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Update on ocular myasthenia gravis in Taiwan

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Abstract:

Myasthenia gravis (MG) is an autoimmune disease involving the neuromuscular junction. Autoantibodies to the acetylcholine receptor or, less frequently, to muscle-specific kinase, attack against the postsynaptic junctional proteins, resulting in fluctuating and variable weakness of muscles. Extraocular, levator palpebrae superioris, and orbicularis oculi muscles are particularly susceptible. The majority of patients with MG present with purely ocular symptoms including ptosis and diplopia initially. About half of these patients progress to generalized disease within 2 years. The prevalence of MG in Taiwan is 140 per million with male to female ratio of 0.7. The incidence rate is higher in the elderly. Several immune-related diseases such as lymphoid malignancy, diabetes, and thyroid diseases are associated with MG in the national population-based studies in Taiwan. Ice pack test, rest test, Tensilon/neostigmine test, circulating antibody measurement, and electrophysiological studies are useful diagnostic tools with variable sensitivity and specificity. For the patients with ocular MG, acetylcholinesterase inhibitors are usually the first-line treatment. Corticosteroids and immunosuppressant could provide better disease control and may reduce the risk of conversion to generalized form although there is still some controversy. A thymectomy is also beneficial for ocular MG, especially in refractory cases. The correction of ptosis and strabismus surgery could improve the visual outcome but should be performed only in stable disease.

Keywords:

Acetylcholine receptor antibody, epidemiology, muscle-specific kinase antibody, ocular myasthenia gravis, thymectomy

Introduction

Myasthenia gravis (MG) is the most common neuromuscular junction disorder. It is an autoimmune disease mediated by antibody attack against the postsynaptic junctional proteins involving in the capture of acetylcholine.[1] The patients may present with fluctuating and variable weakness of ocular, bulbar, respiratory, and limb muscles. Ptosis and diplopia caused by weakness of the extraocular muscles are the most common ocular manifestations of MG. However, this presentation of eye movement can masquerade as any cranial nerve or gaze palsy. The incidence of late-onset MG increased recently,[2-4] and the relationship between MG and other systemic diseases has been widely investigated in the study. This article aims to update the epidemiology, background characteristics, diagnostic tests, and management of MG in Taiwan.

Classification of Myasthenia Gravis

MG could be classified into three types: ocular, bulbar, and generalized. In ocular MG, the disease affects the extraocular, levator palpebrae superioris, and orbicularis oculi muscles with pupillary sparing. Ocular muscles are more susceptible owing to the reduced complement regulation and safety factor and the simplified postsynaptic structure.[5] About half of the patients with ocular MG become generalized within 2 years.[6,7] It is more common in patients with positive acetylcholine receptor antibody (AChRAb) results.[8] However,

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there is no reliable prognostic model to predict the risk of conversion till now. If the disease remains localized for more than 2 years, the likelihood of conversion to generalized MG is rare. In bulbar MG, the disease affects the muscles of mastication and causes dysphagia. For generalized MG, it generally starts by ocular symptoms and then affects the proximal limb muscles (80% occurs within 2 years and 90% occurs within 3 years). Neck weakness or bulbar weakness is a flag implies the risk of respiratory crisis.[8]

For adult patients, it usually presents with ocular symptoms initially, and then about 50% of cases develop generalized form.[6,7] However, for children, 85% of patients have ocular myasthenia and <10% of cases develop generalized form.[9,10] We have to avoid amblyopia due to ptosis and strabismus.

Epidemiology and Background Characteristics in Taiwan

From 2000 to 2007, the incidence rate of MG ranged from 2.0 to 2.2/100,000/year in Taiwan. The prevalence increased gradually from 8.4/100,000 in 2000 to 14/100,000 in 2007. The male to female ratio ranged from 0.6 to 0.7.[9] A systemic review showed that the estimated incidence rate of MG was 3/100,000/year in Europe.[11] The incidences and prevalence of MG in recent epidemiological studies from different countries are summarized in Table 1.[9,12-16]

In regard to the age-specific incidence, there is an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decades (male predominance) in Caucasian populations.[17] In contrast, the incidence rate is higher in 65–79 age group (>4.4/100,000/year) and lower in 0–19 age group (<1/100,000/year) in Taiwan.[9] There is significantly higher incidence in females than males in age groups of 0–4 and 15–54 years.

