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Research Article,

Characteristics of Repetitive Nerve Stimulation (Rns) and Correlation with Severity and Quality of Life of Myasthenia Gravis Patients

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Abstract:

Background: Myasthenia gravis is a rare autoimmune disease due to neuromuscular junction (NMJ) disorders. The diagnosis of myasthenia gravis is based on cardinal clinical symptoms, including fluctuating weakness, worsening with activity, and improving with rest. In addition to clinical signs and antibody tests, other tests that are also crucial for diagnosis are electrodiagnostic examination (EDX) such as repetitive nerve stimulation (RNS) and single fibre electromyography (SFEMG). Recent studies have focused on assessing patients' severity and quality of life, essential for determining the prognosis and subsequent treatment plans.

Objective: To evaluate the characteristic of RNS and its correlation with rigor and quality of life of myasthenia gravis patients.

Methods: Inclusion criteria: patients diagnosed with myasthenia gravis, aged 18-65 years, willing to participate in the study. Exclusion criteria include a history of neuropathy, motor neuron disease, or myopathy and dropping out of the study. Patient demographic data were collected. The results of the RNS examination were divided into two categories, normal and abnormal.

MG severity was assessed by the Myasthenia gravis foundation of America (MGFA) classification, and the patient's quality of life was assessed by Myasthenia Gravis Quality of Life 15 (MG-QOL 15).

Results: Of the 24 samples, 69.1% of RNS were positive. The most sensitive muscle for assessing RNS is the anconeus muscle, followed by the trapezius and nasal. There was no significant relationship between RNS features and severity and the quality of life of myasthenic Gravis patients.

Conclusion: Onconeus muscle is the best location for assessing RNS. Although the number of patients with normal RNS had lower severity and better quality of life, there was no statistically significant relationship. Further studies with larger samples and longer follow-ups are needed.

Introduction:

Myasthenia gravis is a rare autoimmune disease with characteristics fluctuating of muscle weakness and fatigue due to disruption of the neuromuscular junction (NMJ) by autoantibodies that attack the acetylcholine receptor (AChR), muscle-specific kinase (MUSK), lipoprotein-related protein 4 (LRP4), and agrin on the postsynaptic membrane in the NMJ (Juel & Massey, 2007; Trouth et al., 2012; Gilhus & Verschuuren, 2015). Autoimmune myasthenia gravis is a rare disease. The incidence is 40-180 in 1,000,000 world population, with an annual incidence of 4-12 per 1,000,000 (Gilhus & Verschuuren, 2015).

Currently, there is no gold standard for diagnosing myasthenia gravis. The diagnosis of myasthenia gravis is based on cardinal clinical symptoms, including fluctuating weakness, worsening with repetitive activity, and improving with rest (fatiqability). However, some conditions can resemble the clinical picture of MG, such as lambert Eaton myasthenic syndrome (LEMS), botulism, neuromyotonia, myopathy, and miller-fisher syndrome. Other diagnostic tests are needed such as antibody tests against AChR, MUSK, and LRP4 which are specific diagnostic markers for MG. This antibody test, although specific, but very expensive. Apart from clinical symptoms and antibody tests, another test that is also important in myasthenia gravis is electrodiagnostic examination (EDX). There are two types of electrodiagnostic examinations that important

in establishing the diagnosis of myasthenia gravis, namely repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG). Single fiber testing is the most sensitive test while RNS is the most specific for making a diagnosis, but not all EDX laboratories have the SFEMG examination modality, because it requires a large amount of money. In myasthenia gravis there is a decrease in nerve signal transduction due to damage to AChRs. Thus, the low-frequency RNS (2-5 Hz) shows a decrease in the amplitude (decrement) of the compound muscle action potential (CMAP) more than 10% is considered abnormal. However, in clinical practice, the degree of amplitude reduction varies among patients with MG (Jing et al., 2015). Even in conditions where myasthenia gravis has been clinically and convincingly diagnosed and the presence of specific autoantibody tests, RNS and SFEMG examinations are still important in myasthenia gravis patients, especially in seronegative patients (Witoonpanich et al., 2012; Gilhus & Verschuuren, 2015).

