The Seoul Journal of Medicine
Vol. 34, No. 1: 41-48, March 1993

Repetitive Nerve Stimulation and Single Fiber Electromyography Tests for Myasthenia Gravis†

Kwang-Woo Lee and Han-Bo Lee

Department of Neurology, Seoul National University College of Medicine, Seoul 110-744, Korea

=Abstract=**Sometimes it is not easy to make a diagnosis of myasthenia gravis (MG) when the ocular symptoms are the only clinical manifestations. The authors performed this study to understand the significance or the indication of repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG) tests in various stages of MG. The subjects consisted of 15 ocular, 12 generalized, 4 remitted MG, and 5 other neurologic diseases which mimicked it.Positive RNS and SFEMG results were found in 53.3%, 86.7% of ocular type, in 0.0%, 75.0% of remitted type, in 75.0%, 91.7% of generalized type of MG and in 0.0%, 60.0% of other neurologic disease, respectively. When we analysed the results in 15 ocular MG and in 5 non-MG groups, the RNS tests had low sensitivity (53.3%) and high specificity (100%) as they were positive in 8 of 15 ocular MG, and negative in all of 5 non-MG group. Whereas the SFEMG had high sensitivity (86. 7%) and low specificity (40.0%) as it was positive in 13 of 15 ocular MG, and negative in 2 of 5 non-MG group.Therefore it would be concluded that the SFEMG test was much more sensitive than the RNS for the diagnosis of MG, but would not differentiate ocular MG from other neurologic diseases whose clinical features mimicked it. On the other hand, the diagnosis of MG would be promising by a positive RNS test as its specificity was very high.**

Key Words: *Repetitive nerve stimulation, Myasthenia gravis, Single fiber electromyography*

INTRODUCTION

It is generally accepted that the single fiber electromyography (SFEMG) test is extremely sensitive in the diagnosis of myasthenia gravis (Stalberg 1974; Stalberg 1980; Emeryk *et al.* 1985; Keesey 1989). Stalberg and Trontelj (1979) reported that the diagnosis of MG could be abandoned if the abnormal jitter was not present in a weak muscle. The SFEMG tests were abnormal in the extensor digitorum communis (EDC) muscle in 26-66% of ocular MG (Sanders *et al.* 1979; Konishi *et al.* 1981; Sanders *et al.* 1986), and the abnormal rate could be increased up to 54-100% when the frontalis muscles were examined (Sanders *et al.* 1979; Curz Martinez *et al.* 1982), which was in good

Received January 1993, and in final form March 1993.
† Supported by a grant No. 01-92-151 from Seoul National University Hospital Research Fund.
서울대학교 의과대학 신경과학교실: 이광우, 이한보

contrast to 19% abnormality for the repetitive nerve stimulation (RNS) in ocular MG (Horowitz *et al.* 1976; Oh *et al.*1982).

The RNS test is widely used in clinical neurology and helpful for the diagnosis and therapeutic evaluation of MG, but the clinical use of SFEMG is limited since abnormal findings are found in various neuromuscular diseases, including MG, Eaton-Lambert syndrome, myopathy, and neuropathy etc (Stalberg 1979; Oh 1988). Oh *et al.* (1992) reported that the SFEMG was needed in only 9% of MG when the SFEMG was recommended if the RNS and AchR antibody tests were normal. Not infrequently the clinician confronts patients whose clinical features mimic those of ocular MG, but are not suggestive of definite MG and refers them to the electromyographer for the differential diagnosis. Therefore in this study the authors performed the RNS and SFEMG tests in 31 MG and 5 non-MG to understand the significance of RNS and SFEMG for the diagnosis of MG and to clarify the indication and interpretation of SFEMG tests for evaluating ocular MG and borderline non-MG.

METHOD AND MATERIALS

The RNS and SFEMG tests were studied in 31 MG and 5 non-MG neurological diseases which mimicked the clinical features of ocular MG. The data from RNS and SFEMG were analysed in different types of MG, that is, 15 ocular, 4 remitted, and 12 generalized MG, and compared with those in 5 non-MG neurological cases. Finally the diagnostic sensitivity and specificity of RNS and SFEMG tests were calculated in limited MG subjects and in non-MG subjects, respectively.

