Ref: Ro J Neurol. 2023;22(3)
DOI: 10.37897/RJN.2023.3.2

Repetitive nerve stimulation as a predictor of treatment response in myasthenia gravis

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ABSTRACT

Background and objectives. The clinical course of myasthenia gravis (MG) varies and may adversely affect quality of life and limit daily activities. Repetitive nerve stimulation (RNS) can be used to diagnose MG and may predict disease progression. We aim to establish the correlation between RNS and pharmacological treatment response.

Materials and methods. We conducted a cross-sectional study evaluating the correlation between RNS result and pharmacological treatment response as evaluated using the Myasthenia Gravis-Activities of Daily Living (MG-ADL).

Results. RNS positive patients possess greater severity on pre-treatment (9 [5-11] vs. 4 [2-5], p<0.001) and post-treatment (2 [1-4] vs. 1 [0-2], p=0.007) MG-ADL scores. ΔMG-ADL was also significantly greater in RNS positive patients (-6[-7 - -3) vs. -2 [-5 - -1], p=0.004). Spearman's rank-order correlation conducted evaluating the correlation between RNS and ΔMG-ADL demonstrates a significant moderate positive correlation between RNS and ΔMG-ADL (rs=0.495, p<0.001).

Conclusions. A moderate significant correlation was found between RNS and pharmacological treatment response. RNS positive patients are more responsive towards treatment compared to RNS negative patients. Higher fatigability in muscles translates to greater RNS decrements and clinical severity, lending itself to a greater opportunity for improvement following pharmacological. However, this must not be confused with long-term prognosis.

Keywords: myasthenia gravis, treatment response, repetitive nerve stimulation

List of abbreviations

ΔMG-ADL – Difference in Myasthenia Gravis-Activities of Daily Living scores pre and post treatment
MG – Myasthenia Gravis
MG-ADL – Myasthenia Gravis-Activities of Daily Living
RNS – Repetitive Nerve Stimulation

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder involving the neuromuscular junction (NMJ), affecting 15 to 179 per million individuals worldwide [1]. Suspicion for MG begins with a clinical picture suggestive of neuromuscular disorder, which is muscle weakness that increases with repetitive muscle use and felt worse at the end of the day. Ocular muscles are mostly involved, often asymmetrical. Clinical test that supports the diagnosis include Cogan's lid twitch test sign, ice pack test, curtain sign. Antibodies should be tested, however, if negative for anti-AChR antibodies, anti-MuSK antibodies, and anti-LRP4 antibodies, does not merely rule out MG. Neurophysiological testing (Repetitive Nerve Stimulation/RNS) is important when antibody tests are negative, yet can be normal even in patients with severe MG. Single-fibre electromyography is more sensitive but less specific for MG than RNS, and is an invasive procedure. Lastly, response to acetylcholinesterase inhibitors represents diagnostic information, and is seldomly

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Article History:
Received: 14 September 2023
Accepted: 29 September 2023

given as diagnostic confirmation in indecisive ancillary tests.

Due to resource restraints, antibody tests are frequently unattainable across the country. This brings us to the next additional testing, which is RNS. RNS is a fast, non-invasive procedure, and more affordable than antibody tests, therefore, more commonly applied. A previous study has pointed out the use of RNS as a predictor in MG disease progression [2], whereas other studies show that greater RNS amplitude decrements are mostly related to generalized MG and disease severity [3-5]. These findings substantiate the use of RNS more than just a diagnostic tool. In this study, we aim to investigate if there was any correlation between amplitude decrement in RNS and treatment response.

MATERIALS AND METHODS

We conducted a cross-sectional study evaluating the correlation between RNS result and pharmacological treatment response as evaluated using the Myasthenia Gravis-Activities of Daily Living (MG-ADL). This study has been approved by the Research Ethics Committee of the Pelita Harapan University Faculty of Medicine. We collected data on all MG patients who underwent treatment in Siloam Hospitals Lippo Village between September 2018 and April 2021. We included patients between 21 and 70 years of age with electrodiagnostically confirmed MG and have been prescribed pharmacological therapy, willing to sign informed consent forms for participation in this study. Patients were excluded if they have another NMJ disorders besides MG, such as botulism or Lambert-Eaton myasthenic syndrome (LEMS), are non-adherent in taking medications, or are taking immunosuppressants for other comorbid conditions.

