Primary episodic ataxias: diagnosis, pathogenesis and treatment


Introduction

Episodic ataxias are rare neurological conditions characterized by spells of incoordination and imbalance, often with associated progressive ataxia. The genes lesioned in episodic ataxia of early onset include neuronal voltage-gated potassium and calcium channels, which are widely distributed in the nervous system but are particularly abundant in the cerebellum. The genetic identification of these genes broadened the clinical spectrum of episodic ataxia, now known to be variably associated with epilepsy, dystonia, hemiplegic migraine, myasthenia and even intermittent coma. How mutations in these ion channel genes cause a broad spectrum of paroxysmal neurological symptoms and lead to progressive neurodegeneration is not understood. Furthermore, there is much variation regarding clinical manifestations and response to medications even among patients with the same mutations, suggesting that other factors modulate the phenotypic expression of disease-causing mutations. Episodic ataxia is clinically and genetically heterogeneous (Table 1); many patients with episodic ataxia, especially those with onset after early adulthood (Julien et al., 2001) or no interictal signs, await further genetic characterization and mutation identification.

The major symptoms and disability of episodic ataxia are episodic ataxia and progressive, inter-attack weakness, dystonia and ataxia. The symptoms are mainly cerebellar in origin. The cerebellum does not initiate movement, but it compares what the cortex wished to accomplish and what the spinal cord actually executed to modulate cortical activities and orchestrate the timing of contraction and relaxation of the agonist and antagonist muscles to perform complex motor tasks. At the core of the cerebellar computational circuitry are the Purkinje cells, which integrate cortical and sensory excitatory and inhibitory inputs, encode relevant information in their firing rate, then relay the information to the deep cerebellar nuclei for the final output of the cerebellum. There is an enormous convergence of synaptic activity onto each Purkinje cell, with input from mossy fibres, parallel fibres, climbing fibres and noradrenergic fibres. In principle, defects in any of these components can result in cerebellar dysfunction and ataxia.
At least six episodic ataxia (EA) syndromes have been described, but only EA1 and EA2 have been documented in multiple families. Recent genetic discoveries are providing insight into the molecular mechanisms of these dramatic clinical disorders (Table 1). The incidence of episodic ataxia is likely to be less than 1/100 000, based on the cases seen by experts in regional centres.

**EA1**

**Clinical features**

Autosomal dominant episodic ataxia type 1 (EA1) is characterized by brief episodes of ataxia (seconds to minutes) and interictal myokymia (also termed neuromyotonia) (Browne et al., 1994). The onset is typically in early childhood. The episodes of ataxia, which can be associated with dysarthria and a coarse tremor, are typically precipitated by physical and emotional stress, startle or sudden movements (Brunt and Van Weerden, 1990). Aura-like symptoms, including a feeling of falling or weakness, may also occur. The interictal myokymia may be detected clinically or may only be apparent by surface or needle electromyography (EMG). Phenotypic variants such as the combination with partial epilepsy, shortening of the Achilles tendon in children, transient postural abnormalities in infancy, peripheral weakness and neuromyotonia without episodes of ataxia have also been reported (Zuberi et al., 1999; Eunson et al., 2000; Klein et al., 2004). Although the typical duration of attacks is seconds to minutes, recurring up to 30 times a day, atypical variants with prolonged attacks lasting 5 to 12 h have also been described (Lee et al., 2004).

**Genetic characteristics**

The EA1 locus was mapped to chromosome 12q near a cluster of three potassium channel genes (Litt et al., 1994). Missense mutations in KCNA1 were discovered in multiple EA1 pedigrees (Browne et al., 1994, 1995). These were the first report of mutations in a human potassium channel gene and the first known ion channel mutations involving the brain.

