# EPISODIC ATAXIA 1 & 2: CLINICAL CHARACTERISTICS, DIAGNOSIS, AND MANAGEMENT

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**Abstract**

Episodic Ataxias (EAs) are autosomal-dominant inherited ion channelopathies presenting as brief paroxysmal attacks of ataxia with a wide spectrum of associated ictal and interictal neurological symptoms. Episodic Ataxia type 1, (EA1) and Episodic Ataxia type 2(EA2) are the most common forms of EAs, caused by mutations of genes altering the function of the potassium (KCNA1) and calcium (CACNA1A) channels respectively. EA1 is associated with interictal myokymia while EA2 with interictal persistent nystagmus. Moreover, patients with EA2 may present with progressive ataxia and atrophy of the cerebellar vermis. Pharmacological treatments are available for the management of EA1 and EA2.Treatment of choice for EA1 is carbamazepine whereas acetazolamide has a variable effect. In patients with EA2, acetazolamide and 4-aminopyridine seem to be helpful in decreasing the frequency of attacks. Given the genetic and phenotypic heterogeneity of episodic ataxias, next generation sequencing (NGS) could be a diagnostic tool leading to specific and more efficacious therapies.

**Key words**: episodic ataxia type 1, episodic ataxia type 2, genetic channelopathies, KCNA1, CACNA1A

## Introduction

Episodic Ataxias (EAs) represent a group of rare neurological disorders with clinical and genetic heterogeneity. (EAs) are ion channelopathies inherited in an autosomal dominant manner but some sporadic cases have been also described. They are characterized by brief recurrent paroxysmal episodes of ataxia, with a broad spectrum of additional ictal and interictal clinical symptoms [1]. Until now, eight subtypes (EA1-EA8) have been defined by the Online Mendelian Inheritance in Man (OMIM) according to clinical and genetic characteristics. The most common types, EA1 and EA2, are channelopathies caused by mutations of genes altering the function of potassium (KCNA1) and calcium channel (CACNA1A) respectively [2, 3]. Episodic ataxias (EAs)may have also clinical and genetic overlapping with other paroxysmal disorders as familial hemiplegic migraine1 (FHM1), spinocerebellar ataxia type 6 (SCA6) and epilepsy. In this manuscript, we review the literature and focus on the clinical presentation, genetic features and management of the most frequent forms of EAs, EA1 and EA2.

## Clinical and genetic features of episodic ataxia 1 and 2

### *Episodic ataxia type 1*

The prevalence of EA1 is estimated at 1 in 500,000 [4]. EA1 can result from mutations to the potassium channel gene KCNA1, which encodes the voltage-gated potassium channel subunit Kv1.1 [5, 6]. Kv1.1 subunits are expressed in both the central and the peripheral nervous system. However, their highest level is noticed in the Purkinje cells and cerebellar interneurons where they play an important role in nerve repolarization, eventually affecting the inhibitory outputs of the cerebellum [5, 7]. In EA1, a mutation of the KCNA1 gene causes dysfunction of the potassium channel subunit Kv1.1, resulting in excessive inhibition of Purkinje cells outputs, due to hyperexcitability of interneurons [8, 9]. In a small percentage of patients with EA1 symptoms, no mutations were found in the KCNA1 gene, implying the presence of other causative genes [10]. EA1 is characterized by paroxysmal recurrent episodes of vertigo, imbalance and interictal myokymia [11, 12]. Attacks are brief and last from seconds to less than 15 minutes, although longer duration of episodes has been described [13, 14]. During episodes the patients present-cerebellar symptoms, such as incoordination, tremor, dysarthria and imbalance accompanied by diplopia, vomiting, painful body stiffness, diaphoresis and headache [5, 8, 11, 15]. The pathognomonic hallmark of EA1 is the presence of constant interictal myokymia, usually of the perioral, periocular or distal extremities muscles [4, 10, 11]. The frequency of these episodes varies from several times daily to once per month and decreases in adulthood [16]. Episodes can occur spontaneously or may be triggered by stress, physical

