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Interpretation of the repetitive nerve stimulation test results using principal component analysis

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Abstract

Objective: Assessment of the repetitive nerve stimulation (RNS) test parameters has some inherent difficulties, as too many co-dependent variables are involved. To circumvent these problems, we have employed the principal component analysis (PCA) for evaluating the RNS test.

Methods: We performed the RNS test on the abductor digiti quinti (ADQ), flexor carpi ulnaris (FCU) and orbicularis oculi (OO) muscles of 23 myasthenia gravis (MG) patients and 50 controls. For each group, following parameters were chosen for PCA: decremental response of amplitude and area on 2, 3 and 5 Hz stimulation rate, including 5 Hz stimulation, 4 min following tetanus; decremental and incremental response of amplitude and area on 50 Hz stimulation.

Results: Two principal components (PC1 and PC2) for ADQ and FCU muscles and 1 principal component (PC1) for OO muscle were extracted. The mean values of PC1 were significantly increased for all three muscles in the MG group compared to controls ($p < 0.01$). No significant difference between PC2 values of the MG and control groups was observed ($p > 0.05$). PC1 was the most sensitive test in detecting an abnormality on low rates of stimulation.

Conclusions: PCA, which has the advantage of studying a small number of independent parameters on RNS test, seems to be useful for detecting neuromuscular transmission defects.

Significance: By markedly decreasing the number of assessed variables, PCA can give insight to the direction of data distribution abnormalities in the RNS test, which can prove particularly useful in research studies.

Keywords: Repetitive nerve stimulation; Principal component analysis; Decrement; Increment; Area; Myasthenia gravis

1. Introduction

Repetitive nerve stimulation (RNS) test is widely used as a diagnostic tool in disorders of neuromuscular transmission (Oh, 1988). Measurement of the compound muscle action potential amplitude (CMAP) changes following the initial response is useful in the evaluation of results on both low (<10 Hz, LRS) and high rate (>10 Hz, HRS) stimulations in RNS. Because area measurements reportedly provide an additional diagnostic yield in myasthenia gravis (MG) (Lo et al., 2003), it is advisable to examine both variables during the RNS test. Apart from identifying the decremental response, the observation of a significant increment on HRS is equally important especially in the diagnosis of presynaptic neuromuscular transmission disorders (Oh et al., 1996). On the other hand, detecting abnormalities of decremental or incremental response by means of amplitude and area measurements present some difficulties. First, one has to deal with a large number of variables. Second, to conceptualize associations between large numbers of variables simultaneously is not an easy task. Third, some of parameters may reflect similar information about the features of neuromuscular transmission.

Principal component analysis (PCA) is a method of investigating the relationships among multiple variables

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(Mardia et al., 1992). The main applications of PCA are to reduce the number of variables and to detect the structure in the relationships between variables. PCA takes a large number of variables and constructs (a few) sums of subsets of these variables. Combining two correlated variables into one component illustrates the basic idea of PCA. The extraction of principal components amounts to a variance, maximizing rotation of the original variable spaces. After the first component has been extracted, the process runs and another line that maximizes the remaining variability is determined and so on. In this manner, consecutive factors are extracted. Because each consecutive factor is defined to maximize the variability that is not captured by the preceding factor, consecutive factors are independent of each other. Keeping this reasoning in mind, we employed the PCA for the analysis of the RNS test, in search of a few independent parameters (principal components) that would be beneficial for the evaluation of disorders of neuromuscular transmission.

2. Methods

2.1. Patients and control subjects

We retrospectively analyzed the records of 23 MG patients (range 3 to 76, mean age 42) tested before the initiation of immune modulating treatment. The diagnosis was confirmed by a typical history and objective clinical findings of fluctuating ocular, bulbar or extremity muscle weakness, as well as positive pharmacological tests and jitter abnormalities on single fiber EMG. The severity of myasthenia gravis was graded according to the classification recommended by the Myasthenia Gravis Foundation of America, where class I denotes ocular MG and class II–IV, mild, moderate and severe generalized MG, respectively. Patients with a fulminant course, requiring intubation were placed into class V (Jaretzki et al., 2000). There were 3 class I, 9 class II, 6 class III, and 2 class V cases included into the study. However three patients could not be classified due to lack of sufficient data. Fifty other control subjects were identified (range 9–80, mean age: 41), referred to the electrophysiology laboratory for the evaluation of a possible neuromuscular transmission disorder, but found to have none.