**Table 1 Clinical features of the primary episodic ataxia syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Attack duration</th>
<th>Age of onset</th>
<th>Myokymia</th>
<th>Nystagmus</th>
<th>Epilepsy</th>
<th>Tinnitus</th>
<th>Acetazolamide</th>
<th>Inheritance</th>
<th>chr locus</th>
<th>Mutated gene</th>
<th>Mutant protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA1</td>
<td>160120</td>
<td>sec–min</td>
<td>2–15</td>
<td>usual</td>
<td>no</td>
<td>infrequent</td>
<td>occasional</td>
<td>usual</td>
<td>AD</td>
<td>12q13</td>
<td>KCNA1</td>
<td>Kv1.1</td>
</tr>
<tr>
<td>EA2</td>
<td>108500</td>
<td>hours</td>
<td>2–20</td>
<td>no</td>
<td>usual</td>
<td>infrequent</td>
<td>occasional</td>
<td>usual</td>
<td>AD</td>
<td>19p13</td>
<td>CACNA1A</td>
<td>Cav2.1</td>
</tr>
<tr>
<td>EA3</td>
<td>606554</td>
<td>1min–6hr</td>
<td>1–42</td>
<td>usual</td>
<td>usual</td>
<td>usual</td>
<td>no</td>
<td>usual</td>
<td>AD</td>
<td>1q42</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>PATX/EA4</td>
<td>606552</td>
<td>brief</td>
<td>23–60</td>
<td>no</td>
<td>usual</td>
<td>occasional</td>
<td>no</td>
<td>no</td>
<td>AD</td>
<td>2q22-q23</td>
<td>CACNB4</td>
<td>Cav2.1</td>
</tr>
<tr>
<td>EA5</td>
<td>601949</td>
<td>hours</td>
<td>3–teen</td>
<td>no</td>
<td>usual</td>
<td>occasional</td>
<td>no</td>
<td>no</td>
<td>AD</td>
<td>5p</td>
<td>SLCA1A</td>
<td>Unknown</td>
</tr>
<tr>
<td>EA6</td>
<td>600111</td>
<td>hours–days</td>
<td>5</td>
<td>no</td>
<td>usual</td>
<td>occasional</td>
<td>no</td>
<td>no</td>
<td>AD</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1** EA1 mutations in Kv1.1 represented in two dimensions. The predicted structure includes six transmembrane segments (S1–S6). Four such subunits come together to form a functional voltage-gated potassium channel. S4 with regularly spaced positively charged residues is the main voltage sensor. S5, S6 and the re-entrant P loop form the pore with selectivity for K⁺. Circles represent missense mutations; the cross represents a nonsense mutation.

**Genotype–phenotype correlations**

To date, 19 missense mutations and one truncation mutation in KCNA1 have been reported (Browne et al., 1994, 1995; Comu et al., 1996; Scheffer et al., 1998; Zerr et al., 1998; Bretschneider et al., 1999; Zuberi et al., 1999; Eunson et al., 2000; Knight et al., 2000; Kinlai et al., 2004; Klein et al., 2004; Lee et al., 2004; Chen et al., 2006; Poujois et al., 2006) (Fig. 1). The mutations are distributed throughout Kv1.1. *In vitro* expression studies indicate that all mutations impair Kv1.1 function, predicting increased neuronal excitability (Adelman et al., 1995; Bretschneider et al., 1999; Eunson et al., 2000; Rea et al., 2002). The degree and nature of the potassium channel dysfunction appears to explain the phenotypic diversity observed.
Mutations associated with relatively severe phenotypes poorly responsive to medications or associated with seizures tend to show profound reductions in potassium currents when compared to wild type. On the other hand, mutations associated with neuromyotonia alone without ataxia do not alter current amplitude and have only subtle effects on voltage threshold and time course of activation. Mutations associated with the more typical EA1 phenotype show an intermediate pattern; the current amplitude is unaffected but the voltage threshold for activation is significantly increased.

**Pathophysiology**

Kv1.1 is a human homolog of the Shaker channel in Drosophila (Papazian et al., 1987) and is abundantly expressed in the cerebellum and perinodally along motor axons (Wang et al., 1994). Most of the mutations involve the transmembrane segments of the Kv1.1 subunit altering channel dynamics. Well-known triggers for episodes of ataxia include stress, caffeine, hormonal changes and fatigue. The mechanism by which these triggers initiate attacks is largely unknown.

