Episodic Ataxia Type 2

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Summary: Episodic ataxia type 2 (EA 2) is a rare neurological disorder of autosomal dominant inheritance resulting from dysfunction of a voltage-gated calcium channel. It manifests with recurrent disabling attacks of imbalance, vertigo, and ataxia, and can be provoked by physical exertion or emotional stress. In the spell-free interval, patients present with central ocular motor dysfunction, mainly downbeat nystagmus. A slow progression of cerebellar signs accompanied by a slight atrophy of midline cerebellar structures is commonly observed during the course of the disease. EA 2 is caused most often by the loss of function mutations of the calcium channel gene *CACNA1A*, which encodes the $\text{Ca}_v2.1$ subunit of the P/Q-type calcium channel and is primarily expressed in Purkinje cells. To date, more than 30 mutations have been described. Two effective treatment options have been established for EA 2: acetazol-

amide (ACTZ), which probably changes the intracellular pH and thereby the transmembraneous potential, and 4-aminopyridine (4-AP), a potassium channel blocker. Approximately 70% of all patients respond to treatment with ACTZ, but the effect is often only transient. In an open trial, 4-AP prevented attacks in five of six patients with EA 2, most likely by increasing the resting activity and excitability of the Purkinje cells. These findings were confirmed by experiments in animal models of EA 2. Many aspects of the pathophysiology (e.g., induction of the attacks) and treatment of EA 2 (e.g., mode of action of ACTZ and 4-AP) still remain unclear and need to be addressed in further animal and clinical studies. **Key Words:** Episodic ataxia type 2, downbeat nystagmus, P/Q-calcium channel, acetazolamide, aminopyridine.

INTRODUCTION

The first purpose of this review on episodic ataxia type 2 (EA 2) is to describe its clinical features, genetics, and the correlation between mutations and clinical findings, as well as the current treatment options. Special emphasis is placed on the pharmacological effects of the two agents currently used for treatment: acetazolamide (ACTZ) and 4-aminopyridine (4-AP). The second purpose is to address open questions in EA 2, namely the pathophysiology of the induction of the attacks, the mechanisms of action of ACTZ and 4-AP, and the absence of randomized, controlled trials.

The current classification of different types of episodic ataxia (EA) is based on genetics and clinical presentation. To date, there are six genetically defined types of EA, all of them autosomal dominant. Some other diseases that characteristically have the same clinical presentation as EA have not yet been genotyped. Given the variety of their clinical presentations, it seems logical to

classify the EAs on a predominantly genetic basis. More detailed information about the coherence of genotype and phenotype will lead to modifications and expansion in the future.

Episodic ataxia type 1 (EA 1) is characterized by brief attacks of ataxia, lasting for minutes, that are provoked by abrupt postural changes, emotional stress, and vestibular stimulation. Between spells, the patients have neuromyotonia: that is, an ongoing spontaneous high-frequency muscle fiber activity due to axonal hyperactivity.¹ EA 1 is caused by missense point mutations of the voltage-gated potassium channel KCNA1 protein (chromosome band 12p13), which forms the Kv1.1 channels and is expressed in the peripheral and central nervous systems (OMIM #160120). These mutations lead to an altered neuronal excitability by affecting the temporal integration and action potential firing rates.² First-choice treatment options are phenytoin and carbamazepine.³ (For details, see the article by Kordasiewicz and Hanna.⁶⁷)

Patients with EA 2, the focus of this review, present with attacks of imbalance, vertigo, and ataxia. EA 2 is the most frequent subtype of episodic ataxia.

EA 3, a very rare disorder, has so far been described in

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only one family (chromosome 1q 24, OMIM %606554). It is characterized by recurrent attacks (lasting minutes to hours) with vestibular ataxia, vertigo, tinnitus, and headache and (in half of the patients) with interictal myokymia.⁴ Patients respond to ACTZ.

In EA 4, patients have recurrent episodes of vertigo, ataxia, and diplopia, slowly progressive ataxia, and impaired smooth-pursuit eye movements.⁵ These patients do not have myokymia and do not respond to ACTZ. No genetic locus has been identified (OMIM %606552).

