Repetitive nerve stimulation for the evaluation of peripheral nerve hyperexcitability

Michael Benatara a,*, Kristine M. Chapman b, Seward B. Rutkove c

a Department of Neurology, Emory University, 1365A Clifton Road N.E., Atlanta, GA, 30322, USA
b Division of Neurology, University of British Columbia, 1081 Burrard Street, Vancouver, BC Canada V6K 1M8
c Department of Neurology, Harvard University, 330 Brookline Avenue, Boston, MA, 02215, USA

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Abstract

Objective: To examine the utility of repetitive nerve stimulation (RNS) in the evaluation of peripheral nerve hyperexcitability (PNH).

Background: PNH describes a group of disorders characterized by muscle cramps, twitching and stiffness. When severe, PNH may be characterized by the presence of continuous muscle fiber activity on routine needle electromyography (EMG). In milder forms of the disease, nerve hyperexcitability may be evidenced by the presence of after-discharges or cramp potentials following RNS.

Methods: Fifty-four patients were prospectively recruited and classified into one of three groups—PNH, other neuromuscular disease and controls. We recorded and quantified the after-discharges and cramp potentials following RNS at 1, 5, 10 and 30 Hz.

Results: The proportion of nerves with after-discharges and/or cramp potentials was significantly greater in the PNH group than the control group at both 5 Hz (p = 0.03) and 10 Hz (p = 0.01), as well as in the neuromuscular disease group compared to controls at 5 Hz (p = 0.02). There was also a significant concordance between complaints of muscle cramps and fasciculations and the finding of after-discharges and/or cramp potentials at both 5 Hz (p = 0.005) and 10 Hz (p = 0.004). At a stimulation frequency of 10 Hz, the sensitivity of RNS for the diagnosis of PNH (primary or secondary) was 79% and the specificity was 88%.

Conclusion: Our findings suggest that RNS at or below a stimulation frequency of 10 Hz (when positive) is a useful test for the diagnosis of PNH, whether it is primary or secondary.

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1. Introduction

Peripheral nerve hyperexcitability (PNH) is a term that has been used to describe a group of disorders characterized clinically by muscle cramps, muscle twitching (fasciculations or myokymia), muscle stiffness and pseudomyotonia (delayed muscle relaxation after contraction). Acquired neuromyotonia, also known as Isaacs’ syndrome, is one of the better known, albeit rare, examples of PNH. In his description of this disorder in 1961, Isaacs [1] drew attention to the continuous muscle fiber activity on routine needle electromyography (EMG) that characterizes the syndrome. In 1991, Tahmoush and colleagues [2] identified a disorder characterized by less prominent PNH that they called the “cramp-fasciculation syndrome”. Continuous muscle fiber activity was not present in these patients. Instead, the presence of after-discharges following repetitive nerve stimulation (RNS) was taken as evidence of PNH, and this finding was used to define the clinical syndrome [2]. PNH is now recognized to include a spectrum of disorders with varying degrees of nerve hyperexcitability [3,4]. A distinction has also been made between secondary PNH, in which nerve hyperexcitability is the consequence of some other primary nerve pathology (e.g., radiculopathy, peripheral neuropathy), and primary PNH, in which the primary pathology is one of nerve excitability, which may result from the effects of auto-antibodies directed against voltage-gated potassium channels.

Muscle cramps and twitching are common complaints amongst patients seen in the neuromuscular clinic and the electromyography laboratory. The recognition of PNH, either primary or secondary, as the cause of these symptoms is important in that it may spare the patient from further
unnecessary investigations (including muscle biopsy), prompt a search for a primary underlying malignancy (given the occurrence of primary PNH as a paraneoplastic phenomenon), and support symptomatic treatment with membrane stabilizing drugs such as carbamazepine. Tahmoush and colleagues [2] proposed the use of repetitive nerve stimulation as an electrodiagnostic test to identify patients with primary PNH, reporting that after-discharges were observed in PNH, but not in healthy volunteers as well as in a small number of patients with other neuromuscular disorders. This claim was not without controversy. In response to the article by Tahmoush and colleagues, Verdru et al. [5] argued that these discharges were non-specific and could be seen in patients with motor neuron disease, lumbosacral radiculopathy and even in healthy controls.

