Episodic Ataxia Type 1: A Neuronal Potassium Channelopathy

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Summary: Episodic ataxia type 1 is a paroxysmal neurological disorder characterized by short-lived attacks of recurrent midline cerebellar dysfunction and continuous motor activity. Mutations in *KCN1A,* the gene encoding Kv1.1, a voltage-gated neuronal potassium channel, are associated with the disorder. Although rare, the syndrome highlights the fundamental features of genetic ion-channel diseases and serves as a useful model for understanding more common paroxysmal disorders, such as epilepsy and migraine. This review examines our current understanding of episodic ataxia type 1, focusing on its clinical and genetic features, pathophysiology, and treatment.
Key Words: Episodic ataxia, channelopathies, myokymia, potassium channel.

INTRODUCTION

Dysfunction of neuronal ion channels is now understood to cause a number of paroxysmal neurological diseases.[1–5] With advances in molecular biology and the completion of the human genome project, these genetically determined channelopathies are increasingly recognized in clinical practice.

The episodic ataxias are inherited syndromes characterized by intermittent cerebellar dysfunction in individuals with otherwise essentially normal brain function.[2,6–10] Two main forms are recognized, episodic ataxia type 1 and type 2 (EA-1 and EA-2), both of which are autosomal dominant. The episodic ataxias exemplify the phenomenon of phenotypic convergence, in that EA-1 is caused by mutations in the voltage-gated potassium channel gene, *KCNA1*,[11–18] but mutations in the gene *CACNA1A*, which encodes the voltage-gated P/Q-type calcium channel, are associated with EA-2.[19–26] Although individually rare, these disorders have provided unprecedented insight into the complex interplay of ion channels and neuronal circuits, and have raised the possibility that mutations in ion channels underlie some of the more common neurological diseases such as epilepsy and migraine.

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The voltage-gated potassium channel Kv1.1, which is encoded by the *KCNA1* gene associated with EA-1,[11–18] contributes to the regulation of neuronal excitability and is widely expressed in the nervous system. With the identification and characterization of newer mutations of *KCNA1* in EA-1 kindreds, the phenotypic spectrum of the disorder has widened considerably beyond the original description of a purely cerebellar syndrome. This review examines the protean clinic manifestations of EA-1. The mechanistic link between genotype and phenotype is further considered, along with an outline of the molecular and cellular processes involved.

CLINICAL FEATURES

In 1975, Van Dyke et al.[27] first described a family in which 11 members over three generations experienced periodic ataxia and continuous muscle movement. The onset of the disorder was between the ages of 2 and 12 years, and the affected individuals experienced attacks of generalized ataxia, jerking movements of the head, stiffening of the body, and carpal spasms, as well as subjective sensations including vertigo, dizziness, blurred vision, and diplopia. These attacks would last on average 3 minutes and would be provoked by anxiety, excitement, fatigue, hunger, and voluntary movement (kinesigenic stimulation).

Hanson et al.[28] subsequently described in 1976 another family, in which the mother and her two children had intermittent attacks of shaking and titubation with

dysarthria and abnormal hand posturing. The mother, who was born with a clubfoot, described having had episodes of shaking since the age of 4 or 5 years. Episodes occurred several times a month and lasted 10 minutes. During these episodes, her legs would feel weak, her voice would become slurred and she would develop a tremor of the head. In addition, she had continuous rippling muscle movements in her legs, fine twitching of her eyelids, and a tremor involving her hands at rest. Her two children were both born with abnormal posture of the feet. At birth, both the children's hands were clamped shut and described as difficult to pry open. They both went on to develop intermittent episodes of shaking, loss of balance, slurred speech, and stiffening of the body.

Brunt and Van Weerdan[10] in 1990 described the largest family known to date affected by paroxysmal ataxia and continuous myokymia. Twenty-eight members over five generations were diagnosed as having the condition. The onset, frequency, nature of attacks, and precipitants were comparable with previously described families.[8,26] Within the family, there was inter-individual variation with respect to symptoms, duration, and intensity. For example, one boy for many years had attacks of ataxia exclusively during intercurrent illness. The presence of myokymia was also variable. Close examination of half the members demonstrated fine rippling of the muscles, and in another one fourth, myokymia was evident as small lateral finger movements. In all of the affected family members who had EMG examinations, myokymic discharges were clearly demonstrated.

