ABSTRACT: The goal of this retrospective cohort study was to test the hypothesis that the cramp–fasciculation syndrome (CFS) represents a disorder of peripheral nerve hyperexcitability and to evaluate the accuracy of repetitive nerve stimulation (RNS) for its diagnosis. A consecutive series of 108 patients were evaluated with posterior tibial RNS at 1, 2, and 5 Hz. Abnormal peripheral nerve excitability was defined by the presence of afterdischarges, cramp potentials, or continuous motor unit activity. RNS demonstrated abnormal nerve hyperexcitability in 29 of 36 subjects (81%) with CFS, defined operationally by the presence of both muscle cramps and fasciculations. Based on receiver operating characteristic (ROC) curve analysis, tibial RNS correctly classified the presence or absence of CFS in 75% of subjects. These results suggest that CFS represents a form of peripheral nerve hyperexcitability and, furthermore, that RNS is a clinically useful test for CFS.

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ACCURACY OF REPETITIVE NERVE STIMULATION FOR DIAGNOSIS OF THE CRAMP–FASCICULATION SYNDROME

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Peripheral nerve hyperexcitability (PNH) is a term that has been used to describe a group of conditions that range in severity from acquired neuromyotonia (Isaacs' syndrome) to the benign cramp–fasciculation syndrome (CFS).[2,4,7] The evidence for abnormal excitability of peripheral nerves in acquired neuromyotonia is based on the finding of a range of spontaneous electrical discharges that include fasciculation potentials as well as myokymic and neuromyotonic discharges. The presence of antibodies directed against voltage-gated potassium channels—which suppress the outward potassium current and consequently affect neuronal excitability—in a proportion of these subjects adds weight to the contention that acquired neuromyotonia is due to abnormal nerve excitability.[2,3,7] The evidence, however, that CFS is similarly due to hyperexcitability of peripheral nerves is more tenuous: it is based in part on an overlap in symptomatology with that reported in acquired neuromyotonia and in part on the observation that afterdischarges and cramp potentials following repetitive nerve stimulation (RNS) are more readily elicited in these patients than among subjects without symptoms of muscle cramps and fasciculations.[1,4] It is not clear, however, whether all patients with muscle cramps and fasciculations have evidence of abnormal nerve excitability.

The goal of this study was to examine the frequency with which patients complaining of cramps and fasciculations show evidence of abnormal peripheral nerve excitability in the form of afterdischarges and cramp potentials following repetitive stimulation of the tibial nerve and to formally evaluate the accuracy of abnormal RNS for the diagnosis of CFS. Since cramps and fasciculations may also be encountered in association with underlying neuromuscular disorders such as amyotrophic lateral sclerosis, we also examined the question of whether hyperexcitability of peripheral nerves underlies such secondary causes of these symptoms.

MATERIALS AND METHODS

Study Subjects. Subjects from this study were retrospectively identified from an electronic database at our departmental Electromyography Laboratory. The study population comprised subjects consecutively evaluated with posterior tibial RNS during eval-

Abbreviations: CFS, cramp–fasciculation syndrome; LR, likelihood ratio; NPV, negative predictive value; PNH, peripheral nerve hyperexcitability; PPV, positive predictive value; QOL, quality of life; RNS, repetitive nerve stimulation; ROC, receiver operating characteristic

Key words: fasciculations; muscle cramps; peripheral nerve hyperexcitability; ROC curve; sensitivity; specificity

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uation of neurological symptoms between July 2003 and October 2006. RNS was generally performed because of complaints of muscle pain, cramps, or twitching, symptoms that are commonly encountered in other disorders of PNH. All subjects were over 18 years of age. Our Investigational Review Board approved the study protocol and granted an HIPAA (Health Information Portability and Accountability Act) waiver that allowed for review of the electronic medical records.

