

# Episodic vertigo: central nervous system causes

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Episodic ataxia type 2 is a prototypical episodic vertigo and ataxia syndrome that is caused by mutations in the calcium channel gene *CACNA1A*. Recent discoveries regarding the molecular mechanisms that underlie this syndrome provide a model for understanding the more common familial episodic vertigo syndromes, particularly those associated with migraine. Vertigo due to cerebrovascular disease can be of peripheral or central origin, and can mimic more benign peripheral vestibular disorders. Small infarcts in the cerebellum and lateral medulla can present with vertigo without other localizing symptoms.

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## Abbreviations

<b>BPPV</b>	benign paroxysmal positional vertigo
<b>BRV</b>	benign recurrent vertigo
<b>EA</b>	episodic ataxia
<b>FHM</b>	familial hemiplegic migraine
<b>IHS</b>	International Headache Society

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## Introduction

Because vestibular pathways are widely distributed throughout the brain, vertigo can result from central nervous system lesions of many different types and locations [1••]. When there are other neurologic symptoms associated with the vertigo, it is usually relatively easy to localize the lesion and arrive at a diagnosis. When the vertigo occurs in isolation without other associated symptoms, however, a localized lesion is less likely and the differential diagnosis becomes more problematic.

During the past few years the molecular mechanisms that underlie the relatively rare familial syndrome episodic ataxia (EA) type 2 have been elucidated. These mechanisms provide a model for understanding the mechanisms of more common recurrent vertigo syndromes, particularly those associated with migraine. Migraine affects as many as 15–20% of the general population, and it has been estimated that about a quarter of patients with migraine experience spontaneous attacks of vertigo [2]. Several recent reports emphasize that migrainous vertigo is common and underdiagnosed [3,4,5•]. Rapid advances in our understanding of the genetics of migraine should lead to improved diagnosis and treatments for migrainous vertigo in the future.

Since the classical article on vertigo and cerebrovascular disease by Miller Fisher was published in 1967 [6], there has been a general dictum that vertigo is not an isolated symptom of vertebrobasilar insufficiency. In more recent years, however, numerous reports suggest that isolated attacks of vertigo can be the initial and only symptom of vertebrobasilar insufficiency, sometimes a warning of impending stroke [7]. Furthermore, small infarcts in the cerebellum and lateral medulla can present with vertigo and ataxia without other localizing symptoms. These central lesions may be misdiagnosed as a benign peripheral lesion because of the absence of associated neurologic symptoms and signs.

## Familial episodic ataxia

The familial EAs are rare dominantly inherited diseases that are characterized by dramatic episodes of ataxia [8]. EA-1 has brief episodes of ataxia and interictal myokymia, whereas EA-2 is manifested by longer episodes of ataxia with interictal nystagmus. The episodes of ataxia are typically triggered by exercise and stress, and are often relieved by treatment with acetazolamide. These features are reminiscent of the periodic paralysis syndromes that affect muscle, which

suggested to early investigators that an ion channel mutation might be the cause.

In 1994, Browne *et al.* [9] reported four different missense mutations in the potassium channel KCNA1 in four unrelated EA-1 pedigrees. This was the first report of a mutation in a human potassium channel and the first known ion channel mutation involving the brain. The disease locus for EA-2 was localized to a region on chromosome 19p that was previously shown to be the disease locus for familial hemiplegic migraine (FHM) [10]. FHM is a rare inherited type of migraine with aura that is characterized by recurrent episodes of headache and hemiparesis. Recovery between attacks is usually complete but, in some families, there is interictal nystagmus not unlike that seen in EA-2. A calcium channel gene mapped to this locus on chromosome 19p, and Ophoff *et al.* [11] defined the complex structure of the *CACNA1A* gene, which spans 300 000 base pairs and consists of 47 exons that encode the  $\alpha 1A$  subunit of the P/Q calcium channel. Analysis of the exons and flanking introns of *CACNA1A* identified point mutations that resulted in a premature stop codon or interfered with splicing in two families with EA-2 and missense mutations in four families with FHM, thus proving that EA-2 and FHM are allelic disorders.

Episodes in EA-2 vary from pure ataxias to combinations of symptoms, suggesting involvement of cerebellum and brain stem, and even occasionally the cortex. Vertigo, nausea, and vomiting are the most common associated symptoms, being present in more than 50% of patients. About half of the patients report headaches that meet the International Headache Society (IHS) criteria for migraine [10].

