Preoperative Anxiety in Patients With Myasthenia Gravis and Risk for Myasthenic Crisis After Extended Transsternal Thymectomy

A CONSORT Study

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Abstract: A thymectomy can ameliorate the symptoms of myasthenia gravis (MG) and prevent the progression of ocular MG (OMG) to generalized MG (GMG). However, postoperative myasthenic crisis (POMC) is a serious post-thymectomy complication. Preoperative anxiety (POA) is common but typically neglected in MG patients. The association of POA with POMC has not yet been examined.

From June 2007 to December 2013, 541 cases of MG were admitted to the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). All cases underwent extended transsternal thymectomy (ETT). The clinical and pathological characteristics of these patients, including POA and POMC, were analyzed.

A total of 179 patients experienced POA and 67 patients experienced POMC. Patients with POA were more likely to have POMC, a thymoma, and an ectopic thymus. Univariate analysis showed that POMC correlated with POA, presence of an ectopic thymus, dose of pyridostigmine bromide (PYR), presence of a thymoma, MGFA stage, preoperative myasthenic crisis, and postoperative pneumonia. Multivariate logistic regression analysis showed that the independent risk factors for POMC were POA, preoperative myasthenic crisis, higher dose of PYR, and postoperative pneumonia.

Our results suggest that clinicians should consider the risk factors for POMC—especially preoperative anxiety—before performing a thymectomy in patients with MG.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease characterized by muscle weakness and fatigue that may be classified as ocular MG (OMG) or generalized MG (GMG) based on symptoms.1,2 Thymectomy was first employed as a treatment for MG in 1939.3 Now, extended transsternal thymectomy (ETT) is believed as the standard surgical technique,4 and several retrospective studies have shown that ETT contributed to the amelioration of myasthenic symptoms and may inhibit the progression of OMG to GMG.5,6

A potentially life-threatening event, postoperative myasthenic crisis (POMC), defined as a myasthenic crisis induced by thymectomy, is the most common complication after surgery.7,8 On the other hand, MG is a chronic, debilitating, and life-threatening disease, so many patients experience psychological problems, especially anxiety.9 However, physicians and surgeons typically do not consider the psychological status of MG patients, such as preoperative anxiety (POA).10

Since 2000, we have noticed that lots of MG patients suffered depression or anxiety disorders when they came to our hospital and then being performed with surgical treatment. After observation for a long time, and regarding that the relationship of surgical outcome with the different clinical characteristics of patients with MG, and whether POA influences the efficacy of thymectomy are still unclear, we designed and executed questionnaire to evaluate their psychological status since 2007. Moreover, the relationship of POA with POMC has not yet been examined. In an effort to reduce the incidence of POMC, we analyzed the relationship of the perioperative clinical factors of patients with MG and POMC.

PATIENTS AND METHODS

From June 2007 to December 2013, 541 cases of MG were admitted to the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). MG was diagnosed by neurologists.
using the following criteria: (i) unequivocal amelioration of symptoms on pharmacologic testing with edrophonium chloride; (ii) positive result from electrodiagnostic testing of repetitive nerve stimulation or single-fiber electromyography (SFEMG) or both; (iii) clinical manifestations consisting of skeletal or bulbar muscular weakness or both; and (iv) amelioration of symptoms following treatment with anticholinesterase drugs or corticosteroids or both. 

The use of human materials was approved by the Medical Ethical Committee of The First Affiliated Hospital, Sun Yat-sen University.

In all cases, an ETT was performed due to the presence of MG, a diagnosis of thymoma, or poor response to conservative therapy. The clinical characteristics recorded were: age, sex, MG Foundation of America (MGFA) stage, POA, preoperative myasthenic crisis, time from MG onset to surgery, serum level of anti-acetylcholine receptor antibody (AChR-Ab), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), use of prednisone, use of other immunosuppressants (such as azathioprine or cyclophosphamide), daily dose of pyridostigmine bromide (PYR), pleural resection, thymic pathology, presence of ectopic thymus, and postoperative complications. The presence of POA was assessed by the Beck Anxiety Inventory (BAI), and a score higher than 8 was considered positive. 

