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Invited review

Clinical neurophysiology of the episodic ataxias: Insights into ion channel dysfunction *in vivo*

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ABSTRACT

Clinical neurophysiology has become an invaluable tool in the diagnosis of muscle channelopathies, but the situation is less clear cut with neuronal channelopathies. The genetic episodic ataxias are a group of disorders with heterogeneous phenotype and genotype, but share in common the feature of intermittent cerebellar dysfunction. Episodic ataxia (EA) types 1 and 2 are the most widely recognised of the autosomal dominant episodic ataxias and are caused by dysfunction of neuronal voltage-gated ion channels. There are central and peripheral nervous system manifestations in both conditions, and they are therefore good models of neuronal channelopathies to study neurophysiologically. To date most work has focussed upon characterising the electrophysiological properties of mutant channels *in vitro*. This review summarises the role of voltage-gated potassium and calcium channels, mutations of which underlie the main types of episodic ataxia types 1 and 2. The clinical, genetic and electrophysiological features of EA1 and EA2 are outlined, and a protocol for the assessment of these patients is proposed.

1. Introduction

The episodic ataxias were recognised as a heterogeneous clinical syndrome long before ion channel dysfunction was found to be the underlying cause (White, 1969; Van Dyke et al., 1975; Hanson et al., 1977; Griggs et al., 1978; Auger et al., 1984; Gancher and Nutt, 1986; Brunt and Van Weerden, 1990; Vaamonde et al., 1991). Although genetically distinct, both main forms of episodic ataxia (EA1 and EA2) share autosomal dominant inheritance and intermittent cerebellar disturbance and hence were often considered together. The most evident clinical manifestation in the episodic ataxias are the dramatic episodes of acute cerebellar symptoms, but it is clear that there may be more subtle but persistent neurological dysfunction between episodes. In EA1 this is characterised by neuromyotonia, and in EA2 by persistent cerebellar findings in many patients (see Table 1).

EA1 is caused by mutations in the KCNA1 gene encoding the $K_v1.1$ potassium channel alpha subunit (Browne et al., 1994, 1995). EA2 is caused by mutations in the CACNA1A gene encoding the alpha 1A subunit of the $Ca_V2.1$ calcium channel, also known as the P/Q type calcium channel (Ophoff et al., 1996). There have also been descriptions of EA types 3, 4, 5 and 6, (see Table 2) but these variants are exceedingly rare, some only occurring in single families, and gene mutations have not been identified in all.

$K_v1.1$ and $Ca_v2.1$ are both members of the voltage-gated ion channel family. The common feature of proteins in this family is that they consist of domains comprising 6 lipophilic transmembrane alpha helical segments. The fourth segment (S4) contains positively charged residues that sense transmembrane voltage changes, and a loop linking S5 and S6 lines the ion-conducting pore. Four such protein domains [i.e. four gene products] constitute a potassium channel, together with four cytoplasmic beta subunits. The calcium channel has a similar membrane topology comprising four repeated protein domains, but unlike $K_v1.1$ the entire channel is encoded by a single large gene. The potassium channel is also associated with four cytoplasmic β subunits, while the calcium channel is associated with three key auxillary subunits (α2δ, β and γ). The high degree of selectivity for potassium or calcium ions in each channel depends on the precise sequence of amino acids lining the ion-conducting pore.

Abbreviations: EA, episodic ataxia; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; EMG, electromyography; EEG, electroencephalography; NMT, neuromyotonia.

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Table 1
Clinical features of episodic ataxia types 1 and 2.

	Episodic ataxia type 1	Episodic ataxia type 2
Human gene	KCNA1 chromosome 12p13	CACNA1A chromosome 19p13
Channel	Potassium channel, $K_v1.1$	Calcium channel, $Ca_v2.1$
Duration of acute ataxia	Brief: Seconds to minutes	Prolonged: Hours to days
Association with seizures	Yes	Yes
Peripheral nerve features	Neuromyotonia	Occasional reports of intermittent weakness
Headache during acute episodes	No	Sometimes seen
Persistent or progressive cerebellar syndrome	No	Yes

The *in vitro* study of mutant channels associated with the EA phenotype allows characterisation of the functional consequences of specific mutations. Although many different KCNA1 and CACNA1A mutations have been identified, they all appear to result in loss of function, and some have dominant-negative effects on co-expressed wild-type channels (Adelman et al., 1995; Zerr et al., 1998; Zuberi et al., 1999; Eunson et al., 2000; Jouvenceau et al., 2001). Nevertheless the interplay between persistent and paroxysmal features in these conditions remains poorly understood. In part, this may be because these cell models have limitations and cannot fully replicate the *in vivo* biological diversity of channel subunit assembly or posttranslational biophysical processes such as phosphorylation, glycosylation and trafficking to the surface. Furthermore, *in vitro* expression does not mirror the differential topographical expression of the channels observed in central and peripheral neurones (Vacher et al., 2008).

