중증 근무력증의 분류 및 치료 지침

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Subgroup Classification and Therapeutic Guidance for Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disease of neuromuscular blockade, characterized by muscle weakness and fatigue, and is associated with the production of autoantibodies against the skeletal muscle acetylcholine receptor, muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4), and other muscle endplate proteins. In addition, MG may be classified according the location of the affected muscles (ocular vs. generalized), patient age at symptom onset, and thymic pathology. Subgroup classification based on serum antibodies and clinical features include early-onset, late-onset, thymoma-associated, MuSK and LRP4 antibody-negative, and ocular forms of MG, and can help with therapeutic decisions and prognosis. Pyridostigmine is the chosen symptomatic treatment. For patients who do not adequately respond to symptomatic therapy, corticosteroids, other immunomodulating agents, and thymectomy are the first-line immunosuppressive treatments. The treatment of MG is highly individualized and depends on the age of the patient, the type and severity of the disease, and the pace of progression.

Key Words: Myasthenia gravis, Child, Adult, Therapy, Thymectomy

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by weakness and fatigability of skeletal muscles. Most patients who develop MG in adolescence or adulthood have autoantibodies that play a pathogenetically important role by attacking the acetylcholine receptor (AChR), fixing complements, and reducing the number of AChRs over time^{1,2)}. These autoantibodies are believed to originate from hyperplastic germinal centers in the thymus, where myoid cells expressing AChR are gathered.

There are two clinical forms of MG: ocular and generalized. In the generalized type, weakness involves the ocular muscles and variable combinations of the bulbar, limb, and respiratory muscles. The definition of ocular MG is restricted to the ocular symptoms for 2 years without becoming generalized³⁾. Juvenile MG (JMG) patients are subdivided according to the onset of the first symptoms as prepubertal (before the age of 12 years) and postpubertal (after the age of 12 years). Patients who have detectable antibodies to AChR or to the muscle-

specific receptor tyrosine kinase (MuSK) are considered to have seropositive MG, whereas those lacking both AChR antibody (AChR-Ab) and MuSK antibody (MuSK-Ab) on standard assays are considered to have seronegative MG^{1,2)}. About half of the patients with the purely ocular type are seropositive, compared with approximately 90% of those with generalized disease. In contrast to adult MG, young children with JMG presenting generalized symptoms may have no or only slight elevated titer of specific antibodies, the diagnosis is often delayed⁴⁾.

There is an ethnical difference in the presentation and prevalence of the disease. In Asian population, up to 50% of MG patients present with the first symptoms in childhood (age peak between 5 and 10 years, no difference in sex distribution). More than 70% of patients are limited to ocular symptoms and favorable course is common^{5,6)}. Among Caucasian prepubertal patients, presenting only with ocular symptoms, spontaneous remission is frequent and ranges from 15 to 34.7%⁷⁾. In postpubertal children, female predominance is present^{5,6)}. The JMG population among African American shows differences compared to the Asian and European population, and demonstrated poorer response to thymectomy than Caucasian children and lower remission rates⁸⁾. They reveal female predominance in all age groups⁸⁾.

Pathogenesis and subgroups

In most cases, MG is a condition mediated by autoantibodies against AChR^{1,2)}. However, the linkage between AChR antibodies and MG is not absolute. In addition, 10–20% of patients with MG have no measureable levels of autoantibodies against AChR. A proportion of these patients (40–70%) have antibodies directed against MuSK. Young children with JMG presenting generalized symptoms may have no or only slight elevated titer of specific antibodies⁴⁾. The tests of these antibodies, except for AChR-Abs, are available only in specialized laboratories, and have not been performed in our country.

1. AChR-Ab subtypes

AChR-Abs are highly specific for MG. They are directly pathogenic through cross-linking of AChRs, leading to the accelerated degradation of these receptors by complement binding and activation, and by inducing AChR conformational changes or blocking acetylcholine binding. No correlation has been shown between AChR-Ab level and disease severity. However, in individual patients, the titers tend to decrease with successful immunotherapy and parallel clinical improvement^{9,10)}. Individual patients have a mix of immunologically different antibodies to AChR. This is partly due to the heterogeneity of the receptor. In addition, antibodies to the same receptor in a patient with MG can vary in their light-chain and subclass types¹¹⁾. This means that B lymphocytes producing AChR antibodies are also heterogeneous.

Fig. 1. Schematic view of the MuSK-LRP4-ColQ complex¹¹⁾. At the postsynaptic membrane, MuSK is associated with LRP4. MuSK activation through agrin-LRP4 binding triggers a signaling pathway, which includes Dok7 recruitment, leading to AChR clustering. AChE binds through its ColQ tail to perlecan and MuSK. MuSK, muscle-specific tyrosine kinase; LRP4, lipoprotein receptor-related protein 4; AChR, acetylcholine receptor; AChE, acetylcholinesterase; ColQ, collagen Q.