We collected information regarding sex, age, relevant clinical findings, RNS results, Myasthenia Gravis Foundation of America (MGFA) classification, and prescribed pharmacological treatment. Patients were interviewed to determine pre- and post-treatment clinical conditions using the MG-ADL. The MGFA classifications categorize patients into class I for ocular MG, class II for mild generalized MG, class III for moderate MG, and class V for severe cases requiring respiratory intubation [6]. The MG-ADL assesses the impact of MG on daily activities and consists of 8 components (2 activities of daily living and 6 symptoms) each scoring 0-3, with a total score of 24, where higher scores indicate increasing severity. Differences between MG-ADL scores preceding and following treatment (ΔMG-ADL) is calculated to determine treatment response. Patients are said to have a treatment response if there is a minimum of two-point reduction in ΔMG-ADL [7]. RNS was conducted in the distal limb muscles, proximal limb muscles, and facial muscles. RNS measures compound muscle action potential (CMAP), evaluating for decrements or increments in CMAP amplitude. RNS is classified as positive if a CMAP decrement ≥10% is observed in ≥2 muscles.

Statistical analysis

Data was analyzed using IBM SPSS 28.0 for Windows. Categorical data is presented as frequency and percentage. Numerical data is presented with mean and standard deviation. Independent t-test was used to test for the relationship between RNS categories (positive or negative) and age, while non-parametric analyses were used to test for relationships between RNS categories and decrement, median MGFA, pre-, and post-treatment MGADL (using Mann-Whitney U test) and ΔMG-ADL (using Spearman's rank-order correlation test). The relationships between RNS results and MGFA, medications, and treatment response was analyzed using the Chi-square. Relationship between variables is stated as significant if $p < 0.05$.

RESULTS

Fifty MG patients fulfilling the criteria of inclusion and exclusion were included in our study (Table 1). Mean age was 43.8 years, with a female predominance (62%). Most patients (54%) tested positive on RNS with a median decrement of -15.58 (-23.64–-9.98), compared to -3.92 (-5.19–-2.41) in RNS negative patients. All patients received pyridostigmine, while only some were prescribed additional corticosteroids (24%), azathioprine (4%) and mycophenolate mofetil (2%). Compared to patients with negative RNS, patients with positive RNS tend to be younger (39.41 vs. 48.96 years, p=0.019), possess greater severity on MGFA classification (median 3 [2-4] vs. 2 [1-2], p<0.001) and on pre-treatment (9 [5-11] vs. 4 [2-5], p<0.001) and post-treatment (2 [1-4] vs. 1 [0-2], p=0.007) MG-ADL scores. ΔMG-ADL was also greater in RNS positive patients (-6[-7 - -3) vs. -2 [-5 - -1], p=0.004). However, no significant differences were observed in terms of treatment response (p=0.099) and medication use, although immunosuppressant use was higher in RNS positive patients. Spearman's rank-order correlation was conducted to evaluate the correlation between RNS and ΔMG-ADL, with a result of rs=0.495, p<0.001 (Figure 1) demonstrating that a moderate, yet significant, positive correlation exists between RNS and ΔMG-ADL.

DISCUSSION

Electromyography modalities, including RNS, can be used to detect abnormalities in NMJ transmission and diagnose MG. However, its application may transcend diagnosis. Previous studies have demonstrated

TABLE 1. Characteristics of patients included in the study

Variable	All (n=50)	Positive RNS (n=27) n (%)	Negative RNS (n=23) n (%)	p
Age (years), ±SD	43.80±14.58	39.41±13.34	48.96±14.55	**0.019***
Sex, n (%)				0.665
Male	19 (38.0)	11 (40.7)	8 (34.8)	
Female	31 (62.0)	16 (59.3)	15 (65.2)	
RNS decrement (%)	-9.57 (-16.69--4.21)	-15.58 (-23.64--9.98)	-3.92 (-5.19--2.41)	**<0.001***
MGFA classification	2 (1.75-3)	3 (2-4)	2 (1-2)	**<.001***
MGFA classification, n (%)				**0,005***
Class I	12 (24.0)	3 (11.1)	9 (39.1)	
Class IIa, IIb	17 (34.0)	7 (25.9)	10 (43.5)	
Class IIIa, IIIb	14 (28.0)	10 (37.0)	4 (17.4)	
Class IVa, IVb	7 (14.0)	7 (25.9)	0 (0.0)	
Class V	0 (0.0)	0 (0.0)	0 (0.0)	
MG-ADL, median				
Pre-treatment	5 (3-9)	9 (5-11)	4 (2-5)	**<0.001***
Post-treatment	2 (0-3)	2 (1-4)	1 (0-2)	**0.007***
ΔMG-ADL, median	-4 (-7--1)	-6 (-7--3)	-2 (-5--1)	**0.004***
Treatment response				
Responsive	38 (76.0)	23 (85.2)	15 (65.2)	0.099
Non-responsive	12 (24.0)	4 (14.8)	8 (34.8)	
Medications				
Pyridostigmine	50 (100.0)	27 (100.0)	23 (100.0)	-
Corticosteroids	12 (24.0)	9 (33.3)	3 (13.0)	0.094
Azathioprine	2 (4.0)	2 (7.4)	0 (0.0)	0.183
Mycophenolate mofetil	1 (2.0)	0 (0.0)	1 (4.3)	0.274