Electrophysiology. Slow tibial RNS was performed using a Synergy electromyograph system (Oxford Instruments, Eynsham, UK). The recording and reference electrodes were placed according to the standard technique for routine tibial motor nerve conduction studies, with the surface electrode placed over the abductor hallucis brevis muscle and the reference electrode at the base of the first metatarsal. Five supramaximal stimuli at a frequency of 1, 2, or 5 Hz were delivered to the posterior tibial nerve at the ankle 9 cm proximal to the recording electrode. In order to minimize movement artifact, patients were instructed to maintain the foot in a relaxed position and the investigator visually monitored the limb during stimulus administration in order to verify the presence or absence of movement. Recordings were made with the sweep speed set at 1 s per division and a gain of 200 μV per division. Filters were set at conventional settings for motor nerve conduction studies: the low-frequency filter was set at 3 Hz and the high-frequency filter at 10 kHz.

Criteria for the identification of afterdischarges and cramp potentials with surface electrodes following RNS have been described previously.[1] All tracings were reviewed for quality of the baseline recording both prior and subsequent to the train of electrical stimuli. Individual electrical potentials identified following the train of stimuli that were not present at baseline were identified as afterdischarges. When the frequency of afterdischarges was too great to be counted and demonstrated maximal amplitude at onset with a smooth or gradual reduction in amplitude back to baseline, a cramp potential was identified. Continuous motor unit activity was determined to be present when baseline electrical potentials were too numerous to be counted both at baseline and after stimulation with the foot maintained in a relaxed position. RNS results were classified as either normal or abnormal based on a qualitative assessment of the presence or absence of afterdischarges, cramp potentials, or continuous motor unit activity (Fig. 1) by the two study investigators acting independently and blinded to the clinical history. For the purpose of this study, both investigators were required to agree on the assessment of each individual tracing; disagreements were resolved by consensus.

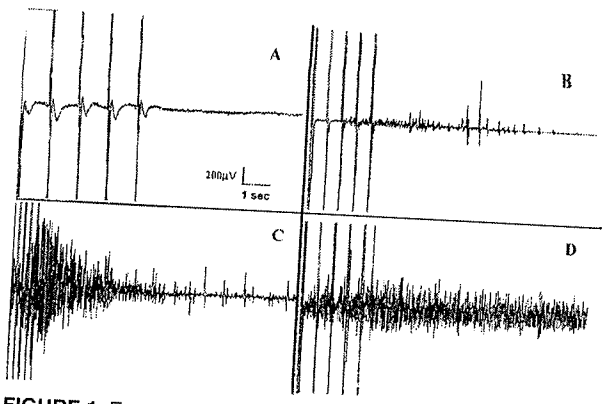

FIGURE 1. Examples of RNS tracings. **(A)** Normal study at 1 Hz. **(B)** Afterdischarges at 2 Hz. **(C)** Cramp potential at 5 Hz. **(D)** Continuous motor unit activity at 1 Hz.

Reference Standard. No gold standard currently exists for a diagnosis of CFS. As such, for the purposes of this study CFS was operationally defined by the presence of both cramps and fasciculations as either clinical complaints or clinical findings. Cramps were defined as sudden, painful, and involuntary contractions of muscle that are associated with palpable hardening of the muscle; their presence was identified by documentation in either the electronic medical record or on a standardized questionnaire furnished by the electrophysiology laboratory. Fasciculations were defined clinically as brief and involuntary arrhythmic muscle twitches and were recognized electrically as characteristic random and spontaneous motor unit action potentials on EMG. CFS was considered either a primary disorder in the absence of other identified pathology or as secondary when both cramps and fasciculations occurred in the context of another underlying neuromuscular disorder. The term benign fasciculation syndrome was used to describe subjects with isolated fasciculations.

Statistical Methods. Descriptive demographic and clinical data were collected with a standardized abstraction sheet. Chi-square analysis and Fisher's exact test were used where appropriate to compare the frequencies of clinical symptoms between those with and without CFS, between those with primary and secondary CFS, and for evaluation of RNS abnormalities by stimulation frequency. Student's *t*-test was used to compare continuous variables between those

Table 1. RNS test characteristics for CFS by stimulation frequency.