Recent studies have focused on assessing the severity and quality of life of myasthenia gravis patients. Severity and poor quality of life have a major impact on the activity of MG patients. In the interest of standardized clinical research of MG, the Myasthenia gravis foundation of America (MGFA) proposed a clinical classification of myasthenia gravis known as the MGFA classification that has been recommended in clinical trials. This classification was developed to be universally applicable in MG studies and is used to identify subgroups of MG patients with distinct clinical features that reflect the severity of MG disease (Jaretzki et al., 2007).

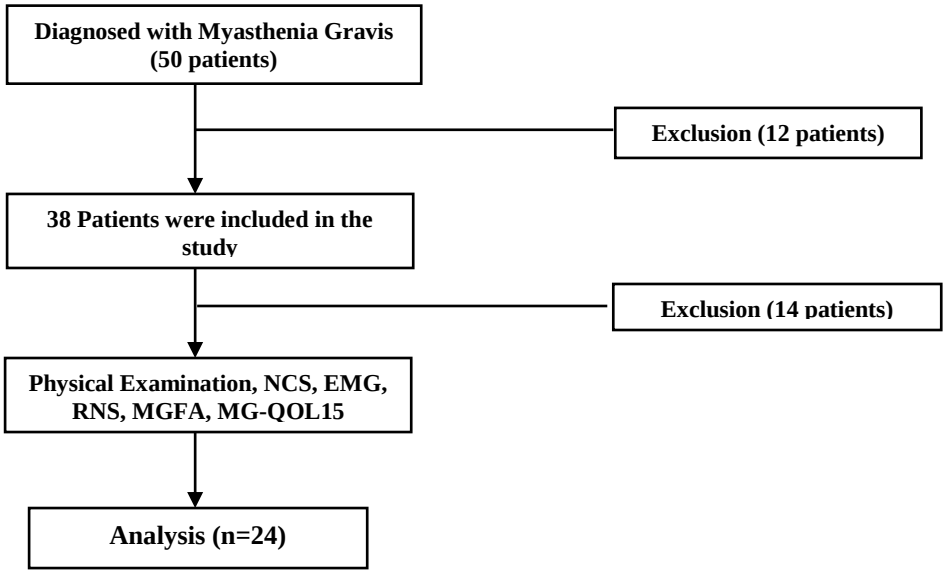
Study by Jing et al. (2015) who examined correlation between clinical severity and electrophysiological finding in 77 myasthenia gravis patients by using RNS and EMG found correlation between severity and decremental RNS amplitude. Severity examine with quantified myasthenia gravis (QMG) and MG activity daily living (MG-ADL). Amplitudo of RNS decrement mainly in the proximal mucles. Myopatic change found in more severe disease characteristic.(Jing et al; 2015).

Myasthenia gravis is a chronic autoimmune disease that greatly affects the patient's quality of life. Studies that focus on the quality of life of MG patients are few and far between. In addition to instruments to assess the severity of MG, many instruments have been developed for MG, including to assess the quality of life of MG patients, one of which is Myasthenia Gravis Quality of Life 15 (MG-QOL 15) which is an instrument with 15 short questions. It only takes two minutes and is easy to use. The study of Kumar et al. (2016) showed that QOL-15 correlated with MGFA classification (Kumar et al., 2016).

