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Abnormal gating of axonal slow potassium current in cramp-fasciculation syndrome

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HIGHLIGHTS

- Cramp-fasciculation syndrome (CFS) can be caused by various etiologies.
- Non-invasive nerve excitability testing identified abnormality in axonal slow K^+ current (I*Ks*).
- Loss of voltage-dependency of axonal I*Ks* may play a key role in axonal hyperexcitability.

ABSTRACT

Objective: Cramp-fasciculation syndrome (CFS) is a heterogeneous condition with multiple underlying causes. Although dysfunction of slow K^+ channels has been reported in patients with CFS, testing all potential candidates for this problem using conventional *in vitro* functional analysis would be prohibitively cost- and labor-intensive. However, relatively economical and non-invasive nerve-excitability testing can identify ion channel dysfunction *in vivo* when combined with numerical modeling.
Methods: Patients with CFS underwent nerve conduction study, needle electromyography, and nerve excitability testing. Mathematical modeling of axonal properties was applied to identify the pathophysiology.
Results: Four patients had distinct electrophysiological findings (i.e., fasciculation potentials, doublet/multiplet motor unit potentials, and sustained F responses); excitability testing showed the following abnormalities: reduction of accommodation during prolonged depolarization, lack of late sub excitability after a supramaximal stimulation, and reduction of the strength–duration time constant. Mathematical modeling showed a loss of voltage-dependence of a slow K^+ current. None of these patients had a mutation in the KCNQ2, 3, or 5 genes.
Conclusions: This study showed that patients with CFS might have abnormal kinetics in a slow K^+ current.
Significance: Nerve-excitability testing may aid the decision to start therapeutic intervention such as administration of slow K^+ channel openers.

Abbreviations: BFNS, benign familial neonatal seizures; CMAP, compound muscle action potential; EA1, episodic ataxia type 1; HCN, hyperpolarization-activated cyclic nucleotide-gated; Ih, HCN current; I*Kf*, fast K^+ conductance; I*Ks*, slow K^+ conductance; INa_p, persistent Na^+ current; *I*/*V*, current–threshold relationship; PNH, peripheral nerve hyperexcitability; RC, recovery cycle; RRP, relative refractory period; SDTC, Strength–duration time constant; SR, Stimulus–response; TE, threshold electrotonus; VGKC, voltage-gated K^+ channels.

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1. Introduction

Abnormal excitability of peripheral axons is known to be associated with various symptoms. Axonal hyperexcitability may manifest as symptoms such as muscle cramp, fasciculations, myokymia/neuromyotonia, and neuropathic pain (Kortman et al., 2012). A number of underlying mechanisms for cramp-fasciculation syndrome (CFS) have been reported, including genetic or autoimmune dysfunction of ion channels (e.g., voltage-gated Na^+ and K^+ channels), peripheral neuropathy, anterior-horn-cell disease, and metabolic abnormality (Liewluck et al., 2014; Rubio-Agusti et al., 2011; Wuttke et al., 2007). However, a large number of patients with CFS do not have an identifiable etiology, that is, the pathogenesis is unclear (“idiopathic CFS”).

Axonal excitability testing assesses the properties of peripheral axons such as resting membrane potential and ion channel function in a non-invasive manner (Bostock et al., 1998; Krishnan et al., 2009; Kuwabara and Misawa, 2008; Nodera and Kaji, 2006). Clinical use of axonal excitability testing in patients with suspected axonal hyperexcitability may be useful for suggesting a potential underlying mechanism that can lead to effective therapy. Here, we present a series of patients with CFS who showed a distinctive pattern of electrophysiological test results and abnormal axonal excitability results that might be associated with abnormal kinetics of a nodal slow K^+ current of the peripheral motor axon.