Stimulation frequency	Sensitivity	Specificity	PPV	NPV	LR +	LR −
1Hz	66% (64%–67%)*	76% (74%–76%)	0.58	0.82	2.75	0.58
1Hz or 2Hz	75% (69%–78%)	67% (64%–67%)	0.51	0.84	2.27	0.37
1Hz or 2Hz or 5 Hz	83% (83%–86%)	58% (57%–58%)	0.50	0.87	1.98	0.29

*Numbers in parentheses represent the confidence boundaries calculated from the sensitivity analyses.

with and without CFS. A series of 2 × 2 tables were constructed in which the threshold for defining RNS as abnormal was varied and the sensitivity and specificity of RNS for the diagnosis of CFS were determined. A sensitivity analysis was performed in order to explore the impact of studies that were uninterpretable due to movement artifact. Sensitivity and specificity were recalculated first by regarding the artifactual recordings as normal and then as abnormal and this facilitated calculation of the confidence limits of the estimates of sensitivity and specificity based on the extremes of data imputation. Sensitivity and specificity estimates allowed for calculation of positive and negative likelihood ratios (LR+ and LR−). Positive and negative predictive values (PPV and NPV), which reflect the proportion of subjects with either positive or negative tests who are found to have disease or to be disease-free, respectively, were calculated. Unconditional logistic regression was used to generate a receiver-operating characteristic (ROC) curve and to estimate the area under the curve. Data were analyzed using SAS v. 8.02 (SAS Institute, Cary, North Carolina).

RESULTS

Study Population. Over a 3-year period, 108 consecutive patients were evaluated with tibial RNS. Of these, 36 (33%) met clinical criteria for the diagnosis of CFS. There were no differences in the basic demographic characteristics of those with and those without CFS with regard to age in years (44 vs. 48, $P = 0.11$) or male sex (61% vs. 57%, $P = 0.68$).

By definition, symptoms of muscle cramps and fasciculations were present in all patients in the CFS group. Muscle stiffness was reported slightly more often among those with CFS (42% vs. 15%, $P = 0.047$), but exercise intolerance, weakness, muscle pain, sensory symptoms, hyperhidrosis, irritability, and hallucinations were no more frequent in those with CFS. Among the 36 subjects with CFS, 12 were found to have an underlying neuromuscular disorder (radiculopathy, 6; motor neuron disease, 4; peripheral neuropathy, 2) and subjects in this group were diagnosed with secondary CFS. CFS was considered primary in the remaining 24 subjects.

Repetitive Nerve Stimulation. RNS of the tibial nerve utilizing at least one stimulation frequency was performed in all study subjects. All subjects were evaluated at 1 Hz, whereas 2 Hz and 5 Hz stimulation was performed in 97 (90%) and 92 (85%) subjects, respectively. The presence of movement artifact precluding interpretation occurred infrequently at all frequencies: 3 (3%) at 1 Hz, 2 (of 97, 2%) at 2 Hz, and 1 (of 92, 1%) at 5 Hz.

Abnormalities in RNS were more frequent among subjects with than without CFS at all stimulation frequencies ($P < 0.002$). The sensitivity of abnormal RNS for the diagnosis of CFS was highest (83%) when afterdischarges, cramp potentials, or continuous muscle-fiber activity at any stimulation frequency were considered abnormal, but specificity was low (58%) (Table 1). Conversely, specificity was highest (76%) when abnormal RNS was defined on the basis of afterdischarges, cramp potentials, or continuous muscle-fiber activity present at 1 Hz, but this elevation of the threshold for defining RNS as abnormal had the effect of reducing sensitivity to 66%. ROC curve analysis illustrates the trade-off between sensitivity and specificity (Fig. 2) with an area