The diagnosis of MG was made by a combination of clinical features and several laboratory work-ups, involving clinical response to anticholinesterase agents, decremental response to repetitive stimulation, the presence of acetylcholine receptor antibodies, negative imaging studies, and thyroid function studies (Kim *et al.* 1991; Lee *et al.* 1992). Those 31 MG subjects were followed up at a minimum 6 months and there was no evidence for the presence of another condition that could explain the weakness. Also the severity of MG was graded according to the modified Osserman's classification. The RNS and SFEMG were performed at the time of MG evaluation regardless of the condition of therapeutic regimens.

The 5 non-MG group initially showed clinical features which mimicked those of MG. 4 subjects complained of ocular symptoms, referred sequentially to the EMG laboratory for the diagnosis or exclusion of MG. They were followed up from 4 to 12 months and classified as "non-MG neurological disease". The remaining one subject complained of easy fatigability without any ocular symptoms, and the final diagnosis was "Eaton-Lambert syndrome" associated with non-small cell lung carcinoma.

RNS and SFEMG tests and interpretation

The RNS test was performed on the abductor digiti quinti (ADQ) and orbicularis oculi (OO) muscles with stimulating electrodes at the wrist on the ulnar nerve and near the facial nerve just distal to its exit from the stylomastoid foramen, respectively (Oh *et al.* 1982). Six responses were obtained at low rate of stimulation (LRS) 2 per, 3 per, and 5 per second, and followed by the high rate stimulation (HRS) of 50 per second for one second, according to the protocol in our EMG laboratory.

To calculate the decremental response, the authors measured the peak-to-peak amplitude of the first and the lowest CMAP among the six and expressed as a percentage of the first CMAP by the following formula:

$$\frac{\text{1st CMAP} - \text{designated CMAP}}{\text{1st CMAP}} \times 100$$

= decrement (%). When decremental response was more than the mean value plus two standard deviation, the result was considered abnormal (Ekstedt and Stalberg 1973; Ekstedt *et al.* 1974).

The SFEMG was performed on the extensor digitorum communis (EDC) muscle following the standard method (Stalberg 1974; Kimura 1983; Oh 1988) using the satellite EMG machine Nicolet Pathfinder II. The patient assumed a supine position on the examining table and was taught to sustain minimal EDC muscle contraction. Then the special SFEMG needle would record single or double EMG potentials by careful movements of the needle. Once the double potentials were obtained, eight superimpositions were recorded. The authors tried to record at least 50 discharges for each pair.

The jitter was best expressed as the mean value of consecutive interpotential differences (MCD) and was calculated by manual method as shown in Fig. 1 (Stalberg 1974). At identical points on the fast negative deflection, the latency difference was measured between the earliest and latest second slave potentials. This time range of 8 discharges (R8) was collected and converted to estimated MCD by multiplying by a conversion factor of 0.40 (Table 1). The manually estimated MCD value was said to be in a good approximation to the actual MCD which was calculated using a computer program (Mihelin *et al.* 1975). The SFEMG test was considered abnormal when either of the following criteria were met; (1) the mean MCD was longer than 36 μsec, (2) individual MCD was greater than 54 μsec.