exercise, alcohol or caffeine intake, hunger, fever, pregnancy or menstruation in women, temperature, and kinesiogenic stimuli [10, 13]. In addition, many patients present symptoms and signs of neuromyotonia, such as muscle stiffness and twitching, reflecting the involvement of the peripheral nervous system [7]. EA1 onset is typically before the age of 20. Later in the disease course, 20% of patients will develop permanent cerebellar signs and symptoms [10]. It is worth mentioning, that EA1 may also manifest with atypical symptoms such as choreoathetosis, skeletal deformities, delayed motor development, isolated myokymia or neuromyotonia, malignant hyperthermia, cognitive dysfunction, dyspnea during episodes and carpal spasms [12, 13, 17-22]. Epilepsy is represented predominantly in Episodic Ataxia type 1. EA 1 may be associated with generalized tonic-clonic seizures as well as focal seizures. There are also reported cases of photo-sensitive epilepsy [23] and seizures with head and eyes deviation, eyelid fluttering and lip-smacking. [24].

### *Episodic ataxia type 2*

EA2 represents the most common and well characterized subtype of episodic ataxias with an estimated prevalence of less than 1 in 100,000 [3]. Typically, disease onset is between 5 and 20 years of age, even though late-onset cases have been described [16, 25].

EA2 is caused by truncating mutations in CACNA1A gene with loss of function effect [26]. The CACNA1A gene encodes the α1 pore-forming subunit of the neuronal voltage-gated P/Q-type calcium channel [27]. The P/Q-type calcium channel is highly expressed in the cerebellum, particularly in Purkinje cells and granular layer neurons. This neuronal calcium channel has a crucial role in CNS synaptic transmission, as it is located on presynaptic nerve terminals leading to the release of neurotransmitters [28].

EA2 is characterized by paroxysmal episodes of cerebellar dysfunction presenting with incoordination, oscillopsia, vertigo, nausea, ataxia, dysarthria, and nystagmus, which is present as an ictal and interictal sign [25, 26]. Additional ictal clinical features include migraine-like symptoms, dystonia, hemiplegia, and generalized weakness. Typically, patients preserve consciousness during the episodes. EA2 is related to an increased risk of absence epilepsy between episodes [23, 29]. According to recent studies, patients with EA2 demonstrate cognitive dysfunction, with impairment in many domains, as well as psychiatric disorders, such as psychosis, autism, depression, and schizophrenia [30, 31]. Of note, some patients can present initially with paroxysmal torticollis or paroxysmal tonic upward gaze, years before the emergence of ataxic episodes [32, 33]. Episodes usually are triggered by heat, alcohol or caffeine intake, phenytoin, stress, startle, physical exercise or fever [25, 26, 32]. On the contrary, sleep or rest seem to attenuate the attacks [26, 32, 33]. The duration of the episodes ranges between hours to days, while the frequency varies from many times per week to once per year [25].

### Other subtypes of episodic ataxias (EA3-EA8)

There are six other rare subtypes of inherited episodic ataxias (EA3 - EA8). These types have been observed in single families. On most occasions the responsible gene was not identified, expect for the types EA5 and EA6.

EA3 was reported in one family and is characterized by ataxia episodes of short duration with additional signs identical to those of EA1 [34]. However, in EA3 the patients present tinnitus as additional feature to the ataxia, in contrast with EA1 [34]. Episodes of ataxia in EA3 are reported as responsive to acetazolamide.

EA4, previously known as periodic vestibulocerebellar ataxia, was found in two multigenerational North Carolina families [35]. EA4 is considered a late onset episodic ataxia that occurs between third to sixth decade. Patients with EA4 share similar clinical characteristics with EA3, expect the presence of oculomotor manifestations, as gaze-evoked nystagmus and defective smooth pursuit [35]. The episodes of ataxia are not responsive to acetazolamide, as opposed to the most of EAs. It's worth mentioning, that in an autopsy of an old patient with EA4, identical neuropathological findings with SCA-6 has been identified, implying a possible role of CAG repeats in the pathophysiology of EA4. [36]. In EA5 a mutation in CACNB4 gene, that codes the β4 subunit of the voltage-dependent calcium channel, was found in three families [37, 38]. Noteworthily, the same mutation was also reported in a German family with epilepsy without symptoms of ataxia [37]. EA5 is characterized by paroxysmal attacks of ataxia similar to those described in EA2, but with later onset of symptoms [15]. In one patient with EA5 permanent cerebellar ataxia was described [38].

EA6 is due to mutations in the SLC1A3 gene. It was described in a 10-year-old boy and a Dutch family with different clinical phenotypes [39, 40].The 10-year-old patient presented with a combination of ataxia, hemiplegic migraine, and seizures, while the three family members had isolated symptoms of episodic ataxia [39-41].

