Movement Disorders
CLINICAL PRACTICE
REVIEW

The Clinical Spectrum of Autosomal-Dominant Episodic Ataxias

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Abstract: Autosomal-dominant episodic ataxias (EAs) represent a clinically and genetically heterogeneous group of disorders characterized by recurrent episodes of cerebellar ataxia (CA). Ataxia episodes are usually of short duration and often triggered by specific stimuli. There are currently seven classified subtypes of EA. EA types 1 and 2 have the highest prevalence and are therefore the clinically most relevant. Between attacks, EA 1 is associated with myokymia. In EA 2, often an interictal downbeat nystagmus with other cerebellar ocular dysfunctions is present; patients with EA 2 may display slowly progessive ataxia and vermian atrophy. EA 1 and 2 are both channelopathies, affecting the potassium channel gene, *KCNA1*, in EA 1 and the PQ calcium channel-encoding gene, *CACNA1A*, in EA 2. The types EA 3 to 7 are very rare and have to be further elucidated. Here, we review the historical, clinical, and genetic aspects of autosomal-dominant EAs and their current treatment, focusing on EA 1 and 2.

In 1986, Gancher and Nutt, from Portland, Oregon, described three distinct syndromes of autosomal-dominant episodic cerebellar ataxias (CAs) in the first volume of *Movement* Disorders.[1] Retrospectively, two of these syndromes correspond to episodic ataxia (EA) type 1 (EA 1) and type 2 (EA 2). The first published reports on the EA disease spectrum date back to 1946 by H.L. Parker from the Mayo Clinic.[2] In 1978, acetazolamide (ACT) treatment was introduced in a subset of EA patients by R. Griggs from Rochester, New York.[3] Missense mutations were first found in a potassium channel gene of EA 1 patients and in a calcium channel gene in patients with EA 2. Thus, EA 1 and 2 are both channelopathies, affecting the potassium channel gene, *KCNA1*, in EA 1 and the PQ calcium channel-encoding gene, *CACNA1A*, in EA 2, respectively. Subsequently, autosomal-dominant EAs were categorized on a clinical and genetic basis in seven subtypes, the most prevalent and clinically relevant being EA 1 and 2.[4] Between ataxia attacks, EA 1 is associated with myokymia. In EA 2, often an interictal downbeat nystagmus with other cerebellar ocular dysfunctions is present; patients with EA 2 may display slowly progessive ataxia and vermian atrophy. Besides ataxia, the various types of EAs are variably associated with a broad spectrum of paroxysmal neurological symptoms, including epilepsy, movement disorders, hemiplegic migraine, and myasthenic syndrome. There is a high variability of these symptoms even among subjects with the same mutations or concordant twins, suggesting that nongenetic factors might modulate the phenotype.[5] There is no such high variability in interictal EA features.

The Clinical Spectrum of EAs

Mutations of the potassium channel-encoding gene (*KCNA1*) result in EA 1, which is characterized by brief attacks of midline cerebellar dysfunction, including limb ataxia, nystagmus, dysarthria, and tremor.[1] The world-wide prevalence is estimated at 1 in 500,000.[6] Onset of EA 1 is typically in early childhood. Attacks consist of ataxia and sometimes are associated with dysarthria and tremor.[7,8] Vertigo is usually absent.[9] Typically attacks are of brief duration (<15 minutes) and may occur up to 30 times per day. Atypical variants with longer duration of episodes have been reported.[7,10] Attacks occur spontaneously or may be triggered by shock, anxiety, exercise, kinesiogenic stimuli, emotional stress, alcohol intake, intercurrent illness, and hunger.[7] Usually, there are no cerebellar deficits between attacks, but ataxia, hearing impairment, and postural tremor of the head and hands have been described.[7,8,11] Approximately 20% of EA 1 individuals will accumlate persistent cerebellar

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symptoms and signs over time.[12] Interictal myokymia is pathognomonic, but not specific for EA 1. It has been speculated that myokymia results from ectopic impulse generators within peripheral nerves.[7,13,14] Other neuromuscular findings include painful stiffness and distal weakness, moderate muscle hypertrophy, and generalized increase in muscle tone associated with hypercontracted posture.[6,8] The fact that some EA 1 patients display cognitive dysfunction, delayed motor development, choreoathetosis, carpal spasms, shortening of the Achilles' tendon, clenching of the fists, and isolated myokymia argues against a pure cerebellar syndrome.[7,8,15–17] Furthermore, skeletal deformities, a higher incidence of tonic-clonic seizures, intermittent head turning and eye deviation to the same side, and breathing disorders during ataxic episodes have rarely been reported in EA 1.[8,15,18,19]