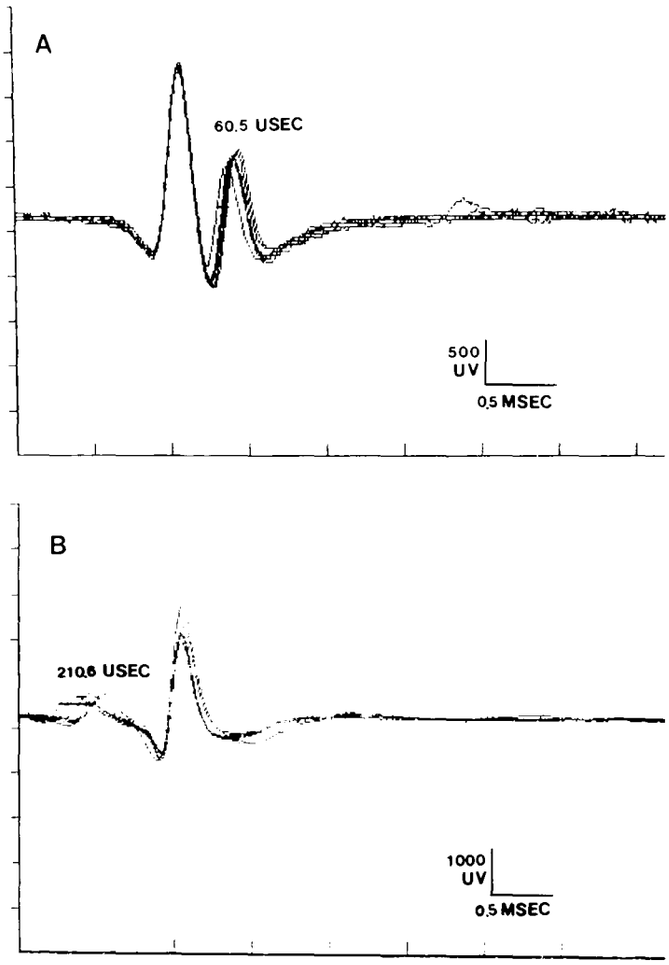

Fig. 1. The SFEMG in case 26 showed normal (A) and abnormal (B) action potential pair. The calculated mean MCD value in A and B was 40.0 μsec and 84.2 μsec, respectively by multiplying a conversion factor (R_8=0.40) to the measured latency difference 60.5 μsec (A) and 210.6 μsec (B).

Table 1. Conversion factors for calculation of MCD

n	2	3	4	5	6	7	8	9	10
F_n	1.0	0.67	0.55	0.49	0.45	0.42	0.40	0.38	0.37

MCD: Mean value of consecutive interpotential differences

MCD = $R_n \times F_n$, where n represents number of superimposed sweeps, F_n is the conversion factor, and R_n is the measured mean value of jitter.

RESULTS

Among 31 MG, there were positive RNS tests 5 in 17 (54.8%) and positive SFEMGs in 27 (87.1%). When we divided the data of the RNS and SFEMG tests according to the clinical severity of MG, positive RNS and SFEMG tests were found in 53.3%, 86.7% of ocular MG, in 0.0%, 75.0% of remitted MG and in 75.0%, 91.7% of generalized MG, respectively (Table 3).

The SFEMG showed positive results in the majority of MG subjects (N=27), regardless of whether the RNS tests were positive (N=16) or negative (N=11). The SFEMG result was also negative in those subjects of ocular (case 1), remitted (case 28), and generalized MG (case

5), who showed negative RNS. But one ocular MG subject (case 9) showed a negative SFEMG, even though the RNS was positive in the orbicularis oculi muscle (Table 2).

In all 5 subjects of the non-MG group, the RNS showed negative results in the ADQ and orbicularis oculi muscle. The SFEMG was positive in two and negative in the other two subjects, who showed clinical features similar to ocular MG. But in case 33 who was diagnosed to have Eaton-Lambert syndrome by the characteristic electrophysiological features, the mean MCD was markedly increased up to 52.0 μsec (Table 3). Thus in the non-MG group positive RNS and SFEMG tests were found in 0.0%, 60.0%, respectively.

When the RNS and SFEMG tests were evaluated in limited groups of the ocular MG and non-MG groups of other neurological diseases, the RNS showed low sensitivity (53.3%) and high specificity (100.0%) as it was positive in 8 of 15 ocular MG and negative in all of the 5 non-MG group. But the SFEMG showed high sensitivity (86.7%) and low specificity (40.0%) as it was positive in 13 of 15 ocular MG, and negative in 2 of 5 non-MG group (Table 4).

The SFEMG test was much more sensitive in diagnosis of MG than the RNS, as shown in table 3. There was no significant difference of positive SFEMG ratio among ocular, remitted, and generalized MG, being positive in 86.7%, 75.0%, 91.7%, respectively (figure 2). Even though the positive SFEMG was found in about 60.0% of non-MG group, the value of mean MCD was small in the non-MG group, compared with that in MG groups (Fig. 2).

