Research Report

Predictive Value of Electrophysiology for Presence of Thymic Pathology in Myasthenia Gravis

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Abstract.
Objective: Single fibre electromyography (SFEMG) and repetitive nerve stimulation (RNS) are routinely performed investigations in evaluation of patients with myasthenia gravis (MG). Significant number of MG patients have a thymic pathology. We aimed to explore the relationship between the SFEMG and RNS findings with the presence of thymic pathology.
Methods: We studied 159 consecutive patients with MG over a 10 year period. The SFEMG parameters – mean jitter (MJ) and percentage of abnormal fibres (POAF) and the RNS result were correlated with the thymic findings.
Results: As compared to patients with normal thymus (MJ:58.3 μsec; POAF:63.5%), patients with thymic pathology had a significantly higher MJ (80.9 μsec; $p < 0.0005$) and POAF (83.5%; $p < 0.0005$). MG patients with thymic hyperplasia had the highest MJ (87.6 μsec) and POAF (84.4%) followed by patients with thymoma (MJ:78.6 μsec; POAF:83.2%). The MJ and POAF did not correlate with the stage of thymoma. Mean jitter values above 34.9 μsec and POAF above 31% had 100% sensitivity for the presence of thymic pathology. A positive RNS increased the risk of thymic pathology (OR = 3.9, CI = 1.8–8.5) and thymoma. (OR = 3.5; CI = 1.5–8.1).
Conclusion: Electrophysiology could be valuable complimentary tool to identify MG patients at high risk for thymic pathology. However, it does not aid us to identify the exact thymic pathology and does not correlate with the stage of thymoma. All OMG patients with higher MJ and PAOF values should also be screened for thymoma.

The results reinforce the immunological role of thymic pathology in neuromuscular transmission interference.

Keywords: Myasthenia gravis, thymic pathology, thymoma, single fibre electromyography, mean jitter, percentage of abnormal fibres, repetitive nerve stimulation

OBJECTIVE

Single fibre electromyography (SFEMG) is of proven value in the diagnosis neuromuscular junction disorders. It has a validated high sensitivity of 85 to 95% for diagnosing neuromuscular transmission defects [1–3]. Thymus abnormalities are common and are seen in up to 70% of myasthenia gravis (MG) patients. Of these, thymic hyperplasia accounts for about 85% and thymomas and other thymic tumors about 15% of abnormalities [4].

There are a few known predictors of thymic tumours in MG. To our knowledge, there are no studies which correlate SFEMG and Repetitive Nerve Stimulation (RNS) parameters with thymic pathology in MG patients. Although a complex interaction between genetic and environmental factors is believed to be

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causative in MG, the thymus has an important role in its pathophysiology [5, 6]. Therefore we explored the relationship between the routinely performed electrophysiologic techniques and thymic pathology in MG patients.

METHODS

Over a 10 year period, we retrospectively reviewed 159 MG patients. Clinical symptoms and signs of fatiguable weakness together with positive electrophysiologic response (SFEMG or RNS) or a postive response to pyridostigmine therapy was the criteria used to diagnose MG in general. Ocular MG was diagnosed in patients with symptoms and signs limited to fluctuating and fatiguable ptosis and/or extraocular movement abnormalities. Generalised MG was diagnosed in patients who had a fluctuating and fatiguable weakness in any one extraocular site not attributable to any other causes. Acetylcholine receptors antibodies were not included in diagnostic criteria as in the earlier half of the study, they were not routinely done as clinical service for all MG patients at our centre.

Thymic status was determined by CT thorax. All patients who had thymic enlargement on CT were classified as having thymic pathology. Patients who did not have a CT thorax were excluded.

Among the patients with a known thymic status, those with SFEMG study were included in the SFEMG arm of study and patients with RNS were included in the RNS arm of the study. There was an overlap of patients in these two groups as many patients had both SFEMG and RNS done.

The thymomas were classified using the Masaoka staging system [7].