**Animal models**

The KCNA1 knockout mouse, which lacks Kv1.1 channels, suffers from epileptic seizures but not episodic ataxia (Smart et al., 1998). More recently, a knockin mouse model bearing the human EA1 mutation V408A was created by homologous recombination. (Herson et al., 2003). In contrast to the KCNA1 null mutation, the V408A mutation is embryonic lethal in the homozygous state. In contrast, heterozygous V408A/+ mice exhibit stress-induced loss of motor coordination that is ameliorated by acetazolamide, similar to human patients with EA1. Consistent with the Kv1.1 localization in GABAergic cells in the cerebellum, recordings of spontaneous inhibitory post-synaptic currents (IPSCs) in Purkinje cells from cerebellar slices of V408A knockin mice reveal an increased frequency and amplitude of IPSCs compared to wild-type littermates; neither the amplitude or frequency of miniature IPSCs nor the frequency of basket cell firing was different. These electrophysiologic data suggest that the behavioural changes are linked to changes in GABA release in the cerebellum. Consistent with Kv1.1 localization in the hippocampus, knockin EA1 mice exhibit impaired spatial learning and memory and a reduced induction of synaptic plasticity in KCNA1-expressing neurons.

**EA2 and allelic disorders**

**Clinical features**

Episodic ataxia type 2 (EA2) is characterized by longer episodes of ataxia (hours) with interictal nystagmus and mildly progressive baseline ataxia (Baloé et al., 1997; Jen et al., 2004a). As with EA1, episodes are commonly triggered by physical and emotional stress. The attacks can be dramatically responsive to acetazolamide. EA2 is by far the most common episodic ataxia syndrome. Like EA1, the onset of EA2 is typically early in life. There has only been one report of EA2 with onset after age 60 years (Imbrici et al., 2005). Episodes can vary from a pure ataxia to combinations of symptoms suggesting involvement of the cerebellum and brainstem and even occasionally the cerebral cortex. Vertigo, nausea and vomiting are the most commonly associated symptoms, occurring in more than 50% of patients. About half of the patients report headaches that meet the International Headache Society (IHS) criteria for migraine. On examination during an acute episode of ataxia, patients typically exhibit a spontaneous nystagmus not seen during the interictal examination. Between episodes, the most common finding is a gaze-evoked nystagmus with features typical of rebound nystagmus. Spontaneous vertical nystagmus, particularly downbeat nystagmus, is seen in about one-third of cases. This may begin with a positional downbeat nystagmus in the head-hanging position that over time becomes a spontaneous downbeating nystagmus.

EA2 is allelic with familial hemiplegic migraine type 1 (FHM1) (Ophoff et al., 1996) and, in some families, episodes of both ataxia and hemiplegic migraine occur in the same patients (Jen et al., 1999; Ducros et al., 2001). EA2 patients can also have progressive ataxia and hemiplegic migraine occur in the same patients (Jen et al., 1999; Denier et al., 1999), fluctuating weakness (Jen et al., 2001), epileptic seizures (Jouvenceau et al., 2001; Jen et al., 2004a; Kors et al., 2004) and dystonia (Spacey et al., 2005).

**Genetic characteristics**

The disease locus of EA2 was mapped to chromosome 19p (Kramer et al., 1995; Vahedi et al., 1995; von Berderlow et al., 1995) in the same region as the disease locus for FHM1 (Joutel et al., 1993). A calcium channel gene CACNA1A mapped to this locus on chromosome 19p. Ophoff and colleagues (1996) characterized the genomic structure of CACNA1A and identified missense mutations in FHM1 and truncation (frameshift and splice site) mutations in EA2.

The gene CACNA1A is extensively alternatively spliced that additional exons have since been identified (Zhuchenko et al., 1997; Bourinet et al., 1999; Soong et al., 2002). A polymorphic stretch of CAG repeats thought to be in the 3’ untranslated region was in fact translated in a longer splice variant that may be the predominant form in the human cerebellum (Ishikawa et al., 1999). Glutamine-encoding CAG-repeat expansion in CACNA1A causes spinocerebellar ataxia type 6 (SCA6), a dominantly inherited pure cerebellar ataxia syndrome of late onset (Zhuchenko et al., 1997). Thus, EA2, FHM1 and SCA6 are allelic disorders, all caused by mutations in CACNA1A.