Table 2. Data of repetitive nerve stimulation and single fiber electromyography in 31 myasthenia gravis and 5 non-myasthenia gravis

Cases	Clinical features	RNS ADQ	RNS OO	SFEMG mean	SFEMG MCD	Case	Clinical features	RNS ADQ	RNS OO	SFEMG mean	SFEMG MCD
1.	I	–	–	24.3	–	19.	II_A	+	+	109.6	+
2.	II_B	+	+	98.3	+	20.	R	-	–	45.0	+
3.	I	–	+	82.6	+	21.	I	–	+	93.8	+
4.	II_B	–	+	38.7	+	22.	I	–	–	42.3	+
5.	II_A	–	–	33.3	–	23.	I	–	+	72.5	+
6.	I	–	+	44.5	+	24.	II_A	–	–	52.0	+
7.	I	–	–	42.5	+	25.	R	–	–	64.3	+
8.	I	+	+	43.9	+	26.	I	+	+	103.1	+
9.	I	–	+	34.7	–	27.	I	–	+	98.6	+
10.	II_A	+	+	50.6	+	28.	R	–	–	31.3	–
11.	II_B	–	+	99.9	+	29.	I	–	–	45.7	+
12.	I	–	+	81.8	+	30.	II_B	–	+	56.5	+
13.	II_A	–	–	107.5	+	31.	II_A	+	+	67.0	+
14.	I	–	–	47.9	+	32.	non-MG	–	–	28.3	–
15.	II_A	–	+	59.2	+	33.	ELS	–	–	52.0	+
16.	R	–	–	41.0	+	34.	non-MG	–	–	22.9	–
17.	I	–	–	42.1	+	35.	non-MG	–	–	46.0	+
18.	II_B	–	+	187.5	+	36.	non-MG	–	–	40.6	+

ADQ: abductor digiti quinti, OO: orbicularis oculi, MCD: mean value of consecutive interpotential differences, +: positive results, –: negative results

Table 3. Comparison of repetitive nerve stimulation and single fiber electromyography tests

Types OF MG	RNS Tesrs on ADQ	RNS Tesrs on OO	SFEMG on EDC
Ocular MG (N=15)	2(13.3%)	8(53.3%)	13(86.7%)
Remitted MG (N=4)	0(0.0%)	0(0.0%)	3(75.0%)
Generalized MG (N=12)	4(33.3%)	9(75.0%)	11(91.7%)
All MG(N=31)	6(19.4%)	17(54.8%)	27(87.1%)

EDC: extensor digiti quinti

Table 4. Comparison of repetitive nerve stimulation and single fiber electromyography between ocular MG and other neurological diseases

	Positive RNS*	Positive SFEMG**
Ocular MG(N=15)	8(53.3%)	13(86.7%)
Other neurological diseases(N=5)	0(0.0%)	3(60.0%)

* RNS: low sensitivity (53.3%), high specificity (100%)
** SFEMG: high sensitivity (86.7%), low specificity (40.0%)

DISCUSSION

It is often not easy to make a diagnosis of MG on clinical grounds. Usually the characteristic clinical features of MG would be the typical distribution of ocular, facial, oropharyngeal or limb muscle weakness, the fluctuating nature of the weakness during the day or hours, and the clinical improvement by the administration of anticholinesterase agents (Penn and Rowland 1989). Thus an unequivocal positive edrophonium test has been thought to be crucial. However the edrophonium test shows low sensitivity, especially in ocular MG and false positive results in various diseases including neuromuscular disease.