EA 2 was mapped to the *CACNA1A* gene on chromosome 19p13, which encodes a calcium channel.[4] EA 2 usually presents with recurrent episodes of vertigo and ataxia lasting for hours to days. The consortium for Clinical Investigation of Neurological Channelopathies estimated the prevalence of EA 2 as less than 1:100,000.[20] In EA 2, attacks usually last longer than 10 minutes and consist of midline CA. The frequency of the attacks ranges from four times per week to once per year. Typical triggers of ataxic episodes are emotional stress and exercise.[21] Other triggers include alcohol or caffeine intake, fever, and phenytoin treatment.[20,22] Clinical onset is typically in the first two decades of life, but late-onset cases have been reported.[23] Vertigo and dizziness (at least half of the patients), nausea, and vomiting are the most common associated symptoms (see Video 1).[21] During attacks, patients may clinically exhibit severe ataxia, dysarthria, and primary position downbeat or gaze-evoked nystagmus.[24] Other attack features include diplopia, dysarthria, dystonia, and weakness. Additionally, there may be symptoms suggestive of brain stem and cortex involvement.[24–26] Approximately 90% of EA 2 subjects show an interictal nystagmus, mainly gaze-evoked or primary position downbeat nystagmus.[27] Other neuro-ophthalmological findings include impairment of visual tracking, optokinetic nystagmus, and suppression of the vestibulo-ocular reflex (see Video 2). Saccade dysmetria and slowing of mean saccade velocity have been reported.[22,24,28] Furthermore, patients with EA 2 display an increased epilepsy risk, compared to the background population.[29] Gradual progressive baseline ataxia occurs in up to 50% of EA 2 patients.[30] Approximately 50% of EA 2 subjects complain of frequent headaches, which fulfill the International Headache Society (IHS) criteria of migraine.[30] Unusual features of EA 2 include cognitive deficits, abdominal pain, and possibly strabismus and hyperactivity disorders.[31] Focal and segmental dystonia was reported in carriers of truncating *CACNA1A* mutations.[32] Furthermore, there are several reports on paroxysmal torticollis and blepharospasm.[33–36] Animal models using *CACNA1A*-mutant mice suggest that paroxysmal dystonia may result from disruption of a motor network involving both the basal ganglia and cerebellum.[37]

EA type 3 (EA 3), for which no specific mutations have been identified thus far, is characterized by attacks of vertigo, tinnitus, and ataxia.[38] EA type 4 (EA 4) does not link to EA 1 and 2 loci and is accompanied by episodes of generalized ataxia, diplopia, imbalance, and vertigo.[39] EA type 5 (EA 5) results from a mutation of a gene (*CACNB4*) encoding for voltage-activated Ca^{2+} channels, which results in ACT-responsive recurrent episodes of vertigo and ataxia.[40] Mutations in the *SLC1A3* gene impair glutamate transporter function and lead to EA type 6 (EA 6), which is associated with episodic and progressive ataxia.[41] EA type 7 (EA 7) is associated with long-lasting attacks of weakness and dysarthria; no specific mutations have been identified as yet.[42] EA 2, EA 3, EA 5, and, to some extent, EA 1 are considered to be ACT-responsive disorders.[43] An overview of clinical features of EA 1 to 7 is given in Table 1 and Supporting Table 1.

Furthermore, several reports on unclassified familial EAs have been published recently; Conroy et al. describe a three-generation Irish family with an EA phenotype associated with ictal slurred speech and an unreported locus (candidate gene *UBR4*) on chromosome 1.[44] Proline-rich transmembrane protein gene (*PRRT2*) mutations have also rarely been associated with an EA phenotype.[45,46] Cha et al. reported late-onset episodic vertical oscillopsia with interictal downbeat nystagmus and slowly progressive gait ataxia.[47] Genetic testing for EA 1 and 2 and for SCA 1, 2, 3, and 6 were negative. A region of suggestive linkage was identified on chromosome 13.