EA 5 is caused by mutations of the calcium channel CACNB4B4 protein (chromosome region 2q22~q23; OMIM +601949), which lead to attacks of vertigo, ataxia, and seizures. One mutation causes juvenile myoclonic epilepsy.⁶ The onset of symptoms is in the third and fourth decades. The attacks last hours (sometimes weeks); between the attacks patients have downbeat nystagmus, postural imbalance, and ataxia. Symptoms respond to ACTZ.

Another form with recurrent attacks of ataxia with seizures, migraine, and alternating hemiplegia has been reported more recently in one patient; it was classified as EA 6. Symptoms began in early childhood, due to a missense mutation in the *SLC1A3* gene encoding a glutamate transporter EAAT1 protein on chromosome band 5p13. The mutations lead to a reduced capacity of the glial glutamate transporter and less glutamate uptake, which may result in neural hyperexcitability and cause seizures and alternating hemiplegia.⁷

It must be emphasized that other diseases characterized by the clinical presentation of episodic ataxia exist that have not yet been formally classified as EA. For example, episodic ataxia lasting approximately 20 min-

utes but with large variability in attack frequency associated with paroxysmal choreoathetosis, paresthesias and spasticity, has been described with a locus on chromosome 1p. Attacks are precipitated by emotional and physical stress as well as by alcohol and fatigue.⁸ Patients respond to ACTZ.

CLINICAL FEATURES OF EPISODIC ATAXIA TYPE 2

Episodic ataxia type 2 (EA 2) usually begins in early childhood, most often before the age of 20. Rarely, however, symptoms may first manifest in patients older than 50 years.^{7,9-11} Such late onset may be related to certain mutations, such as, for example, multiple-base pair insertions in *CACNA1A*.¹² Clinically, EA 2 is characterized by recurrent attacks of ataxia lasting for several hours to days, which are provoked by physical exertion, emotional stress, or alcohol.^{9,13} Several patients also have mild myasthenic symptoms (due to impaired neuromuscular transmission; see below). Attacks may occur daily or over longer intervals, even years in some patients. The most recent large case series from Jen et al.¹⁴ described the clinical spectrum in 18 families and nine sporadic cases; 64 patients were genetically defined. All but 2 of these 64 patients reported episodes of ataxia; two members of one family had only progressive ataxia. All but one had experienced onset before age 20. Migraine headaches occurred in more than half.¹⁴ These findings indicate that the clinical patterns of EA 2 and vestibular migraine are related (Table 1). Both disorders are characterized by a combination of episodic vertigo or ataxia as well as ocular motor disturbances in the spell-free

TABLE 1. Differentiation of Episodic Ataxia Type 2 and Vestibular Migraine

	Picture of EA 2	Picture of VM
Clinical features	<ul style="list-style-type: none"> • Recurrent attacks of vertigo, imbalance and ataxia (minutes to hours) • Migraine headaches (>50%) • Familial history in the majority 	<ul style="list-style-type: none"> • Spontaneous recurrent attacks of vertigo/dizziness (minutes to hours) • Associated headache or other migrainous symptoms (60%–70%) • Individual or familial history of migraine in the majority
Examination findings during attacks	<ul style="list-style-type: none"> • Pathological positional nystagmus (70%) • Ataxia/postural imbalance (>90%) 	<ul style="list-style-type: none"> • Pathological spontaneous or positional nystagmus (70%) • Postural imbalance (90%)
During attack-free interval	<ul style="list-style-type: none"> • Central ocular motor signs (>90%) 	<ul style="list-style-type: none"> • Central ocular motor signs (>60%) • Peripheral vestibular deficit (10%–20%)
Genetic background	<ul style="list-style-type: none"> • <i>CACNA1A</i> mutations (60%) 	<ul style="list-style-type: none"> • <i>CACNA1A</i> mutations in FHM • None found to date in VM
Treatment of choice	<ul style="list-style-type: none"> • Acetazolamide, 4-aminopyridine 	<ul style="list-style-type: none"> • Beta-blockers, valproate

EA 2 and VM cannot be differentiated solely by clinical presentation. Both disorders are characterized by a combination of episodic vertigo or ataxia as well as ocular motor disturbances in the spell-free interval. Monosymptomatic presentations of VM without headaches occur in up to 30% of patients. In a subgroup of patients with FHM, there is a genetic linkage to the *CACNA1A* gene, which is the locus most often mutated in EA 2. The frequency of *CACNA1A* gene mutations in ordinary vestibular migraine is not known. Data adapted from Jen et al., 2004,¹⁴ and Brandt and Strupp, 2006.¹⁵