Regarding the associated diseases of MG in Taiwan, 12% of patients have thymoma.[9] There is 2.27-fold risk of lymphoid malignancies and 118.47-fold risk of thymus cancer in MG patients.[18] In a population-based cohort study in Taiwan, there is 1.26-fold risk of diabetes mellitus (hazard ratio [HR] =1.26, 95% confidence interval [CI] = 1.04–1.53).[19] The risk is higher in patients with corticosteroids use (HR = 1.46, 95% CI = 1.15–1.86). MG is also associated with a higher risk of osteoporosis regardless of corticosteroid use (HR = 1.96, 1.52 in corticosteroid-naïve patients, 2.37 in corticosteroid-treated patients, 95% CI = 1.57–2.44, 1.11–2.08 in corticosteroid-naïve patients, 1.82–3.07 in corticosteroid-treated patients).[20] MG is also associated with allergic conjunctivitis, allergic rhinitis, Hashimoto's thyroiditis, and Graves' disease.[21] The relationships between the associated diseases and MG in Taiwan are summarized in Table 2.

Clinical Manifestations of Ocular Myasthenia Gravis

Double vision and ptosis are the most common symptoms of ocular MG.[1] It is generally bilateral but could be sequential and asymmetric. Diagnosing MG could be a challenge to the ophthalmologist. Ophthalmoparesis may occur and mimic almost any pattern of ocular misalignment. Exotropia with vertical heterotropia is the most common type.[22] The symptoms may progress in the evening and improve with rest. Comprehensive history taking could provide an important clue and raise the suspicion of MG. Enhancement of ptosis may develop on sustained upward gaze. Cogan's lid twitch is another sign of ocular MG. It means a small downward movement of an eyelid while the patient changing gazes from the downward position to the primary position. While the more ptotic eyelid is lifted by the examiner, the contralateral eyelid may become more ptotic.

Pain, blurred vision, and tearing may also occur in patients with ocular MG. It is caused by incomplete blinking due to weakness of the orbicularis muscles. Dry eye syndrome is noted in 21% of ocular MG and 28% of generalized MG.[23] Exposure keratopathy could be noted as the result of poor eyelid closure.

Diagnostic Tests of Myasthenia Gravis

The diagnosis of MG is based on the clinical diagnostic tests, electrophysiological studies, and antibody

Table 1: Recent epidemiological study of myasthenia gravis in different countries

First author	Year	Region	Incidence per million/year	Prevalence per million
Lai[9]	2000-2007	Taiwan	20-22	140
Cetin[12]	2009	Austria		156.9
Park[13]	2010-2011	Korea	24.4 (2011)	96.7 (2010) 106.6 (2011)
Boldingh[14]	2010	Norway		138
Boldingh[14]	2012	Netherlands		167
Breiner[15]	1996-2013	Ontario, Canada	23-34	320
Santos[16]	2013	Northern Portugal		111.7

Table 2: Associated diseases of myasthenia gravis in Taiwan

Disease entity	HR	95% CI
Any cancer[18]	1.74	1.47-2.05
Lymphoid malignancies[18]	2.27	1.06-4.88
Thymus cancer[18]	118.47	42.57-329.71
Diabetes mellitus[19]	1.26	1.04-1.53
Osteoporosis[20]	1.96	1.57-2.44
Disease entity	**Adjusted OR**	**95% CI**
Allergic conjunctivitis[21]	1.93	1.71-2.18
Allergic rhinitis[21]	1.26	1.09-1.45
Hashimoto's thyroiditis[21]	2.87	1.18-6.97
Graves' disease[21]	3.97	2.71-5.83

CI = Confidence interval, HR = Hazard ratio, OR = Odds ratio

measures. Clinical diagnostic tests are useful in the diagnosis of ocular MG. In outpatient clinic, we can use edrophonium test (Tensilon test, intravenous injection of Tensilon), neostigmine test (intramuscular injection), ice pack test, and rest test to help us to make the diagnosis. The sensitivity of neostigmine test is 98% in generalized MG and 79% in ocular MG.[23] However, we need to monitor the vital signs of the patients and take notice of the side effect of bradyarrhythmia. The activity of acetylcholinesterase decreased in low temperature. Therefore, the application of ice for 2 min can improve ptosis in 80% of MG patients.[24] Rest test could also be a safe alternative. Muscle function may improve after 10–30 min of rest.[25] These noninvasive procedures are the first choices in outpatient clinic and could avoid the possible complications of edrophonium test and neostigmine test.