Since the description of the first EA-1 kindred by Van Dyke et al.,[27] a further 19 unrelated families have been described in the literature.[8,11–18,28–31] Within this group, more than 100 individuals have been identified as having the phenotype of episodic ataxia and myokymia, the two cardinal features of EA-1. It is becoming increasingly apparent that wide phenotypic differences exist both between families and between individuals of the same family. Although the full spectrum of phenotypic variations remains to be established, a number of core clinical features have emerged.

Clinically, EA-1 usually declares itself in the first or second decade of life. Patients experience disabling attacks of midline cerebellar dysfunction, manifesting as truncal and limb ataxia, dysarthria, and visual symptoms such as oscillopsia and visual blurring. These symptoms are often accompanied by nausea and headache. A coarse tremor of the arms and head titubation are clinically evident in certain kindreds. These attacks are triggered by physical and emotional stress, chemical stressors, startle, and sudden postural changes and can last from seconds to minutes. The frequency of these ataxic spells can vary among individuals, from recurrent daily ictal episodes to infrequent attacks occurring a few times a year. The episodes terminate spontaneously. Some patients find that resting or sleeping at the onset helps curtail the episode. Interictally, patients are asymptomatic, with a normal neurological examination. The disease is nonprogressive, and the attack frequency commonly decreases with age.

The second cardinal feature of EA-1 is the presence of continuous interictal motor activity in the form of myokymia or neuromyotonia that is a consequence of peripheral nerve hyperexcitability. The term *myokymia* denotes spontaneous skeletal muscle contractions that produce a rippling quality. These fine, rippling movements of muscle can be observed in the limbs and around the eyes, and are also evident as small-amplitude side-to-side movements of the fingers in the outstretched hands. Myokymia in EA-1 patients is often subclinical, although invariably evident on electromyography studies (FIG. 1).

Episodic ataxia type 2 is the other well-characterized paroxysmal cerebellar disorder.[2,6,32,33] Although it has

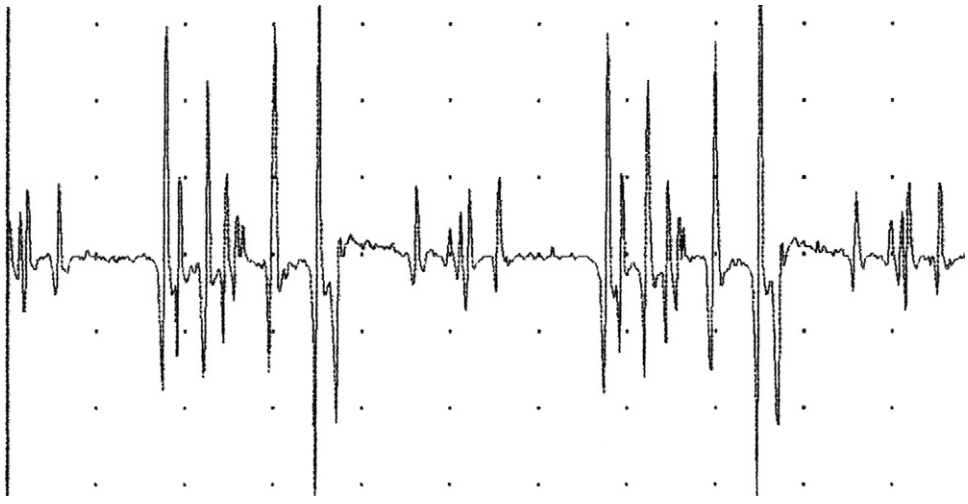

FIG. 1. Electromyographic tracing of myokymia.