Table 1. Subgroup Characteristics and Antibodies of Myasthenia Gravis

Abs	Subtypes	Ab isotype	Thymic pathology	HLA associations	Distinctive features
AChR	Early onset (<50 years)	IgG1, IgG3	Hyperplasia	DR3-B8-A1, DR9 (in Asians)	Female, favorable
AChR	Late onset (>50 years)	IgG1, IgG3	Normal, hyperplasia	Diverse, DR2-B7	Male, Ab to muscle Ag (severe course)
AChR	Thymoma	IgG1, IgG3	Neoplasia	None identified	Ab to muscle Ag, other paraneoplastic disorders
AChR	Ocular	IgG1, IgG3	–	–	50% - AChR Ab
MuSK		IgG4	Normal	DR14, DR16, DQ5	Female, severe course (crisis), facial & bulbar weakness
LRP4		IgG1	–	–	Similar to AChR myasthenia, favorable, May be seen with AChR & MuSK Abs
Others	Agrin, Cortactin	–	–	–	

Abs, antibodies; AChR, acetylcholine receptor; MuSK, muscle-specific tyrosine kinase; LRP4, lipoprotein receptor-related protein 4; HLA, human leukocyte antigen.

2. MuSK antibodies

MuSK autoantibodies have been found in 40–70% of Caucasian patients with AChR-seronegative MG¹²⁾. There are significant differences between MuSK-Ab-positive MG and AChR-Ab-positive MG in pathologic mechanism, clinical features, and response to pharmacologic treatments; onset at any age, female predominance, oculobulbar form, restricted myopathic form with prominent respiratory and/or proximal weakness, no thymic pathology (thymoma), and lower responsiveness to acetylcholinesterase inhibitors (Table 1)^{9,12)}. The MuSK protein is a transmembrane component of the postsynaptic neuromuscular junction. The nerve-derived proteoglycan agrin binds to lipoprotein-related protein 4 (LRP4), leading to the activation of MuSK13). Activated MuSK interacts with the cytoplasmic adaptor protein Dok7, leading to recruitment of rapsyn to promote clustering of AChRs (Fig. 1)^{13,14)}.

3. Seronegative myasthenia

A subset (6–12%) of patients with MG who have no detectable antibodies directed to AChR or MuSK are classified as having seronegative MG¹⁵⁾. Patients with seronegative MG are more likely to have purely ocular disease than those who are seropositive. Antibodies to other self-antigens have been detected in various reports on patients with seronegative MG (Table 1). (a) Antibodies to LRP4, the agrin-binding receptor of the MuSK complex (Fig. 1), inhibit AChR clustering in the membrane, and have been found in up to 50% of patients with seronegative MG^{16,17)}. (b) Agrin antibodies have been detected in a few patients with MG and AChR, MUSK, or LRP4 antibody¹⁸⁾. (c) Cortactin is a protein that mediates clustering of AChR at the neuromuscular junction¹⁹⁾. Titin and ryanodine receptor antibodies occur in some patients with AChR-associated MG. These antibodies are present with a high frequency in thymoma-associated MG, with an intermediate frequency in late-onset MG, and very rarely in early-onset and ocular MG²⁰⁾.

4. Thymus and the origin of autoimmunity in myasthenia

Most patients with AChR-Ab-positive MG have thymic abnormalities including hyperplasia in 60–70% and thymoma in 10–12%¹⁾. The thymus contains a small number of “myoid” cells. These cells are distinguished by striations and the presence of AChR on their surface. In addition, thymic epithelial cells produce unfolded AChR subunits that are hypothesized to prime helper T cells. These “autoimmunized” T cells then attack AChR on myoid cells and create infiltrating germinal centers in the hyperplastic thymus²⁾.

Clinical features

MG is a relatively uncommon disorder with an annual incidence of approximately 7–23 new cases per million population²¹⁾. There tends to be a bimodal distribution to the age of onset, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance). Early in the disorder, the symptoms may be transient in many patients and even spontaneously go into remission for weeks or longer. However, the manifestations typically worsen and become more persistent. The maximum range of the symptoms was seen by 3 years from onset in 77%²²⁾. In postpubertal children, the clinical course is similar to adult-onset MG. The patients often present with ocular symptoms at the onset; generalized weakness develops in up to 80% in the course of the disease^{4,5,7)}.