On examination during an acute episode of ataxia, patients often exhibit a spontaneous nystagmus that is not seen during the interictal examination. In between episodes, the most common finding is that of a gaze-evoked nystagmus with features typical of rebound nystagmus [10]. 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 downbeat nystagmus. Later in the course a mild truncal ataxia may be seen, along with impaired smooth pursuit and saccadic dysmetria.

#### Molecular mechanisms of episodic ataxia type 2

*CACNA1A* encodes for the  $\alpha 1A$  subunit of the P/Q calcium channel [8]. Each of four homologous domains of the  $\alpha 1A$  calcium channel subunit has six putative  $\alpha$ -helical membrane-spanning segments (S1–S6; Fig. 1 [12]). The pore-forming region (pore loop) is between segments 5 and 6, and segment 4 is the voltage-sensing

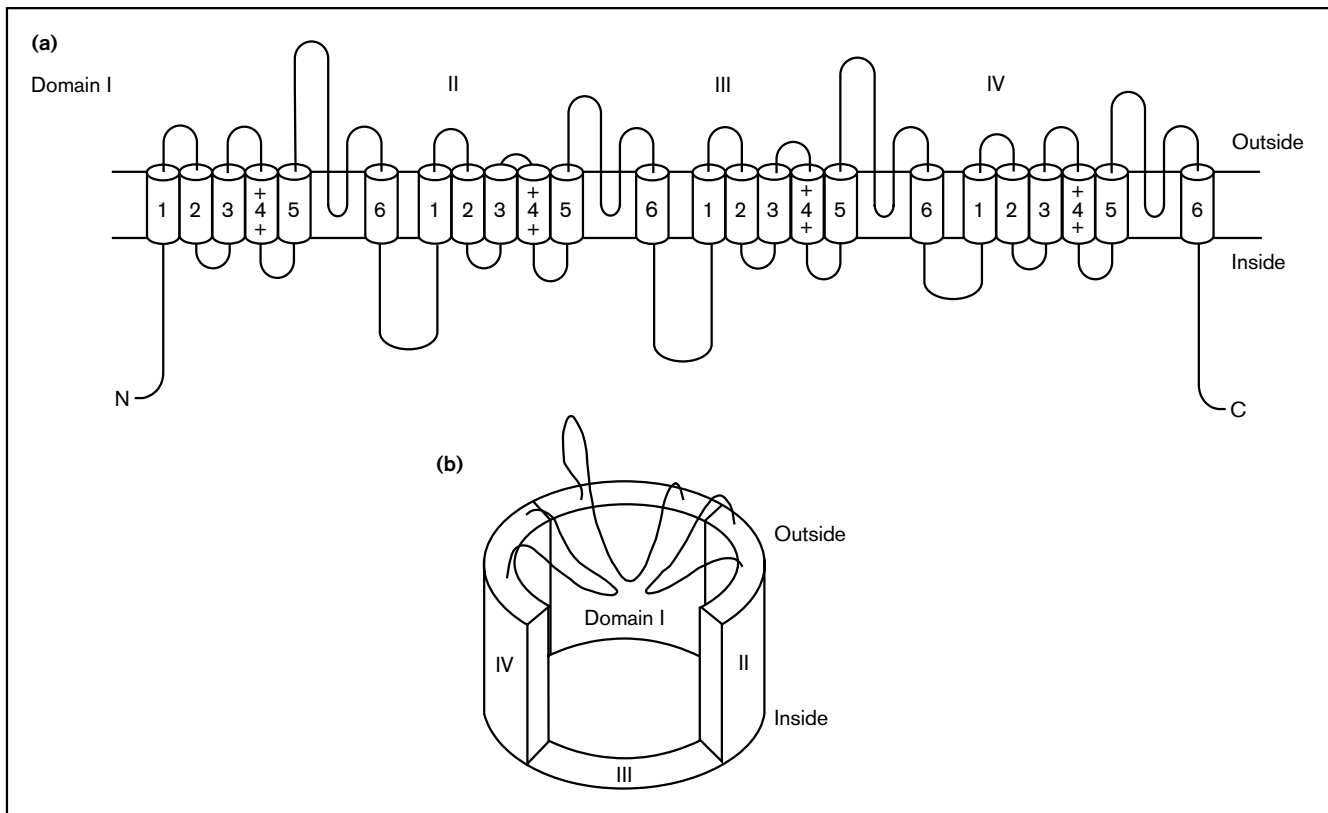
region. The central pore is formed by the pore loops from each of the four subunits. *CACNA1A* is expressed throughout the brain, but is particularly heavily expressed in the Purkinje and granular cells of the cerebellum. It is also heavily expressed in the neuromuscular junction, where it is tightly coupled with neurotransmitter release.