similarities to EA-1, several features help to distinguish it. First, EA-2 is more prevalent. The duration of the attack in EA-2 is measured in hours to days, and each ictus is commonly associated with nausea, vomiting, vertigo, and occasionally diplopia. More than half of patients with EA-2 experience a severe migrainous headache during an attack. The migrainous component is notable, in that familial hemiplegic migraine is an allelic disorder of the P/Q-type calcium channel[34,35] and patients often have overlapping features. Weakness during or preceding an attack has also been described. Although myokymia is not a feature in EA-2, patients often develop persistent interictal downbeating nystagmus that is present in all directions of gaze. Moreover, in these patients, a progressive cerebellar syndrome often supervenes in later years. Indeed, cerebellar atrophy, notably of the anterior vermis, is evident on MRI.[36] Attacks in EA-2 patients may be precipitated by stress or intercurrent illness but not by sudden movements (in contrast to EA-1). The efficacy of drugs such as acetazolamide is also more marked in EA-2 patients.[7]

With the discovery of novel mutations in EA-1, the phenotypic spectrum of the disorder has widened. In addition to the classical description, phenotypic variants include EA-1 with partial epilepsy,[14,17] EA-1 without myokymia,[37] and even isolated severe neuromyotonia.[14] Eunson et al.[14] described a family with a *KCNA1* gene mutation in which the proband, a 3-year-old boy, presented with increased tone in his limbs, his fists partially clenched, and small semirhythmical lateral movements of his fingers and rippling movements of his calf and hamstrings. His EMG confirmed continuous generalized myokymic activity. His 39-year-old father had no history of episodic ataxia or muscle stiffness, but displayed subtle myokymia of his dorsal interrossei. Isolated neuromyotonia has been previously described in autoimmune Isaacs' syndrome or acquired neuromyotonia, in which antibodies against the voltage-gated potassium channel result in its dysfunction; however, this family represents the first reported case of isolated neuromyotonia caused by a mutation in the *KCNA1* gene.

In a few patients with EA-1, longer lasting episodes have also been reported. A number of different neuromuscular findings are recognized, including distal wasting with contractures, shortening of the Achilles tendon in children, and transient postural abnormality in infants such as flexion of the fingers, wrists, elbows, and knees.[16]

Kinali et al.[38] reported a case in one family in which the same mutation of the *KCNA1* gene in the mother and son resulted in two different clinical phenotypes. The son presented in infancy with generalized muscle stiffness and motor developmental delay. He was also found to have mildly dysmorphic features, short stature, and an abnormal gait. His increased muscle tone resulted in marked kyphoscoliosis, elbow contractures, and shortening of the Achilles tendon. His EMG demonstrated marked generalized myokymia. The boy's mother presented some years later with typical features of EA-1. On examination, she had myokymia and mild skeletal abnormalities.

This family[38] was found to have the same mutation as another family[17] with EA-1 accompanied by contractures and epilepsy (see next section). Recently, a 10-year-old girl with EA-1 was found to have distal weakness with paresis of the extensors of the feet and prolonged spells of limb stiffness lasting up to 12 hours.[39] There is also heterogeneity in the response to treatment[40] with some kindreds being particularly resistant to drugs.[14]

EPILEPSY AND EA-1

The prevalence of seizures is overrepresented in EA-1 family members, compared with unaffected members. To date, 11 individuals from four unrelated families have been reported to have epilepsy.[10,17,27,37] Van Dyke et al.[27] described a female with generalized motor seizures and an abnormal EEG who had a partial response to phenytoin. Brunt and van Weerdan[10] in 1990 identified three members of an EA-1 family with 28 affected members who had abnormal EEGs. The family harbored the V174F missense mutation in the *KCNA1* gene.

Zuberi et al.[17] described a Scottish family with EA-1 in whom a point mutation (T226R) in *KCNA1* was identified. Of the five affected individuals in the family, two had epilepsy supported by ictal EEG recordings. The propositus was a 3-year-old boy who presented at 7 weeks with recurrent episodes of apnea and cyanosis. The episodes consisted of head-turning and eyes deviating to the same side, flickering of the eyelids, and lip-smacking. The ictal EEG demonstrated rhythmical slow-wave activity over the right hemisphere, becoming spike-and-wave complexes that subsequently spread to the left hemisphere. A diagnosis of complex partial seizures was made, and the patient was successfully treated with carbamazepine. The boy's paternal aunt was also diagnosed with EA-1 and epilepsy. She presented in early infancy with marked postural deformities and was initially diagnosed as having atypical familial arthrogryposis. Between the ages of 9 and 10 years, she began having attacks of episodic ataxia and seizures, clinically considered to be partial followed by secondary generalization. Although the ataxic episodes were clearly distinguished from seizures, her EEGs on two occasions were normal and she did not respond well to phenytoin or sodium valproate.