The cardinal feature of MG is fluctuating skeletal muscle weakness with diurnal alternation, often with true muscle fatigue²³⁾. More than 50% of patients present with ocular symptoms of ptosis and/or diplopia²⁴⁾. Ptosis usually aggravates after physical activity. Children may complain about double vision, particularly during prolonged reading or in the course of the day. About 50% of children with ocular symptoms develop systemic or bulbar muscle involvement within 2 years^{25,26)}. About 15% of patients present with bulbar symptoms, including dysarthria, dysphagia, and fatigable chewing. Imminent risk of aspiration may produce a “myasthenic crisis”²⁷⁾. Facial muscles are frequently involved and make the patient appear expressionless. Myasthenic crisis is a life-threatening situation in which respiratory muscle weakness leads to respiratory insufficiency and pending respiratory failure.

Diagnostic approach

To diagnose JMG, the combination of a thorough history, repeated physical examination, and neurophysiological investigations, as well as serology tests are helpful clues. Postpubertal children may present with very indicative symptoms and have in up to 90% positive AChR antibodies in generalized MG²⁸⁾. The diagnosis in younger children constitutes a particular challenge as nonspecific symptoms may be present or the antibodies are only minimal elevated or even normal, also in case of severe generalized myasthenia. MG remains a clinical diagnosis. The approximate diagnostic sensitivity of the confirmatory laboratory tests in adult MG is shown in Table 2.

1. Serologic testing

Detection of AChR-Ab or MuSK-Ab, which is possible in approximately 90% of adult patients with generalized disease, provides the laboratory confirmation of MG^{10,29}. In those with purely ocular myasthenia, the sensitivity of AChR-Ab testing is considerably lower (i.e., AChR-Ab is detectable in about half of the patients). In JMG patients with seronegative MG, most often young children with an ocular myasthenia, antibodies are not helpful because they may be negative in up to 50%^{8,25,26}. MuSK antibodies are also rare in children and appear to be associated with a more severe disease, affecting mostly facial and bulbar weakness as well as frequent respiratory crises^{5,28}. The detection of these antibodies is available only in specialized laboratories and could be initiated in seronegative JMG patients with distinct clinical symptoms and abnormal neurophysiological findings¹⁶. Here, larger number of patients and long-term follow-up are necessary to clarify the clinical and therapeutic implications of low-sensitivity AChR-Ab and LRP4-Ab in pediatric population.

2. Electrophysiologic studies

Electrophysiologic tests usually allow the confirmation of diagnosis in patients with seronegative MG. Repetitive nerve stimulation (RNS) is the most frequently used test. Single-fiber electromyography is more technically demanding in children than RNS, and could be only performed in sedated children or in postpubertal patients with good compliance. Both the RNS test and single-fiber electromyography have a diagnostic sensitivity in generalized MG of about 75–95%^{10,30}. However, the

sensitivity of RNS is much lower (15–45%) in patients with ocular myasthenia (Table 2).

3. Pharmacological testing

In edrophonium testing, edrophonium chloride (Tensilon), a short-acting cholinesterase inhibitor, is administered intravenously (IV)²⁹. An IV infusion should be started for rapid medication in the adverse events for the test. In children younger than 1 year, recommended dose is 0.15 mg/kg IV, preceded by a test dose of 0.01 mg/kg and then depending on effects increasing with 0.15 mg/kg steps to a maximum of 0.6 mg/kg. In children older than 1 year and weighing <34 kg, the dose is 0.5 mg IV initially, followed by subsequent 1 mg doses, repeated every minute to a maximum total dose of 5 mg. In adolescents with weighing >34 kg, the dose is 1–2 mg IV initially, then repeated every minute to a maximum total dose of 10 mg⁷. These doses may be given intramuscularly or subcutaneously. Effects should be seen within 10 s and disappear within 120 s. Adverse effects include nausea and emesis, headache, and bronchospasm. Atropine (0.01 mg/kg) should be prepared in a separate syringe before the administration of edrophonium, to block acute muscarinic effects of the cholinesterase inhibitor.

As a good alternative regimen, neostigmine methylsulfate (prostigmine) is administered intramuscularly at a dose of 0.04 mg/kg. If the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 h after the first dose (typical dose, 0.5–1.5 mg). The peak effect is seen in 20–40 min. IV prostigmine is contraindicated because of the risk of cardiac arrhythmias, especially in young infants.

Table 2. Approximate Sensitivity of the Confirmatory Tests for Myasthenia Gravis in Adult

Tests	Generalized MG (%)	Ocular MG (%)
AChR Antibodies ²⁹	80-90	40-55
MuSK antibodies ¹² (in AChR Ab negative patients)	40–55	<10
Repetitive nerve stimulation ^{10,30}	75	<50
Single fiber electromyography ^{10,30}	92-99	80-95

MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase.