The serum level of anti-AchR Ab was determined by enzyme-linked immunosorbent assay (ELISA), with 0.2 mmol/L as the cut-off. The surgery was extended transsternal transthoracic thymectomy, as described by Jaretzki and Wolff, and included removal of the thymus and clearance of perithymic fat from the lower end of the thyroid to the diaphragm and laterally from the bilateral mediastinal pleura to the phrenic nerves. 

Pleural resection was performed when the pleura adhered to perithymic fat or invaded by a thymoma. Thymus pathology was classified as thymoma, thymic hyperplasia, or thymic atrophy. An ectopic thymus was defined by the presence of thymus tissue in the perithymic fat, based on microscopy. Finally, the complications after surgery were categorized as pneumonia, pleural effusion, mediastinitis, and others.

A POMC was defined by the presence of: (i) respiratory failure induced by neuromuscular weakness after surgery with a prolonged postoperative intubation (more than 48h); (ii) extubation within 24 hour after surgery, but recurrence of neuromuscular weakness that required reintubation or resuscitation support in the following 2 weeks; and (iii) exclusion of cholinergic crisis or respiratory failure due to phrenic paralysis or other diseases.

Statistical Analysis

The Mann–Whitney U test was used to analyze categorical data and Student’s t-test to analyze continuous data (expressed as means ± SDs). Individual variable risk factors for POMC were identified by univariate regression analyses, and the significant factors from this univariate analysis were entered into a stepwise binary logistic regression analysis. All statistical analyses were performed with SPSS software (SPSS version 19.0; IBM SPSS Inc., Chicago, IL). A P-value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Patients With and Without POA

There were 557 patients initially enrolled, but 16 patients were excluded because of concomitant diseases such as hyperthyroidism and systemic lupus erythematosus. Table 1 showed the characteristics of patients who did and did not experience POA. A total of 253 (46.8%) were men and 288 (53.2%) were women, and the mean age was 27.0 ± 9.80 years (range: 10–57 years). The average time from diagnosis of MG to surgery was 58.0 ± 34.3 months (range: 3–120 months). Based on the MGFA classification, 62 cases (11.5%) were stage I, 89 cases (16.5%) were stage II A, 121 cases (22.4%) were stage IV B, 73 cases (13.5%) were stage III A, 60 cases (11.1%) were stage III B, 51 cases (9.4%) were stage IV A, 51 cases (9.4%) were stage IV B, and 34 cases (6.3%) were stage V. All 541 patients used PYR tablets for control of symptoms (average daily dose: 175.73 ± 35.31 mg), 191 cases (35.3%) used corticosteroids, and 86 cases (15.9%) used other immunosuppressants such as azathioprine or cyclophosphamide. Before the ETT, evaluation of POA by the BAI indicated that 179 cases (33.1%) had anxiety and 88 cases (16.3%) had a history of a myasthenic crisis. Preoperative testing showed that 440 cases (81.3%) were anti-AChR positive. Pulmonary function testing indicated that the FEV1 was 84.26 ± 19.62% and the FVC was 86.23 ± 17.11%. A total of 179 cases (33.1%) had POA and 67 cases (12.4%) experienced a POMC according to the criteria described above. Pleural resections were performed in 325 cases (60.1%). Pathological data indicated that 134 cases (24.8%) had thymoma, 345 cases (63.8%) had thymus hyperplasia, and 62 cases (11.5%) had thymus atrophy. An ectopic thymus was present in 171 cases (31.6%). A comparison of groups that did and did not experience POA indicated that the only statistically significant differences were that patients with POA were more likely to have a thymoma (P < 0.001) and an ectopic thymus (P = 0.005).

Characteristics of Patients with and without POMC

Table 2 shows the characteristics of patients who did and did not experience a POMC. These results indicate that patients in the POMC group were more likely to have a more advanced MGFA stage (P = 0.003), POA (P = 0.016), a preoperative myasthenic crisis (P = 0.03), a thymoma (P = 0.006), an ectopic thymus (P = 0.028), use of a higher dose of PYR (P < 0.001), and postoperative pneumonia (P < 0.001).