2.2. Repetitive nerve stimulation

A Dantec Counterpoint electromyograph was used for the studies. Anticholinesterase agents were discontinued at least 12 h before test. The following muscles were studied: abductor digiti quinti (ADQ, 50 control, 21 MG), flexor carpi ulnaris (FCU, 39 control, 10 MG), orbicularis oculi (OO, 39 control, 16 MG). In 2 ADQ muscles another electromyograph that was unable to make area measurements were used. All patients underwent a RNS test on the ADQ muscle. A second distal muscle (FCU) was tested in some cases. The two ADQ muscles without area measurements were excluded from the study. The RNS test on OO was carried out in patients with prominent ocular weakness.

RNS testing of the ADQ muscle was performed by stimulating the ulnar nerve at the elbow with surface electrodes, the intensity being supramaximal with 100 μs duration. Stimuli at rest and after 30 s of isometric exercise was given, followed by 2, 3, 5 and 50 Hz trains, with at least 1 min of rest between each train, which consisted of at least 9 pulses at LRS and 50 pulses at HRS. Another 5 Hz train was given 4 min following tetanus. CMAPs were recorded with Dantec 13 L 20 disposable surface electrodes, utilizing the belly–tendon method. Filters were set at 20–10,000 Hz. Skin temperature was controlled above 31 °C. In order to obtain artifact-free tracings, the forearm and hand were immobilized by means of velcro straps on a heavy board, the so called 'Jolly board'. Peak–peak amplitude of the CMAP at rest, percentage of the post-exercise increment of CMAP amplitude, peak–peak amplitude and negative peak area in RNS were measured. Decrement was calculated automatically on LRS, by measuring the lowest response and expressed as the percentage of the first potential. On HRS, both the decrement and the increment were measured if they were identified on the same tracing. RNS testing on the FCU muscle was performed in the same manner, except that exercise was not performed, as the immobilizing board and straps restricted wrist flexion. Zygomatic branch of the facial nerve, anterior to the tragus was stimulated for the OO muscle. Same stimulus duration and filter settings were used. One stimulus at rest and 2, 3 and 5 Hz trains of nine pulses were delivered with 1 min of rest between each train. The muscle was not exercised to avoid displacement of the electrodes during the maneuver. Recording was made by means of Dantec 13 L 20 disposable surface electrodes; the active electrode placed on the midpoint of the lower portion of the muscle, referenced to an electrode on the same vertical plane above eyebrow. Measurements were similar to those made in the distal muscles, where the decrement of the lowest response on LRS was calculated automatically and expressed as the percentage of the first potential.

Mean values of amplitude and area decrement on LRS for ADQ, FCU and OO muscles, as well decrement and increment on HRS for ADQ and FCU muscles were calculated. Interrelations between any of the evaluated variables were expressed as Pearson's correlation coefficients. For each group following parameters were chosen for PCA: amplitude and area decrement on 2, 3 and 5 Hz ($D2_{amp}$, $D3_{amp}$, $D5_{amp}$, $D2_{area}$, $D3_{area}$, $D5_{area}$) and 5 Hz 4 min following tetanus (DPT_{amp} DPT_{area}); decrement and increment on 50 Hz stimulation rate (TD_{amp}, TD_{area}, TI_{amp}, TI_{area}), except for the OO muscle, where only decrement on LRS was evaluated. PCA was first performed on controls and MG groups together, followed by a separate analysis for each group. The software program MINITAB 13.0 was used to calculate results.