Eunson et al.[14] reported a further family in which the mother had a phenotype of both tonic-clonic and partial seizures with long-standing myokymia; her 3-year-old son had nonfebrile tonic-clonic seizures. Both family

members were found to have a mutation in the *KCNA1* gene (A242P) but neither had any ataxic episodes.

Patients with EA-1 are approximately 10 times more likely to develop epilepsy than are normal individuals, implicating *KCNA1* mutations as a pathogenic susceptibility factor for epilepsy.[17] In support of this, a mouse knock-out of *KCNA1* has been described to have an epilepsy phenotype.[41] Moreover, mutations in two related voltage-gated potassium channel genes, *KCNQ2* and *KCNQ3* on chromosome arms 20q and 8q, respectively, have been implicated in the pathogenesis of benign familial neonatal convulsions (BFNC).[42–46] The seizure type in EA-1 patients includes both generalized[41] and partial seizures. Potassium channels determine the excitability of neurons, and drugs that block potassium channels are proconvulsant in humans.[47,48] It is possible that dysfunction of potassium channels may be relevant to other epilepsies in humans, particularly if they lower seizure threshold. It is still unclear why only certain individuals with EA-1 mutations develop epilepsy—although epigenetic factors may influence the phenotype.

A further link between *KCNA1* and epilepsy is suggested by a recent study of the role of LGI-1, implicated in a rare autosomal dominant form of temporal lobe epilepsy, in modulating fast inactivation of Kv1.1.[49] Other cellular roles of LGI-1 have been reported,[50] however, and so this mechanistic link remains to be confirmed.

Diagnosis of EA-1

The most valuable investigation in patients suspected of having EA-1 is the EMG. An abnormal myokymic EMG is found in nearly all patients with EA-1, regardless of whether they have visible myokymia on examination. Typical features include continuous spontaneous repetitive motor unit discharges. Recurrent grouped discharges (doublets, triplets, and multiplets) are also seen.[28] In some patients, a myokymic EMG is evident after the application of regional ischemia.[40] Laboratory blood tests including creatine kinase are not affected by EA-1. A muscle biopsy is generally unhelpful in aiding diagnosis. An EEG may be informative, given the overrepresentation of epilepsy in EA-1 patients. In contrast to EA-2, in which cerebellar atrophy may be visible on MRI with progression of disease, EA-1 patients have unremarkable MRI features. Now that the gene defect responsible for EA-1 has been identified, screening for mutations in the *KCNA1* gene on chromosome 12 can help to provide genetic confirmation of the disorder.

Molecular biology of EA-1

Genetic linkage studies[11,12,51] have mapped the EA-1 syndrome locus to chromosome band 12p13 and to mutations in the *KCNA1* gene, which encodes the voltage-gated potassium channel subunit Kvα1.1. This is the mammalian ortholog of the Shaker channel, the first potassium channel to be identified in the fruit fly, *Drosophila melanogaster*. Eighteen missense mutations and one premature stop codon in the carboxyl terminus have been identified in EA-1 patients[11–18] (Table 1). These mutations are understood to be pathogenic, and not polymorphisms, because they are not present in large numbers of control chromosomes in the background population, nor are they present in family members without EA-1. The mutations all affect highly conserved residues in the channel and are distributed throughout the peptide chain.

A detailed description of the structure and function of the voltage-gated potassium channel is beyond the scope of this review.[3,52] A few basic principles, however, are necessary to appreciate the effects of mutations on the biophysical properties of the channel.