EA7 was reported only in a single family with similar ictal but without the interictal features of EA2 [42]. EA7 gene locus has been identified to chromosome 19q13.

EA8 was recently identified in an Irish family with symptoms of episodic ataxia [43].The attacks were

characterized by generalized weakness, dysarthria, and unsteadiness, while some of the affected members presented myokymia, twitching around the eyes and nystagmus. Interestingly, these patients responded only to clonazepam with no benefit from acetazolamide. EA8 is considered to be related to a heterozygous mutation in UBR4 gene [43]. In addition, two unrelated cases with symptoms of episodic ataxia and mutation in UBR4 have been described [44].

## Diagnosis

Diagnosis of EA1 and EA2 is mainly based on clinical presentation and molecular genetic testing for KCNA1 and CACNA1A mutations respectively [10]. EA molecular testing should be applied in the presence of paroxysmal or chronic cerebellar signs, particularly in patients with positive family history [8, 36]. In many cases the genetic test has revealed de novo mutations, so the presence of positive family history is not mandatory for the application of CACNA1A or KCNA1 sequencing [22]. EA2 should be considered also in cases with developmental delay, early onset paroxysmal dystonia, epilepsy, or epileptic encephalopathies when family history for EAs or chronic cerebellar signs coexist [32]. Furthermore, during CACNA1A sequencing all the exons must be screened for mutations. Until to date >100 mutations in CACNA1A have been reported, while in EA1 only 47 mutations [46]. In EA1, brain MRI is often normal, while in EA2 cerebellar atrophy, particularly of the vermis is evident [10, 15]. Routine nerve conduction studies in both EA1 and EA2 are normal [33]. However, EMG in patients with EA1 is characterized by the presence of myokymia and the typical findings of neuromyotonia, especially in the muscles of the hand [10, 12]. In EA2, EMG and nerve conduction studies are without significant findings, even though abnormal jitter in single fiber EMG has been described, indicating neuromuscular dysfunction [23, 47]. In addition, epileptiform EEG activity is common in EA2. However, the key clinical diagnostic features for EA1 and EA2 are mainly the interictal manifestations. EA1 presents with interictal myokymia whereas patients with EA2 exhibit interictal nystagmus (downbeat, gaze-evoked or rebound nystagmus) [4].

Finally, EA1 and EA2 –as paroxysmal movement disorders (PxDs)– must be also distinguished from other genetic syndromes with PxDs, mainly from kinesigenic dyskinesia and paroxysmal non kinesigenic dyskinesia [45]. EAs, as mentioned above, are characterized by episodes of cerebellar dysfunction, while PxDs present with attacks of hyperkinetic movements.

A summarized overview of clinical features and differential diagnosis between EA1 and EA2, is provided in Table 1.

## Therapeutic management

### *Episodic ataxia type 1*

Numerous drugs can improve EA1 symptoms but until now, in the absence of comparative studies and trials, no drug has been shown to be strongly effective. In addition, responses to treatment are variable. It is worth noting that the therapeutic response varies even among genotypically similar individuals [8, 10].

The pharmacological treatment of EA1 is mainly based on carbamazepine (CBZ). Occasional response has also been described in treatment with phenytoin or acetazolamide [48]. In addition to the pharmacological treatments mentioned above, the known factors that cause attacks should be avoided. Behavioral measures such as avoiding stress, sudden movements, loud noises, and caffeine can be applied to reduce the manifestations of the disease. Physical and occupational therapies are recommended to enhance mobility, improve fine motor skills and reduce the risk of complications such as contractions, scoliosis or hip dislocation [49].

CBZ is a voltage-gated sodium channel blocker that reduces synaptic transmission of excitatory stimuli by stabilizing overstimulated nerve membranes. CBZ has been used in EA1 in doses up to 1,600 mg/day, with significant improvement in symptoms as well as frequency, severity and duration of attacks. However, CBZ's initial response was not maintained in some cases [50].