TABLE 1 Main features of episodic ataxia types 1 to 7

	EA1	EA2	EA3	EA4	EA5	EA6	EA7
Gene	*KCNA1*	*CACNA1a*	Unknown	Unknown	*CACNB4*	*SLC1A3*	Unknown
Gene product	Kv1.1	Cav2.1	—	—	Cav2.1	EAAT1	—
Attack duration	<15 minutes	>10 minutes to hours	Minutes to hours	Brief	Hours	Hours to days	Hours to days
Frequent ictal symptoms*	Vertigo	Nystagmus, dysarthria, vertigo	Tinnitus, vertigo	Vertigo, diplopia, imbalance	Vertigo	Seizures, migraine, hemiplegia	Weakness, dysarthria
Interictal symptoms	Myokymia, epilepsy	Nystagmus, migraine epilepsy	Myokymia, nystagmus, epilepsy	Nystagmus	Nystagmus, epilepsy, ataxia	Ataxia, epilepsy	None
Acetazolamide response	Occasionally	Usually	Usually	No	Occasionally	No	Occasionally

*Excluding ataxia.

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Genetic and Molecular Aspects of EAs

The Online Mendelian Inheritance of Man (http://www.omim.org) currently lists seven clinical EA phenotypes (Table 1). Thus far, four causative genes have been identified.

EA 1 represents the first discovered human brain-specific channelopathy.[14] Heterozygous, usually missense mutations in the *KCNA1* gene on chromosome 12p13 cause this autosomal-dominant disorder.[14] The *KCNA1* gene consists of one single exon and encodes the alpha subunit of Kv1.1, a voltage-gated potassium channel, which plays a crucial role in controlling neuronal excitability.[14] Thus far, at least 28 (mostly missense) mutations have been described.[4,5,11,16,18,19] In vitro studies suggest that Kv1.1 mutations impair channel function and increase neuronal excitability.[17,48] The degree and severity of these dysfunctions may explain the various EA 1 phenotypes.[4] Kv1.1 channels are preferentially localized on gamma-aminobutyric acid (GABA)-ergic cerebellar interneurons and are highly expressed in the hippocampus and in myelinated peripheral nerves.[49] Electrophysiological recordings from cerebellar Purkinje cells (PCs) in a *KCNA1* knock-in mouse model suggest that *KCNA1* mutations alter the excitability of the cerebellum. In myelinated nerves, Kv1.1 channels are densely expressed in the juxtaparanodal region of the axon.[50] Activation of these K^+ channels reduces resistance of the intermodal membrane and limits axonal hyperexcitability after an action potential.[51] Mutant channels thus are expected to lead to excessive excitability of neurons.[52]

EA 2 is caused by a wide range of mutations in the *CACNA1A* gene, which contains 47 exons and is located on chromosome 19p13. *CACNA1A* encodes a voltage-gated Cav2.1 P/Q-type calcium channel (Cav2.1 channel).[20,53] In 1996, Ophoff et al. found four missense *CACNA1A* mutations in familial hemiplegic migraine type 1 (FHM1) and two *CACNA1A* mutations disrupting the reading frame in unrelated patients with EA 2.[53] Thus, EA2 and FHM1 are allelic disorders. Subsequently, expansion of a polymorphic CAG repeat segment in *CACNA1A* was reported in patients with SCA6.[54] The great majority of *CACNA1A* mutations associated with an EA 2 phenotype are nonsense mutations or defects in splice sites predicting a premature stop, resulting in a truncated protein product.[55,56] Cav2.1 channels are abundantly expressed in the cerebellum and at the neuromuscular junction. Because EA 2 is most often caused by loss-of-function mutations, it is associated with reduced calcium currents.[57] Mutant channels probably lead to an altered or reduced calcium-dependent neurotransmitter release, which, in turn, leads to altered intrinsic firing properties of the inhibitory effect of GABA-ergic PCs.[57,58] However, markedly decreased calcium currents resulting from reductions of calcium conductance, as found in EA 2–causing mutations, have not been observed in mutations causing SCA6 or FHM1.[21] Dysfunction of Cav2.1 channels has also been associated with altered time-varying responses to transient increases in corticomotor excitability.[59] Fluctuating muscle weakness of EA 2 patients is most probably the result of a presynaptic defect in neuromuscular transmission. In vitro microelectrode studies showed an increased jitter and blocking on single-fiber electromyography (EMG).[60] Most EA 2 cases are familial, but sporadic mutations were also described.[24,30] To date, at least 77 different mutations in *CACNA1A* have been associated with an EA 2 phenotype, but specific *CACNA1A* mutations do not strictly predict the EA 2 phenotype.[25,61] In line with this, a novel *CACNA1A* missense mutation has been recently associated with nonepisodic SCA with slow progression.[62] To date, approximately only one third of suspected EA 2 cases could be associated with a detectable *CACNA1A* mutation.[11,35]

Candidate genes have yet not been identified for EA 3, 4, and 7 (Supporting Table 1).