MG-ADL: Myasthenia Gravis-Activities of Daily Living, ΔMG-ADL: Difference in Myasthenia Gravis-Activities of Daily Living scores pre and post treatment, MGFA: Myasthenia Gravis Foundation of America, RNS: repetitive nerve stimulation, SD: standard deviation

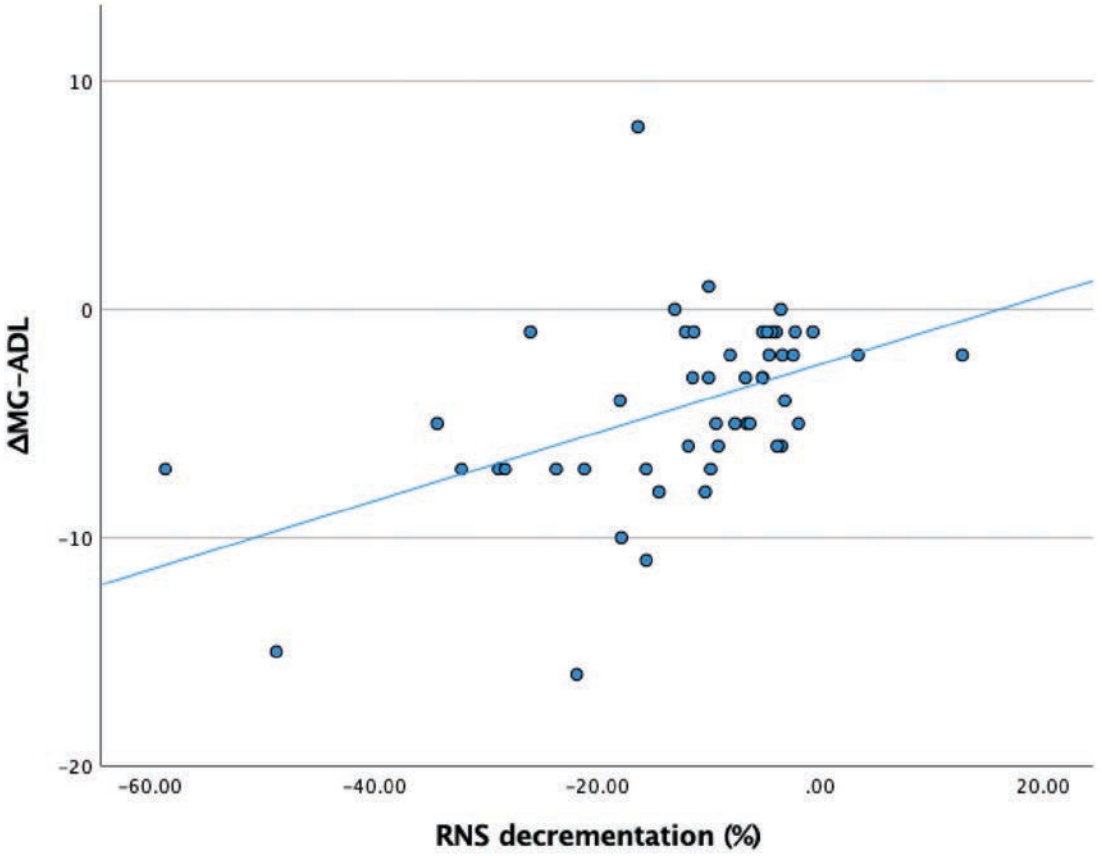

FIGURE 1. A scatter plot demonstrating the distribution of RNS decrement (%) compared with ΔMG-ADL. (R2 linear = 0.222) ΔMG-ADL: Difference in Myasthenia Gravis-Activities of Daily Living scores pre and post treatment, RNS: repetitive nerve stimulation

