Nagoya J. Med. Sci. **55.** 103 ~ 113, 1993

REMISSION OF MYASTHENIA GRAVIS: CLINICAL, ELECTROPHYSIOLOGICAL AND IMMUNOLOGICAL STUDIES

KAZUO MANO[1*], TOSHIHIKO TAKEGAMI[1], SUSUMU OKAMOTO[1] and AKIRA TAKAHASHI[2]

[1]*Department of Neurology, Nagoya National Hospital, Nagoya, Japan*
[2]*Department of Neurology, Nagoya University, School of Medicine, Nagoya, Japan*

ABSTRACT

The prognosis of 142 patients with myasthenia gravis (MG) was clinically investigated. Forty-nine (35%) had clinical remission (CR) and 23 (16%) good improvement (GI), while 70 (49%) remained in poor condition. Favorable clinical factors for CR were the onset of MG before the age of 20 years, a pre-thymectomy period of less than one year, and a post-thymectomy period of six years or more. Single-fiber electromyography (SFEMG) showed abnormal jitter in nine (47%) of the 19 CR patients, while abnormal jitter was shown in 13 (81%) of the 16 GI patients. Abnormal jitter in CR patients was correlated with the following clinical factors: complication with the thymoma, a period of three or more years from thymectomy to remission, and a remission period of less than six years. An anti-acetylcholine receptor (anti-AChR) antibody was positive in 12 CR patients (63%) as well as in 13 GI patients (81%). Based upon these facts, we point out that true remission seldom occurs in MG patients, and that there exist clinical features that may favorably induce clinical remission. We would like to postulate that electrophysiological and immunological follow-up is indispensable even in CR patients to predict recurrence.

Key Words: Myasthenia gravis, remission, electromyography, antiacetylcholine receptor antibody

INTRODUCTION

Remission is defined as a temporary but marked reduction in severity or disappearance of the symptoms of a disease. In case of myasthenia gravis (MG), thymectomy is a useful treatment and the remission rate has been reported to be between 21% and 51% among thymectomized patients[1–9]. Remission in MG, however, may reveal electrophysiological or immunological abnormalities, which possibly result in a recurrence of the illness. Remission must be strictly distinguished from recovery. We studied the clinical remission of MG patients from the clinical, the electrophysiological and the immunological points of view to clarify the clinical features favorable to remission, and to show the importance of repeated examinations to ascertain good prognosis.

Correspondence: Kazuo Mano, M.D., Department of Neurology, Nagoya First Red Cross Hospital, 3-35 Michishita-cho, Nakamura-ku, Nagoya 453 Japan
Accepted for Publication on November 21, 1992

PATIENTS AND METHODS

Patients We studied a series of 142 patients with MG treated in the Department of Neurology, Nagoya National Hospital, and who were followed up for two years or more. The clinical features of the patients are shown in Table 1. Their clinical courses were observed for two to 15 years (with an average of 9.2 years).

The prognosis was classified into three groups according to the criteria described below:

Clinical remission (CR) − a condition in which myasthenic symptoms have not been identified for 20 months or longer after the active stage, thus allowing patients to have a normal life without medication.

Table 1. Clinical Features of Patients

	Total	CR[a)]	GI[b)]	PI[c)]	
Patients	142	49	23	70	
Sex ♀/♂	96/46	30/19	15/8	51/19	
Onset age (yr)					
<20	39	20	4	15	e)
20–40	60	17	10	33	e)
40≦	43	12	9	22	e)
Clinical classification					
ocular	21	10	2	9	
generalized mild	32	12	8	12	
generalized severe	89	27	13	49	
Therapy					
anti-ChE[d)] only	21	7		14	
steroid only	16	6	4	6	
thymectomy	105	36	19	50	
Period of disease until thymectomy (yr)					
<1	39	18	6	15	e)
1–3	29	11	5	13	e)
3–5	15	4	2	9	e)
5≦	22	3	6	13	e)
Histology of thymus					
thymoma	23	8	4	11	
non-thymoma	82	28	15	39	
Follow-up period after thymectomy (yr)					
<2	5			5	e)
2–4	17	3	5	9	e)
4–6	14	4	5	5	e)
6–8	21	6	5	10	e)
8–10	21	8	1	12	e)
10≦	27	15	3	9	e)

a) CR, clinical remission; b) GI, good improvement; c) PI, poor improvement; d) anti-ChE, anticholinesterase; e) $p < 0.05$.