The occurrence and severity of EA1 paroxysmal attacks can be alleviated by acetazolamide (ACTZ), a carbonic anhydrase inhibitor. While some patients show improvement with ACTZ, the response to treatment is only occasional. It's mechanism of action in EA1 is unclear. ACTZ exhibits a regulatory effect on intracellular pH. Therefore, ionic channels and ionic conductivity in neuronal membranes can be regulated, causing both hyperpolarization and reduced excitability, which can in turn lead to reduced attacks. Alternatively, ACTZ may decrease the excitability of GABAergic neurons as a consequence of intracellular alkalinization. The usual starting dose is 125 mg with a gradual increase up to 1000 mg maximum in 1-4 divided doses [51]. Eventually the reduced effectiveness of ACTZ and the development of adverse effects lead to the discontinuation of treatment in many patients. Long-term side effects include neuropsychiatric manifestations, hallucinations, nephrolithiasis, rash, fatigue, hyperhidrosis, and gastrointestinal disorders. Treatment with ACTZ should be avoided in people with either hepatic or renal/adrenal insufficiency [50, 52, 53].

Phenytoin is another potent regulator of Na + channels that can also reduce symptoms of ataxia and myokymia in EA1 patients. Phenytoin is usually a second-line drug for typical attacks, at a dose of

**Table 1**. Clinical features/Differential diagnosis of Episodic Ataxias type 1 and 2

| | EA1 | EA2 |
|---|---|---|
| **Gene** | KCNA1 | CACNA1A |
| **Chromosome** | 12p13 | 19p13 |
| **Channel type** | Potassium channel, Kv1.1 | Calcium channel, Cav2.1 |
| **Inheritance** | Autosomal dominant | Autosomal dominant |
| **Age of onset** | 1st to 2nd decade | 2nd to 3rd decade |
| **Attack duration** | Seconds to minutes | Hours to days |
| **Frequent ictal symptoms** | Vertigo | Incoordination, vertigo, dysarthria |
| **Interictal symptoms** | Myokymia | Nystagmus, late onset persistent cerebellar syndrome |
| **Episode triggers** | Stress, physical exercise, alcohol or caffeine intake, hunger, fever, pregnancy or menstruation in women, temperature and kinesiogenic stimuli. | Heat, alcohol or caffeine intake, phenytoin, stress, startle, physical exercise or fever. |
| **Associated features** | Neuromyotonia, distal weakness, epilepsy, dysarthria | Migraine, dystonia, tremor, cognitive impairment, generalized weakness, tonic upward gaze |
| **Treatment of choice** | Carbamazepine<br><br>Acetazolamide (variable response) | Acetazolamide (adequate response)<br><br>4-aminopyridine Dalfampridine |
| **Brain MRI** | Usually, normal | Cerebellar vermian atrophy |
| **EMG** | Neuromyotonia, myokymic discharges | Usually normal, abnormal jitter on single fiber EMG in patients with episodic weakness |

Abbreviations: MRI: Magnetic resonance imaging, EMG: Electromyography

3.7 mg/kg/day. In some cases, phenytoin but not acetazolamide has been shown to be effective for both ataxia and dyskinesias. In some cases, however, phenytoin had no therapeutic effect. Phenytoin should be used cautiously especially in younger ages, as it can cause permanent cerebral atrophy and dysfunction.

Diphenylhydantoin at doses of 150-300 mg/day led to a reasonable seizure control in a number of patients. Sulthiame is a carbonic anhydrase inhibitor that reduces the occurrence of seizures, at doses of 50-200 mg/day. However abortive attacks of a few seconds can still be observed during treatment. Paresthesias and paroxysmal carpal spasms are some of the side effects associated with sulthiame use [50, 52].

Valproic acid and Lamotrigine are sometimes used as an alternative treatment, as they lead to a reduction in seizures in some patients. Recently, some authors suggested the use of riluzole as a possible treatment option for type 1 episodic ataxia. Although there are no reports of the use of riluzole in EA1, riluzole has been used successfully in patients with cerebellar ataxia of other causes, spinocerebellar and Friedrich's, ataxia without significant side effects. Its effectiveness must be confirmed by further studies in EA1 [50, 52, 53].

### *Episodic Ataxia 2*

For the most common subtype of EA, episodic ataxia type 2, two treatment options have been described: acetazolamide, and 4-aminopyridine (4-AP). The general therapeutic principles that apply to all episodic ataxias include physiotherapy, kinesiotherapy, occupational therapy, speech therapy and special education as well as orthotic devices for gait disturbances. Patients should be encouraged to avoid any triggers that could exacerbate the symptoms. All patients and families should receive genetic counseling.