Stimulated SFEMG was performed on the orbicularis oculi muscle of the affected eye or on either side if no specific ocular signs were present. A Dantec 9013K0872 needle (Dantec, Skovlunde, Denmark) 40 mm in length and 0.45 mm in diameter was inserted at the edge of the muscle. To make single fibre recordings, axonal stimulation of the VII cranial nerve branch was achieved with a Teca disposable monopolar needle (Teca, Old Woking, Surrey, UK) placed 2.5 cm away from the recording needle and a silver chloride disc as an anode at the malar prominence to produce visible twitches. Stimulation was made with square pulses of 0.04 ms duration at 10 Hz and intensity ranging from 8 mA to 15 mA. Amplifier settings were fixed at 500 to 10 kHz. All studies were performed with a Dantec Keypoint Machine. Single fibre responses were selected based on criteria of short rise times (<300 msec), clear separation from other discharges, and stable waveform morphology. For each study, individual mean consecutive differences (MCD) of a minimum of 20 single fibre responses were averaged to obtain a final MJ value. Responses with MCDs less than 5 μsec are not included due to the possibility of direct muscle fibre stimulation. Based on our laboratory controls, individual single fiber jitter values above 30 μsec and a final mean jitter above 23 μsec were regarded as abnormal [8]. Percentage of abnormal fibres were calculated as ratio of individual fibres with abnormal jitter to total fibres studied (minimum 20 for every patient).

RNS was performed at 3 Hz with a square pulse 0.3 ms in duration. Recordings from the orbicularis oculi, nasalis, trapezius, and abductor pollicis brevis muscles were obtained. We utilized handheld Dantec 9013L0221 bipolar electrodes and 9013S0211 adhesive surface electrodes for stimulation and recording, respectively. A positive RNS was designated as decremental response above 10% in any of the muscles studied.

SFEMG, RNS and CT thorax were performed within 4 to 6 weeks of MG diagnosis. None of the patients was on acetylcholinesterase inhibitors at the time of SFEMG or RNS.

STATISTICAL ANALYSIS

Simple arithmetic mean values were calculated for MJ and for POAF for different patient groups – patients with normal thymus, patients with thymoma, patients with thymic hyperplasia, and the latter two groups taken together (thymic pathology group). These groups were then compared in terms of MJ and POAF. For the RNS arm, these groups were compared with respect to the positivity and negativity of the study.

Mann Whitney test was used to compare the difference in the values between two groups. Scatter plot graphs and Spearman's correlation coefficient was used to examine the relationship between the MJ and POAF with the stage of thymoma. Receiver operating characteristic (ROC) curves were plotted to estimate the maximum sensitivity of the SFEMG in predicting thymic pathology.

RESULTS

Amongst the 159 patients, 19 patients were excluded due to unknown thymic status.

Of the remaining 140 patients, single fiber EMG was not done in 34 patients who were excluded. Finally, 106 patients with known thymic status and who also had a SFEMG performed were included in the SFEMG arm of study.

Similarly, among the 140 patients, RNS was not done in 12, who were excluded. The remaining 128 patients were included in the RNS arm of our study.

The diagnosis of MG was confirmed in all except 5 patients on the basis of clinical symptoms and signs and a positive electrophysiology study. The 5 patients who had normal SFEMG and RNS study but were diagnosed to have MG were included on the basis of a good response to pyridostigmine as mentioned earlier.

SFEMG arm (Table 1)

Of the 106 patients in this arm, 74 (69.8%) had normal thymus while 32 (30.1%) patients had a thymic pathology (thymoma: 24; Thymic hyperplasia: 08).

For MG patients with normal thymus, the MJ was 58.3 μsec (CI 50.3–66.2) and the POAF was 63.5% (CI 56.4–70.7). The MJ and POAF for patients with thymic pathology were 80.9 μsec (CI 69.3–92.5) and 83.5% (CI 75.5–91.4) respectively. The MJ was thus significantly higher in the patients with thymic pathology ($p < 0.0005$) (Fig. 1). The thymic pathology group also showed significantly higher POAF ($p < 0.0005$) (Fig. 2).

When MG patients with thymoma alone were compared to patients with normal thymus, the MJ and POAF were still significantly higher in the thymoma group. The MJ and POAF in thymoma group were 78.6 μsec (Fig. 1) and 83.2% (Fig. 2) respectively ($p = 0.001$ for both MJ and POAF).