The electrophysiological studies include repetitive nerve stimulation and single-fiber electromyogram (EMG). Decrement on nerve stimulation in the orbicularis oculi could be noted during repetitive stimulation of the facial nerve. The sensitivity of repetitive nerve stimulation test is around 78% but the specificity is low.[26] With single-fiber EMG, we can observe increased jitter in patients with MG. In generalized MG, we choose extensor digitorum communis as the first target. However, in ocular MG, the orbicularis oculi or frontalis may be examined first. Single-fiber EMG has much higher sensitivity (96.4%) and specificity than repetitive nerve stimulation test.[27]

In regard to antibody measurement, autoantibody to AChR has high sensitivity (80%–90%) in patients with generalized MG but only 60% in ocular MG.[28] The use of cell-based assay with clustered AChRs significantly increase the sensitivity of AChRAb detection.[29] The autoantibody test is the most specific test for MG; no false-positive results have been reported. However, the levels of autoantibody correlate poorly with the clinical condition.[30] The presence of AChRAb increases the probability of developing generalized form.[31] Antibody against muscle-specific kinase (MuSKAb) is detected in 40% of AChRAb-negative MG Caucasians[32] but only in 4%–12% of Taiwanese.[33,34] MuSKAb is more often in female patients. Patients with positive MuSKAb tended to have more severe impairment and frequent bulbar muscles involvement, more often experienced crisis and respiratory difficulty.[35] MuSKAbs have been reported in patients with ocular MG.[35-37] On the other hand, antibodies to receptor-related low-density lipoprotein-4 (anti-LRP-4) is detected in 10%–40% of double-seronegative patients.[38] Anti-LRP4 antibodies were detected in three reported cases of ocular MG.[39]

For a patient with the suspicion of ocular MG, we could perform noninvasive clinical diagnostic tests first. Then, we usually need antibody measurement to confirm the diagnosis. Since the sensitivity of autoantibody test is lower in ocular MG, for the seronegative patients, electrophysiological studies could help us to make the final diagnosis. Single or multiple cranial neuropathy, thyroid eye disease, chronic progressive external ophthalmoplegia, and myotonic dystrophy are some differential diagnosis of ocular MG and should be ruled out when the diagnosis is uncertain.

Case Series of Myasthenia Gravis in Taiwan

From 1970 to 1983, Woung *et al*. collected 197 patients with MG (78 males, 119 females) with average follow-up periods of 4.5 years in National Taiwan University Hospital.[22] The average onset was the age of 17 in ocular MG and age of 27 in generalized MG. About 31.5% of patients were diagnosed as having MG before the age of 10. Among all the patients with MG, 54.2% had only ocular involvement. Ptosis was the most common symptoms. The involvement of extraocular muscle was the most common in lateral rectus. Regarding the diagnostic methods, 57.4% of patients were diagnosed by neostigmine test. Nearly 12.7% of them were diagnosed by Tensilon test, and 29.9% of them were diagnosed by EMG and repetitive stimulation test. Around 72.9% of patients with generalized MG transit from ocular to generalized form within 1 year of disease onset.

There was another study in Southern Taiwan conducted by Hsu *et al*.[40] They collected 65 patients with average follow-up time of 30.4 months. Among all the patients, 53.8% had only ocular involvement. Ptosis and diplopia were also the most common symptoms. Lateral rectus and levator muscle were the most common involving extraocular muscles. Neostigmine test was positive in 93.8% of patients. AChRAb was positive in 96.2% of generalized MG and 66.7% of ocular MG.

According to the results of these two studies, the percentage of ocular MG was higher in Taiwan. However,

the clinical presentation, clinical course, and sensitivity of diagnostic tests were similar to the observation in the previous studies.

Treatment Options

The treatment options of MG includes medical treatment, thymectomy, intravenous immunoglobulin (IVIG), and plasmapheresis. Regarding medical treatment, we usually start with acetylcholinesterase inhibitors, such as pyridostigmine and neostigmine.[41] Pyridostigmine has rapid onset of action but the effects only last for 4 h. It has a better effect on ptosis than on diplopia. The common starting dose of pyridostigmine is 30 mg three times a day. The maximal dose is usually 120 mg every 4 h while awake. We should titrate the dose by its effects and adverse effects. The adverse effects of acetylcholinesterase inhibitors include increased secretions, abdominal cramps, diarrhea, sweating, nausea, and bradycardia. In one case series, pyridostigmine treatment could induce resolution of diplopia in only 6.9% of patients.[42] Besides, it does not influence the development of generalization. If acetylcholinesterase inhibitors could not provide enough disease control or the adverse effects preclude effective dosing, we may shift to corticosteroids. Steroid can reduce the rate of generalization in several retrospective studies[43,44] and appear to be well tolerated, safe, and effective in treating ocular MG.[45] However, there are still some debates about the risk-modifying effect of steroid. Further randomized clinical trial is indicated to clarify the effect of steroid on disease conversion. The onset of effect often begins within 2–3 weeks. The dose of prednisone can be started at 20 mg daily and then increased by 5 mg every 3–5 days to the target dose of 1.0 mg/kg/day.[46] Once an effective response is obtained, tapering of the dose should be slow. The daily dose could be reduced by 5–10 mg each month. It could be necessary to go back to a higher dose if the symptoms recur during the taper.