In recent years the diagnosis of MG has

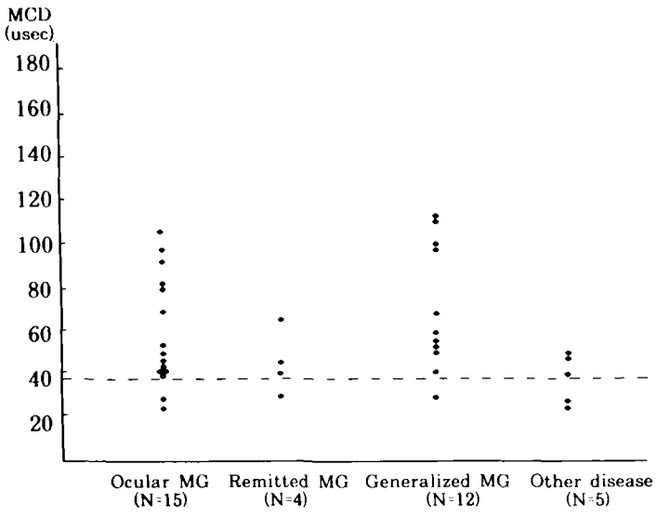

Fig. 2. The distribution of mean MCD in 31 MG and 5 non-MG groups revealed no significant difference among various types of MG. However the abnormal mean MCD value was very small in these non-MG, compared with those values in MG subjects.

improved using several laboratory tests, the serum acetylcholine receptor antibody (AChR-Ab) assay, the repetitive nerve stimulation (RNS), and the single fiber electromyography (SFEMG). Oh *et al.* (1992) reported that at least one of AChR-Ab assay, the RNS test, and the SFEMG test was abnormal in all 120 cases of MG, and the SFEMG was most sensitive in the diagnosis of MG. However the report did not say how the diagnosis of MG was established or what proportions of different severity of MG were involved.

In our study the diagnosis of "definite MG" was established if the following criteria were met; (1) there was fluctuating weakness of ocular, extraocular, facial, oropharyngeal and/or limb muscles which were compatible with MG, (2) clear improvement on anticholinesterase was documented by the physician and reported by the patient which was sustained for at least three months, (3) there was no evidence of the presence of another condition that could explain the clinical symptoms. However we did not establish a final diagnosis in these subjects in the non-MG group, except for one with Eaton-Lambert syndrome. These 4 subjects did not

show any clinical features suggestive of ocular MG and did not fulfill the aforementioned diagnostic criteria of MG during the six months follow-up period. So we could say that we ruled out other diagnosis, such as thyroid opthalmopathy, subtle brainstem infarcts, multiple sclerosis, or mitochondrial myopathy etc, even though definite diagnoses were not made.

Our study showed that the SFEMG was much more sensitive than the RNS, even though each test revealed a higher percentage of positive results in generalized MG than in ocular MG. The RNS test in the ADQ muscle was nonproductive, showing positivity in 2 of 15 ocular MG (13.3%), which was compatable with various reported data (Horowitz *et al* 1976; Krarup 1977; Oh *et al.* 1982). But the diagnostic sensitivity of RNS was higher in the orbicularis oculi in ocular MG (53.3%). According to Oh's data, a higher yield (64%) in the RNS test was noted in the orbicularis oculi due to their unique technique. Thus RNS on the proximal muscle is often recommended to increase the diagnostic sensitivity when the RNS on distal muscles shows negative results (Ozdemir *et al.* 1976).

On the contrary, the SFEMG was very sensitive in ocular (86.7%), generalized (91.7%), and remitted MG (75.0%). The normal mean MCD (less than 36 μsec) was found in 2 ocular, 1 remitted, and 1 generalized MG. It was not an unusual finding because the SFEMG test was performed only in EDC muscles in those patients. The diagnostic sensitivity became high up to 54-100% when the frontalis muscle was also examined in ocular and generalized MG (Stalberg *et al.* 1974; Jablecki 1978; Sanders *et al.* 1979; Curz Martinez 1982). Stalberg and Trontelj (1979) said that they could rule out the diagnosis of MG if the increased jitter was not found in weak muscle.

Our results for positive SFEMG in ocular MG were high (86.7%), compared with previously reported data of Stalberg and Sanders (1981), Cruz Martinez *et al.* (1982), Sanders and Howard (1986), Sunwoo (1988), being 59%, 66%, 57%, 88%, respectively. It could be possible that some of those subjects classified into ocular MG might have subclinical limb weakness or a long history of ocular MG. The SFEMG technique and interpretation could be other factors because this test requires fairly elaborate equipment and patient cooperation.