EA 2 = episodic ataxia type 2; FHM = familial hemiplegic migraine; VM = vestibular migraine.

interval (see below). It should be noted that headaches do not occur in up to 30% of patients with vestibular migraine.^{15–17}

Between spells, more than 90% of patients exhibit central ocular motor disturbances such as gaze-holding deficits, saccadic smooth pursuit, impaired visual suppression of the vestibulo-ocular reflex, especially down-beat nystagmus,¹⁸ or rarely bilateral internuclear ophthalmoplegia.¹⁹ Some of these patients develop subtle and slowly progressive limb ataxia and postural imbalance later in life. Mental retardation has also been reported.²⁰ Several patients have complained of generalized (myasthenic) weakness; patients rarely suffer from dystonia, which may be a late feature of the disease.²¹ Others have hemiplegic episodes or absence seizures. EEG abnormalities were reported in patients with acetazolamide-responsive ataxia.²² Imbrici et al.²³ described a family in which absence seizures segregate in an autosomal dominant fashion through three generations. Five members exhibited a combination of absence epilepsy (with 3-Hz spike-waves) and cerebellar ataxia.

Cerebellar atrophy, especially of the anterior vermis, can be detected on MRI.^{24,25} Decreased high-energy phosphate ratios, reduced total creatine, increased pH (most likely due to an intracellular alkalosis), and high lactate peaks have also been found in the cerebellum of patients with EA 2.^{26,27}

GENETICS AND PATHOPHYSIOLOGY

The autosomal dominant hereditary disorder EA 2 is commonly (see below) caused by mutations of the calcium channel gene *CACNA1A* on chromosome 19p13.^{10,28,29} This gene encodes the Ca_v2.1 subunit of the P/Q-type calcium channel (2261 amino acids), which acts as the voltage sensor and ion-conducting pore.³⁰ More than 30 mutations distributed throughout the gene have been described. Most of them are nonsense or frameshift mutations that lead to a disruption of the reading frame, or intronic mutations that predict aberrant splicing.^{10,31,32} There have also been reports of missense mutations (T4747C transition in the highly conserved transmembrane segment S6; AY1593/1594D), which result in a loss of function of the expressed *CACNA1A* protein.^{33,34} At least two families with CAG-repeat expansions of the *CACNA1A* gene (defining the SCA 6 genotype) have been reported whose clinical presentation was indistinguishable from EA 2.³⁵

EA2 is allelic with familial hemiplegic migraine type 1, which is almost exclusively caused by gain-of-function mutations, resulting in an increase of calcium flow through the *CACNA1A* channel.³⁶ The spinocerebellar ataxia type 6 is also caused by a genetic alteration of the *CACNA1A* gene, with small, characteristic expan-

sions of a CAG repeat within the last exon of this gene.³⁷ (For further details, see article by Rajakulendran et al.⁶⁸)

Despite the loss-of-function mutations in EA 2, one intact gene still expresses the normal ion-channel protein due to heterozygosity; however, the channel density and the calcium currents are reduced,³⁴ and thus neurotransmitters are released (namely, GABA in Purkinje cells and acetylcholine at the neuromuscular junction).^{38,39} For this reason, it is assumed that ataxia is caused by impaired neurotransmission. It was also shown that the misfolded mutant *CACNA1A* protein impairs plasma membrane trafficking and targeting of the functioning *CACNA1A* proteins in a pronounced and basically negative way in both nonsense and missense *CACNA1A* mutations.³² These mutations were associated with a more pronounced and progressive ataxia between the attacks.

Some mutations are associated with certain additional clinical features, such as absence epilepsy.^{12,40} Ataxic spells induced by fever or high environmental temperature were associated with a certain *CACNA1A* mutation (nucleotides 1253+1 G→A). Overall, however, there is no simple genotype-phenotype correlation as different types of mutations (missense vs. nonsense) at distinct loci within the *CACNA1A* gene lead to similar symptoms.¹⁴