Kv1.1 channels open upon depolarization and mediate neuronal repolarization following the action potential, thus regulating the electrical excitability of nerve and muscle fibers. Native Kv1.1 channels consist of four homologous pore-forming α-subunits (Kvα1.1), each containing six transmembrane-spanning segments (S1–S6), which are linked by intracellular and extracellular loops (FIG. 2A). The α-subunits of the potassium channel share a similar structure with the other members of the voltage-gated channel superfamily, with each Kv subunit homologous to a single domain of sodium and calcium channels—each comprised of four homologous, potassium channel-like domains within a single molecule.

The crystal structure of mammalian Kv α-subunits has recently been resolved,[53] revealing how the six transmembrane segments fold together to make a functional subunit (FIGS. 2B and 2C). The α-subunits of these channels determine their ion selectivity and control the voltage-sensing functions of the ion channels. The S4 segment of the α-chain contains several positively charged amino acids and acts as the voltage sensor of the channel, linking changes in membrane voltage to the opening of the channel pore. The S5–S6 loop forms the selectivity filter that ensures the channel is impermeable to all other ions except potassium. The N- and C-termini of each subunit are cytoplasmic and play important roles in channel assembly and targeting. In addition to the four α-subunits, the Kv1.1 channel also contains accessory cytoplasmic β-subunits,[54] which associate with the α-subunit in a 1:1 stoichiometry, such that four α-subunits and four β-subunits combine to form the complete Kv channel complex.

The α- and β-subunit composition is subject to variability, such that Kvα1.1 (the channel implicated in EA-1) may coassemble with other members of the Kv

TABLE 1. *Mutations identified in EA-1 patients*

Mutation (Segment Involved)	Phenotype	Functional Consequences	References
V174F (S1)	EA-1 with epilepsy	Mutant channels are not functional	Adelman et al.,[58] 1995
I177N (S1)	EA-1	Reduction in K^+ current amplitude; alters channel kinetics	Imbrici et al.,[63] 2003
F184C (S1)	EA-1	Alters voltage dependence and kinetics of activation	Adelman et al.,[58] 1995
T226A (S2)	EA-1	Profound reduction in K^+ current amplitude. Slowed activation and deactivation kinetics	Zerr et al.,[61] 1998
T226R (S2)	EA-1 with epilepsy and infantile contractures, postural abnormalities, skeletal deformities	Reduction in K^+ current, with mutant subunits exerting a dominant negative effect	Zuberi et al.,[17] 1999
T226M (S2)	EA-1	Profound reduction in K^+ current amplitude; shift in threshold of activation	Zerr et al.,[61] 1998
T226K (S2)	Isolated myokymia	No K^+ current, with mutant subunits exerting a dominant negative effect	Hisama et al.,[69] 2006
R239S (S2)	EA-1	Minimal K^+ current	Adelman et al.,[58] 1995
A242P (S2)	Myokymia and seizures	Profound reduction in K^+ current amplitude	Eunson et al.,[14] 2000
P244H (S2–S3 linker)	Isolated neuromyotonia	Functionally no difference between wild-type and mutant channels	Eunson et al.,[14] 2000
F249I (S2–S3 linker)	EA-1	No detectable K^+ current	Zerr et al.,[62] 1998
I262T (S3)	EA-1 with distal weakness	N/A	
G311S (S4–S5 linker)	EA-1	Reduction in K^+ current	Zerr et al.,[61] 1998
E325D (S4–S5 linker)	EA-1	Altered kinetics of activation and voltage dependence	Adelman et al.,[58] 1995
L329I (S5)	EA-1	N/A	
S342I (S5)	EA-1 without myokymia seizures	N/A	
V404I (S6)	EA-1	Relatively small effect on channel properties; responds well to treatment	Eunson et al.,[14] 2000
V408A (S6)	EA-1	Minor alterations in kinetics of activation and voltage dependence	Adelman et al.,[58] 1995
R417X (C-terminus)	Drug-resistant EA-1	Profound reduction in K^+ current amplitude	Eunson et al.,[14] 2000

EA-1 = episodic ataxia type 1; N/A = data not available.

subfamily, notably Kvα1.2 and Kvα1.4.[55–57] There is also some variability in the identity of the β-subunit, thus increasing the range of channel stoichiometries. Depending on the identity of the α- and β-subunits making up the channel, it can exhibit fast inactivation in the presence of continued depolarization. This is mediated by the insertion of a cytoplasmic peptide (which corresponds to the N-terminus of an α-subunit or of an accessory β-subunit) into the pore of the channel. The β-subunits also promote the surface expression of α-subunits, enhance potassium current amplitude, and may modulate channel kinetics.