Method:

This study is a cross-sectional study. Samples collected from July 2017 to December 2017. Data collection was carried out in the EMG laboratory of M.Djamil Hospital Padang, Indonesia. The population is all patients who come to outpatient clinic of M Djamil hospital with a diagnosis of myasthenia gravis. Inclusion criteria were MG patients aged 18-65 years who were willing join with this study. Exclusion criteria were patients with clinical features resembling lambert Eaton myasthenic syndrome and botulinum toxin, history of neuropathy, motor neuron disease, drop out for any reason. All patients who met the inclusion criteria underwent RNS examination on the abductor digiti minimi, onconeus, trapezeus and nasal muscles. Severity and quality of life collected with MGFA classification and MG-QOL15. Data is presented with percentages, categorical data and continuous data. To assess the relationship between RNS with severity and quality of life, a t-test was performed and Mann Whitney as alternative test. P value <0.05 was considered statistically significant. Statistical analysis using SPSS version 21. The study was approved by the ethics committee of the Faculty of Medicine, Andalas University.

Results:



Patients who included in the study were patients who from the physical examination supported the direction of Myasthenia Gravis and patients who had complete data. The number of samples included in the study were 24 patients.

The characteristics of MG patients include age, gender, onset (in years), results of NCS examination, EMG, RNS, past illness history. Nerve conduction study and electromyography (EMG) were performed to rule out other possible diagnoses. The basic characteristics of the patients are shown in table 1.

Table 1 Basic Characteristic of Patients with Myasthenia Gravis

Title	Amount	%
Gender		
- Man	4	16.6
- Woman	20	83.4
Age,mean(min-max),years	33.7 (16-65)	
Onset, mean (min-max),year	3.75 (1-16)	
Nerve conduction study		
• Normal	23	96
• Abnormal	1	4
EMG		
• Normal	24	100
• Abnormal	0	0
RNS		
• Positive	19	79.1
• Negative	5	20.9
Muscles with positive RNS		
• Abductor Digiti Minimi	1	5.26
• trapezeus	14	73.68
• Onconeus	15	78.95
• Nasal	11	57.89
MGFA		
• I	9	37.5
• IIA	6	25
• IIB	7	29.2
• IIIA	0	0
• IIIB	3	12.5
Other illnesses suffered		
• DM	2	8.3
• Hypertension	3	12.5
• Hypertoid	3	12.5
• Thymoma	1	4.1

Table 1 shows the basic characteristics of the study where the most gender is female (83.4%). The mean age of patients at this time was 33.7 years, with a median onset of 3.75 years. On examination of the nerve conduction study, only 1 abnormality was found, namely carpal tunnel syndrome, while for electromyography examination there were no abnormalities. Nerve conduction study and electromyography were performed to screen for possible diseases or other peripheral nerve disorders experienced by the patient. For the RNS examination, there were 5 people (20.9%) with negative results. The muscle that showed the most positive results was the onconeus (78.95%) followed by the trapezeus 73.68%. Based on the MGFA classification 37.5% of patients were pure ocular MG.

To find out whether there is a relationship between repetitive nerve stimulation and the patient's quality of life using the MG QOL, the Kolmogorov Smirnof and Shapiro-Wilk normality tests were conducted first. It is necessary to know what kind of statistical test can be used in this research. After the test, the data obtained were normally distributed (significance value 0.49). The statistical test used was the independent T-test.

Table 2 Relationship between Repetitive Nerve Stimulation and Quality of Life of Myasthenia Gravis patients

	RNS	N	mean	Std. Deviation	Std. Error Mean
MGQOL	positive	19	16.21	9.572	2.196
	negative	5	11.40	5,941	2,657

p= 0.3

Table 5.2 shows that the mean MG QOL for patients with positive RNS is 16.21. While the MG-QOL value of 15 patients with negative repetitive nerve stimulation results was 11.4. This means that patients with negative RNS value have a better quality of life than patients with a positive RNS, but statistically, there is no significant value (p>0.5).

Table 3. The Relationship between Repetitive Nerve Stimulation and Severity of Myasthenia Gravis Patients

		MGFA				Total
		I	IIA	IIB	IIIB	
RNS	negative	3	2	0	0	5
	Positive	6	4	7	2	19
Total		9	6	7	2	24

p = 0.141

To determine the relationship between the RNS examination and the severity of myasthenia gravis, the Chi square test was used. The statistical test did not find a significant relationship between repetitive nerve stimulation and the severity of Myasthenia Gravis which was assessed on the Myasthenia Gravis Foundation of America scale.