The use of RNS as a means to identify PNH amongst patients with symptoms of muscle cramps and twitching is an attractive idea. The appeal derives in large part from the simplicity of the test and the ease with which it can be incorporated into routine electrodiagnostic studies. But the precise role of RNS as a tool to identify after-discharges and the appropriate interpretation of such discharges remain unclear. In this study, we have sought to identify the value of after-discharges following RNS for the diagnosis of PNH by evaluating its use in a cohort of individuals presenting to an electromyography laboratory. Specifically, we examined the effects of stimulation frequency, the relative threshold at which different nerves (e.g., tibial vs. median) fire after-discharges in response to RNS and whether diseased nerves, such as those in patients with polyneuropathy or radiculopathy, are more or less prone to generate such after-discharges as compared to a group of patients with primary PNH.

2. Methods

Approval for this study was obtained from the Committee on Clinical Investigation at the Beth Israel Deaconess Medical Center and written informed consent was obtained from all subjects.

2.1. Patient selection and classification

All patients seen in our electrodiagnostic laboratory by one of the investigators over the period of several months were eligible for inclusion in the study. This prospective cohort included four patients with primary PNH; an additional three subjects with previously diagnosed primary PNH were also recruited from our clinic population. Serological testing for the presence of voltage-gated potassium channel antibodies was not performed.

There is no gold standard for the diagnosis of primary PNH. Tahmoush et al. [2] used the presence of after-discharges following RNS to define a cohort of patients with muscle cramps and exercise intolerance as having the cramp-fasciculation syndrome. In order to evaluate the sensitivity and specificity of RNS for the diagnosis of this syndrome, it was necessary to use a clinical definition for the syndrome of primary PNH. For the diagnosis of primary PNH, therefore, we required (i) that patients report symptoms of muscle cramps and/or twitching as their primary complaint, (ii) that fasciculations be visible on examination and (iii) that routine NCS and motor unit potentials on EMG in symptomatic extremities were normal. Patients were designated as having secondary PNH if they reported symptoms of muscle cramps and/or twitching (although often not as the primary complaint) and had fasciculations on examination, but if routine NCS and EMG showed evidence of underlying neuromuscular disease. For the purposes of the classification used, a normal EMG was taken to imply normal motor unit potential morphology and recruitment in the absence of abnormal spontaneous/insertional activity. Continuous muscle fiber activity and/or myokymia were not observed in any patients.

Patients were therefore primarily assigned to one of three groups based on the presence or absence of symptoms of muscle cramps and twitching and the results of routine NCS and EMG:

1. The normal control group—normal routine NCS and EMG without symptoms of muscle cramps and twitching in any extremity.
2. The neuromuscular disease group—abnormalities on routine NCS and EMG, irrespective of the presence or absence of symptoms of muscle cramps and twitching. Symptoms were identified and subsequently used to divide these patients into two groups, those with and without secondary PNH.
3. The primary PNH group—normal routine NCS and EMG with symptoms of muscle cramps and twitching.

2.2. Protocol

Repetitive nerve stimulation was performed following routine nerve conduction studies and electromyographic examination using a Synergy electromyograph (Oxford Instruments, Eynsham, Great Britain). The recording and reference electrodes were placed according to standard procedure for motor nerve conduction studies. For examination of the median and ulnar nerves, the stimulating electrode was positioned over the relevant nerve 7 cm proximal to the recording electrode. A distance of 9 cm was used for study of the peroneal and tibial nerves. Recording electrodes were placed over abductor pollicis brevis, abductor digiti minimi, extensor digitorum brevis and abductor hallucis for the median, ulnar, peroneal and tibial nerves, respectively. The time sweep was set to 1 s per division (total of 10 s) and the gain was set at 100 μV per division. The subject was instructed to relax the limb being studied and tried to maintain the relaxed state during and after the administration of the stimulus. Each nerve was stimu-
lated supramaximally (pulse duration of 0.1 ms) at 1 Hz (for 5 s), 5 Hz (for 1 s), 10 Hz (for 1 s) and 30 Hz (for 1/2 s). The stimulating electrode was secured in position over the nerve to minimize movement and the potential for submaximal stimulation. An interval of approximately 30–60 s was allowed between trains of stimuli. At least one nerve was examined in each patient, depending on individual tolerance for the test procedure. Up to four nerves (median, ulnar, peroneal or tibial) were examined in some patients. All patients were asked to complete a questionnaire indicating the presence or absence of symptoms that might suggest PNH, such as muscle cramps and twitching.