**Genotype-phenotype correlations**

A wide range of phenotypes have been associated with mutations in CACNA1A (Fig. 2; Table 2). There is much
The majority of patients with FHM1 have cerebellar symptoms and signs (Ducros et al., 2001). Overall, they found nine mutations in CACNA1A, all of which were missense mutations. Eighty-nine percent of subjects with mutations had attacks of hemiplegic migraine. Six mutations were associated with hemiplegic migraine and cerebellar signs and 83% of the subjects with these six mutations had nystagmus, ataxia or both. Only three mutations were associated with pure hemiplegic migraine. Jen et al. (2004a) found a wide range of mutations associated with the EA2 phenotype. Most commonly, mutations predicted premature termination of the open reading frame, with a range of truncation sites from the shortest having only domain 1 intact, to the longest having all four domains intact with only a truncation of the C terminus. Missense mutations typically involved the pore loop region of the protein. Functional studies of the mutated channel in EA2 have shown a marked reduction in current expression and deficiencies in plasma membrane targeting (Guida et al., 2001; Wan et al., 2005b). As with EA1, more severe mutations are generally associated with more severe functional effects, both with regard to current expression and plasma membrane targeting.

**Pathophysiology**

CACNA1A encodes the pore-forming and voltage-sensing subunit Cav2.1 of the P/Q type voltage-gated calcium channels. These channels are abundantly expressed in the
cerebellum and presynaptically at the neuromuscular junction (Mori et al., 1991; Ludwig et al., 1997). Genetic analysis in EA2 families have revealed over 50 mutations in CACNA1A with more than two-thirds predicting a premature stop owing to nonsense mutations or defects in splice sites (Denier et al., 1999; Jen et al., 2004a; Wan et al., 2005a; Eunson et al., 2005). Cav2.1 is highly expressed at the neuromuscular junction, where calcium entry through P-type calcium channels triggers acetylcholine release at motor nerve terminals. Unlike the cerebellum, which is inaccessible for in vivo electrophysiological investigation, the neuromuscular junction is easily accessible and has proven informative in unraveling not only the peripheral manifestations but also synaptic remodelling in the periphery. Although EA2 patients complain of fluctuating weakness but typically do not manifest weakness at baseline, electromyographic studies demonstrate a reduced safety factor of neuromuscular transmission and increased jitter and blocking on voluntary single fibre electromyography (Jen et al., 2001). In vitro microelectrode studies in patients with genetically characterized EA2 showed marked reduction of end plate potential quantal content, confirming a presynaptic defect in neuromuscular transmission (Maselli et al., 2003). Interestingly, the end plate potentials showed high sensitivity to N-type blockade with omega conotoxin not seen in controls. The finding of impaired neuromuscular transmission in EA2 patients is consistent with a loss-of-function mechanism for EA2 mutations. The presence of N-type calcium channels in the neuromuscular junction of EA2 patients reflects a possible compensatory mechanism to restore normal activity both at the neuromuscular junction and at central neuronal synapses.

As in the case of EA1, the mechanism for the episodic features with EA2 is largely unknown. Understanding the mechanism of these rare episodic neurological disorders should provide insight into understanding the pathophysiology of the more common episodic neurological disorders such as epilepsy and migraine. Although channelopathies underlie several neurological disorders characterized by episodic symptoms, mutations in genes that do not encode ion channels have been found to cause recurrent episodic symptoms, emphasizing indirect ways by which neuronal excitability can be modulated. For example, a mutation in casein kinase 1-δ (CK1δT44A) which causes a familial form of advanced sleep phase syndrome (FASPS) also causes migraine with aura (Xu et al., 2005). Cortical spreading depression (CSD) is thought to be the pathophysiologic mechanism underlying migraine with aura and a lower threshold for CSD could be a common mechanism for episodic neurological dysfunction. Mice transgenic for human CK1δT44A were found to have a significantly decreased threshold for CSD compared to controls and a significantly increased number of CSD events per level of stimulus compared to controls. Mutations in ion channels can also lead to a decreased threshold for CSD and spontaneous neuronal discharge (see later).

Animal models

The recessive mouse models tottering, leaner, rolling Nagoya and rocker harbouring mutations in murine Cacna1a have epilepsy, dystonia and ataxia (Fletcher et al., 1997; Mori et al., 2000; Zwingman et al., 2001). In tottering mice, the attacks of dyskinesia are triggered by clinically relevant precipitants such as stress and caffeine (Fureman et al., 2002). Function studies in tottering mice show reduced current density from Cav2.1 channels, which are expressed abundantly in cerebellar Purkinje and granule cells. This would result in a general reduction in Purkinje cell firing rates and a loss of inhibition of deep cerebellar nuclei. These mouse models are consistent with the loss-of-function hypothesis for Cav2.1, as has been proposed for its human EA2 mutations.