Univariate Analysis of Factors Associated with POMC

Table 3 shows a univariate logistic regression analysis of factors associated with POMC. These results indicate that POMC was significantly associated with a more advanced MGFA stage (OR = 2.43, 95% CI: 1.43–4.14, P = 0.001), POA (OR = 2.18, 95% CI: 1.30–3.66, P = 0.003), preoperative myasthenic crisis (OR = 1.93, 95% CI: 1.05–3.53, P = 0.033), high daily dose (<180 mg) of PYR (OR = 0.65, 95% CI: 3.52–10.41, P < 0.001), thymoma (OR = 2.10, 95% CI: 1.23–3.59, P = 0.007), an ectopic thymus (OR = 1.78, 95% CI: 1.06–3.01, P = 0.03), and postoperative pneumonia (OR = 4.68, 95% CI 2.50–8.76, P < 0.001).

Multivariate Analysis of Factors Associated with POMC

Table 4 shows the multivariable analysis of factors associated with POMC. These results indicate that POMC was significantly and independently associated with POA (OR = 2.40, 95% CI: 1.33–4.34, P = 0.004), preoperative myasthenic crisis (OR = 2.37, 95% CI: 1.19–4.73, P = 0.014), high daily dose (>180 mg) of PYR (OR = 5.99,
| Variable                                      | With POA n (%) | Without POA n (%) | P-value |
|-----------------------------------------------|----------------|-------------------|---------|
| N                                             | 179            | 362               |         |
| Age (years)                                   | 26.8 ± 5.6     | 27.1 ± 6.3        | 0.567*  |
| Sex                                           |                |                   |         |
| Male                                          | 78 (43.6%)     | 175 (48.3%)       | 0.296*  |
| Female                                        | 101 (56.4%)    | 187 (51.7%)       |         |
| MGFA classifications                           |                |                   |         |
| Stage I                                       | 26 (14.5%)     | 36 (9.9%)         | 0.834*  |
| Stage II                                      | 76 (42.4%)     | 134 (37.0%)       |         |
| Stage IIA                                     | 38 (21.1%)     | 51 (14.1%)        |         |
| Stage IIB                                     | 38 (21.1%)     | 83 (22.9%)        |         |
| Stage III                                     | 33 (18.4%)     | 100 (27.6%)       |         |
| Stage IIIA                                    | 19 (10.6%)     | 54 (14.9%)        |         |
| Stage IIB                                     | 14 (7.8%)      | 46 (12.7%)        |         |
| Stage IV                                      | 31 (17.3%)     | 71 (19.6%)        |         |
| MGFA stage I+II                              | 135 (75.4%)    | 370 (74.6%)       | 0.141†  |
| MGFA stage IV+V                              | 44 (24.6%)     | 108 (25.4%)       |         |
| Preoperative myasthenic crisis                |                |                   |         |
| With                                          | 25 (14.0%)     | 63 (17.4%)        | 0.309*  |
| Without                                       | 154 (86.0%)    | 299 (82.6%)       |         |
| Onset of MG to surgery (months)               | 58.6 ± 7.9     | 57.7 ± 8.4        | 0.261†  |
| Anti-AchR level (nmol/L)                      | 6.6 ± 1.4      | 6.1 ± 2.5         | 0.133†  |
| FEV1 (%)                                      | 82.7 ± 27.3    | 85.0 ± 25.8       | 0.451†  |
| FVC (%)                                       | 86.6 ± 33.6    | 86.1 ± 25.7       | 0.277†  |
| Preoperative usage of prednisone              |                |                   |         |
| Yes                                           | 70 (39.1%)     | 121 (33.4%)       | 0.194*  |
| No                                            | 109 (60.9%)    | 241 (66.6%)       |         |
| Preoperative usage of other immunosuppressants|                |                   |         |
| Yes                                           | 26 (14.5%)     | 60 (16.6%)        | 0.541*  |
| No                                            | 153 (85.5%)    | 302 (83.4%)       |         |
| Preoperative daily dose of pyridostigmine (mg)| 176.8 ± 33.5   | 175.2 ± 38.6      | 0.895*  |
| Pleural resection                             |                |                   |         |
| With                                          | 109 (60.9%)    | 216 (59.7%)       | 0.784*  |
| Without                                       | 70 (39.1%)     | 146 (40.3%)       |         |
| Thymic pathology                              |                |                   |         |
| Thymoma                                       | 50 (27.9%)     | 84 (23.2%)        | 0.001†  |
| Hyperplasia                                   | 129 (72.1%)    | 278 (76.8%)       |         |
| Ectopic thymus                                |                |                   |         |
| Yes                                           | 71 (39.7%)     | 100 (27.6%)       | 0.005†  |
| No                                            | 108 (60.3%)    | 262 (72.4%)       |         |
| POMC                                          |                |                   |         |
| With                                          | 33 (18.4%)     | 34 (9.4%)         | 0.003†  |
| Without                                       | 146 (81.6%)    | 328 (90.6%)       |         |
| Postoperative other complications              |                |                   |         |
| None                                          | 115 (64.2%)    | 343 (67.1%)       | 0.552*  |
| Pneumonia                                     | 20 (11.2%)     | 36 (9.9%)         |         |
| Pleural effusions                             | 16 (8.9%)      | 28 (7.7%)         |         |
| Mediastinitis                                 | 16 (8.9%)      | 32 (8.8%)         |         |
| Other                                         | 12 (6.7%)      | 23 (6.4%)         |         |