Ocular complications of long-term steroid use include glaucoma, posterior polar cataract, and central serous chorioretinopathy. Other complications of steroid include aseptic bone necrosis, hyperglycemia, osteoporosis, immune compromise, hypertension, growth retardation in children, and proximal myopathy.[47] If the disease is still under poor control or steroid is not tolerance to the patients, we can add azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, or another immunosuppressant. Immunosuppressant can reduce the risk of progression to generalized MG.[48-50] Azathioprine could improve MG symptoms significantly in most patients, but the onset of beneficial effect is delayed for about 6 months to 1 year.[51,52] Mycophenolate mofetil is well tolerated with few side effects. The efficacy of mycophenolate was supported by several large retrospective studies,[53,54] but the benefit was not proved by some short-term prospective clinical trials.[55,56] Cyclosporine has faster onset of action (1–2 months) and its efficacy was proved by several clinical trials.[57-59] However, the renal toxicity of cyclosporine and frequent interaction with other medications limit its applications. Tacrolimus has similar effect to cyclosporine and results in a significant reduction in the steroid dose.[60-62] It has less nephrotoxicity in comparison with cyclosporine. Methotrexate, rituximab, cyclophosphamide, and etanercept may also provide beneficial effects.[63-66]

Thymic hyperplasia is found in 69% of seronegative MG and 88% of seropositive MG.[67] Thymectomy is recommended for patients with thymoma. In a recent randomized control trial of patients with generalized nonthymomatous MG, the patients in the thymectomy group had lower prednisone dose and fewer requirement for immunosuppressant use.[68] Thymectomy can decrease the need for continuing medical treatment. There is also a lower rate of progression to generalized MG and more opportunity to undergo complete remission.[69-73] In the past, thymectomy was not recommended for ocular MG as the first-line treatment. It should be considered if medical treatment has failed.[74] However, the minimally invasive procedures such as robotic surgery make thymectomy a more acceptable therapeutic option for patients with ocular MG.[75]

IVIG is indicated in acute exacerbations including myasthenic crisis or the perioperative period of thymectomy. It accelerates the catabolism of immunoglobulin G, suppresses the antibody production, and neutralizes autoantibodies.[76,77] About 70% of patients have improvement of symptoms with IVIG.

Double-filtration plasmapheresis is another treatment option to reverse an exacerbation of myasthenia. It modulates cellular immunity, decreases natural killer cell cytotoxicity.[78,79] Besides, it is effective for AChRAb or MuSKAb removal and amelioration of muscle weakness.[80,81] Both IVIG and plasmapheresis are reserved for refractory MG and seldom used in ocular MG.

Surgical correction can be performed for stable ptosis. However, the degree of ptosis should be stable for 3–4 years before repair.[82,83] Otherwise, the recurrence of ptosis could develop as the nature of myasthenia. Since the levator muscle function is usually fluctuating, the choice of levator muscle resection may cause under correction and require repeat surgery. Frontalis slings are the alternative method, but the surgeon needs to pay attention to the exposure-related complications. For patients presenting with diplopia, we can use prism glass or occlusion therapy.[84] Strabismus surgery is indicated

when the deviation is too large and no substantial change in the degree of deviation for at least 12 months.[85] The patients should be informed regarding the possibility of repeat surgeries, especially in those with older age, positive AChRAb, more severe disease, or coexistent muscle restriction.[86]

Conclusions

Ocular MG is a localized form of MG involving the extraocular, levator palpebrae superioris, and orbicularis oculi muscles. The prevalence of MG in Taiwan is comparable to Caucasian populations. The incidence rate is higher in the elderly and the percentage of ocular MG was higher in Taiwan. The clinical manifestations include diplopia and ptosis. Ice pack test, rest test, Tensilon/neostigmine test, circulating antibody measurement, and electrophysiological studies could help the ophthalmologist to make the diagnosis. For the patients with ocular MG, acetylcholinesterase inhibitors are usually considered as the first-line treatment. Corticosteroids and immunosuppressant should be used in patients with poor disease control. The ophthalmologists must decide the sequence of treatment based on the level of disease activity and patient tolerability. Surgical correction of ptosis and strabismus could be performed while the condition is stable for a long time.

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Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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