A mutant mouse model harbouring a human FHMI mutation R192Q (with no associated cerebellar symptoms in human) complicates the quandary of whether these mutations lead to a gain- versus a loss-of-function (van den Maagdenberg et al., 2004). Early expression studies of R192Q in HEK293 cells demonstrated a gain of channel function, with increased channel density and open probability, which differed from other FHMI mutations that demonstrated impaired channel function (Hans et al., 1999). In contrast, when expressed in cerebellar granule cells isolated from mice lacking Cav2.1, the same R192Q mutant channel was found to show a reduced channel density but enhanced (estimated) single channel calcium influx, which appeared to be a shared feature among several FHMI mutants (Tottene et al., 2002). In the mouse model harbouring R192Q, there was an overall gain-of-function, with increased mutant channel density, increased neurotransmission at the neuromuscular junction and enhanced cortical glutamate release. In addition, the threshold for eliciting CSD was reduced in R192Q mice, and the propagation velocity of CSD was increased. By comparison, Cav2.1 null mice show a higher threshold and slower propagation speed of CSD (Pietrobon, 2005).

An alternative hypothesis links migraine with loss-of-function Cav2.1 mutations and weakened neurotransmission. Cao and Tsien (2005) observed a reduction in both channel density as well as calcium influx when they expressed FHMI mutant constructs in hippocampal neurons from a Cav2.1-knockout mouse model. In the presence of endogenous Cav2.1 channels, the mutant Cav2.1 (P/Q type) channels interfered with the wild type in mediating both excitatory and inhibitory synaptic transmission (Cao et al., 2004; Cao and Tsien, 2005). Furthermore, there was a compensatory increase in the contribution to synaptic transmission from N-type channels, with potentially increased sensitivity to G-protein-mediated presynaptic inhibition (Cao and Tsien, 2005). This disease model of migraine allows for trigger-driven neuromodulation and further impairment of already defective mutant-expressing synapses.
Emerging data also point to alterations in the intrinsic properties of Purkinje neurons in addition to synaptic dysfunction caused by mutations in the P/Q type voltage-gated calcium channels (Bond et al., 2005). Irregular Purkinje firing has been observed in mouse models of EA3: an animal model of idiopathic bilateral episodic ataxia (Hoebeek et al., 2005). This loss in the precision of Purkinje pacemaking was demonstrated to be a direct consequence of mutant calcium channels and could be rescued by increasing the activity of small-conductance calcium-dependent potassium channels (K_{Ca}) (Walter et al., 2006). Chronic in vivo perfusion of K_{Ca} agonists into these mutant mice markedly reduced the frequency and severity of intermittent dystonic posturing and improved motor performance (Walter et al., 2006).

EA3–EA6

Online Mendelian Inheritance of Man (OMIM) currently records six episodic ataxia clinical phenotypes, each with distinctive genetic features (Table 1). EA3 was described in a single large Canadian family with episodic vertigo, tinnitus and ataxia and episodes typically lasting minutes (Steckley et al., 2001). The disease locus was distinct from EA1 and EA2 and mapped to chromosome 1q42 (Cader et al., 2005). Interestingly, there is clear overlap in clinical features between EA3 and migraine-associated vertigo. Currently it is unclear whether this syndrome represents a distinct episodic ataxia or a migraine-vertigo syndrome.

EA4, also called periodic vestibulocerebellar ataxia, was described in two North Carolina kindreds with late-onset vertigo and ataxia as well as interictal nystagmus (Farmer and Mustian, 1963; Damji et al., 1996). The attacks typically last hours and are not relieved by acetazolamide. Linkage analysis ruled out EA1 and EA2 loci, but so far no genome-wide scan has been reported.

EA5 was identified when a series of families with episodic ataxia were screened for mutations in the calcium channel β4 subunit CACNB4, on chromosome 2q (Escayg et al., 2000). This family had clinical features similar to EA2 but mutations in CACNA1A were ruled out. Complicating matters, the same mutation was found in a German family with generalized epilepsy (but no ataxia) and functional studies showed only subtle changes in calcium channel function.