* Mann–Whitney U test; AchR = acetylcholine receptor.
† Student’s t-test; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; POA = preoperative anxiety; POMC = postoperative myasthenia gravis crisis.
| Variable | With POMC n (%) | Without POMC n (%) | P-value |
|----------|----------------|-------------------|---------|
| Age (years) | 26.4 ± 11.7 | 27.06 ± 13.5 | 0.503* |
| Sex | Male 30 (44.8%) | 226 (47.7%) | 0.257* |
| | Female 37 (55.2%) | 248 (52.3%) | |
| MGFA classifications | | | |
| Stage I | 4 (6%) | 58 (12.2%) | 0.001* |
| Stage II | 18 (26.9%) | 192 (40.5%) | |
| IIA | 3 (4.5%) | 86 (18.1%) | |
| IIB | 15 (22.4%) | 106 (22.4%) | |
| Stage III | 17 (25.4%) | 116 (24.5%) | |
| IIIA | 11 (16.4%) | 62 (13.1%) | |
| IIIB | 6 (9.0%) | 54 (11.4%) | |
| Stage IV | 21 (31.3%) | 81 (17.1%) | |
| IVA | 12 (17.9%) | 39 (8.2%) | |
| IVB | 9 (13.4%) | 42 (8.9%) | |
| Stage V | 7 (10.4%) | 27 (5.7%) | |
| Stage I+II+III | 39 (58.2%) | 366 (77.2%) | 0.003* |
| Stage IV+V | 28 (41.8%) | 108 (22.8%) | |
| Preoperative anxiety (POA) | With 31 (46.3%) | 149 (31.4%) | 0.016* |
| | Without 36 (53.7%) | 325 (68.6%) | |
| Preoperative myasthenia crisis | With 17 (25.4%) | 71 (15.0%) | 0.031* |
| | Without 50 (74.6%) | 403 (85.0%) | |
| Onset of MG to surgery (months) | 63.6 ± 8.7 | 57.2 ± 12.9 | 0.111* |
| Anti-AchR level (nmol/L) | 6.52 ± 1.14 | 6.21 ± 1.75 | 0.869* |
| FEV1 (%) | 82.3 ± 20.1 | 84.6 ± 32.5 | 0.262* |
| FVC (%) | 86.3 ± 30.2 | 86.2 ± 25.9 | 0.995* |
| Preoperative usage of prednisone usage | With 28 (31.8%) | 163 (34.4%) | 0.236* |
| | Without 39 (58.2%) | 311 (65.6%) | |
| Preoperative usage of other immunosuppressants | With 9 (13.4%) | 77 (16.2%) | 0.556* |
| | Without 58 (86.6%) | 397 (83.8%) | |
| Preoperative daily dose of pyridostigmine (mg) | 196.6 ± 90.1 | 172.8 ± 82.9 | 0.001* |
| Pleural resection | With 41 (61.2%) | 284 (59.9%) | 0.842* |
| | Without 26 (38.8%) | 190 (40.1%) | |
| Thymus pathology | Thymoma 26 (38.8%) | 108 (22.8%) | 0.006* |
| | Thymic hyperplasia 41 (61.2%) | 366 (77.2%) | |
| Ectopic thymus | With 29 (43.3%) | 142 (30.0%) | 0.028* |
| | Without 38 (56.7%) | 332 (70.0%) | |
| Postoperative other complications | None 29 (43.3%) | 329 (69.4%) | 0.001* |
| | Pneumonia 19 (28.4%) | 37 (7.8%) | |
| | Pleural effusions 8 (11.9%) | 36 (7.6%) | |
| | Mediastinitis 7 (10.4%) | 41 (8.6%) | |
| | Others 4 (6.0%) | 31 (6.5%) | |