Good improvement (GI) − a condition in which a normal life has been restored, but short occurrences of transient, easy fatiguability and a mild fluctuation of muscular strength are observed such that occasional medication is required.

Poor improvement (PI) − a condition in which a patient cannot be taken off medication, which is used periodically to sustain life.

Electrophysiological study The electrophysiological study was conducted on 35 patients (19 CR patients and 16 GI patients). SFEMG, the method advocated by Ekstedt and Stålberg[10–12], was applied to the extensor digitorum communis (ECD) because it favored myasthenic manifestations in the active stage. SFEMGs were recorded with an electrode Medelec SF25 and analysed using a Medelec MS6 with an AA6 amplifier. Fifty discharges or more were recorded, and five to 10 discharges were superimposed on to light-sensitive paper. Variations in interpotential intervals were measured manually, and the mean consecutive difference (MCD) was calculated in microseconds (Fig.1). The jitter value, equivalent to the grand total mean MCD of each patient, was obtained from 12 to 26 potential pairs, or an average of 19.4 pairs. The jitter value was used to compare the patients. This test was performed on 11 healthy adults (six men and five women between 26 and 67 years old), and showed the jitter value to be 39.0±7.1(mean±SD)μsec. Therefore a jitter value of more than 54μsec was considered to be abnormal. Blocking was considered to be positive when it was observed in 10% or more of the potential pairs[12–14].

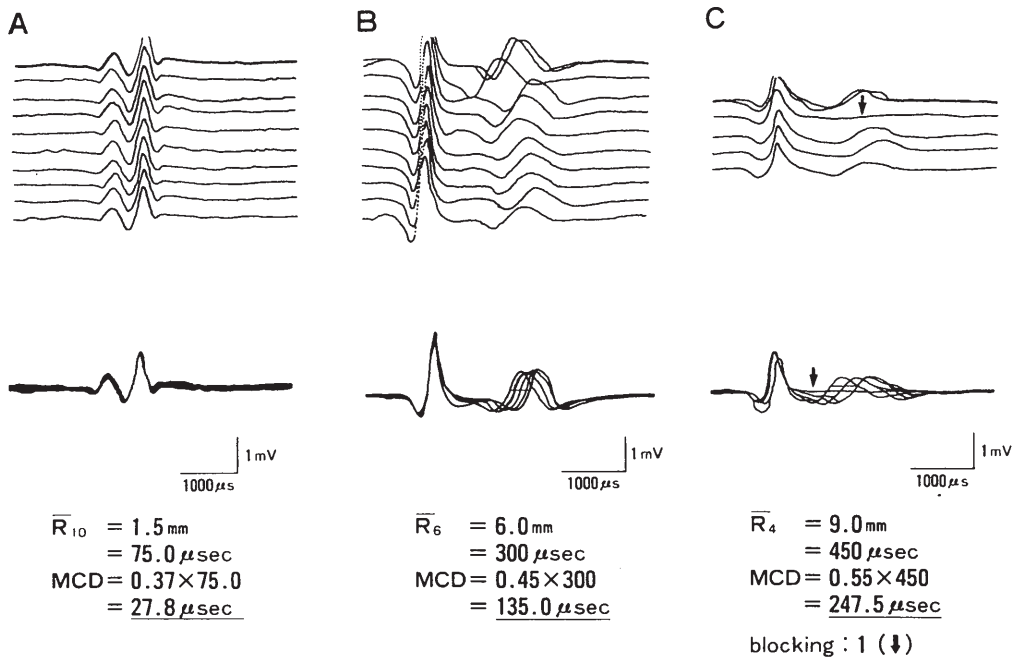

Fig. 1. Three examples of SFEMG findings.
A: normal jitter; B: abnormal jitter without blocking; C: abnormal jitter with blocking