When MG patients with thymoma were compared to MG patients with thymic hyperplasia in terms of their MJ and POAF values, (Figs. 1 and 2) there was no significant difference (Thymoma group: MJ = 78.6; CI 65.9–91.3; POAF = 83.2%; CI 73.1–93.2 vs.

Thymic hyperplasia group: MJ = 87.6 (CI 54.9–120.3), POAF = 84.4%; CI 70.5–93.2). ($p = 0.578$ for MJ; 0.821 for POAF). The number of patients in thymic hyperplasia group was very small.

46 patients had Generalized MG (GMG) (43.4%) and 45 had ocular MG (OMG) (42.4%). The clinical pattern of MG was uncertain in 15 patients (14.1%). The MJ was 85 μsec in patients with GMG and 49.7 μsec in patients with OMG ($p = <0.0005$). The POAF in patients with GMG and OMG were 83.1% and 59% respectively ($p < 0.0005$).

Subgroup analysis of GMG patients with thymic pathology (MJ 85.5 μsec; POAF 85.8%) and without thymic pathology (MJ 84.4 μsec; POAF 79.8%) showed no statistical difference ($p = 0.55$ and 0.49 respectively). However, subgroup analysis for the OMG patients with (MJ 76.4 μsec; POAF 85.8%) and without thymic pathology (MJ 46.3 μsec; POAF 54.9%) showed significant difference in both MJ ($p = 0.02$) and POAF ($p = 0.01$).

When the MJ and POAF were compared in subgroup of GMG patients with thymic pathology
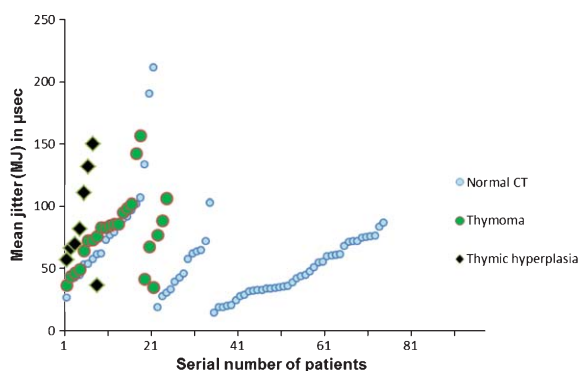

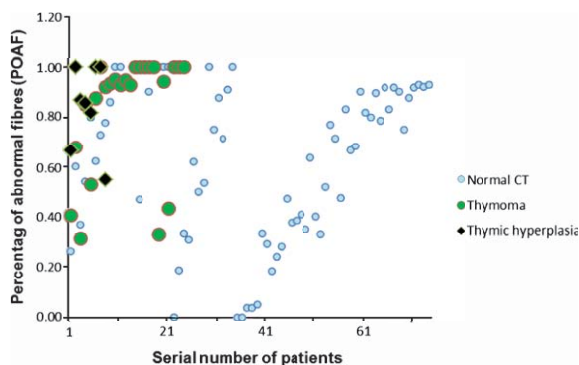Fig. 1. Individual MJ values in patients from different groups.

Fig. 2. Individual POAF values in patients from different groups. (1 = 100%).

Table 1
Table showing MJ and POAF values across different groups of patients and their comparison