Functional effects of EA-1 mutations in Kv1.1

In vitro electrophysiological methods have helped considerably in elucidating the mechanisms by which mutations in the Kvα1.1 channel subunit result in the EA-1 phenotype. Most studies of this nature have used heterologous expression systems in which channels containing the mutations associated with EA-1 are introduced into cells, such as *Xenopus* oocytes, that normally do not express abundant voltage-gated channels. The effects of these mutations on potassium channel function are then investigated by voltage-clamping and measuring the electrical current flowing in response to imposed changes

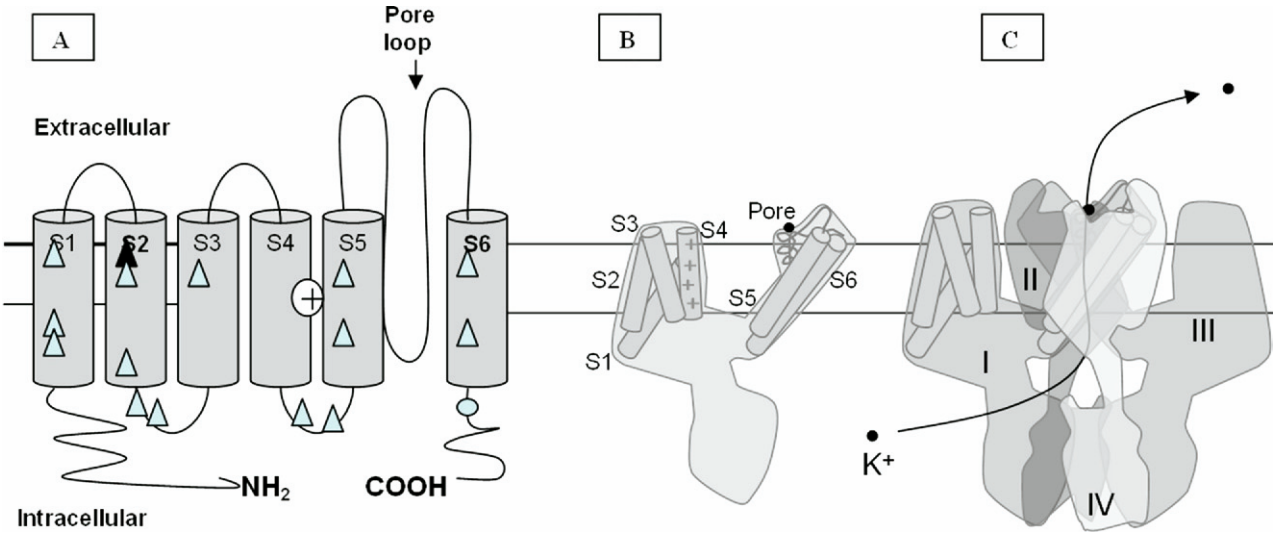

FIG. 2. (A) Structure of the Kvα1.1 channel subunit showing the six transmembrane segments (S1–S6), the voltage-sensing S4 segment, and the pore-lining loop between S5 and S6. Triangles indicate the positions of known missense mutations; the circle represents the R147 stop, which truncates most of the C-terminus. The black triangle represents the highly variable T226 site (for details, see text under Epilepsy and EA-1). (B) A depiction of the predicted structure of a single Kv1.1 subunit channel showing the position of the six transmembrane segments and the pore. (C) The predicted assembly of four α-subunits to form a functional channel, with the location of the pore. For simplicity, the approximate locations of the transmembrane segments are indicated in domain I only.

in transmembrane voltage. Several studies have shown that mutant Kv1.1 subunits result in a significant reduction in peak potassium current amplitude relative to wild-type currents.[14,17,58–64] The reduction varies, depending on the mutation, and ranges from virtually undetectable to a current amplitude comparable with wild-type channels. Thus far, no mutations have been found that increase the currents from these channels.