Discussion:

Myasthenia gravis is a disease with autoimmune disorders due to disorders of muscle and nerve junctions. Clinical symptoms are often chronic, and significantly affect the patient's quality of life due to the severity of the disease itself. Table 1 shows the basic characteristics of myasthenia gravis patients. The highest gender was female (83.3%), the average age of the patient was 33.7 years, the youngest age was 16 years, and the oldest age was 65 years. The onset of myasthenia gravis was 3.75 years. From the nerve conduction study, one person showed abnormalities in the form of carpal tunnel syndrome and all electromyography examinations were within normal limits. The data obtained in this study are almost the same as those obtained in an epidemiological study of Myasthenia Gravis in Stockholm, Sweden. Where the age at onset is 34 years old. (Kalb B, 2002). Study by Estevez conclude that MG prevalency rate 260 cases per 100.000 population and early onset ≤ 50 years old was recorded in 29,1 % cases. This study get highly prevalent for MG in older population than current study (Estevez, 2020). Study epidemiology by Lee in Korea population also increase in the prevalence of MG and a predominance of elderly MG patients (Lee, 2002). This difference probably due to longer life expectancy.

On repetitive nerve stimulation examination, positive results were obtained in 79.1% of patients. This is in accordance with the literature which states that RNS is found to be positive in 75-80% of generalized MG

(Saphiro, 2014). RNS examination has become one of the most useful electrodiagnostic examinations in assessing disorders of the neuromuscular junction. Of all the muscles examined in the patient, the muscle that gave the most positive RNS values was the onconeus, followed by the trapezeus and nasalis. There were only 1 patients who had positive results on the abductor digiti minimi muscle. This study consistent with Jing (2015) which found that positif response rate for ulnar being lower than those the other 3 nerves ($p<0,001$) (Jing,2015). Different results were found in the Costa study, 2004. In one study, the trapezeus was abnormal on RNS examination of ocular MG patients, while the onconeus and nasalis were more sensitive for generalized myasthenia gravis Costa J, 2004). Study by Kim concluded that abnormality of extremity RNS can be independent predictor patient ocular MG to become generalized MG (Kim, 2021).

Assessment of the quality of life patients with myasthenia gravis is an important tool in assessing clinical outcomes. A more specific scale for fluctuating patient complaints can be used as a guide for non-motor complaints and can also be used as a guide in treatment. Currently, several questionnaires have been developed that can be used to assess the quality of life of patients with myasthenia gravis, including the MG QOL 15. A study in Brazil found that the MG QOL 15 had high internal consistency and good validity in assessing the quality of life of patients with myasthenia gravis (Aline, et al; 2016). Study by Jing found that quality of life MG patient (examine with QMG and MG-ADL) correlated well with the magnitude of the decremental response to RNS for multiple nerves. These relationships were more apparent in the facial, accessory, and axillary nerves than in the ulnar nerve.This finding suggesting the relationship more apparent for the proximal muscles (i.e. orbicularis oculi, trapezius, deltoid) than for the distal muscles (abductor digiti minimi) (Jing, 2015).

Until now, research on the relationship between repetitive nerve stimulation and the severity of myasthenia gravis is still lack. This may occur because repetitive nerve stimulation is not the only modality or gold standard in establishing the diagnosis of myasthenia gravis and the repetitive examination of nerve stimulation does not have standardized cut off point. Research by Abraham et al (2017) provides a different cut off point value for each muscle examined, where the facial muscles are given a cutoff point value of 7-8%, while the other muscles examined are 10%. A study in India that first linked the severity and quality of life of patients with Myasthenia Gravis got significant results, where the more severe the severity of the disease, the higher the MG QOL value (Kumar, 2016). This study obtained different results when compared to the study by Kumar. This may be due to the number of samples which are significantly different in number and possibly also due to different socio-cultural backgrounds. A study by Kumar was conducted on ethnic Indians; a review found that ethnic Indians had a lower threshold for pain and complaints of other diseases when compared to other ethnic groups (Campbel, 2012).