As shown in table 2, the SFEMG was positive in the majority of MG subjects when they showed positive RNS (N=6) or negative RNS (N=11). In case 9, the mean jitter was 34.7 μsec and the RNS was positive in the orbicularis oculi muscle. This patient had complained of intermittent diplopia for several years and was unlikely to require treatment. The data in this patient supported Sanders *et al.*'s report that they increased the positive rate of SFEMG from 38% on EDC to 100% on frontalis muscles in 13 cases of ocular MG (Sanders *et al.* 1979; Sanders and Howard 1986). In this connection, it is a good idea that the SFEMG should be performed in a weak muscle such as the frontalis when the test did not show abnormal jitter on EDC muscles, especially in ocular MG.

In the non-MG group the RNS and the SFEMG tests showed positive results in none (0%) and in 3 (60.0%) of 5 subjects, respectively. Rouseev *et al.* (1992) reported that they found abnormal SFEMG in 6 of 18 patients with a "definite other diagnosis" (33.3%), and concluded that the abnormality might be rather mild, compared with that in "definite MG".

When we analysed the data of ocular MG (N=15), and non-MG (N=5) groups, the RNS showed low sensitivity (53.3%) and high specificity (100%) and the SFEMG showed high sensitivity (86.7%) and low specificity (40.0%). Roussev *et al.* (1992) also reported the results similar to our data, in which they used as abnormal SFEMG criteria 2 or more pairs of 20 with jitter > 45 μsec, or mean jitter > 34 μsec, and maximized the sensitivity and specificity of the SFEMG tests for "definite ocular" MG from other conditions causing ocular symptoms. Further they concluded that it was possible to predict that if the test is abnormal, the patient

has ocular MG and is likely to require therapy, or if the test is normal, the patient has some other condition, or has mild ocular MG that is unlikely to require medication. When they improved the specificity by taking the criteria to mean jitter greater than 50 μsec. But there was no significant difference of abnormal mean MCD value among different severities of MG in our study (Fig. 2).

The RNS test has also several advantages e.g., relative simplicity, rapid results, and a good correlation between electrophysiological and clinical assessment of disease severity in MG, even though its sensitivity is low. Oh *et al.* (1992) said the RNS on proximal muscles was recommended to increased the diagnostic yield by 15%.

In conclusion, the authors believe that RNS and SFEMG have unique value for the diagnosis of MG. The RNS would be recommended to be done in those patients suspected of MG on the ADQ and orbicularis oculi muscles first. The diagnosis of MG could be confirmed if the RNS test was positive. If the RNS is normal even in the proximal muscle, SFEMG is needed. It is said that SFEMG is indicated in only limited numbers of suspected MG (9%) when we follow the testing guideline.

If the SFEMG is positive in first the EDC or second the frontalis muscle, the diagnosis of MG may be possible, but not confirmative because its specificity is very low, especially in those patients with ocular symptoms. In this situation, it could be the most important step that we can identify the classical SFEMG pattern in MG, characterized by, (1) definite increased jitter with or without neuromuscular blocking, (2) increasing jitter abnormality with a higher discharge rate, and (3) normal fiber density (Schwartz and Stalberg 1975).

ACKNOWLEDGEMENT

The authors wish to thank Mr. Gil-Hyeon Cha for his technical assistance.

REFERENCES

Cruz Martinez A, Ferrer MT, Perez Conde MC, Diez Tejedor E, Barbeiros P, Ribacoba R. Diagnostic yield of single fiber EMG and other electrophysiological technique in myasthenia gravis: Clinical remission and thymectomy evaluation. Electromyogr Clin Neurophysiol 1982; 22:395-417

Ekstedt J, Stalberg E. Single fiber electromyography for the study of the microphysiology of the human muscle. In Desmedt JE (Ed): New Development in Electromyography and Clinical Neurophysiology. S Karger, Basel, 1973, vol 1:89-112

Ekstedt J, Nilsson G, Stalberg E. Calculation of the electromyographic jitter. J Neurol Neurosurg Psychiatry 1974; 37:526-39

Emeryk B, Rowinska K, Nowak-Michalska T. Do true remissions in myasthenia really exist?: An electrophysiological study. J Neurol 1985; 231:331-5

