very mild axial ataxia only noticeable during tandem gait.

Brain MRI was normal (Figure 1). Diffuse slow waves with no epileptic spikes were observed on electroencephalogram. Laboratory assays, neurosonologic examination, and complete cardiologic screening were normal. The cognitive profile was normal.
Given his history, highly suggestive of EA2, he was started on acetazolamide 250 mg/day with an excellent response. Our patient did not experience further EA spells in the 3 years following the introduction of acetazolamide, which was optimally tolerated. The very mild ataxia was no longer appreciable, whereas the nystagmus persisted.

Genetic testing showed a novel heterozygous variant in exon 6 of the CACNA1A gene, c.889G>A (p.G297R). The amino acid modified in our patient (glycine) is well conserved through the species, and in silico analysis (PolyPhen) showed that this missense variant is probably damaging, with the highest possible score of 1.00; the same results were obtained with other bioinformatic tools (Panther, Mutation Tester). This mutation was absent in both parents, who were examined and did not show any features of EA nor other neurological signs. This genetic finding confirmed the diagnosis of EA2 in our patient, who had a highly suggestive clinical picture. The excellent responsiveness to acetazolamide further supported the diagnosis of EA2 (see later).

**Therapy of episodic ataxias**

The mainstays of treatment of degenerative cerebellar ataxia (including EA patients with stabilized ataxia) are currently physiotherapy, occupational therapy, and speech therapy. Specific pharmacological therapies are available for EA1 and especially EA2.

**Episodic ataxia type 1**

Several drugs could improve symptoms in some EA1 patients but, so far, no medication has been proven effective. Furthermore, the responses are variable. Responsiveness to acetazolamide treatment is only occasional in EA1 patients. The antiepileptic drug, phenytoin, is a modulator of voltage-gated Na+ channels that is also capable of decreasing ataxia and myokymia in EA1 patients. However, phenytoin can cause permanent cerebellar dysfunction and atrophy and should be used with extreme caution in these patients. Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, making fewer of these channels available to subsequent opening. It could significantly reduce the frequency of attacks in members of several large families. Even if in some cases the initial response was not sustained, carbamazepine is currently the treatment of choice for EA1.

**Episodic ataxia type 2**

Acetazolamide is the pharmacological treatment of choice for EA2; a dosage between 250 and 1000 mg/day is usually effective. Acetazolamide 250 mg/day could fully suppress EA episodes in our EA2 patient. Alternatively, 4-aminopyridine can be used. Other drugs, including dalfampridine, have been proposed as potential treatment options, but further studies are still needed.

As previously seen, EA2 is a dominant genetic disease caused by mutations in the CACNA1A gene encoding the CaV2.1 subunit of the PQ-type calcium channel, highly expressed in Purkinje cells. The loss in the precision of Purkinje cell pacemaking likely contributes to EA2 symptoms. In a mouse model, Purkinje cells exhibit high-frequency burst firing during attacks. The changes induced by the mutation, resulting in a reduced calcium current, are considered to decrease the inhibitory effect of Purkinje cells. This may result in disinhibition of the deep cerebellar nuclei and therefore ataxia, and also in disinhibition of vestibular nuclei neurons receiving anterior semicircular canal pathways. As aminopyridines (potassium channel blockers) improve nystagmus, their effects on the frequency of attacks in EA2 were evaluated. Specifically, 4-aminopyridine was reported to reduce the frequency of attacks and improve the quality of life in EA2, likely restoring the diminished precision of pacemaking in Purkinje cells, by
increasing the action potential after hyperpolarization and prolonging the action potential.16

A recent systematic review has concluded that for patients with EA2, 4-aminopyridine 15 mg/day probably reduces ataxia attack frequency over 3 months,21 based on one randomized, double-blind, placebo-controlled, crossover, class 1 study performed on 10 patients.22 This study showed that EA2 subjects receiving placebo had a median monthly attack frequency of 6.5, whereas patients taking this drug had a frequency of 1.65 (significant difference, \( p<0.03 \).22 Considering that further controlled trials on 4-aminopyridine are still strongly needed,23 the same review acknowledged that ‘historical treatment approaches, such as the use of acetazolamide for the treatment of EA2, can have clinical value even in the absence of clinical trial evidence’.21 Potential side effects of long-term acetazolamide use include kidney stones; therefore, ultrasound monitoring is warranted. Acetazolamide can be safely administered to patients with a history of antibiotic allergic reactions.24

Recently, an EA2 patient with poor response to acetazolamide has been reported to significantly improve with a combination of acetazolamide 750 mg/day and levetiracetam 750 mg/day.25 Levetiracetam could be effective by inactivating calcium channels,25 but further studies are needed. Furthermore, the muscle relaxant agent, chlorzoxazone, has been proposed as a new potentially effective treatment of EA2.14 In a mouse model of EA2, chlorzoxazone could restore the precision of Purkinje cell pacemaking in a dose-dependent manner.14 Oral administration of chlorzoxazone could improve interictal motor performance and reduce the duration, severity, and frequency of spells of motor imbalance in this mouse model, with no adverse effects.14 Studies in human patients are still needed.

**Conclusion**

We reported here an EA2 case with a novel de novo CACNA1A mutation. Eye movement disorders, including congenital nystagmus as in our patient, are an early manifestation of CACNA1A mutations26 and may strongly help in the diagnostic approach of EA2 patients.

Acetazolamide and 4-aminopyridine are reported to decrease severity and frequency of spells in EA2,27 and represent two valid and generally safe treatment options. A clinical trial focusing on the comparison of acetazolamide and 4-aminopyridine therapy in EA2 patients is ongoing in Munich (EAT2TREAT study). In fact, acetazolamide could fully suppress EA episodes in our patient. Further studies are needed to clarify the potentialities of acetazolamide and 4-aminopyridine in EA2 patients: for instance, can these two drugs be combined? Are their effects synergistic? Studies focusing on the possible utility of levetiracetam and chlorzoxazone are also needed.

For EA1 (and for rarer EAs), the therapeutic options are more limited. To date, carbamazepine is probably the treatment of choice for EA1, but this conclusion is based only on some case reports and case series,18 and the optimal treatment plan is unknown. EAs are still underdiagnosed. Therefore, improved recognition and understanding of EAs is necessary. NGS techniques will represent a useful, time-saving, and cost-effective diagnostic tool for the diagnosis of a patient with an EA phenotype.28 An improved diagnostic approach may help determine early therapeutic intervention strategies and directly affect patient care.29 A greater understanding of the molecular processes involved in the mediation of episodic ataxias (as well as of other paroxysmal movement disorders)30 will lead to more specific and efficacious therapies for this still elusive group of disorders.31,32

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**Correspondence:** Daniele Orsucci, Unit of Neurology, San Luca Hospital of Lucca, Via Lippi-Francesconi, 55100 Lucca, Italy. orsuccid@gmail.com

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