Measurement of anti-AChR antibody titer In all 35 patients for whom SFEMG was employed, the serum anti-acetylcholine receptor (anti-AChR) antibody was measured by the anti-human IgG method using the AChR of a monkey (normal value < 0.16pmol/ml)[15]. The measurement of anti-AChR antibody and SFEMG were conducted on patients on the same day. The results of these tests were compared.

Statistical analysis Results between the various groups were compared using the χ^2 test and the mean values of two groups were compared using the two sample *t* test.

RESULTS

Clinical factors affecting the prognosis (Table 1) The prognosis was significantly related to the age when the illness began, the length of the pre-thymectomy period and the length of the post-thymectomy period, but not to sex, therapy or histology of the thymus.

In the group of 39 patients who were less than 20 years old when the illness began, 20 patients (51%) were in CR, 4 (10%) were in GI, and 15 (39%) were in PI. While, in the group of 103 patients with onset after the age of 20, 29 (28%) were in CR, 19 (18%) were in GI, and 55 (54%) were in PI. The difference between the two groups was significant ($\chi^2=6.55$, $p < 0.05$).

In the group of 39 patients who had a thymectomy less than one year from onset of the illness, 18 (46%) were in CR, 6 (15%) were in GI, and 15 (39%) were in PI. Of 37 patients who had had the illness three years or more before a thymectomy, 7 (19%) patients were in CR, 8 (22%) were in GI, and 22 (59%) were in PI. The difference between the two groups was significant ($\chi^2=6.01$, $p < 0.05$). The remission rate was obviously lower as the pre-thymectomy period became longer. In the group of 36 patients who had had a thymectomy less than six years ago, there were 7 (19%) in CR, 10 (28%) in GI, and 19 (53%) in PI. In the group of 69 patients who had had a thymectomy six years ago or more, 29 (42%) were in CR, 9 (13%) were in GI, and 31 (45%) were in PI. An increase in CR patients and a decrease in PI patients were observed in the latter group. The difference between the two groups was significant ($\chi^2=6.68$, $p < 0.05$).

Electrophysiological study (Tables 2 and 3) The results of the SFEMG examinations are shown in Tables 2 and 3 correlative to the clinical features of the patients. The number of patients who had both normal jitter and normal anti-AChR antibody was extremely small —3 (16%) of the 19 patients in CR and 1 (6%) of the 16 patients in GI, or a total of 4 (11%) of 35 patients examined. The incidence of patients with abnormal jitter in GI was significantly higher ($\chi^2=4.27$, $p < 0.05$) than that of those in CR. Both the appearance and degree of blocking were higher in GI.

Abnormal jitter was correlated with the histology of the thymus, with the thymectomy-to-remission period, as well as with the period of remission.

Correlation with the histology of the thymus: All five thymoma patients demonstrated abnormal jitter. Of the 12 non-thymoma patients, only four (33%) demonstrated abnormal jitter. The difference between the patients with thymoma and those without thymoma was significant ($\chi^2=3.90$, $p < 0.05$).