EA 5 is caused by a mutation in the *CACNB4* gene on chromosome 2q22-13.[40] This gene encodes an isoform of the beta subunit of voltage-activated Ca^{2+} channels. Mutations in *CACNB4* are also found in generalized epilepsy and juvenile myoclonic epilepsy.[63]

EA 6 is caused by mutations in the *SLC1A3* gene, encoding glial excitatory amino acid transporter 1 (EAAT1). EAAT1 is primarily expressed in the cerebellum, caudal brainstem, and diencephalon, mediates secondary active glutamate transport, and functions as an ion channel. A disease-associated point mutation (P290R) has been shown to result in a reduced number of this transporter in the surface cell membrane and to impair its associated glutamate uptake.[64] Nevertheless, the mutant channel shows larger anion currents than wild-type cells, which argues for a gain of function. EA 6 represents the first human disease found to be associated with altered function of excitatory amino acid transporter anion channels.[64]

Recently reported EA phenotypes, which are associated with *PRRT2* (and possibly *UBR4*) mutations demonstrate that ion channel dysfunction is not the unique pathophysiological mechanism of EA.[45]

Diagnostic Approach and Differential Diagnosis in EAs

Commercially genetic testing is currently available only for EA 1 and 2. In genetically negative EA 2 cases, mutations in *CACNA1A* promotor regions and introns, as other EA types (especially EA 6), have to be considered.

In EA 1, progressive ataxia occurs in a small proportion of individuals, but cerebellar atrophy seems to be rare.[12,16] EMG at rest of EA 1 subjects may show continuous spontaneous activity or afterpotentials and myokymic discharges.[13,52] In addition, the diagnostic utility of nerve excitability studies has been demonstrated in EA 1 recently.[52] In EA 2, brain MRI may display an atrophy of the midline cerebellum, which is more accentuated in patients with long-standing disease with persistent interictal ataxia.[20] A small proportion of EA 2 patients complain of weakness during attacks, which is probably the result of presynaptic failure of neuromuscular transmission and synaptic remodeling. However, routine EMG and nerve conduction studies in EA 2 usually are unremarkable, but single-fiber EMG and morphological studies of the neuromuscular

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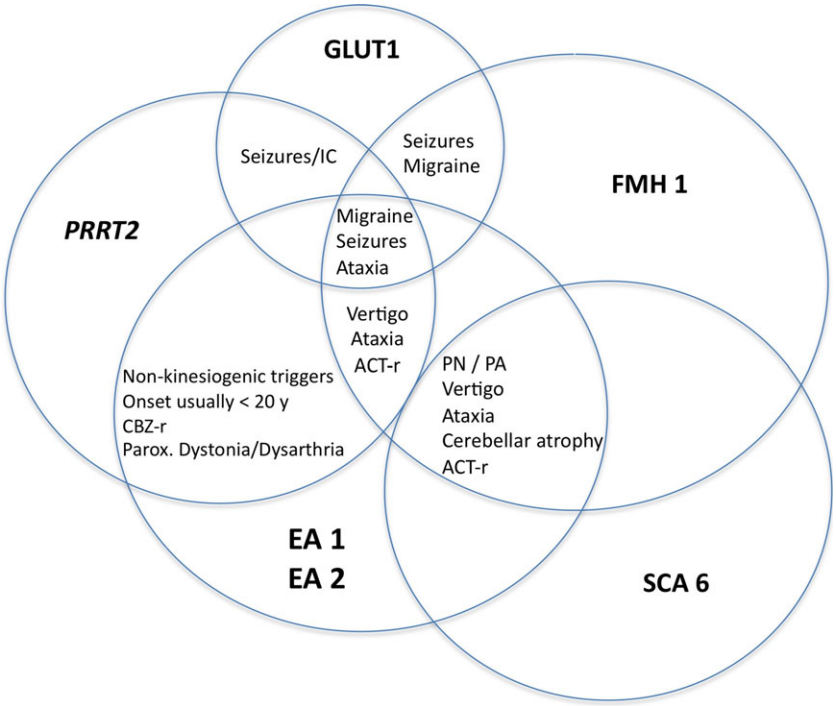