This is the first study to examine the features of repetitive nerve stimulation in patients with myasthenia gravis in West Sumatra and also the first study related with repetitive nerve stimulatio feature with quality of life of MG patients. No significant results were obtained in this study, possibly due to the relatively small number of samples and the cutoff point used in this study, where this study provided a cutoff point of 10% in Myasthenia Gravis patients.

Conclusion:

The basic characteristics of myasthenia gravis patients, the sexes were mostly women in the third decade of age, and more than 70% of patients had positive RNS results. RNS positif predominanly in onconeus and trapezues as medial and proximal muscle. There was no significant relationship between the severity of myasthenia gravis and the patient's quality of life. Research is needed with more samples and a longer period of time to observe characteristic of RNS in relation with quality of life and severity wi

Bibliography:

[1] Abraham A et al. 2017. Repetitive Nerve Stimulation cutoff values for the diagnosis of myasthenia gravis. Muscle nerve.55 (2):166-17

[2] Aline MM, Rodrigo SG, Luiz SM, Denise DSF, Elizabeth RCF, Arthur K, Stella MSL, Antonio LT. 2016. Determinant of quality of life in Brazilian patients with myasthenia gravis. PubMed central.71(7):370-374

[3] Campbell CM, Robert RE. 2012. Ethnic difference in pain and pain management. Pain Manag.2012 May;2(3):2019-230

[4] Costa I, Evangelista T, Conceigo I, Catvalho M. 2004. Repetitive nerve stimulation in myasthenia gravis-relative senseitivity in difference muscle.

[5] Estevez ADG, Lopez DM, Pardo PG, Prez LNA, Sebastian CG, Ozaiya AD, Rodriguest G. 2020. Epidemyologi of Myasthenia Gravis in the province of Ourense. Neurologia.

[6] Gilhus NE, Verschuuren JJ. 2015. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14:1023-36

[7] Jaretzki A, Barohn RJ, Ernstoff RM, Kamisnki HJ, Keesey JC, Penn AS, et al. 2000. Myasteni Gravis: Recomendation for Clinical Research Standarts. Ann Thorac Surg 70:327-34

[8] Jing F, Cui F, Chen Z, Yang F, Ling L, Huang X. 2015. Clinical and Electrophysiological Markers in Myasthenia Gravis Patients. Eur Neurol 74:22-27

[9] Juel VC, Massey JM. 2007. Myasthenia Gravis. Orphanet journal of rare diseases 2:44.

[10] Kim KH, Kim SW, Shin HY.2021. Initial Repetitive Nerve Stimulation Test Predic Conversion of Ocular Myasthenia Gravis to Generalized Myasthenia Gravis. J Clin Neurol.17(2):265-272

[11] Kumar R, Nagappa M, Sinha S, Taly AB, Rao S. 2016. MG-Qol-15 scores in treated myasthenia gravis: Experience from a university hospital in India.

[12] Lee HS, Lee HS. 2016. The Epidemiology of Myasthenia Gravis in Korea. Yonsei Medical Journal.57(2):419

[13] Preston CD, Shapiro B. 2013. Electromyography and neuromuscular disorders. Clinical electrophysiological correlation. Third edition. Pg 52-61.

[14] Trouth AJ, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. 2012. Myasthenia Gravis: A Review. Autoimmune diseases Volume 2012

[15] Witoonpanich R, Dejthevaporn C, Sriphrapradang A, Pulkes T. 2011. Electrophysiological and immunological study in myasthenia gravis: diagnostic sensitivity and correlation. Clinical neurophysiology 122:1873-1877