Correlation with the thymectomy-to-remission period: Of the 12 patients whose remission began less than three years after thymectomy, normal jitter was in 8 (67%) and abnormal jitter in 4 (33%). Of five patients who had had a thymectomy three years or more before remission began, jitter was abnormal in all of them. The difference between the two groups was of

Table 2. Correlation Between SFEMG Findings and Clinical Features

Jitter	CR[a] Normal	CR[a] Abnormal	GI[b] Normal	GI[b] Abnormal
Paitents	10	9[2][d]	3	13[5][e]
Sex ♀/♂	7/3	6[1]/3[1]	2/1	8[5]/5
Onset age (yr)				
<20	1	2		3
20–40	7	3[1]	1	6[4]
40≦	2	4[1]	2	4[1]
Clinical classification				
generalized mild	4	2	2	4[1]
generalized severe	6	7[2]	1	9[4]
Therapy				
steroid only	2			1[1]
thymectomy	8	9[2]	3	12[4]
Period of disease until thymectomy (yr)				
<1	4	4		5[1]
1–3	3	4[1]	2	2[2]
3–5	1			2
5≦		1[1]	1	3[1]
Histology of thymus				
thymoma		5[1] ┐ e)	2	2[1]
non-thymoma	8	4[1] ┘	1	10[3]
Period between thymectomy and examination (yr)				
<2			1	1
2–4	3	1[1]	1	2[1]
4–6	1	5		1
6–8	2	1		4[2]
8–10	1	2[1]		2[1]
10≦	1		1	2
Period between thymectomy and remission (yr)				
<1	2	2[1] ┐		
1–2	4	┐		
2–3	2	2 ┘ e)		
3≦		5[1] ┘		
Period of remission (yr)				
<2	3	1 ┐		
2–4	3	5[1] ┐		
4–6		3[1] ┘ e)		
6≦	4	┘		
Anti-AChR[c] antibody titer (pmol/ml)				
<0.16	3	4	1	2[1]
0.16–0.5		1	1	5[1]
0.5–1.0	2			2
1.0–5.0	5	4[2]	1	3[2]
5.0≦				1[1]

a) CR, clinical remission; b) GI, good improvement; c) anti-AChR, anti-acetylcholine receptor; d) [ ]: no. of patients with blocking; e) $p < 0.05$.

Table 3. Correlation Between Anti-AChR[a] Antibody Titer and Clinical Features of Patients in Clinical Remission

	Normal jitter		Abnormal jitter	
Antibody titer	Normal	Abnormal	Normal	Abnormal
Patients	3	7	4	5
Sex ♀/♂	2/1	5/2	3/1	3[1]/2[1][b]
Onset age (yr)				
<20		1		2
20–40	2	5	2	1[1]
40≦	1	1	2	2[1]
Clinical classification				
generalized mild	2	2	2	
generalized severe	1	5	2	5[2]
Therapy				
steroid only	2			
thymectomy	1	7	4	5[2]
Period of disease until thymectomy (yr)				
<1	1	3	2	2
1–3		3	2	2[1]
3–5		1		
5≦				1[1]
Histology of thymus				
thymoma			2	3[1]
non-thymoma	1	7	2	2[1]
Period between thymectomy and examination (yr)				
2–4	1	2		1[1]
4–6		1	3	2
6–8		2	1	
8–10		1		2[1]
10≦		1		
Period between thymectomy and remission (yr)				
<1		2	1	1[1]
1–2	1	3		
2–3		2	1	1
3≦			2	3[1]
Period of remission (yr)				
<2	1	2		1
2–4	2	1	3	2[1]
4–6			1	2[1]
6≦		4		

a) anti-AChR, anti-acetylcholine receptor; b) [ ]: no. of patients with blocking.

noticeable importance ($\chi^2=3.90$, $p<0.05$).

Correlation with the period of remission: Of 15 patients who had been in remission for less than six years, 6 (40%) had normal jitter and 9 (60%) had abnormal jitter. All four patients who had been in remission for six years or more showed normal jitter.

The SFEMG re-examination was performed after seven to 13 months (an average of 11.2 months) on five CR patients with abnormal jitter values. The jitter values improved in 4 (80%) patients and blocking disappeared in all five patients.

