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Different neurologic outcomes of myasthenia gravis with thymic hyperplasia and thymoma after extended thymectomy: A single center experience☆

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ABSTRACT

This study aimed to reveal the clinical course and outcomes of myasthenia gravis (MG) in patients with thymic lymphoid hyperplasia and thymoma undergoing extended thymectomy and to identify the clinical prognostic factors of remission for MG. In total, 73 patients undergoing extended thymectomy were divided into two groups: group A with lymphoid hyperplasia (n = 39) and group B with thymoma (n = 34). According to the MG Foundation of America (MGFA) post-intervention status, the primary endpoint was a composite measure defined as achievement of complete stable remission (CSR), pharmacologic remission (PR), minimal manifestations (MM) or improvement (IM). The secondary endpoint was CSR. The cumulative probabilities of reaching the primary endpoint were 71.8% in group A and 85.3% in group B ($p = 0.164$), respectively. Using Kaplan-Meier survival analysis, the probability of reaching the primary endpoint in group B was remarkably greater than group A ($p = 0.036$). Cox multivariate analysis indicated that pre-operative MGFA class I (HR: 3.019, 95% CI: 1.084–8.410) and MGFA II (2.665, 95% CI: 1.033–6.873) compared to MGFA III and presence of thymoma (HR: 2.229, 95% CI: 1.079–4.606), showed the most consistent association with remission of MG after thymectomy. Finally, thymic lymphoid hyperplasia and severe symptoms may negatively affect prognosis of MG following thymectomy.

1. Introduction

MG (myasthenia gravis) is characterized by undulant skeletal muscle weakness and fatigability, which is a T cell dependent and antibody mediated autoimmune disorder of the neuromuscular junction. Thymic abnormality plays a key role in the pathogenesis of MG [1]. 50–60% of MG patients have concomitant thymic hyperplasia and 10–20% have thymoma [2]. MG represents a spectrum of variants according to thymic histology [3]. The presence of thymoma has been frequently considered an adverse prognostic marker for MG outcome following thymectomy [4–8]. In contrast, thymic lymphoid hyperplasia, including follicular and diffuse hyperplasia, is generally regarded as a more favorable prognostic indicator over thymoma [9]. A possible explanation is that the site of anti-AChR antibody production is located in hyperplastic thymus, but the source of this antibody in patients with thymoma may be peripherally located [9]. However, several recent investigations have shown that clinical outcomes of the thymomatous MG were not worse than those with non-thymomatous MG after thymectomy [10,11].

In the context of previous studies, an obvious limitation is that the group of non-thymomatous MG patients generally presented with thymic hyperplasia, as well as atrophic, involuted cysts or normal thymus. Composite histological features may augment the confounding differences amongst MG patients. To reduce the confounders, we included MG patients with only thymic lymphoid hyperplasia or thymoma to determine the relationship between thymic abnormality and

Abbreviations: MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; CSR, complete stable remission; PR, pharmacologic remission; MM, minimal manifestations; IM, improvement; VATS, video-assisted thoracoscopic surgery; OMG, ocular form MG; GMG, generalized form MG; EOMG, early onset MG; WHO, World Health Organization; SD, standard deviation; HR, hazard ratio; CI, confidence interval

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MG. To our knowledge, long-term neurologic outcomes of MG after thymectomy have been rarely compared between MG patients with thymic hyperplasia and those with thymoma. The aim of the current study was to study the pathological and clinical characteristics of MG with thymic hyperplasia or thymoma undergoing extended thymectomy and to reveal independent prognostic factors of MG.

2. Materials and methods

2.1. Patients

Between January 2013 and March 2016, seventy-three MG patients who underwent video-assisted thoracoscopic surgical (VATS) extensive thymectomy at West China Hospital were enrolled in our retrospective cohort. MG sufferers with atrophic or an involuted thymus, thymic cyst, normal thymus or thymic carcinoma were excluded. In addition, four patients were excluded due to coexistence of thymoma and lymphoid hyperplasia and 8 patients were lost at follow-up. None of the patients developed MG for the first time after thymectomy in our study. According to the histopathologic features, all subjects were classified into two groups: group A with lymphoid hyperplasia (n = 39) and group B with thymoma (n = 34). We retrospectively analyzed the clinical data from the database at the Department of Thoracic Surgery at West China Hospital. Diagnosis of MG was provided by the neurologists based on clinical manifestations of skeletal muscles and at least one of the following tests, including the neostigmine reaction test, the repetitive nerve stimulation test and a laboratory assay for anti-muscle antibody [12]. The local ethics committee approved the study and all of the participants were recruited following informed consent to join the present study and publish their clinical data for academic purposes.