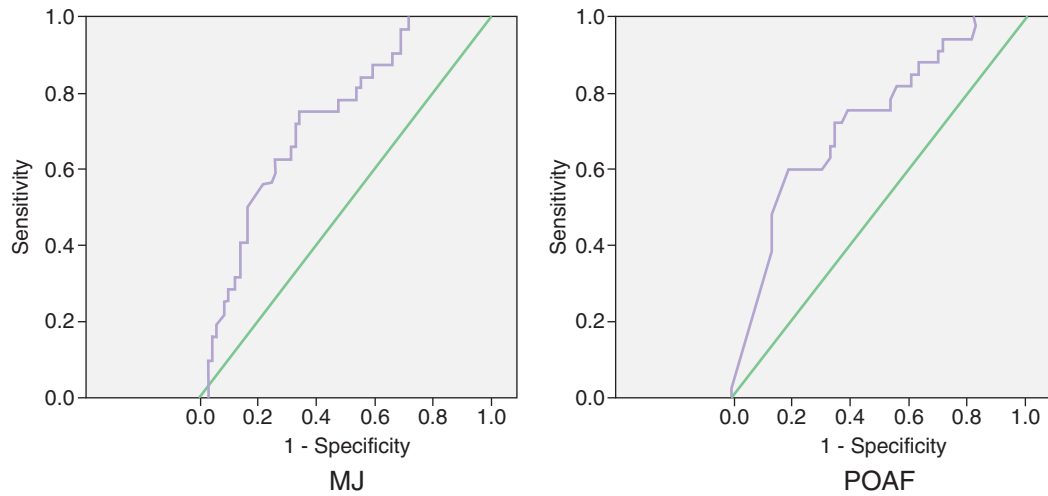| Thymic status	No. of patients	MJ (μsec)	POAF (%)	*p* value (compared to normal thymus group)
Normal thymus	74	58.3	63.5	
Thymic pathology	32	80.9	83.5	<0.0005 for MJ and POAF
Thymoma	24	78.6	83.2	0.001 for MJ and POAF
Thymic hyperplasia	8	87.6	84.4	

Fig. 3. The ROC curve to compute sensitivity and specificity of MJ and POAF for thymic pathology.

(MJ = 85.5 µsec; POAF = 85.8%) and OMG patients with thymic pathology (MJ = 76.4 µsec; POAF = 85.8%), there was no significant difference ($p = 0.92$ and 0.40 for MJ and POAF respectively).

Both MJ and POAF were computed for detection of thymic pathology. Mean jitter above 34.9 µsec and POAF above 31% had 100% sensitivity in detecting a thymic pathology. The Area under curve for the ROC curve was 0.731 for MJ (CI 0.63–0.83) and 0.719 for POAF (CI 0.61–0.82) (Fig. 3).

RNS arm

Of the 128 patients in this arm, 83 had no thymic pathology, 11 had thymic hyperplasia and 28 had thymoma. 63 patients (49.2%) had GMG and 50 patients (39%) had OMG. The clinical MG type was uncertain in 15 patients (11.71%) (Table 2).

Patients with a positive RNS test had a higher likelihood of having a thymic pathology as against patients with negative RNS (OR = 3.9, CI = 1.8–8.5).

Patients with a positive RNS test also had a higher likelihood of having thymoma as compared to patients without thymoma (OR = 3.5; CI = 1.5–8.1).

Table 2
Comparison of RNS findings in patients with normal thymus, thymic pathology and thymoma

	Normal thymus	Thymic pathology	Thymoma
Postive RNS	26	29	21
Negative RNS	57	16	13
Odds ratio (CI)		3.9 (1.8–8.5)	3.5 (1.5–8.1)

DISCUSSION

Recently, there is an increasing interest in predicting thymic tumors based on immunological profile in MG patients. The predictors of thymoma in MG are presence of striated muscle antibodies and acetylcholine receptor antibodies in patients with early onset MG [9] presence of anti-titin and anti-ryanodine antibodies [10, 11], intermediate titres of acetylcholine receptor antibodies [12] and a clinical pattern of non-limb symptom profile at MG onset, characterized by bulbar, ocular, neck, and respiratory symptoms [13].

Although electrophysiology, including SFEMG and RNS, are routinely used for evaluation of MG in clinical setting, to our knowledge, there is no study examining the predictive value of electrophysiological studies for thymic pathology.

SFEMG is a highly sensitive test for diagnosing MG and is routinely performed for this purpose where the expertise is available. MJ, POAF and blocking are its parameters used for interpretation. In our study both higer MJ and higher POAF were associated with the presence of a thymic pathology. These finding reaffirms the relationship between thymus and neuromuscular transmission defect in the pathogenesis of MG.