Routine neurophysiological tests have the advantage of assessing ion channel function *in vivo*. Clinical neurophysiology has proven a useful tool in the diagnosis of muscle channelopathies (Miller et al., 2004; Michel et al., 2007). Exercise protocols and cooling studies may even help direct genetic investigations in these conditions (McManis et al., 1986; Fournier et al., 2004; Fournier et al., 2006). Neuronal channelopathies are becoming increasingly recognised and a structured approach to electrodiagnosis may also prove important in the clinical assessment of these patients. However, as yet, neurophysiological tests are only useful adjuncts to the clinical and genetic characterisation of these disorders. EA1 and EA2 have both peripheral and central nervous system manifestations, and both have distinctive *in vivo* neurophysiological characteristics which can guide genetic testing. This review collates the evidence for paroxysmal and persistent channel dysfunction *in vivo* in patients with $K_v1.1$ and $Ca_v2.1$ channelopathies and documents the neurophysiological abnormalities expected in the episodic ataxias.

2. Clinical features of episodic ataxia

Only 15 years ago these conditions were biologically unexplained and often labelled psychogenic. Epileptiform, metabolic or mitochondrial hypotheses were suggested in an attempt to explain paroxysmal neurological dysfunction in structurally normal tissue. The term 'episodic ataxia' is perhaps now a misnomer, because the phenotype of patients with KCNA1 and CACNA1A mutations continues to expand, and subjects may present with features other than paroxysmal incoordination.

2.1. Episodic ataxia type 1

The initial descriptions of EA1 recognised that nearly all subjects exhibited neuromyotonia of varying degrees as well as episodic ataxia (Van Dyke et al., 1975; Hanson et al., 1977; Griggs et al., 1978; Gancher and Nutt, 1986; Brunt and Van Weerden, 1990; Vaamonde et al., 1991). It was also observed that isolated neuromyotonia could be an inherited disease (Auger et al., 1984) although the basis for this was not understood (see below). The *episodic cerebellar dysfunction* typically manifests in the first or second decades, and may be precipitated by startle, sudden movement or a change in stance, vigorous exercise or emotional stress (Zuberi et al., 1999). These features may result from loss of the membrane-stabilizing action of $K_v1.1$ channels on the function of cerebellar neurons. The acute ataxic episodes are brief, lasting seconds to minutes. They are variable in severity and may be associated with dysarthria and sometimes titubation. Fever or intercurrent illness may reduce a patient's threshold to having an event, and during fever these episodes may be of greater severity than usual. Persistent cerebellar signs may occasionally be seen interictally, although these are usually subtle (Van Dyke et al., 1975; Hanson et al., 1977; Gancher and Nutt, 1986; Brunt and Van Weerden, 1990; Zuberi et al., 1999; Eunson et al., 2000). Brain imaging is usually normal (Eunson et al., 2000; Brunt and Van Weerden, 1990; Zuberi et al., 1999; Vaamonde et al., 1991; Chen et al., 2007). The presence of *neuromyotonia* is an expected consequence of the K^+ channel dysfunction in peripheral nerve axons, much as with acquired neuromyotonia caused by antibodies against voltage-gated K^+ channels (Newsom-Davis and Mills, 1993). Neuromyotonia is clinically apparent in nearly all patients to varying degrees, and is characterised by muscle stiffness, twitching, flickering and sometimes muscle hypertrophy. The fingers, calves and face (particularly around the eyes and mouth) are commonly affected, but involvement may be subtle, sometimes only observed as fine involuntary movements of the fingers (Hanson et al., 1977; Gancher and Nutt, 1986; Zuberi et al., 1999; Eunson et al., 2000; Rajakulendran et al., 2007).

The severity of neuromyotonia in EA1 can vary significantly between patients, and even within families. Neuromyotonia may be present at birth, producing infantile contractures (e.g. shortened Achilles' tendons) or postural limb deformities such as fixed finger clenching, thumb adduction, lower limb fixed knee flexion or fixed plantar flexion (Zuberi et al., 1999). Postural deformities may be minor, such as toe walking or toe running alone, and may gradually resolve with supportive care. In contrast, progressive kyphoscoliosis in childhood has been reported (Kinali et al., 2004). Some subjects undergo orthopaedic intervention prior to the diagnosis of EA1. Episodes of acute worsening of neuromyotonia may produce

Table 2
Reported episodic ataxia phenotypes with genetic heterogeneity.

	EA type 3	EA type 4	EA type 5	EA type 6
Phenotype	Ataxia lasting minutes (sometimes several hours), tinnitus	Brief episodes of ataxia, nystagmus	Ataxia lasting several hours. One family manifests epilepsy but no EA	Episodic and progressive ataxia, hemiplegia, epilepsy
Genotype	Autosomal dominant. Maps to chromosome 1q42	Autosomal dominant, gene not identified	Autosomal dominant, chromosome 2q22-q23. Missense mutations in CACNB4 ($Ca_v2.1$)	Sporadic missense mutation; chromosome 5p SLC1A3; glutamate transporter gene
Number of reports	Single kindred	2 families	Several families	Case report