Horowitz SH, Genkins G, Kornfeld P, Papatestas AE. Electrophysiologic diagnosis of myasthenia gravis and the regional curare test. Neurology 1976; 26: 410-7

Jablecki CK. Single fiber electromyography, AAEE Minimonograph No. 6, Rochester, MN, American Association of Electromyography and Electrodiagnosis, 1978

Keesey JC. Electrodiagnostic approach to defects of neuromuscular transmission. Muscle Nerve 1989; 12:613-26

Kim BJ, Lee NS, Lee KW, Lee SB, Myung HJ. Clinical studies on associated autoimmune disease with myasthenia gravis. J Korean Neurol Asso 1991; 9: 432-8

Kimura J. Electrodiagnosis in disease of nerve and muscle: Principle and Practice. FA Davis. Philadelphia, 1983: pp.305-19

Konishi T, Nishitani H, Matsubara F, Ohta M. Myasthenia gravis: Relation between jitter in single-fiber EMG and antibody to acetylcholine receptor. Neurology 1981; 31:386-92

Krarup L. Electrical and mechanical responses in the platysma and adductor pollicis: In patients with myasthenia gravis. J Neurol Neurosurg Psychiatry

1977; 40:241-9

Lee KW, Lee NS, Kim BJ, Lee DS, Chung JK, Lee MC, Lee SB, Myung HJ. Changes of acetylcholine receptor antibody concentration and disease severity in myasthenia gravis. J Korean Neurol Asso 1992; 10:162-72

Mihelin M, Trontelj JV, Trontelj JK. Automatic measurement of random interpotential intervals in single fiber electromyography. Int J Bio-Med Comp 1975; 6:181-90

Oh SJ, Eslami N, Nishihira T, Sarala PK, Kuba T, Elmore RS, Sunwoo IN, Ro YI. Electrophysiological and clinical correlation in myasthenia gravis. Ann Neurol 1982; 12:348-54

Oh SJ. Electromyography: Neuromuscular Transmission study. Williams & Wilkins, Baltimore, 1988: pp. 243-91

Oh SJ, Kim DE, Kuruoglu R, Bradley RJ, Dwyer D. Diagnostic sensitivity of the laboratory tests in myasthenia gravis. Muscle Nerve 1992; 5:720-4

Ozdemir C, Young RR. The result to be expected from electrical testing in the diagnosis of myasthenia gravis. Ann NY Acad Sci 1976; 274:203-22

Penn AS, Rowland LP. Myasthenia gravis. In Rowland LP (Ed): Merritt's Textbook of Neurology, 8th edition, Lea & Febiger, Philadelphia London, 1989: pp. 697-704

Rouseev R, Ashby P, Basinski A, Sharpe JA. Single fiber EMG in the frontalis muscle in ocular myasthenia: specificity and sensitivity. Muscle Nerve 1992; 15:399-403

Sanders DB, Howard JF. Single-fiber electromyography in myasthenia gravis. Muscle Nerve 1986; 9:809-19

Sanders DB, Howard JE, Johns TR. Single-fiber electromyography in myasthenia gravis. Neurology 1979; 21:68-76

Schwartz MS, Stalberg E. Myasthenic syndrome studied with single fiber electromyography. Arch Neurol 1975; 32:815-7

Slomic A, Rosenfalk A, Buchthal F. Electrical and mechanical responses of normal and myasthenic muscle. Brain Res 1968; 10:1-78

Stalberg E. Single fiber electromyography. DISA Information Department, Copėnbagen, Denmark, 1974

Stalberg E, Trontelj JV. Single fiber electromyography. Old Working, Surrey, UK, Mirvalle Press, 1979: pp. 33-83

Stalberg E. Clinical electrophysiology in myasthenia gravis. J Neurol Neurosurg Psychiatry 1980; 43:622-33

Stalberg E. Sanders DB. Electrophysiologial tests of neuromuscular transmission. In Stalberg E, Young R (eds): Clinical Neurophysiology. London, Butter-Worths, 1981, pp.88-116.

Sunwoo IN. Diagnostic value of single fiber electromyography in myasthenia gravis in Korea. J Korean Neurol Asso 1988; 6:210-7