EA6 was identified in a single child with episodic and progressive ataxia, episodes of hemiplegia and seizures. Through a candidate gene approach, a de novo mutation was identified from a screen of the candidate gene SLC1A3, a glutamate transporter localized to astrocytes (Jen et al., 2005). The mutation altered a strictly conserved amino acid residue, and functional studies of the mutated protein showed an almost complete loss-of-function with a dominant negative effect on the wild type allele.

There is a clear pattern to the genetic mutations associated with episodic ataxia and hemiplegic migraine. All of the currently identified genes play an important role in excitatory neurotransmission in the nervous system (Fig. 3). A second hemiplegic migraine syndrome (FHM2) is caused by mutations in ATP1A2 that codes for the alpha subunit of a Na+/K+-ATPase (De Fusco et al., 2003). The ion channel proteins coded by KCNA1, CACNA1A and CACNB4 are important for presynaptic glutamate release. The SLC1A3-encoded glial transporter EAAT1 is important for glutamate reuptake from the synaptic cleft. The ATP1A2-encoded ion pump is important in maintaining the appropriate electrochemical gradient in neurons and glia. We consider genes coding for other ion channels, pumps, transporters and proteins important in GABAergic neurotransmission as good candidates causing episodic ataxia and hemiplegic migraine syndromes.

Differential diagnosis

The main differential diagnosis of the episodic ataxia syndromes is between other episodic neurological disorders such as epilepsy, paroxysmal dyskinesia and migraine. Complicating matters, epileptic seizures can be seen with both EA1 and EA2. The key to the diagnosis of EA1 and EA2 is to find the characteristic interictal findings of myokymia with EA1 and baseline nystagmus and ataxia with EA2. Occasionally patients with one of the spinocerebellar ataxias syndromes (SCAs) may have episodic fluctuations in their baseline ataxia. This has been best documented with the EA2-allelic disorder SCA6 in which
discrete episodes may be responsive to acetazolamide (Jen et al., 1998).

Since EA2 and FHM1 are allelic disorders and since migraine is common with EA2, investigators have questioned whether mutations or polymorphisms in CACNA1A or other episodic ataxia genes may be responsible for more common varieties of migraine (Terwindt et al., 2001). In families with FHM1, some members with documented mutations in CACNA1A have only migraine headaches (with or without aura). Also, episodic vertigo is a common migraine symptom and vertigo commonly accompanies episodes of ataxia in patients with EA2. However, preliminary studies of patients with migraine with and without aura and of patients with migraineous vertigo have not found polymorphisms in CACNA1A that are enriched in patients (Jen et al., 2004b; von Brevern et al., 2006).

**Diagnostic testing**

Currently diagnostic genetic testing is commercially available for EA1 and EA2, which can also be tested by various research laboratories. The entire coding regions of KCNA1 and CACNA1A are sequenced since mutations occur throughout the genes without any consistent hot spots. 

KCNA1 is much easier to screen for mutations than CACNA1A since it has only a single exon compared to the 48 exons of CACNA1A. Even with sequencing of the entire coding regions of these two genes, deletions, duplications and cryptic mutations in untranslated or intronic regions important for gene expression could be missed. In cases where multiple family members are available, preliminary linkage analysis can help decide whether it is worth sequencing the suspect genes.

**Who should be screened for mutations in KCNA1 and CACNA1A?**

The majority of patients will present with the characteristic phenotype of these two syndromes (Table 1), however, phenotypic variations have been reported with both syndromes. Age of onset is a key differential, since onset after age 20 years is rare with both EA1 and EA2. Sporadic cases (spontaneous mutations) occur with both EA1 and EA2, therefore, the lack of a family history does not rule out the diagnosis. Patients with later onset and progressive baseline ataxia should be screened for the CAG repeat expansion in CACNA1A (SCA6).