Our study also suggests that highest MJ values and POAF were seen in patients with thymic hyperplasia although the number of patients were very few in this group. Patients with thymoma had intermediate MJ values while patients with normal thymus had lowest values. This correlates with earlier studies

which found that highest titre of Ach-receptor antibodies were found in patients with thymic hyperplasia followed by intermediate levels in patients with thymoma [12]. However, the clinical relevance of this observation remains uncertain and warrants further examination. The lower incidence of thymic hyperplasia in our cohort could be due to the fact that only patients with a suspicious thymic mass identified on CT thorax had undergone thymectomy and thus had a histologic diagnosis.

SFEMG, though helpful in predicting occurrence of thymic pathology, was not useful in predicting whether the pathology was hyperplasia or thymoma. Consequently, the MJ and POAF were not significantly different in patients with thymoma as compared to patients with thymic hyperplasia. Amongst patients with thymoma, there was no correlation between the stage of thymoma and MJ or POAF. This suggests that factors other than the invasiveness of the thymoma may play crucial roles in the pathogenesis of MG.

Out of the cohort of our 159 patients, 74 patients had known acetylcholine antibody levels, of which 42 (56.7%) had positive antiobodies. This was irrespective of the type of MG, which would be consistent with the known incidence of antibody positivity in generalised and ocular myasthenic patients considered together. Patients with positive antibodies more likely had a thymic pathology (OR = 7; CI = 2.08–23.46) as compared to those with negative antibodies. This is inkeeping with the known positive predictivity of thymic pathology in antibody positive patients.

We found that MJ value above 35 μsec and POAF above 32% had 100% sensitivity in detecting thymic pathology although at a low specificity (30% and 18% respectively). This correlates well with the fact that SFEMG only detects neuromuscular transmission defects, regardless of the underlying pathology causing it. However, it is clinically important to accept a higher sensitivity for detecting a potentially treatable thymic lesion in the real clinical situation. Our findings imply a need to screen all patients with values mentioned above for presence of thymic pathology regardless of the type of MG. This would particularly be true for MG patients whose initial radiologic imaging misses a small thymoma [14]. It would also be relevant in patients who may not be routinely screened for thymic pathology – eg. patients with ocular MG or elderly patients with generalized MG. This view is further supported by subgroup analysis of our OMG patients. The OMG group with thymic pathology had a significantly higher MJ and POAF values when compared to their counterparts without thymic pathology. Although the number of

patients with OMG with thymic pathology was small, this is probably a reflection of the known fact that OMG patients do not commonly have thymic pathology. Hence our findings suggest the need to screen the subgroup of OMG patients who have a higher MJ and POAF values for the presence of thymoma, contrary to the common practice.

With respect to the RNS arm, in our study, MG patients with positive RNS study were more likely to be associated with thymic pathology. RNS positivity was also associated with likelihood of having a thymoma. Thus detection of thymoma should be of clinical priority in RNS positive patients.

Our study has some limitations. This is retrospective study and the patient numbers are small when it comes to subgroup analysis. The patients included are those specifically referred to neurology clinic and we have not included MG patients followed up in other medical departments of our hospital. This may alter the comparability of the observed population to the general population of MG. We have not taken into account the clinical and entire serologic data. In the absence of a complete serologic data, a potential bias might arise due to the fact that true MG was present in patients with thymic pathology thus giving a higher MJ and POAF in this group and some cases without thymic pathology might have been misdiagnosed as MG. However, all our patients had a thorough clinical and electrophysiologic workup done before MG was diagnosed, they had strict inclusion criteria and were followed up for sufficient period of time during which no alternative diagnoses had emerged. This makes the possibility of wrong MG diagnosis to be negligible.

In conclusion, SFEMG parameters of mean jitter and percentage of abnormal fibres are significantly higher in patients with thymic pathology. Electrophysiology could be complimentary (and not a substitute) to CT chest to identify MG patients at high risk for thymic pathology. All OMG patients with higher MJ and PAOF values should also be screened for thymoma. MJ and POAF values do not help to predict exact pathology and also do not correlate to stage of thymoma.

The results reinforce the immunological role of thymic pathology in neuromuscular transmission interference.

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DISCLOSURE STATEMENT

None.

CONFLICTS OF INTEREST AND SOURCES OF FUNDING

None.

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