Anti-AChR antibody titer (Tables 2 and 3) Anti-AChR antibody titers (normal value <0.16pmol/ml), as well as SFEMG, were measured simultaneously in 19 CR patients. There were 7 (37%) normal patients and 12 (63%) abnormal patients. The distribution of antibody titers in abnormal patients fell between 0.18 and 3.97pmol/ml (mean 1.72pmol/ml). While in 16 GI patients, 3 (19%) were normal and 13 (81%) were abnormal. Distribution of the titer ranged from 0.21 to 18.2pmol/ml with a mean of 2.14pmol/ml. The difference in incidence and degree of anti-AChR antibody titer abnormality, however, was not significant between CR and GI patients.

Correlation between abnormality in anti-AChR antibody titer and clinical features among patients in CR was examined. No significant differences could be detected for any of the clinical features.

Chronological follow-up was done on 11 of 19 patients in CR. Seven of them showing an abnormal titer at the active stage showed a tendency for the titer to decrease even during the period of remission.

DISCUSSION

(1) Does true remission exist in MG patients?

In our study 49 (35%) of the 142 patients had clinical remission, i.e., no myasthenic symptoms have been noticed for more than 20 months without medication following the active stage. This means that a stable condition in which medication is unnecessary can frequently be obtained.

However, such a stable condition does not always mean that electrophysiological or immunological abnormalities have disappeared. SFEMG is the most sensitive clinicality applicable examination and the most reasonable electrophysiological method to evaluate the neuromuscular transmission quantitatively[13]. Sanders et al.[14] observed abnormal jitter in 7 of 9 patients in remission, while they could detect no abnormality in repetitive stimulation tests conducted on 4 of the 9 patients. Emeryk et al.[16] found abnormal jitter in 17 (85%) of 20 patients in remission. We obtained a lower rate of abnormal jitter than these previous reports because we more strictly defined both clinical remission and the criteria for abnormal jitter.

Existence of the anti-AChR antibody is the cardinal cause of MG. The titer of the antibody indicates the activity of the disease especially in case of patients who have shown a positive antibody in the active stage. Limburg et al.[17] found a positive anti-AChR antibody in 19 (79%) of 24 MG patients in remission. It was positive in 12 (63%) of our 19 CR patients, showing a similar result.

So far there has been no comparative study on jitter values and anti-AChR antibody titers occurring simultaneously in CR patients. Our study, however, has proven that true remission with normal jitter and without the antibody may occur only rarely in MG patients.

(2) Clinical features necessary to obtain CR

In our patients, the following factors were proved necessary to have a 40% or higher remission rate: onset before the age of 20 years, a period of less than one year before thymectomy, a period of less than three years from thymectomy to remission, and a remission period of longer than six years after thymectomy.

Based upon the previous reports[8,18–22] and our own results, age of initial onset and pre-thymectomy period are considered to be the most important factors in predicting the prognosis of MG patients. Clinical observations disclose that the age of onset is closely related to clinical severity, therapeutic effects and histology of the thymus[8,23,24]. Remission rate is known to be high in patients with a pre-thymectomy period of less than three years[8,9,18–20], and it becomes higher as the post-thymectomy period becomes longer[5,25,26].

The previous reports are not always consistent on the correlation between the prognosis and the thymic histology exclusive of thymoma. In some reports[2,19,26,27] the effect of thymectomy was better in patients with an atrophic thymus, while in others[4,28,29,30] thymectomy was more effective among patients with a hyperplastic thymus. Thus, the thymus must play a key role in the occurrence of MG; nevertheless, the significance of thymic lesion remains unclear and further study is required.

Spontaneous remission may occasionally occur only in patients with an ocular or a mild, generalized type of MG and with juvenile onset. We should follow up patients who develop MG as a juvenile and who have an ocular or a mild, generalized type, for two to three years after its onset. In a severe, generalized type, the sooner the thymectomy is performed the better the prognosis is because no spontaneous remission can possibly occur without it. Our study revealed that it would be reasonable to evaluate thymectomy in six years.