that RNS has a role in predicting disease progression in MG [2], and we aim to ascertain its role in correlating with pharmacological treatment response as measured by ΔMG-ADL. Our study demonstrates patients with positive RNS results are more significantly likely to be younger, possess greater disease severity as demonstrated by greater MGFA classification as well as pre-treatment and post-treatment MG-ADL scores, consistent with results from previous studies stating MG patients with jitters and greater decrements are more likely to have generalized MG, bulbar, respiratory, and extremity weakness, as well as higher Quantitative Myasthenia Gravis Score scores [3-5]. Treatment response (categorized as ΔMG-ADL ≥2) was also observably higher in the RNS positive group compared to the negative group (85.2% vs. 65.2%), although it was not statistically significant (p=0.099). However, RNS positive patients has significantly greater ΔMG-ADL compared to RNS negative patients, indicating a higher degree of treatment response (-6[IQR -7 - -3) vs. -2 [IQR-5 - -1], p=0.004). Furthermore, a statistically significant moderate positive correlation was found between RNS and ΔMG-ADL (rs=0.495, p<0.001). Taken together, the data suggests that in MG, a higher degree of fatigability in muscles translates to larger decrements detected on RNS, and greater clinical severity (as documented by MGFA/MGADL), which lends itself to a greater opportunity for improvement following pharmacological treatment (as seen on ΔMG-ADL). These findings are concordant with a previous study by Zinman et al., who reported that MG patients in whom ≥10% blocking was found on SFEMG demonstrated greater improvements in QMSG compared to patients with minimal blocking on SFEMG [8]. However, differences in pharmacological treatment between groups may have a partial effect on degree of treatment response. Although no significant differences were seen in medication use (as our study is not powered for this purpose), immunosuppressant use was higher in RNS positive patients, most likely due to greater severity [4]. However, while RNS positivity may be correlated with a better response towards treatment, it should not be confused with a better prognosis. Our results still demonstrate a significant difference in post-treatment MG-ADL scores between the two groups, wherein median post-treatment MG-ADL remains higher in the positive RNS group (2 [IQR 1-4]) compared to the RNS negative group (1 [IQR 0-2]), although the disparity is greatly diminished compared to pre-treatment scores (9 [IQR 5-11] and 4 [IQR 2-5] respectively). Of note, a previous study have found that RNS results did not significantly correlate with AChR-Ab titers nor long-term prognosis [9].

Therefore, the authors propose that RNS can be used as a surrogate to predict treatment response in MG patients. However, it has lower sensitivity compared to SFEMG, at 60-70% for proximal muscles in cases of generalized MG, and 35–38% for facial muscles in ocular MG [10]. Furthermore, previous studies evaluating RNS sensitivity in MG yielded conflicting results between different muscle groups. A study by Amandusson et al. found abnormal decrement in 54% of patients with ocular MG, 77% with predominant bulbar fatigue, and 83% with predominant limb fatigue [11], and a study by Abraham et al. found abnormal decrements were associated with more severe clinical disease [3]. However, another study by Liik reported that RNS in proximal muscles may be normal even in cases of severe MG [12]. These results illustrate that interpretation of RNS results in MG must be done carefully, and selection of tested muscle group is crucial.

To the best of the authors' knowledge, this is the first study evaluating the correlation between RNS and the treatment response in the Indonesian MG population. However, due to its retrospective design, there may be recall bias and dose of medication may vary. We hope that further similar studies in the field – taking into account other possible confounding factors – could be conducted in the future,.

CONCLUSION

A moderate, yet significant, correlation was found between RNS and treatment response. RNS positive patients are more responsive towards treatment compared to RNS negative patients. A significant relationship was also found between MGFA classification with RNS results, and between MG-ADL scores and RNS findings.

Conflict of interest

I undersign and certificate that I have/ do not have any financial or personal relationships that might bias the content of this work.

Author's contributions

Conceptualization, PYG and SC.; methodology, PYG and RS.; software, RS.; validation, PYG, SC and RS.; formal analysis, RS.; investigation, SC.; resources, PYG and SC.; data curation, SC and RS.; writing—original draft preparation, SC and RS; writing—review and editing, PYG; visualization, PYG.; supervision, PYG; project administration, PYG; funding acquisition, SC. All authors have read and agreed to the published version of the manuscript.

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