Alterations in the voltage threshold and gating properties of potassium channels have also been demonstrated. Some mutations alter the rate of activation and inactivation, and others shift the activation threshold to more depolarized levels.[62] The end result is a reduction in potassium flux through the channel. If one considers that patients with EA-1 are heterozygous and that Kv1.1 is a tetrameric protein, then the Kv1.1 channels in patients are likely to be assembled from a mix of normal and mutant subunits encoded by their two copies of *KCNA1*. Studies attempting to reproduce the *in vivo* condition have coexpressed mutant and normal Kvα1.1 subunits, and this has resulted in potassium current densities that were intermediate between homomeric mutant and normal channels on their own.[17,62] The view that mutant channels exerted a dominant negative effect on current amplitude is inferred when the mixture of mutant and normal channels gives less current than half the normal channels alone.

Some mutations interfere with fast inactivation, by hampering the insertion of the inactivating peptide into the cytoplasmic pore.[65,66] Thus, depending on whether Kvα1.1 coassembles with subunits that confer fast inactivation, a given mutation may have highly variable effects on neuronal excitability. Because the normal partners of Kvα1.1 show cell-type and regional diversity in the nervous system,[67] this phenomenon, together with differences in the degree of loss of function, may go some way toward explaining the phenotypic differences associated with distinct mutations.

A further insight into the effects of altered potassium channel function in terms of Kvα1.1 mutations may be deduced from animal studies. Kvα1.1-null mice, which have had the *KCNA1* gene deleted, have a phenotype of ataxia, seizures, and myokymia.[41] In one study, a mouse knock-in model of the V408A mutation was constructed by introducing the mutation by homologous recombination.[68] Homozygous V408A/V408A mice died on embryonic day 3, but heterozygous V408A/+ mice were viable and had stress-induced loss of coordination and showed improvement with acetazolamide similar to that seen for EA-1 in humans.

Evidence linking the degree of potassium current impairment to the severity of disease has come from studies in which mutations associated with a severe phenotype including seizures and drug-resistance (R147 stop which truncates the C-terminus) dramatically reduce the potassium current, whereas mutations associated with a relatively benign phenotype of neuromyotonia alone with no ataxia (P244H) did not alter the current amplitude. This may in part explain the phenotypic variability observed with EA-1. To date, no mutations in patients have been found that would be expected to cause a complete deletion of the gene. The single mutation that truncates the subunit, R147stop, is found at the extreme end of the subunit. It is likely that severe phenotypes, such as those

TABLE 2. *The response of EA-1 families to medications*

Mutation	Phenotype	Response to Medication	References
F184C	EA-1 and myokymia	Partial response to phenytoin	Van Dyke et al.,[27] 1975
V174P	EA-1 and myokymia	ACZ ineffective in one member; phenytoin reduced myokymia in one member	Gancher and Nutt,[8] 1986
V174P	EA-1 and myokymia	In 12 members tested, ACZ reduced frequency of attacks in 8	Brunt and van Weerdan,[10] 1990
E325D	EA-1 and myokymia	ACZ reduced frequency and severity of attacks in 3 members	Lubbers et al.,[40] 1995
T226R	EA-1 and partial seizures, postural abnormalities	ACZ reduced attacks in 1 member	Zuberi et al.,[17] 1999
A242P	Partial epilepsy and myokymia	Antiepileptic medication improved myokymia	Eunson et al.,[14] 2000
P244H	Isolated neuromyotonia	N/A	Eunson et al.,[14] 2000
R417X	Drug-resistant EA-1	No improvement with ACZ and antiepileptics	Eunson et al.,[14] 2000
V404I	EA-1 and myokymia	Carbamazepine improved attacks	Eunson et al.,[14] 2000
L329I	EA-1 and myokymia	Carbamazepine significantly reduced frequency of attacks in 8 members	Hand et al.,[30] 2001
T226R	Severe neuromyotonia and skeletal deformities	In 1 member, phenytoin improved neuromyotonia; in 1 other member, carbamazepine reduced frequency and severity of ataxic attacks	Kinali et al.,[38] 2004

ACZ = acetazolamide; EA-1 = episodic ataxia type 1; N/A = data not available.

seen in mouse knockouts, would result from earlier truncations and that these would extend the phenotypic range further.