* Mann–Whitney U test; AchR = acetylcholine receptor.

† Student's t-test; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; POA = preoperative anxiety; POMC = postoperative myasthenia gravis crisis.
TABLE 3. Univariate Logistic Regression Analysis of Risk Factors Associated With POMC

| Variable                                | With POMC n (%) | Without POMC n (%) | OR       | 95% CI       | P-value |
|-----------------------------------------|-----------------|--------------------|----------|--------------|---------|
| Age (years)                             |                 |                    |          |              |         |
| < 50                                    | 65 (97.0%)      | 465 (98.1%)        | 0.63     | 0.13–3.00    | 0.562   |
| ≥ 50                                    | 2 (3.0%)        | 9 (1.9%)           |          |              |         |
| Sex                                     |                 |                    |          |              |         |
| Male                                    | 30 (44.8%)      | 226 (47.7%)        | 0.74     | 0.44–1.25    | 0.741   |
| Female                                  | 37 (55.2%)      | 248 (52.3%)        |          |              |         |
| Higher MGFA classification              |                 |                    |          |              |         |
| Stage I+II+III                          | 39 (58.2%)      | 366 (77.2%)        | 2.43     | 1.43–4.14    | 0.001   |
| Stage IV+V                              | 28 (41.8%)      | 108 (22.8%)        |          |              |         |
| POG                                     |                 |                    |          |              |         |
| With                                    | 31 (46.3%)      | 149 (31.4%)        | 2.18     | 1.30–3.66    | 0.003   |
| Without                                 | 36 (53.7%)      | 325 (68.6%)        |          |              |         |
| Preoperative myasthenia crisis          |                 |                    |          |              |         |
| With                                    | 17 (25.4%)      | 71 (15.0%)         | 1.93     | 1.05–3.53    | 0.033   |
| Without                                 | 50 (74.6%)      | 403 (85.0%)        |          |              |         |
| Onset of MG to surgery (months)         |                 |                    |          |              |         |
| < 12                                    | 5 (7.5%)        | 54 (11.4%)         | 1.43     | 0.86–2.37    | 0.172   |
| 12–24                                   | 4 (6.0%)        | 56 (11.8%)         |          |              |         |
| > 24                                    | 58 (86.6%)      | 364 (76.8%)        |          |              |         |
| Anti-AchR level (nmol/L)                |                 |                    |          |              |         |
| > 0.2                                   | 54 (80.6%)      | 386 (81.4%)        | 0.95     | 0.50–1.81    | 0.871   |
| ≤ 0.2                                   | 13 (19.4%)      | 88 (18.6%)         |          |              |         |
| FEV1 (%)                                |                 |                    |          |              |         |
| < 80%                                   | 33 (49.3%)      | 235 (49.6%)        | 0.95     | 0.50–1.81    | 0.882   |
| ≥ 80%                                   | 34 (50.7%)      | 239 (50.4%)        |          |              |         |
| FVC (%)                                 |                 |                    |          |              |         |
| < 80                                    | 25 (37.3%)      | 196 (41.4%)        | 0.84     | 0.50–1.43    | 0.533   |
| ≥ 80                                    | 42 (62.7%)      | 278 (58.6%)        |          |              |         |
| Prednisone usage                        |                 |                    |          |              |         |
| With                                    | 28 (31.8%)      | 163 (34.4%)        | 1.79     | 0.98–3.25    | 0.056   |
| Without                                 | 39 (58.2%)      | 311 (65.6%)        |          |              |         |