Notably, no mutation of the *CACNA1A* gene can be detected in approximately 30% to 50% of all patients presenting with typical clinical features of EA 2.^{14,31,41} In some of these patients, other EA 2 genes have been postulated: for example, on chromosome band 1q42 (peak 2-point lod score of 4.14).⁴² A mutation in the “Ca_v2.1α subunit” leads to cerebellar ataxia and absence epilepsy. Its coexpression with *CACNA1A* resulted in an impairment of the channel function Ca_v2.²³ Further, a novel mutation of the *KCNA1* gene causes EA without myokymia, highlighting the heterogeneity of phenotypic effects.⁴³

The P/Q-channel (the P stands for Purkinje, Q for granular cells) is expressed mainly in the cerebellum and (presynaptically) at the neuromuscular junction.³⁰ This anatomical pattern of expression of the P/Q-channel may explain the ataxia, cerebellar atrophy, and the (mild) myasthenic symptoms. These latter symptoms correlate with electrophysiological findings, which revealed a reduction of the endplate potential and quantal release of acetylcholine at the neuromuscular endplate, leading to a presynaptic failure. Single-fiber electromyography showed that jitter was blocked, which improved with increased stimulation frequency.³⁸

Mutations lead to changes not only in ion currents and the release of neurotransmitters, but also in pH and metabolism, which may be related to the induction of the attacks and neurodegeneration. Localized phosphorus (³¹P) and proton (¹H) magnetic resonance spectroscopy

were performed in the cerebellum and the occipital lobe of six patients with EA 2. The ^{31}P magnetic resonance spectroscopy showed decreased high-energy phosphate ratios in the cerebrum and increased pH in the cerebellum and cerebrum in untreated patients. The ^1H magnetic resonance spectroscopy revealed high lactate peaks in three of the six patients. These metabolic alterations were probably induced by the calcium channelopathy and may characterize EA 2.⁴⁴

Such abnormalities on cerebellar MRI spectroscopy have been interpreted to indicate intracellular alkalosis.^{26,44} Harno et al.²⁷ used proton MR spectroscopy to examine cerebellar and thalamic metabolism of nine mostly nonataxic EA 2 family members (all with proven *CACNA1A* mutation) and nine healthy control subjects. Cerebellar total creatine was lower in the patient group ($P = 0.005$) than in control subjects, possibly reflecting an early sign of calcium channel dysfunction in EA 2.²⁷

It is still unclear how the mutations and additional changes are related to the precipitation of attacks by physical and emotional stress or alcohol. Changes in pH or transmitters are assumed to underlie the attacks, but this is still an open question, one that can best be evaluated in animal models of EA 2.

ANIMAL MODELS OF EPISODIC ATAXIA TYPE 2

There are several animal models of mutations in the *CACNA1A* gene (e.g., the tottering mouse, leaner mouse, rolling mouse Nagoya).⁴⁵ The tottering mouse mutant contains a homozygous spontaneous C-to-T change at position 1802, which leads to a nonconservative proline-to-leucine amino acid substitution near the conserved P domain of the *CACNA1A* protein.⁴⁵ This mutation alters the pore function of the P/Q calcium channel and thereby reduces calcium currents, particularly in cerebellar Purkinje cells, where these channels are most abundant.³⁹ Like patients with EA 2, the tottering mouse suffers from episodic attacks of ataxia induced by emotional and chemical stress. This animal model is most suitable for systematically analyzing the mechanism underlying attack precipitation (e.g., withdrawal or caffeine) and the principles of treatment. To date, it has been demonstrated that attacks are prevented by noradrenergic blockade; however, agents that facilitate noradrenergic neurotransmission failed to induce attacks.⁴⁶ Thus, we must assume that alterations of noradrenergic neurotransmission contribute to attack initiation but in themselves alone are insufficient to induce attacks.⁴⁶ Another study showed that aminopyridines (4-AP; 3,4-DAP) effectively prevent attacks in tottering mice.⁴⁷

The leaner mouse mutant also harbors a homozygous spontaneous mutation in the gene encoding the voltage-activated Ca^{2+} channel $\alpha 1\text{A}$ subunit, the pore-forming

subunit of P/Q-type Ca^{2+} channels.⁴⁸ On the basis of this mutation, an out-of-frame splicing event in the carboxy terminus occurs which results in dramatic reductions in P-type Ca^{2+} channel function in cerebellar Purkinje neurons. These mice show degeneration of differentiated granule, Golgi, and Purkinje cells within the cerebellum. Leaner mice show features similar to those of tottering mice but have more severe ataxia.⁴⁵

Another mutation of the $\alpha 1\text{A}$ gene has been identified in the rolling Nagoya mouse mutant. It leads to a charge-neutralizing arginine-to-glycine substitution at position 1262 in the voltage sensor-forming segment S4 in repeat III.⁴⁹ These mice represent an intermediate phenotype, one that develops a more severe ataxia than the tottering mouse but lacks motor seizures.