(3) Pathophysiology of CR patients

The pathophysiology of each group will be discussed, based upon abnormalities in jitter and anti-AChR antibody.

The normal jitter/normal anti-AChR group (three patients) Since SFEMG was done on EDC only, false negative cannot be completely denied. However, it has been proven that only a small number of patients can have a remission without any abnormalities in their examination results.

The normal jitter/abnormal anti-AChR group (seven patients) It has been assumed that the acting site of the antibody does not coincide with the ACh binding site since correlation is not always seen between myasthenic symptoms and anti-AChR antibody titer[17,32,33]. Diversity of the antibody binding site is known, and it has been proven that discrepancy between the titer of antibody and dysfunction of neuromuscular transmission can occur[34–36].

The abnormal jitter/normal anti-AChR group (four patients) Waning in amplitude of motor endplate potential during repetitive muscle contraction is likely to cause jitter abnormality[13]. Amplitude of endplate potential shows a decline in the number of ACh receptors at the endplate. This decline is caused either by an anti-AChR antibody, which promotes destruction and degradation, or by immunopharmachological blocking. These findings suggest normal anti-AChR antibody titer is false negative; therefore, it is of importance to measure the blocking antibody.

The abnormal jitter/abnormal anti-AChR group (five patients) Abnormal jitter reflects the action of an anti-AChR antibody against an ACh receptor. There may be a similarity in the pathophysiology between CR patients and active MG patients. Konishi et al.[37] reported that muscular strength was more closely correlated to the degree of blocking than to the extension of jitter values. Slight blocking of 10.0% to 16.7% in our CR patients is not supposed to reflect on their daily activities or muscle strength. But this group can be regarded as the group with the greatest potential of disease recurrence.

(4) Chronological change in electrophysiological and immunological parameters

Little is known about the chronology of electrophysiological and immunological parameters in the clinical remission patients. Our longitudinal investigation of jitter values and anti-AChR antibody titer leads us to believe that both electrophysiological and immunological functions are apt to improve continuously in CR patients. It is also suggested that abnormal jitter exists in most patients at the beginning of CR. The SFEMG examination, therefore, is considered to be useful in predicting recurrence through quantitative evaluation of neuromuscular transmission. Conclusively, we would like to point out the necessity for repeated and careful SFEMG examinations with measurement of anti-AChR antibody, especially in patients who have been in CR less than six years and who have abnormal jitter values.

ACKNOWLEGEMENTS

The authors would like to express their sincere gratitude to Prof. Erik Stålberg, University Hospital, Uppsala, for his invaluable advice and criticism of the manuscript, and to Prof. Norio Fujiki, Fukui Medical School, for encouraging us to realize this study.

REFERENCES

1) Simpson, J.A.: An evaluation of thymectomy in myasthenia gravis. *Brain*, 81, 112–144 (1958).
2) Perlo, V.P., Arnason, B., Poskanzer, D., Castleman, B., Schwab, R.S., Osserman, K.E., Papatestis, A., Alpert, L. and Kark, A.: The role of thymectomy in the treatment of myasthenia gravis. *Ann. N. Y. Acad. Sci.*, 183, 308–315 (1971).
3) Emeryk, B. and Strugalska, M.H.: Evaluation of results of thymectomy in myasthenia gravis. *J. Neurol.*, 211, 155–168 (1976).
4) Buckingham, J.M., Howard, F.M.Jr., Bernatz, P.E., Payne, W.S., Harrison, E.G.Jr., O'Brien, P.C. and Weiland, L.H.: The value of thymectomy in myasthenia gravis: A computer-assisted matched study. *Ann. Surg.*, 184, 453–458 (1976).
5) Rodriguez, M., Gomez, M.R., Howard, F.M.Jr. and Taylor, W.F.: Myasthenia gravis in children: long-term follow-up. *Ann. Neurol.*, 13, 504–510 (1983).
6) Mulder, D.G., Herrmann, C.Jr., Keesey, J. and Edwards, H.: Thymectomy for myasthenia gravis. *Am. J. Med.*, 146, 61–66 (1983).
7) Scadding, G.K., Havard, C.W.H., Lange, M.J. and Domb, I.: The long term experience of thymectomy for myasthenia gravis. *J. Neurol. Neurosurg. Psychiatry*, 48, 401–406 (1985).
8) Papatestas, A.E., Genkins, G., Kornfeld, P., Eisenkraft, J.B., Fagerstrom, R.P., Pozner, J. and Aufses, A.H.Jr.: Effects of thymectomy in myasthenia gravis. *Ann. Surg.*, 206, 78–88 (1987).
9) Durelli, L., Maggi, G., Casadio, C., Ferri, R., Rendine, S. and Bergamini, L.: Actuarial analysis of the occurrence of remissions following thymectomy for myasthenia gravis in 400 patients. *J. Neurol. Neurosurg. Psychiatry*, 54, 406–411 (1991).
10) Ekstedt, J., Nilsson, G. and Stålberg, E.: Calculation of the electromyographic jitter. *J. Neurol. Neurosurg. Psychiatry*, 37, 526–539 (1974).