Ophoff *et al.* [11] initially reported two mutations disrupting the reading frame of *CACNA1A*, thus predicting a truncated  $\alpha 1A$  subunit in two families with EA-2. Yue *et al.* [13] identified a missense mutation in a family with a severe progressive ataxia in some members, and superimposed episodes of vertigo and ataxia in others. This mutation predicted a substitution of a highly conserved amino acid in the critical pore loop region of the  $\alpha 1A$  transmembrane subunit. Subsequently, numerous different mutations in *CACNA1A* were identified in patients with EA-2, with the majority predicting truncated proteins caused by premature stop codes [14]. However, a few missense mutations have also been associated with the EA-2 phenotype [15,16]. Although most cases have been familial, sporadic cases of EA-2 with *CACNA1A* mutations have been reported [14,17]. By contrast, only missense mutations in *CACNA1A* have been associated with the FHM phenotype [18\*\*]. Most patients with FHM due to missense mutations in *CACNA1A* also have cerebellar signs on examination (nystagmus and ataxia). Only a small minority of patients with pure hemiplegic migraine (without cerebellar signs) have been found to have mutations in *CACNA1A*.

There clearly is genetic heterogeneity for both FHM and EA-2. Some families with FHM have been linked to chromosome 1q, whereas others are not linked to either the 19p or 1q loci [18\*\*]. Escayg *et al.* [19] identified a missense mutation in the calcium channel  $\beta 4$  subunit gene *CACNB4* in a family with generalized epilepsy and in a family with EA-2. This could represent a second genotype for EA-2, although, because of the different phenotypes in the two families, the mutation must be considered a candidate disease mutation until the in-vivo consequences of the mutation can be determined. Initial efforts to assess the functional consequences of EA-2-causing mutations in *CACNA1A* have resulted in either a complete loss of P/Q channel function or a marked loss of voltage sensitivity [16,20].

#### Relationship between mutations in *CACNA1A* and uncomplicated migraine

In some families with FHM due to known mutations in *CACNA1A*, members with the mutation can have only migraine with aura or migraine without aura as the only manifestation of their mutation. It is therefore reasonable to question whether other mutations in *CACNA1A* may

Figure 1. Structure of the calcium channel encoded by the *CACNA1A* gene

(a) The  $\alpha 1A$  subunit of a calcium channel encoded by *CACNA1A*. Each of the 4 domains (I–IV) has six transmembrane segments (1–6). The pore-forming regions (pore loops) are between segments 5 and 6. (b) Illustration of how the central pore of the channel is believed to be formed by the pore loops from the four domains. Adapted from Baloh and Jen [12].

cause just these more common varieties of migraine [18••].

Sandor *et al.* [21] found subtle subclinical cerebellar impairment using a three-dimensional analysis of reaching movements in patients with common variety migraine. The abnormalities were more pronounced in patients with migraine with aura than in those without aura. Montagna *et al.* [22] pointed out the similarities between the magnetic resonance spectroscopy findings in EA-2 and in patients with uncomplicated migraine. Those investigators raised the possibility of a common pathophysiologic mechanism for EA-2 and uncomplicated migraine, such as an altered calcium channel. Terwindt *et al.* [23] performed an affected sibling pair analysis using flanking and *CACNA1A* intragenic markers, and found that sibling pairs with any form of migraine inherited the same chromosome 19p *CACNA1A*-containing region significantly more frequently than would be expected on the basis of chance. The result was almost completely dependent on the increased sharing found in sibling pairs with migraine

with aura, suggesting that *CACNA1A* may be an important gene in production of migraine with aura. However, Kim *et al.* [24] screened *CACNA1A* for mutations in seven probands from families with migraine and episodic vertigo, and found no mutations.