| Usage of other immunosuppressants       |                 |                    |          |              |         |
| With                                    | 9 (13.4%)       | 77 (16.2%)         | 0.75     | 0.31–1.77    | 0.512   |
| Without                                 | 58 (86.6%)      | 397 (83.8%)        |          |              |         |
| Daily dose of pyridostigmine (mg)       |                 |                    |          |              |         |
| > 180                                   | 34 (50.7%)      | 69 (14.6%)         | 6.05     | 3.52–10.41   | <0.001  |
| ≤180                                    | 33 (49.3%)      | 405 (85.4%)        |          |              |         |
| Pleural resection                       |                 |                    |          |              |         |
| With                                    | 41 (61.2%)      | 284 (59.9%)        | 1.06     | 0.59–1.90    | 0.855   |
| Without                                 | 26 (38.8%)      | 190 (40.1%)        |          |              |         |
| Thymus pathology                        |                 |                    |          |              |         |
| Thymoma                                 | 26 (38.8%)      | 108 (22.8%)        | 2.10     | 1.23–3.59    | 0.007   |
| Thymic hyperplasia                      | 41 (61.2%)      | 366 (77.2%)        |          |              |         |
| Ectopic thymus                          |                 |                    |          |              |         |
| With                                    | 29 (43.3%)      | 142 (30.0%)        | 1.78     | 1.06–3.01    | 0.031   |
| Without                                 | 38 (56.7%)      | 332 (70.0%)        |          |              |         |
| Postoperative complications             |                 |                    |          |              |         |
| None                                    | 29 (43.3%)      | 329 (69.4%)        | 0.336    | 0.20–0.57    | 0.001   |
| Pneumonia                               | 19 (28.4%)      | 37 (7.8%)          |          |              |         |
| Pleural effusions                       | 8 (11.9%)       | 36 (7.6%)          |          |              |         |
| Mediastinitis                           | 7 (10.4%)       | 41 (8.6%)          |          |              |         |
| Other                                   | 4 (6.0%)        | 31 (6.5%)          |          |              |         |

AchR = acetylcholine receptor; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; POA = preoperative anxiety; POMC = postoperative myasthenia gravis crisis.
The results of this study confirm previous studies that a preoperative myasthenic crisis, high dose of PYR (>180 mg), and postoperative pneumonia were independently associated with POMC. Our study is the first to document a relationship between POA and POMC, and confirms POA as an independent risk factor for POMC. Regarding that clinicians may ignore anxiety disorders in MG patients because they believe that anxiety is a common disorder and has no negative effects on surgery or treatment of MG, surgeons in particular should heed these findings and pay more attention to the psychological status of MG patients, especially POA before surgery. POA can be successfully managed by antianxiety agents and psychotherapy and this may reduce the incidence of POMC.

In conclusion, the results of this study confirm previous studies that a preoperative myasthenic crisis, high dose of PYR, and postoperative infection (pneumonia) are the independent risk factors for POMC. Our novel finding is that POA is also an independent risk factor for POMC. These results should alert physicians and thoracic surgeons that they should consider the psychological status of their MG patients. The relationship between POA and POMC in patients with MG suggests that psychotherapy that decreases POA in these patients may also lower the incidence of POMC. A randomized controlled trial will be needed to test this hypothesis.

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