11) Stålberg, E., Ekstedt, J. and Broman, A.: Neuromuscular transmission in myasthenia gravis studied with single fibre electromyography. *J. Neurol. Neurosurg. Psychiatry*, 37, 540–547 (1974).
12) Stålberg, E. and Trontelj, J.V.: Single fiber electromyography. pp.33–64 (1979), The Mirvalle Press Ltd., Ols Working, Surrey.
13) Stålberg, E.: Clinical electrophysiology in myasthenia gravis. *J. Neurol. Neurosurg. Psychiatry*, 43, 622–633 (1980).
14) Sanders, D.B., Howard, J.F.Jr. and Jones, T.R.: Single-fiber electromyopraphy in myasthenia gravis. *Neurology*, 29, 68–76 (1979).
15) Lindstrom, J.M., Seybold, M.E., Lennon, V.A., Whittingham, S. and Duane, D.D.: Antibody to acethylcholine receptor in myasthenia gravis. *Neurology*, 26, 1054–1059 (1976).
16) Emeryk, B., Rowińska, K. and Nowak-Michalska, T.: Do true remissions in myasthenia gravis really exist? An electrophysiological study. *J. Neurol.*, 231, 331–335 (1985).
17) Limburg, P.C., The, T.H., Hummel-Tappel, E. and Oosterhuis, H.J.G.H.: Anti-acethylcholine receptor antibodies in myasthenia gravis. Part 1. Relation to clinical parameters in 250 patients. *J. Neurol. Sci.*, 58, 357–370 (1983).
18) Seybold, M.E., Howard, F.M.Jr., Duane, D.D., Payne, W.S. and Harrison, E.G.Jr.: Thymectomy in juvenile myasthenia gravis. *Arch. Neurol.*, 25, 385–392 (1971).
19) Genkins, G., Papatestas, A.E., Horowitz. S.H. and Kornfeld, P.: Studies in myasthenia gravis: Early thymectomy. Electrophysiologic and pathologic correlations. *Am. J. Med.*, 58, 517–524 (1975).
20) Oosterhuis, H.J.: Observations of the natural history of myastheia gravis and the effect of thymectomy. *Ann. N. Y. Acad. Sci.*, 377, 678–690 (1981).
21) Monden, Y., Nakahara, K., Kagotani, K., Fujii, Y., Nanjo, S., Masaoka, A. and Kawashima, Y.: Effects of preoperative duration of symptoms on patients with myasthenia gravis. *Ann. Thorac. Surg.*, 38, 287–291 (1984).
22) Donaldson, D.H., Ansher, M., Horan, S., Rutherford, R.B. and Ringel, S.P.: The relationship of age to outcome on myasthenia gravis. *Neurology*, 40, 786–790 (1990).
23) Compston, D.A.S., Vincent, A., Newsom-Davis, J. and Batchelor, J.R.: Clinical pathological, HLA antigen and immunological evidence for disease heterogeneity in myasthenia gravis. *Brain*, 103, 579–601 (1980).
24) Fukuyama, Y., Hirayama, K. and Osawa, M.: Epidemiological and clinical features of childhood myasthenia gravis in Japan. In *Myasthia gravis*, edited by Jpn. Med. Res. Found. pp.19–27 (1981) Univ. of Tokyo Press, Tokyo.