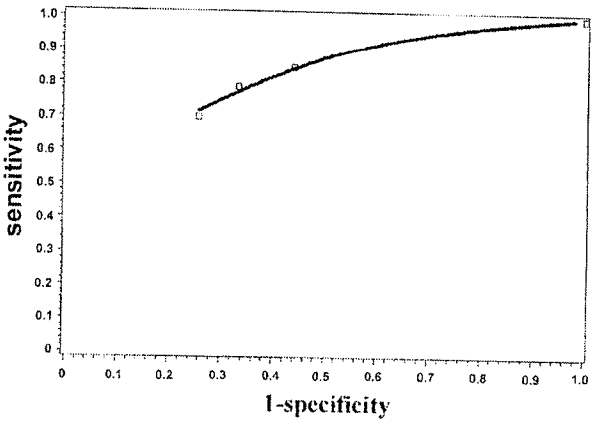

FIGURE 2. ROC curve for RNS in CFS.

under the curve of 0.751, which implies an overall probability of a correct diagnosis in 75% of patients. The relative frequency of abnormal RNS did not distinguish between those with primary or secondary CFS at 1 Hz (79% vs. 83%, $P = 1.00$), 2 Hz (75% vs. 91%, $P = 0.38$), or 5 Hz (72% vs. 89%, $P = 0.63$). None of the five study subjects diagnosed with benign fasciculation syndrome were noted to have abnormal RNS.

Clinical Features Associated with Primary CFS. In an effort to define a syndrome of primary CFS due to PNH, we selected those patients without an underlying neuromuscular disorder who demonstrated afterdischarges or cramp potentials at 1 Hz RNS, the stimulation frequency with the highest specificity for the diagnosis of CFS. Muscle stiffness was reported more frequently with primary CFS than in those without CFS (60% vs. 0%, $P < 0.001$), and both positive and negative sensory symptoms showed a trend toward being less frequent in primary CFS than in those without CFS (40% vs. 48%, $P = 0.06$). Exercise intolerance, muscle weakness, muscle pain, hyperhidrosis, and irritability or visual hallucinations were not more frequent in primary CFS than those without CFS. When comparing symptoms between those with primary and secondary CFS, only muscle stiffness was more common in primary CFS (60% vs. 0%, $P = 0.02$); all other symptomatic complaints failed to distinguish between groups. Myokymic discharges were identified in 2 of 14 (14%) of those with primary CFS, the only subjects in whom myokymia was present in the entire study population. Of the CFS subjects specifically queried regarding the impact of cramps on quality of life (QOL) by a standardized questionnaire, 6 of 10 indicated impaired QOL, each of whom had abnormal RNS at 1 Hz. Cramps tended to impact QOL more frequently in patients with primary than secondary CFS, although only a trend was noted (100% vs. 33%, $P = 0.08$).

DISCUSSION

Symptoms of muscle cramps and fasciculations are common among patients seen by neuromuscular specialists. As the etiology of these symptoms is diverse, it is often difficult to discern the underlying cause. Cramps and fasciculations may be symptomatic of an underlying neuromuscular disorder such as amyotrophic lateral sclerosis, but may also occur as part of a group of conditions characterized by primary hyperexcitability of peripheral nerves. The prototypic disorder of PNH, Isaacs' syndrome, or acquired neuromyotonia, can be recognized by the presence of characteristic myokymic and neuromyotonic discharges. A more difficult question has been how to identify those patients whose symptoms of cramps and fasciculations might be due to a more benign form of PNH in which these characteristic electrical discharges are absent.