2.2. Peri-operative managements

Preoperative severity of symptoms of MG was evaluated according to the Myasthenia Gravis Foundation of America (MGFA) classification [13]. MGFA class I is defined as weakness and fatigability only of eyelids, class II as mild generalized neurologic symptoms, class III as moderate generalized neurologic symptoms, class IV as severe generalized neurologic symptoms, and class V as a MG crisis requiring intubation and respirator support. Class I is a subgroup which is mainly ocular form MG (OMG). Classes II to V are another subgroup which are a generalized form of MG (GMG) which indicates that manifestation involves at least one of limbs, trunk, oropharynx or respiratory muscles. Chest computed tomographic or magnetic resonance imaging scanning was received before performing extended thymectomy.

Preoperative laboratory blood examinations, electrocardiogram examination and respiratory function tests were all routinely performed. In addition, thyroid function was examined and corrected if necessary. Thymectomy was recommended for GMG patients and for OMG patients with a possible thymoma on chest imaging or ocular symptoms refractory to medical management. A consistent treatment protocol of pre-operative preparation was conducted by neurologists and thoracic surgeons. Specifically, routine intravenous immunoglobulin administration for at least 5 days prior to operation was recommended in patients with GMG to reduce the risk of myasthenic crisis (400 mg/kg/day). Oral pyridostigmine was administered to control symptoms in all patients prior to and after thymectomy at the lowest active dosage (generally 120–180 mg/day). If the treatment failed to show satisfactory efficacy, an oral steroid was taken (generally 40 mg/day). Other immuno-suppressants did not need to be discontinued.

We tried to ensure that MGFA class was not more than III at least one month before thymectomy. For GMG patients, intravenous human immunoglobulin was occasionally administrated to alleviate preoperative symptoms. If necessary, plasmapheresis was conducted (three times one week, if the efficacy was minor, subsequently once a week for 5–7 weeks). In addition, promptly and appropriately post-operative management was necessary.

To treat the MG sufferers planning to receive thymectomy, a multidisciplinary clinical team consisting of experienced neurologists and thoracic surgeons at our hospital was formed. The neurologists were responsible for the diagnosis, pharmaceutical management and assessment of MG patients and the thoracic surgeons were in charge of the operation and peri-operative care. All neurological follow-up investigations that aimed to classify MG severity were done by one of the authors (the first co-author, Yu Zheng).

All extended thymectomies were performed with VATS with 80% of patients using a right-side approach as described previously [14]. Extended thymectomy was defined as en bloc resection of the thymus and all adipose tissue anterior to both phrenic nerves. All patients were regularly sent to the intensive care unit soon after the operation to prevent asphyxia and respiratory failure, and then extubated before backing to the ward.

2.3. Classification standards

Histologic examination was carried out by professional pathologists in our institution and confirmed by a pathologist skilled in thymic histology. Thymic lymphoid hyperplasia includes follicular (characteristic of ectopic germinal center) and diffuse hyperplasia (medullary lymphoid cell infiltration only). The World Health Organization (WHO) histologic classification system of thymoma was used [15], which includes total five subtypes: A, AB, B1, B2, B3, from subtype A to B3 there is a progressive deterioration of the prognosis. The thymus glands from the patients undergoing heart operations served as the control specimens. The Masaoka's staging system was employed when examining thymic specimens [16], which includes total six substages: I, IIa, IIb, III, IVa, IVb. From stages I to IV there is also progressive invasion and poor prognosis. Two patients with Masaoka's stage IV and one with stage III received post-operative adjuvant radiation therapy.

2.4. End-points

Each patient was regularly followed once every three months during the following-up period. Five patients with thymoma and 3 patients with hyperplasia were lost to follow-up and they were therefore excluded for the study. According to the MGFA post-intervention status [13], the primary neurologic endpoint was a composite measure defined as achievement of complete stable remission (CSR), pharmacologic remission (PR) or minimal manifestations (MM) or improvement (IM). Secondary endpoints were CSR which indicates no fatigable muscle weakness of MG for at least one year and being free of medication for MG. PR shows that patients with the same clinical criteria as for CSR take some form of drug for MG excluding cholinesterase inhibitors. MM indicates The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination. IM indicates A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol [13].

2.5. Statistical methods

Descriptive statistics were used to describe the patients' baseline. Univariate analysis was conducted using non-parametric test, the Chi-square (χ^2) test and the Student *t*-test. If necessary, fisher's exact test was conducted for the categorical variables. Survival analysis was conducted by using Kaplan-Meier approach. Multivariate analysis and dummy variable analysis were carried out using Cox's proportional hazards regression model. The p values of < 0.05 were defined as significant.