### Vertigo and migraine

Neuhauser *et al.* [5•] compared the prevalence of migraine according to IHS criteria in 200 patients from a dizziness clinic with that in an age-matched control group of 200 orthopedic patients. They found that the prevalence of migraine was significantly higher in the group from the dizziness clinic than in the control group ( $P < 0.01$ ). In 15 out of 33 patients with migrainous vertigo, vertigo was regularly associated with migraine headaches. In 16 patients vertigo occurred both with and without headaches, and in two patients headache and vertigo never occurred together. The duration of vertigo attacks ranged from minutes to days. In an accompanying editorial, Stahl and Daroff [25] suggested that it is time for neurologists to pay more attention to migrainous vertigo.

Oh *et al.* [26\*] studied the families of 24 patients who presented with benign recurrent vertigo (BRV) and who reported a family history of similar attacks of vertigo. Of 220 relatives who participated in the study, 37% reported BRV and 50% met the diagnostic criteria for migraine. By contrast only one out of 43 (2%) unrelated spouses reported BRV, whereas 10 out of 43 (23%) met the diagnostic criteria for migraine. More than two-thirds of relatives with BRV met the diagnostic criteria for migraine, and the majority reported that they had typical migraine headaches with at least some of their episodic vertigo. Those investigators concluded that familial BRV is a migraine syndrome, probably inherited in an autosomal-dominant manner with decreased penetrance in men.

Ishiyama *et al.* [27] reviewed the records of 247 patients with a confirmed diagnosis of benign paroxysmal positional vertigo (BPPV) involving the posterior semi-circular canal. Migraine was three times more common in patients with BPPV of unknown cause than in those with BPPV secondary to trauma or surgical procedures. More than 50% of patients who developed BPPV under the age of 50 years met the IHS criteria for migraine. Those investigators concluded that patients with migraine suffer recurrent damage to the inner ear (due to vasospasm or some other mechanism) that predisposes them to developing recurrent BPPV.

Clinical-pathological correlation in a patient with migraine, sudden deafness, and delayed endolymphatic hydrops showed findings consistent with ischemic infarction in one ear and delayed endolymphatic hydrops in the other ear [28]. Those authors speculated that these changes probably resulted from ischemia, possibly due to migraine-associated vasospasm.

### Vertigo and stroke

Since the circulation to the inner ear arises from the vertebrobasilar system (usually from the anterior inferior cerebellar artery), vertigo due to cerebrovascular disease can be of peripheral or central origin [1\*\*].

Kim [29] described three patients with lateral medullary infarction who presented with isolated vertigo and gait ataxia without the other typical symptoms and signs of lateral medullary infarction. Magnetic resonance imaging scans of the brain showed small infarcts that selectively involved the most dorsolateral portion of the rostral medulla corresponding to vestibulocerebellar pathways. That author emphasized that these patients may be initially misdiagnosed as having a labyrinthine disorder.

Kang *et al.* [30\*] described 12 patients with acute bilateral cerebellar infarcts in the distribution of the posterior inferior cerebellar artery. All of the patients

exhibited gait ataxia and 83% had acute vertigo. None of the patients had associated Wallenberg's syndrome. Those patients illustrate that not infrequently a single artery supplies both medial posterior inferior cerebellar artery territories.

Saeed *et al.* [31] reviewed the records of 26 patients who presented with vertebral artery dissection. Both sexes were equally involved with a mean age of onset of 48 years. Possible precipitating factors were identified in 14 patients (53%), with sport-related injury and chiropractic manipulations being most common. Headache or neck pain was a prominent feature in 88% of patients and the most common focal neurologic symptom was vertigo, which occurred in 57% of patients. Those investigators emphasized that headache or neck pain followed by vertigo or unilateral facial paresthesias is an important sign of vertebral artery dissection and may precede onset of stroke by several days.

Brandt *et al.* [32\*] found that spontaneous cervical artery dissections were associated with ultrastructural connective tissue abnormalities, mostly without other clinical manifestations of the connective tissue disease. A structural defect in the extracellular matrix of the arterial wall leading to a genetic predisposition was suggested. These findings explain why vertebral artery dissections can occur spontaneously in young, apparently healthy people without major injury.

### Conclusion

Patients presenting with vertigo often pose a diagnostic dilemma, particularly if there are no other associated neurological symptoms. Episodic vertigo is common with migraine and can be the initial symptom of brain stem or cerebellar stroke.

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