Although most studies in mice have focused on synaptic transmission, some recent studies show that the precision of Purkinje cell pacemaking is lost in all the mutant mouse models. This loss causes degradation of synaptic information.³⁹ The restoration of the aberrant pacemaking also alleviated symptoms, thus providing a new target for treatment.⁴⁷

TREATMENT OPTIONS AND PRINCIPLES

Based on the pathophysiological understanding of EA 2, two established pharmacologic approaches focus on modulating the pH level and membrane ion conductance: ACTZ and 4-AP.

Acetazolamide

Currently, ACTZ is the drug of first choice for preventive treatment of EA, with dosages of 250 to 1000 mg per day, although its efficacy has never been proven in a randomized controlled trial.^{50–52} ACTZ is a carbonic anhydrase inhibitor, which was initially shown to decrease the number of attacks in hypokalemic periodic paralysis patients.^{53–56} Its efficacy, discovered accidentally in a patient with EA 2 misdiagnosed as having periodic paralysis,⁵¹ was later confirmed by others.^{57,58} ACTZ effectively prevents or attenuates the attacks in approximately 50% to 75% of all patients. Clinical experience, however, shows that many patients stop treatment with this agent in the long run, because it is either no longer effective or they develop adverse effects (unpublished observation).

ACTZ has several effects. It inhibits the carbonic anhydrase interconversion of $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$. It causes diuresis, initial kaliuresis, and metabolic acidosis. ACTZ also lowers serum bicarbonate levels and reduces the amount of brain lactate and pyruvate, resulting in subsequent brain acidosis.⁵⁸ The mechanism by which ACTZ prevents attacks—most likely via changes in pH—may be a key to understanding the disease pathomechanism, especially how the attacks are triggered.

Changes in extracellular and intracellular pH cause alterations of the transmembrane conductance: for instance, a decrease in intracellular pH reduces potassium conductance, an increase in pH raises it.³⁰ As we have noted, magnetic resonance spectroscopy showed that abnormal intracellular pH levels in the cerebellum of untreated patients with EA 2 normalized with ACTZ treatment.^{26,44} Thus, one hypothesis is that attacks are secondary to abnormally high intracellular pH values and that it is by reducing this pH level that ACTZ may prevent attacks.¹¹ Lower pH values reduce potassium conductance of the cell membrane and have an effect on the activation and inactivation of sodium and calcium channels, respectively.³⁰ Thus, the excitability and resting activity of neurons are restored. Without ACTZ, attacks may be precipitated by exercise and stress (hyperventilation), raising intracellular pH further.

As already noted, ACTZ is also effective for treating hypokalemic periodic paralysis, which is caused by mutations of a sodium channel gene (*SCN4A*).⁵⁵ Here, the mechanism might also involve regulation of potassium ion and proton concentrations. To determine whether a change of the proton concentration influences the gating of *SCN4A* mutants, Kuzmenkin et al.⁵⁹ used pH values ranging from 6.4 to 8.4 in bath or pipette solutions. The change of extracellular pH had profound effects on steady-state activation and inactivation of the wild-type channels, probably due to the change in surface potential but also to a direct blockade of the sodium channels.⁶⁰ The effect of intracellular pH on wild-type sodium channels was rather small. This suggests that ACTZ-induced metabolic acidosis probably has a therapeutic effect only by changing the steady-state properties of the mutants, and not their level of expression. Finally, Spacey et al.⁶¹ also demonstrated that ACTZ does not have a direct effect on either the wild-type or the mutated P/Q-channel. Thus, its mechanism of action most likely involves changes of pH that alter the transmembrane potential and excitability of neurons.⁶¹

Possible adverse effects of ACTZ include nephrolithiasis, hyperhydrosis, paresthesia, muscle stiffness with easy fatigability, and gastrointestinal disturbances. Side effects are dose-related and can be partially reduced by potassium chloride supplementation. Sulthiame, another carbonic anhydrase-inhibiting drug, has also been used successfully. It caused fewer side effects and was most effective in dosages between 50 and 300 mg daily.⁶² Nevertheless, ACTZ is the drug of first choice, with sulthiame as an alternative treatment option. Recently, Scoggan et al.⁶³ identified a new missense mutation in exon 12 of the *CACNA1A* gene from a patient with EA 2; the symptoms were controlled with a combination of ACTZ and valproic acid.