**Treatment of episodic ataxia**

Several different drugs are reported to improve symptoms with EA1 and EA2, but so far there have been no controlled studies documenting or comparing efficacy of these different drugs. Carbamazepine, valproic acid and acetazolamide have been effective for EA1 (Eunson et al., 2000; Klein et al., 2004) and acetazolamide (Griggs et al., 1978), flunarizine (Boel and Casaer, 1988) and 4-aminopyridine (Strupp et al., 2004) have been effective in EA2. The response to acetazolamide is often dramatic with EA2 (Griggs et al., 1978; Jen et al., 2004a). The carbonic anhydrase inhibitors were initially tried in patients with periodic paralysis based on their kaliuretic effect for hyperkalemic periodic paralysis and then, based on an observation made serendipitously, in hypokalemic periodic paralysis. Acetazolamide was used in a single blinded study for treatment of hypokalemic paralysis over 30 years ago, which focused on prevention of attacks (Resnick et al., 1968). A subsequent study even suggested that acetazolamide may improve interictal weakness (Griggs et al., 1970). Acetazolamide was also serendipitously found to be effective in controlling episodes of ataxia with EA2 (Griggs et al., 1978) and there have been multiple reports in the literature since the 1970s reporting excellent results in patients with EA2. Acetazolamide has been shown to increase extracellular proton concentration (Bain et al., 1992), which strongly inhibits ion permeation through open calcium channels. In another study, acetazolamide was found not to directly alter wild type or mutant calcium channel properties, suggesting that acetazolamide may exert its therapeutic effects on other channels (Spacey et al., 2004).

4-aminopyridine was recently found to be effective in stopping attacks in three patients with episodic ataxia, two genetically confirmed to be EA2 (Strupp et al., 2004). Furthermore, 3,4-diaminopyridine was demonstrated in a placebo-controlled study to improve downbeat nystagmus, which is often observed in patients with EA2 (Strupp et al., 2003). The mouse models of EA2 provide an excellent system to test the efficacy of currently used drugs and the potential to develop new drugs for treating the episodic ataxia syndromes. 4-aminopyridine and 3,4-diaminopyridine were effective in preventing attacks in the mouse model *tottering*, but the drugs did not affect the severity of ‘break through’ attacks that occurred in the presence of the drug (Weisz et al., 2005). Thus the aminopyridines appear to increase the threshold for attack initiation without mitigating the character of the attack. Drugs that blocked noradrenergic neurotransmission prevented attacks in *tottering* mice but agents that facilitated noradrenergic transmission failed to induce attacks (Fureman and Hess, 2005). Therefore, while noradrenergic transmission is important for attacks, norepinephrine is not sufficient to induce attacks. As noted earlier, Purkinje cell pacemaking is lost in the mouse mutant *leaner*, resulting in a significant degradation of the synaptic information encoded in their activity. This irregular pacemaking is caused by reduced activation of calcium-activated potassium channels (K<sub>Ca</sub>) which could be reversed by pharmacologically increasing their activity with 1-ethyl-2-benzimidazolinone (EBIO). Infusion of EBIO into the cerebellum of ataxic mice significantly improved motor performance (Walter et al., 2006). Thus drugs that activate K<sub>Ca</sub> channels might be
effectively in controlling episodic ataxia in patients with EA2. Interestingly, therapeutic concentrations of acetazolamide activate $K_{Ca}$ channels which could be another mechanism of action of acetazolamide in EA2 (Walter et al., 2006).

**Ongoing and proposed clinical trials**

A pilot study on 4-aminopyridine in EA2 with a total of 10 patients and a cross-over design was recently completed in Germany (M. Strupp, C. Jahn and T. Brandt, personal communications). As part of the NIH-supported CINCH program, there is an ongoing study of the natural history of the episodic ataxia syndromes. Patients are initially defined phenotypically and genetically and then followed for a minimum of 2 years. Episode rates are carefully monitored and disease progression documented. A controlled pilot study on the safety and tolerability of 4-aminopyridine as an add-on treatment to acetazolamide in EA2 is scheduled to begin soon. We hope to improve diagnosis and understanding of the disease mechanism to stratify patients with episodic ataxia for future clinical trials. Details regarding these and future studies can be obtained at the CINCH website [http://rarediseasesnetwork.epi.usf.edu/cinch/index.htm](http://rarediseasesnetwork.epi.usf.edu/cinch/index.htm).

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**Conflict of interest statement.** None declared.

**References**


Appendix

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Participants of the meetings listed alphabetically:

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