Individual electrical potentials following the train of stimuli were designated after-discharges. The number of after-discharges within 500 ms of the end of the stimuli were counted. When the frequency of after-discharges was too high for individual potentials to be identified and counted, the after-discharge was described as a cramp potential. The duration of the cramp potential was measured and expressed in seconds. To calculate the area of the cramp, the signal was rectified and the area of the rectified baseline of an epoch of identical length to that of the cramp potential was subtracted from the measured area of the potential.

Meaningful interpretation of the results of repetitive nerve stimulation requires the ability to distinguish between involuntary after-discharges and cramp potentials, which are thought to represent true nerve hyperexcitability versus voluntary motor activity that might result from withdrawal or muscle contraction by the test subject in response to the discomfort of the repetitive stimulation (especially at higher stimulation frequencies). This distinction is not always straightforward. In order to minimize bias, two of the investigators (M.B. and K.M.C.) developed rules (see below) to best distinguish between voluntary and involuntary motor activity and the third investigator (S.B.R.) then evaluated all of the recordings, using these rules, to determine how they should be classified. This examiner was blinded to the clinical data and the results of routine electrodiagnostic testing.

2.3. Statistical analysis

The sensitivity and specificity of repetitive nerve stimulation at each of 1, 5, 10 and 30 Hz were calculated. Chi-square analysis and Fisher’s exact test were used, as appropriate, to compare the proportion of positive results in patients in each group.

3. Results

3.1. Population demographics

Fifty-one patients were recruited in the electromyography laboratory over a period several months to participate in the study and an additional three patients with primary PNH were recruited from our clinic population during the same period. Patient demographics are summarized in Table 1. A total of 71 nerves were studied in 54 patients. The neuromuscular disease group included 16 patients with a median neuropathy at the wrist (carpal tunnel syndrome), 1 patient with an ulnar neuropathy, 3 patients with cervical radiculopathy, 9 patients with lumbosacral radiculopathy, 3 patients with polyneuropathy and 1 patient with the stiff-man syndrome. Out of these 33 patients with underlying neuromuscular disease, 12 reported experiencing troublesome muscle cramps. Under the assumption that clinical criteria are sufficient for the diagnosis, these 12 patients would be classified as having secondary PNH.

3.2. Distinguishing between genuine after-discharge/cramp potentials and “artifacts” due to incomplete relaxation

The distinction between these two forms of electrical potentials was defined operationally. The designation of motor activity as after-discharge/cramp potential required that (1) it be clearly distinct from the baseline motor activity, (2) it begin during or immediately following the train of repetitive stimuli, and (3) the baseline fluctuation characteristic of voluntary motor activity, had to be absent. Fig. 1 illustrates what was regarded as involuntary after-discharges (Fig. 1a) and a cramp potential (Fig. 1b). Examples of what was considered voluntary withdrawal or muscle contraction are illustrated in Fig. 2. When the blinded examiner could not determine whether true after potentials or cramp potentials were present because of the presence of excess contaminating voluntary motor activity, the tracings were designated as uninterpretable and the data excluded from analysis. Using these criteria, data from 16 recordings (i.e., any single nerve at any single stimulation frequency) had to be excluded (i.e., 6% of a total of 262 recordings that were made during the study).

3.3. Sensitivity and specificity of the presence of after-discharges and cramp potentials

Neither after-discharges nor cramp potentials were elicited in healthy nerves at low stimulation frequencies (1 and 5 Hz) (Table 2). Either after-discharges or cramp potentials (or both), however, were observed in a relatively small proportion (7–23%) of healthy nerves at higher stimulation frequencies (10 and 30 Hz). After-discharges or cramp potentials were designated as having secondary PNH.