There are only a few reports on the effect of ACTZ on interictal nystagmus and progressive cerebellar degener-

ation. The original ACTZ-responsive family has not shown any progression of ataxia for more than 20 years.⁹ Others have reported an improvement of interictal cerebellar signs.¹³ More recently ACTZ was demonstrated to improve neuro-otological abnormalities such as saccadic hypermetria and gaze-evoked nystagmus in a family with EA 2. These observations need to be investigated in a long-term randomized controlled trial.

4-Aminopyridine

It was recently shown that aminopyridines (such as potassium channel blockers) improve downbeat nystagmus,⁶⁴ most likely by increasing the inhibitory influence of the Purkinje cells, a hypothesis that findings in animal experiments have supported.⁶⁵ Because Purkinje cell function is assumed to be impaired in EA 2 and downbeat nystagmus, the effects of 4-AP on the occurrence of attacks were evaluated in three patients with EA 2. Attacks of ataxia were completely prevented in two patients with EA 2 (who no longer responded to ACTZ) and markedly reduced in a third by the potassium channel blocker 4-AP. All patients fulfilled the recently published diagnostic criteria for EA 2¹⁴; the diagnosis was confirmed in two patients in whom mutations in the *CACNA1A* gene were detected. Cessation of the treatment led to a recurrence within 1 to 2 days. Subsequent therapy with 4-AP alleviated the symptoms. In the meantime, four patients with genetically proven EA 2 and two patients with the clinical picture of EA 2 have been treated with 4-AP; five of the six had a full response.

The question arises as to how to explain the effects of 4-AP. As already noted, the loss-of-function mutations lead to the reduction of calcium-dependent neurotransmitter release, especially of the Purkinje cells.⁶⁶ It is, therefore, assumed that ataxia in EA 2 is due to a dysfunction of the Purkinje cells, which leads to a reduced release of the inhibitory transmitter GABA. Thus, 4-AP may prevent attacks in EA 2 and improve downbeat nystagmus by increasing the release of GABA in the Purkinje cells. The following mechanisms also appear to be involved: 1) Animal experiments have shown that 4-AP increases the excitability of Purkinje cells; 1 to 10 micromolar concentrations of 4-AP markedly shortened the latency of calcium spike firing after the onset of depolarizing pulses.⁶⁵ 2) 4-AP prolongs the duration of action potentials and increases the release of neurotransmitters by blocking several potassium currents: for example, the A-current and the delayed-rectifier current.³⁰

These effects of 4-AP were further evaluated in animal models of EA 2. It is remarkable that 4-AP was observed to completely prevent attacks of ataxia in the tottering mouse, but it did not affect the severity of breakthrough attacks that occurred in the presence of a drug. These results suggest that the aminopyridines increase the threshold for attack initiation without mitigating the

character of the attack.⁴⁷ From a clinical point of view, a prospective randomized controlled study is necessary to prove the short- and long-term effects of 4-AP and to compare them with ACTZ, which remains the standard treatment for EA 2.

Future treatment trials

First of all, it will be necessary to improve our knowledge of the pathophysiology of EA 2, especially of the mechanisms underlying attack provocation. As a second step, the mechanisms of action of ACTZ and 4-AP should be investigated more thoroughly. Both issues are best addressed by electrophysiological and genetic examination in the animal models.

The therapeutic effects of ACTZ and 4-AP should be evaluated and compared in randomized controlled treatment trials. The focus should be on the short-term effects (e.g., attack prevention and improvement of interattack central ocular motor dysfunction), as well as on the long-term effects on progressive cerebellar signs and symptoms. It will also be necessary to correlate different genotypes to the pharmacologic responses.

Finally, these studies should include approaches to clearly differentiate EA 2 from vestibular migraine on a genetic basis, because the clinical manifestations of both may be indistinguishable in many patients (Table 1).

Acknowledgments: We thank Judy Benson for copyediting this manuscript.

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