Figure 1 Clinical overlap of EA 1 and 2 and its differential diagnoses. ACT-r, (possibly) acetazolamide responsive; CBZ-r, (possibly) carbamazepine responsive; IC, infantile convulsions; PA, permanent ataxia; parox., paroxysmal; PN, permanent nystagmus; *PRRT2*, proline-rich transmembrane protein gene (*PRRT2*) mutations.

junction may demonstrate signs of impaired neuromuscular transmission.[65] Abnormal epileptiform EEG findings are frequent in EA 2 patients.[29]

The differential diagnoses of the EA spectrum diseases mainly include migraine, in particular, vestibular migraine, glucose transporter type 1 (GLUT1) deficiency syndrome, and *PRRT2* mutations (Fig. 1). Preliminary studies show no higher frequencies of *CACNA1A* mutations in migraine with or without aura.[66]

Interictal clinical key features are of important diagnostic value. Because EA 1 and 2 represent the majority of diagnosed EA cases, one should systematically look for interictal myokymia, nystagmus, and ataxia. Onset of EA 1 and 2 is very rare after the age of 20. A negative family history does not rule out EA because sporadic cases have been described both in EA 1 and 2.[24]

CACNA1A allelic disorders such as FHM1 and SCA6 are common differential diagnoses of EA 2 and are sometimes (FHM1) or usually (SCA6) associated with progressive ataxia. Especially in FHM1 patients, a progressive cerebellar dysfunction may lead to a phenotype that is clinically indistinguishable from EA 2 (Fig. 1).[67] Moreover, fluctuating disease course with treatment response to acetazolamide in SCA6 is possible.

Therapy

ACT, carbamazepine (CBZ), and valproic acid have been shown to be effective in some EA 1 subjects.[68] Phenytoin is contraindicated in EA 2, but one article reports good control of symptoms in EA 1.[69] Approximately two thirds of EA 2 patients respond to ACT treatment (250–1,000 mg/day).[3,30] However, placebo-controlled trials about the efficacy of ACT are lacking, and side effects (e.g., kidney stones) limit its therapeutic use.

Efficacy of the potassium channel blocker, 4-aminopyridine (4-AP), in EA 2 was shown in an observational study in 2004.[70] 4-AP treatment was safe and associated with a reduction of attacks. Furthermore, positive effects of 4-AP on ataxia attacks have been confirmed in studies using an animal model of EA 2, the tottering mouse.[58,71] In 2011, a randomized, placebo-controlled, double-blind, crossover trial demonstrated a significant effect of this agent on the number of attacks and quality of life.[72] Therefore, we recommend 4-AP in a dosage of 5 to 10 mg 3 times a day in EA 2 patients with no, or a declining, ACT treatment response. Recent results from an observational study suggest that the sustained release form of 4-AP is also effective and well tolerated.[73] Furthermore, segmental dystonia in EA 2 has recently been successfully treated by DBS.[36]

Perspectives

There are several promising ongoing and proposed clinical trials in EA research. Performing a next-generation sequencing study, E. Mantuano from Rome tries to identify new genes involved in EA syndromes. To achieve this, whole-genome sequencing in a series of extended multigenerational EA pedigrees (in which known EA-causative genes were excluded) will be used.

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Furthermore, there are two ongoing placebo-controlled trials with the sustained release form of 4-AP (University of California, NCT01543750) and a randomized, controlled three-arm phase III trial comparing the sustained release form of 4-AP with ACT and placebo (EAT2TREAT; EudraCT-Nr.: 2013-000107-17; University of Munich, EAT-2-TREAT, EudraCT-Nr.: 2013-000107-17).

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

S.K.: 1A, 1B, 1C, 3A

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Supporting Information

A video accompanying this article is available in the supporting information here.

SUPPORTING TABLE 1. Overview of genetic aspects and clinical features of episodic ataxia types 3 to 7.

Video 1. EA 2 patient history.

Video 2. Downbeat nystagmus syndrome: typical finding in patients with episodic ataxia type 2. A downbeat nystagmus occurs in the primary position; it intensifies during convergence or when looking to the side. It is typically associated with a gaze-evoked nystagmus and saccadic smooth pursuit, in particular, in the vertical plane. These are typical ocular motor findings for a dysfunction of the cerebellum, namely, the flocculus and paraflocculus. Nystagmus is superimposed over gaze pursuit. When testing the vertical optokinetic nystagmus, the downbeat nystagmus appears to be lessened when the stimulus pattern is turned downward.

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