<table>
<thead>
<tr>
<th>Table 1 Patient demographics</th>
<th>Control</th>
<th>Neuromuscular disease</th>
<th>Primary PNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Number of nerves studied</td>
<td>15</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>44 (23–69)</td>
<td>52 (27–89)</td>
<td>42 (21–60)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>5:9</td>
<td>14:19</td>
<td>4:3</td>
</tr>
</tbody>
</table>
potentials, however, were elicited in a greater proportion of nerves in the neuromuscular disease and primary PNH groups at all stimulation frequencies. The proportion of nerves with after-discharges and/or cramp potentials was significantly greater in the primary PNH group than the control group at both 5 Hz (p = 0.03) and 10 Hz (p = 0.01) and in the neuromuscular disease group compared to the control group only at 5 Hz (p = 0.02).

Having observed that a substantial proportion of nerves from patients in the neuromuscular disease group showed evidence of hyperexcitability, we tried to determine whether there was, in general, a correlation between the report of symptoms of muscle cramping/twitching in the affected limb and the presence of after-discharges or cramp potentials. All subjects were, therefore, divided into two groups—those with and without symptoms of muscle cramps/fasciculations, irrespective of the results of routine NCS and EMG. As shown in Table 3, there is a significant concordance between the presence of symptoms of muscle cramps/twitching and the finding of either after-discharges or cramp potentials at stimulation frequencies of 5 Hz (p = 0.005) and 10 Hz (p = 0.004), occurring in only 7 of the 66 RNS tests without cramping vs. 33 of the 74 RNS tests with cramping.

### Table 3

<table>
<thead>
<tr>
<th>Stimulation (Hz)</th>
<th>Control</th>
<th>Neuromuscular disease</th>
<th>Primary PNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0/11</td>
<td>1/28 (4%)</td>
<td>2/19 (11%)</td>
</tr>
<tr>
<td>5</td>
<td>0/15</td>
<td>9/35 (26%)</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>10</td>
<td>1/14 (7%)</td>
<td>11/34 (32%)</td>
<td>13/21 (62%)</td>
</tr>
<tr>
<td>30</td>
<td>3/13 (23%)</td>
<td>16/32 (50%)</td>
<td>11/19 (58%)</td>
</tr>
</tbody>
</table>

PNH: peripheral nerve hyperexcitability.

a  Neuromuscular vs. control (p = 0.02).

b  Primary PNH vs. control (p = 0.03).

c  Primary PNH vs. control (p = 0.01).

3.4. Nerve-specific susceptibility to fire after-discharges or cramp potentials following RNS

Overall, after-potentials in response to RNS were observed more often in the tibial nerve (88% at 30 Hz) than in the median nerve (23% at 30 Hz). Therefore, in order to minimize the potential bias that could result from the study of more tibial nerves in patients with symptoms of muscle cramps and twitching than amongst those without such symptoms, we separately compared the frequency of after-potentials in the tibial and median nerves in patients in the
different groups. While this data (summarized in Table 4) hints at a potential association between presence of symptoms and the finding of after-discharges/cramp potentials following RNS of the tibial nerve, it is not significant, likely given the small number of nerves analyzed. A similar, non-significant trend was observed for the median nerve (data not shown).

3.5. Quantification of after-discharges and cramp potentials

In accordance with the method described by Tahmoush and colleagues, we attempted to quantify the degree of nerve hyperexcitability by counting the number of individual after-discharges within the first 500 ms of the train of stimuli. With two exceptions, after-discharges were only recorded in patients with symptoms of muscle cramps/twitching; amongst those with cramps or twitching, there was no clear correlation between the stimulation frequency and the number of after-discharges (data not shown). For the analysis of cramp potentials, we calculated both the duration and the rectified area of the measured potentials, as described in Methods. Although there was a trend showing increasing area of the cramp potential with incremental rate of stimulation in all three patient groups, there was no clear correlation between the area of the cramp potential and the diagnostic category; this is largely due to the high variance of the data.