The treatment of choice for ataxic attacks in EA2 is ACTZ with a response rate around 50-70%. Initial dose is usually 250 mg/day in two divided doses. The effective daily dose may be between 250 and 1000

**Table 2**. Treatment of Episodic Ataxias type 1 and 2

| | Drug | Dose | Comments |
|---|---|---|---|
| **EA1** | Carbamazepine | up to 1,600 mg daily | Initial response not maintained in some cases. |
| | Acetazolamide (ACTZ) | 250- 1000 mg max in divided doses | Response to treatment is only occasional |
| | Phenytoin | 3.7 mg/kg | Second-line drug for typical attacks<br>Caution especially in younger ages<br>Contraindicated in EA2. |
| | Diphenylhydantoin | 150-300 mg daily | Adequate seizure control in some patients with epilepsy. |
| | Sulthiame | 50-200 mg daily | Abortive attacks |
| | Valproic acid (VPA) & Lamotrigine (LMT) | VPA: 750mg daily,<br>LMT:75-100mg daily | Alternative treatments |
| | Riluzole | 50 mg bid | Possible treatment. No reports in EA1 |
| | | | |
| **EA2** | Acetazolamide (ACTZ) | 250-1000 mg daily in divided doses | Treatment of choice<br>Higher doses may be required |
| | 4-aminopyridine (4-AP) | 5 mg tid. | For non-responders or having side effects from ACTZ. Contraindicated in patients with epilepsy |
| | Dalfabridine | 10 mg bid | Further studies are needed |
| | Levetiracetam | 250-1500 mg daily | Reports of a good response in combination with ACTZ |
| | Acetyl-DL-leucine | 5 gr/day | In combination with 4-AP<br>Further studies are needed n EA2 |
| | Benzodiazepines | Low doses | Symptomatic relief (dizziness, nausea, sleep disorders) |
| | Chlorozoxazone | – | Only in mice models with EA2.<br>Studies in human patients still needed. |

mg, and higher doses may be required. Acetazolamide can stop attacks by lowering the abnormally high intracellular pH by subsequently activating and deactivating the sodium and calcium channels respectively. It is worth noting that some patients have no or only transient symptomatic benefit while others discontinue acetazolamide treatment due to adverse reactions [45].

4-AP is a selective potassium channel blocker that is believed to restore Purkinje cells pacemaking in the cerebellum [49]. 4-AP can be used in patients with EA2 who are non-responders to acetazolamide treatment or discontinued therapy due to side effects. The efficacy of 4-aminopyridine has been confirmed in a randomized controlled trial in adolescents and adult patients with EA2.This study showed a significant reduction in number, severity and duration of ataxia attacks compared to the placebo group as well as a significant improvement in the quality of life of patients. The usual dosage is 5-10 mg tid. 4-AP is contraindicated in patients with epilepsy due to dose-dependent risk of seizures [54-56].

Other drugs, including dalfabridine (prolonged-release 4-aminopyridine, fabridine), have been suggested as possible treatment options with positive results at 10 mg twice daily, but further studies are needed [57].

There are also reports of a good response with the combination of levetiracetam and acetazolamide [58]. This favorable outcome is believed to be due to the inactivation of calcium channels, induced by levetiracetam [59]. A good clinical response has been also described with the combination of 4-AP with the amino-acid acetyl-DL-leucine (5 gr day). Three case series that included different types of cerebellar ataxias showed that Acetyl-DL-leucine has considerably improved cerebellar symptoms, but further studies are needed for its efficacy in EA2 [60]. In addition, the

muscle relaxant chlorozoxazone has been proposed as a potentially new treatment based on mice models with EA2, but its effectiveness remains to be studied in humans [48]. Low-dose benzodiazepines can be used for symptomatic relief, in order to minimize symptoms of severe dizziness and nausea, but also to improve sleep disorders in patients.

## Conclusions

EAs are underdiagnosed neurologic disorders. A better diagnostic approach is needed for the recognition and early treatment of patients with an EA phenotype. Next generation sequencing (NGS) will represent a diagnostic tool leading to specific and efficacious therapies for this heterogeneous group of genetic disorders [48]. Given the different gene mutations that are implicated in the pathogenesis of EAs, gene therapy could be a promising therapeutic option in the future by using splicing-based strategies [46].

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