2. Methods

2.1. Patients

This prospective study, performed from January, 2008 to August, 2013, was approved by the Institutional Review Board of Tokushima University and Chiba University and was performed in accord with the principles embodied in the Declaration of Helsinki. Informed consent was obtained from all participants before the start of the study. The inclusion criteria were the presence of muscle cramps (painful and involuntary contractions associated with palpable hardening of the muscle) and evidence on the neurologic exam of fasciculations involving muscle groups other than calf and foot muscles (Liewluck et al., 2014). Patients who had electrolyte disturbance or electrophysiological and clinical findings suggestive of motor neuron disease were excluded. Assays for the autoantibody against voltage-gated K^+ channels (VGKC) were performed at the Department of Neurology, Kagoshima University (Arimura et al., 2006). Sequential analysis of the KCNQ2, 3, and 5 genes were performed at the Department of Pediatrics, Fukuoka University (Ishii et al., 2009).

2.2. Nerve conduction study and needle electromyography

Nerve conduction studies of the motor and sensory nerves were performed using routine techniques, at least in the median, ulnar, tibial, and sural nerves (Kimura, 2013). Needle electromyography of gastrocnemius, tibialis anterior, vastus medialis, and other muscles when clinically indicated, was performed using a concentric needle.

2.3. Nerve excitability measurements

Immediately after the nerve conduction study and needle electromyography, the excitability of the median motor nerve was recorded over the abductor pollicis brevis, with the stimulation electrode placed 3 cm proximal to the wrist crease and the remote electrode at 10 cm proximally. The median nerve was chosen because the normative excitability values have been established. Multiple excitability measurements were recorded using commercially-available software (QtracW; Digitimer, UK) (Bostock et al., 1998). The current required to produce a predetermined amplitude (response level) of the compound muscle action potential (CMAP) was defined as “threshold current.” In threshold electrotonus (TE) tests, long depolarizing or hyperpolarizing sub threshold conditioning currents up to 100 ms in duration and with amplitudes of ±40% of the threshold current were used. S2 accommodation was defined as the change of threshold from the time of its maximum within the depolarizing subthreshold electrotonus to pulse end. The strength–duration time constant (SDTC) was estimated based on the thresholds at different durations of stimulus according to Weiss’s law. The current–threshold relationship (I/V) was recorded with a 1-ms test stimulus applied 200 ms after the onset of a long-lasting subthreshold polarizing current. Recovery cycle (RC) was recorded by delivering the test stimulus at different intervals (from 1.6 to 200 ms) after a supramaximal conditioning stimulus. The hand and forearm were wrapped in a blanket during testing to maintain skin temperature at >32 °C.

The control excitability data were obtained from healthy individuals who had no neurological symptoms or signs ($N = 19$ [6 women and 13 men]: age 55.6 ± 15.4 years [mean ± SD: range 34–78]). Notably, the reported effect of age on nerve excitability was found to be minimal in this study (Bae et al., 2008), such that we did not have to adjust excitation parameters to offset age effects.

2.4. Mathematical modeling of the excitability data

The commercially available Bostock model of the human motor axon was used in the simulation of axonal excitability (Memfit, QtracP). Parameter adjustments were made to improve the fit to normal human RC, strength–duration, I/V, and TE (Howells et al., 2012; Kiernan et al., 2005). To reflect better the characteristic waveform changes (see Section 3), the weighting factors were set as follows: TE, 3; RC, 3; SDTC, 1; and I/V, 1.

2.5. Data analysis

The excitability parameters of patients and control subjects were compared using the Mann–Whitney U test (QtracP version 31/5/2013, Digitimer, UK). The P-value significance threshold was set at 0.05.

3. Results

3.1. Clinical presentation, nerve conduction study, and electromyography

We identified four patients who met the inclusion criteria. Table S1 presents the clinical summary. We describe two representative patients in detail: (1) Patient 1 was a 22-year-old woman with no history of seizure disorder or developmental delay, who experienced muscle cramps in the legs at age 10 after running. She developed heaviness of the legs and difficulty running after age 12. Carbamazepine was prescribed by a local pediatrician at age 16 and her leg symptoms were relieved. Her family history was unremarkable. Her general physical exam was unremarkable. Her neurological exam was normal in cognition, cranial nerves, muscle tonus and bulk, muscle strength, sensation, muscle stretch reflexes, and coordination. Visible fasciculation was present in the calves and rarely in the arms at rest. Brief exercise provoked painful muscle cramps. The motor and sensory nerve conduction studies showed normal latencies, conduction velocities, and amplitudes.