3.6. RNS as a test of diagnostic utility in individual patients

The preceding analysis has focused on the results of RNS testing of individual nerves. In the use of RNS for diagnosis of PNH, however, individual nerves are of less interest than the cumulative results in a given patient. That is to say, what is the sensitivity and specificity for the diagnosis of PNH of finding after-discharges and/or cramp potentials in any nerve? As shown in Table 5a, at a stimulation frequency of 10 Hz, the sensitivity for the diagnosis of primary PNH is 100%. The specificity is 92% if the results of routine NCS and EMG are normal and falls to 65% in the routine NCS and EMG reveal the presence of some underlying neuromuscular disorder. Slower rates of stimulation provide a higher specificity, but at the expense of lower sensitivity. If only one nerve is tested, the tibial nerve seems to offer the greatest sensitivity and specificity.

An alternative approach is to classify patients based on the presence or absence of muscle cramps (i.e., divided into those without PNH and those with PNH [primary or secondary combined]). As shown in Table 5b, at a stimulation frequency of 10 Hz, the sensitivity and specificity for the diagnosis of PNH (based on the presence of after-discharges and/or cramp potentials) are maximized at 79% and 88%, respectively. Based on these data, the positive and negative predictive values of finding after-discharges and/or cramp potentials are optimal at 10 Hz, being 79% and 88%, respectively.

4. Discussion

Muscle cramps and fasciculations, which result from the spontaneous discharge of motor nerves [6], are amongst the most common symptoms of PNH. The same symptoms may occur in normal healthy persons, particularly under certain circumstances including exercise, dehydration and pregnancy; this is perhaps not surprising.
given that the capacity to fire after-discharges and/or a cramp potential in response to RNS is not restricted to hyperexcitable nerves. Stone et al. [7], for example, were reliably able to induce cramp potentials in healthy volunteers using a stimulus duration of 1 ms, administered at a frequency of 16–18 Hz for 2 s. Warmolts and Mendell [8] were similarly able to induce repetitive discharges in mixed peripheral nerves in patients with a peripheral neuropathy. It seems likely (and indeed, it is intuitive), therefore, that nerve excitability represents a spectrum and that hyperexcitability represents one end of the spectrum at which it is relatively easy to elicit an after-discharge or a cramp potential.

It is against this background that we have examined the utility of RNS as an electrodiagnostic tool in a population of patients seen in our electrophysiologic laboratory over a period of several months. The protocol we used, described by Tahmoush and colleagues [2], is easily administered, adding only 3–5 min to routine electrodiagnostic testing, and is well tolerated up to a stimulation frequency of 10 Hz.

We have found that after-discharges and cramp potentials were elicited with similar frequency amongst patients with primary PNH and a group of patients with other neuromuscular disease, but very infrequently in the control group, especially at stimulation frequencies at 10 Hz or below. Our data suggest that it is the qualitative presence or absence of after-discharges and/or cramp potentials at a particular stimulation frequency that is particularly useful as a diagnostic test. Quantitative measures, such as the number of after-discharges within 500 ms and the area of the cramp potential, are not as helpful.

We also noted a concordance between the finding of after-discharges and/or cramp potentials and the presence of symptoms of muscle twitching and cramps. Our findings, therefore, suggest that RNS may be a useful test for the electrodiagnosis of both primary and secondary PNH, but that it is less helpful for distinguishing the two. Results of the RNS should be interpreted in conjunction with routine NCS/EMG to make this distinction. The problem of (especially nocturnal) leg cramps in the elderly is a common one. Given the high prevalence of lumbosacral radiculopathy in this population, it seems reasonable that such cramping may reflect nerve hyperexcitability related to this disorder. Our finding that such patients do show evidence of PNH suggests an explanation as to why membrane stabilizing drugs like carbamazepine are effective.

In conclusion, repetitive nerve stimulation for the diagnosis of PNH (either primary or secondary) performs with reasonably good sensitivity and specificity—79% and 88%, respectively, at a stimulation frequency of 10 Hz. There is a 79% chance of having PNH if the test is positive (i.e., the positive predictive value) and the likelihood of not having PNH if the test is negative (i.e., the negative predictive value) is 88%. RNS, therefore, seems to be a useful test for the diagnosis of both primary and secondary PNH. Results of RNS should be interpreted in conjunction with routine NCS and EMG in order to distinguish primary from secondary PNH.

References