25) Jaretzki, A. III, Penn, A.S., Younger, D.S., Wolff, M., Olarte, M.R., Lovelace, R.E. and Rowland, L.P.: "Maximal" thymectomy for myasthenia gravis. *J. Thorac. Cardiovasc. Surg.*, 95, 747–753 (1988).
26) Papatestas, A.E., Alpert, L.I., Osserman, K.E., Osserman, R.S. and Kark, A.E.: Studies in myasthenia gravis: Effects of thymectomy. Results on 185 patients with nonthymomatous and thymomatous myasthenia gravis, 1941–1969. *Am. J. Med.*, 50, 465–474 (1971).
27) Vetters, J.M. and Simpson, J.A.: Comparison of thymic histology with response to thymectomy in myasthenia gravis. *J. Neurol. Neurosurg. Psychiatry*, 37, 1139–1145 (1974).
28) Cohn, H.E., Solit, R.W., Schatz, N.J. and Schlezinger, N.: Surgical treatment in myasthenia gravis. A 27 year experience. *J. Thorac. Cardiovasc. Surg.*, 68, 876–885 (1974).
29) Sambrook, M.A., Reid, H., Mohr, P.D. and Boddie, H.G.: Myasthenia gravis: clinical and histological features in relation to thymectomy. *J. Neurol. Neurosurg. Psychiatry*, 39, 38–43 (1976).
30) Rubin, J.W., Ellison, R.G., Moore, H.V. and Pai, G.P.: Factors affecting response to thymectomy for myasthenia gravis. *J. Thorac. Cardiovasc. Surg.*, 82, 720–728 (1981).
31) Tindall, R.S.A.: Humoral immunity in myasthenia gravis: biochemical characterization of acquired clinical correlations. *Ann. Neurol.*, 10, 437–447 (1981).
32) Roses, A.D., Olanow, C.W., McAdams, M.W. and Lane, R.J.M.: No direct correlation between serum anti-acetylcholine receptor antibody levels and clinical state of individual patients with myasthenia gravis. *Neurology*, 31, 220–224 (1981).
33) Vincent, A., Newsom-Davis, J., Newton, P. and Beck, N.: Acetylcholine receptor antibody and clinical response to thymectomy in myasthenia gravis. *Neurology*, 33, 1276–1282 (1983).
34) Newson-Davis, J., Willcox, N., Schluep, M., Harcourt, G., Vincent, A., Mossman, S., Wray, D. and Burges, J.: Immunological heterogeneity and cellular mechanisms in myasthenia gravis. *Ann. N. Y. Acad. Sci.*, 505, 12–26 (1987).
35) Vincent, A., Whiting, P.J., Schluep, M., Heidenreich, F., Lang, B., Roberts, A., Willcox, N. and Newsom-Davis, J.: Antibody heterogeneity and specificity in myasthenia gravis. *Ann. N. Y. Acad. Sci.*, 505, 106–120 (1987).

36) Lennon, V.A. and Griesmann, G.E.: Evidence against acetylcholine receptor having a main immunogenic region as target for autoantibodies in myasthenia gravis. *Neurology*, 39, 169–176 (1989).
37) Konishi, T., Nishitani, H., Matsubara, F. and Ohta, M.: Myasthenia gravis: Relation between jitter in single-fiber EMG and antibody to acetylcholine receptor. *Neurology*, 31, 386–392 (1981).