The relationship between mutation and phenotype is further complicated by the finding that four different mutations in *KCNA1* change the amino acid threonine 226 (Table 1). This amino acid is conserved widely, from fruit fly to humans.[69] Although functional studies indicate that altering this amino acid in all cases causes a drastic reduction in potassium current (in two cases with dominant negative effects), the phenotype is highly variable, ranging from typical EA-1 to isolated myokymia to EA-1 with epilepsy and abnormal posturing. This suggests that virtually identical defects in channel function can lead to diverse manifestations of disease.

The question to be answered is how the observed reduction in potassium current results in the EA-1 phenotype. The Kv1.1 channel is widely expressed both in the CNS and peripheral nerves, particularly in GABAergic basket cells of the granule cell layer and in the juxtaparanodal regions of motor axons.[70,71] The continuous motor fiber activity in neuromyotonia is generated by hyperexcitability of motor axons. The mechanism is similar to that which has been proposed in acquired neuromyotonia, which is associated with antibodies against the voltage-gated potassium channels in the peripheral motor nerves. The mutations in the Kvα1.1 channel subunit lead to a reduction in potassium permeability that results in prolongation of the action potential and failure to repolarize.[72] This failure to repolarize gives rise to the repetitive myokymic discharges.

The mechanism of ataxia is harder to explain. GABAergic basket cells have a marked inhibitory effect on Purkinje cells and are therefore ideally placed to regulate cerebellar output. If Kv1.1 is normally enriched in these cells, then mutations in the *KCNA1* gene resulting in dysfunction of the Kv1.1 channel function might be hypothesized to impair the cerebellar modulation of movement and so result in ataxia.[73] This model, however, fails to explain why cerebellar dysfunction is intermittent, or indeed why attacks are precipitated by stress or startle.

It has recently been proposed that spreading acidification, akin to cortical spreading depression, may occur in the cerebellar cortex.[74] Whether this occurs during an ictus remains to be determined, let alone the cellular triggers and underlying mechanisms. Although the broad expression of the channel in the cerebral cortex and the hippocampus may account for the increased incidence of epilepsy in certain kindreds with EA-1, the presence of Kv1.1 in the heart, skeletal muscle, retina, and pancreatic cells is noteworthy, in that no impairment of any of these tissues has been reported in EA-1 kindreds.

TREATMENT

Acetazolamide, a carbonic anhydrase inhibitor, is effective in reducing the frequency of ataxic episodes in some individuals. Lubbers et al.[40] studied the response of an EA-1 family to acetazolamide. All six members were affected by paresthesia (in accordance with reports from other families[10]), and this caused the medication to be

stopped in three patients. In the remaining three, acetazolamide reduced the number and severity of attacks, although some loss of efficacy did occur after 1 or 2 weeks.

The precise mechanism of action in EA-1 is unknown, although it has been postulated to alter the pH in the vicinity of the ion channel, causing hyperpolarization of the cell membrane and thus reducing neuronal excitablilty.[10] In support of this model, an abnormally high pH, correctable by acetazolamide, has been reported in the cerebellum by nuclear magnetic resonance spectroscopy of patients with episodic ataxia.[75,76] However, these studies were performed in patients without genetic characterization, and thus were likely to be biased toward EA-2 because of its higher prevalence, so their relevance to EA-1 is unclear.

Long-term acetazolamide use can result in the formation of renal calculi. Hence, regular monitoring of renal function is necessary. Some patients also respond to various antiepileptic medications, including carbamazepine, phenytoin, and phenobarbitone. In one large Australian family, 8 of the 19 affected members were taking prophylactic carbamazepine and all noticed a significant reduction in the frequency of attacks. This response is comparable to that of a large Scottish family (described by Eunson et al.[14]) harboring the V404I mutation who all responded to carbamazepine. Again, the mechanisms of action remain to be elucidated, although these observations suggest that treatment may be specific to the mutations present, in that not all patients with EA-1 respond to these therapies.

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