The basic hypothesis underlying the use of RNS to identify patients with CFS due to PNH is that, while the more severe forms of PNH are characterized by frequent spontaneous electrical (myokymic and neuromyotonic) discharges, a milder form of nerve hyperexcitability is evidenced by the presence of afterdischarges or cramp potentials that are triggered by repetitive stimulation of a peripheral nerve.[1] However, since even normal nerves may be induced to fire such afterdischarges and cramp potentials,[1,6] the crucial question relates to the threshold frequency of repetitive stimulation that best discriminates between normal nerves and those that are hyperexcitable. In an effort to address this question we performed a retrospective cohort study in which a clinical definition was used as the gold standard for the diagnosis of the CFS, i.e., the presence of both muscle cramps and fasciculations. Using this definition, we evaluated the diagnostic utility of RNS of the tibial nerve at 1, 2, and 5 Hz, with the selection of these test parameters based on prior observations.[1] We found that RNS provides reasonably good discrimination between those with and without CFS, as evidenced by an area under the ROC curve of 0.75. In evaluating the utility of a diagnostic test it is appropriate to vary the threshold for defining a test as abnormal depending on the clinical context. Thus, when a test is being used to screen for a particular condition, it is important to maximize sensitivity. For RNS, this can be accomplished by defining the test as abnormal based on the presence of afterdischarges or cramp potentials at 1, 2, or 5 Hz. By contrast, when a test is being used to confirm the presence of a condition and high specificity is required, the threshold for defining pathology can be raised such that afterdischarges or cramp potentials following only 1 Hz stimulation are regarded as abnormal. Under this paradigm, RNS offers a maximal sensitivity of 83% and a maximum specificity of 76%. These estimates of sensitivity and specificity as well as the area under the ROC curve, which represents the overall diagnostic accuracy of the test across a range of cut-points for defining abnormality, are comparable to those reported for accuracy of nerve conduction studies for the diagnosis of carpal tunnel syndrome in the presence of axonal polyneuropathy.[5]

The discrimination between those with and without CFS afforded by RNS is incomplete, for several possible reasons. One possibility, as noted before, is that symptoms of muscle cramps and twitching are of diverse etiology, with only some being due to PNH and these are the patients with abnormal RNS. A second possible explanation might be that the symptom of muscle cramping is somewhat nonspecific in that different people may use the term "cramp" to mean different things. Strictly speaking, we define a cramp as a spontaneous involuntary muscle contraction that is associated with palpable hardening of the muscle. Given the retrospective nature of this study it is not possible to be confident that such a strict definition was employed uniformly.

Methodological differences between this study and a prior study of the utility of RNS for the evaluation of patients with muscle cramps and fasciculations[1] preclude a direct comparison of the results. However, the approach adopted in the current study of including a consecutive series of patients in whom RNS was used for the evaluation of symptoms suggestive of PNH, with an independently applied reference standard, provides a more accurate reflection of the clinical utility of this test. As few series on CFS exist and diagnostic criteria vary, it is likewise difficult to directly compare clinical features between our study and previous literature. It is interesting, however, to note that in the series reported by Tahmoush et al.[4] 8 of 9 patients were unable to work secondary to their neurological symptoms. We were not able to remark on functional status but did observe an interesting trend toward an adverse impact of cramps on health-related QOL. Future study is needed to investigate formally the impact of cramps on functional status and health-related QOL to substantiate these preliminary observations.

The results of this study suggest several conclusions. First, the RNS protocol utilized in this study is fairly simple in terms of its performance and interpretation, and is well tolerated by the vast majority of patients. Second, the presence of afterdischarges or cramp potentials following RNS of the tibial nerve at stimulation frequencies ranging from 1–5 Hz provides reasonably good discrimination between those with and those without abnormal nerve excitability. The clinical significance of abnormal RNS is unclear, but RNS may be a useful test to document the presence or absence of CFS (due to abnormal nerve excitability) in patients with clinical complaints of cramps and muscle twitching. It is possible that such patients may better respond to sodium channel antagonists, but this remains a hypothesis in need of confirmation. Third, clinical complaints outside of muscle stiffness may fail to distinguish between those with and without CFS. Fourth, it is interesting to note that evidence of abnormal neuronal excitability was not found in any of the patients in this study who complained only of fasciculations, suggesting that patients with the benign fasciculation syndrome do not represent a form PNH. Finally, abnormal neuronal excitability appears to underlie both the primary and secondary forms of CFS, suggesting that PNH may result from several distinct pathophysiologic processes.

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