Treatment

Therapeutic standards for treatment of JMG have been adopted from adult patients³¹. Treatment options in JMG can be classified into three main categories: (a) symptomatic treatments

Table 3. Immune-modulating Agents Used in Myasthenia Gravis

Treatment	Onset of action	Time to maximal effect	Initial dosing/frequency	Monitor
Immunomodulator				
Plasmapheresis	1-5 days	1-3 weeks	4-6 exchanges on alternate days	BP, coagulation parameters
IVIg	3-10 days	1-3 weeks	1-2 g/kg (over 2-5 days)	BP, renal/cardiac status
Prednisone	2-6 weeks	5-6 mo	0.5-1 mg/kg/d (maximum 30 mg/d), increase up to 2 mg/kg/d (maximum 60-80 mg/d)	BP, glucose, bone density
Azathioprine	6-12 months	1-2 years	0.5-1 mg/d, increase of 0.5 mg/kg/d every 4 weeks up to 2.5 mg/kg/d	CBC, liver function
MMF	4-12 months	1-2 years	2.0-2.5 g/d in divided twice	CBC
Cyclosporin	2-6 months	6-12 months	4-6 mg/kg/d in divided twice	BP, renal function
Tacrolimus	1-2 months	6-12 months	3-5 mg/d	BP, renal function, potassium
Surgery (thymectomy)	1-10 years	1-10 years		

IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; BP, blood pressure; CBC, complete blood count

(anticholinesterase agents), (b) chronic and rapid immunomodulating treatments, and (c) surgical treatment (thymectomy). The time of onset of the clinical effect of each of these therapies for MG varies considerably (Table 3).

1. Symptomatic treatment

Acetylcholinesterase inhibitors are the first-line treatment for long time use owing to their safety. Pyridostigmine (Mestinon) is the usual choice and is administered orally³²⁾. In general, limb and bulbar symptoms (dysphagia, fatigable chewing, and dysarthria) respond better to acetylcholinesterase inhibitors than the ocular manifestations (ptosis and diplopia). For adults and older adolescents, a common starting dose is 30 mg three times a day. The dose is titrated according to its effect, increasing to usually 120 mg every 4 h while the patient is awake. Almost all adult patients require a total daily dose of ≤ 960 mg. For children and younger adolescents, the initial dose is 0.5–1 mg/kg every 4–6 h, up to a total daily dose of 5–7 mg/kg (maximum of 300 mg/day)^{7,33)}. When a patient has significant persistent weakness despite the use of pyridostigmine in sufficient doses, or when the adverse effects prohibit effective dosing, then immunotherapy is generally warranted.

The most inconvenient muscarinic adverse effects include abdominal cramping and diarrhea. Others are increased salivation and bronchial secretions, nausea, sweating, and bradycardia. The nicotinic adverse effects include fasciculations and muscle cramping.

2. Immunomodulation/Immunosuppression

The second therapeutic modality in MG is the administration of immunomodulating agents (Table 3). Prednisone and prednisolone are the first-line therapy in children with persisting symptoms, and are widely used as well as other agents, most commonly azathioprine, mycophenolate mofetil, and cyclosporine³⁴⁾. The administration of moderate or high doses of glucocorticoids leads to marked improvement or remission in about 70–75%. Prednisone is usually administered at high doses (0.75–1.0 mg/kg/day) for several months during the initial treatment of moderate or severe MG. In children, the starting dose is 0.5–1 mg/kg/day (maximum 30 mg/day), possibly increasing up to 2 mg/kg/day (maximum 60–80 mg/day) with often alternate day to minimize side effects. Several immunosuppressive drugs are effective in MG (Table 3)³⁴⁾. To maximize the effects and minimize the adverse effects, a combination of immunosuppressive drugs is preferable for most patients.

Both plasmapheresis and intravenous immunoglobulin (IVIG) work quickly (over days) from initiation; however, the benefits

are only short term (weeks)³⁵⁾. These rapid immunotherapies are used most often in the following situations: (a) in the presence of myasthenic crisis, (b) preoperatively before thymectomy or other surgery, (c) as a “bridge” to slower-acting immunotherapies, (d) periodically to maintain remission in patients with MG that is not well controlled despite the use of chronic immunomodulating drugs⁴⁾.

A typical course of plasmapheresis consists of five exchanges every second day (3–5 L of plasma each) during 7–14 days. The beneficial clinical effect of plasmapheresis is usually seen within days; however, the benefit typically lasts only 3–6 weeks. IVIG is used in the same setting as plasmapheresis to quickly reverse an exacerbation of myasthenia³⁵⁾. The total dose of IVIG is 2 g/kg, usually during 2–5 days (maximum dose 150 g). The effect of IVIG is seen typically in less than a week, and the benefit can last for 3–6 weeks. This regimen can be repeated every 4–8 weeks in patients who have failed to respond to other therapies.

3. Thymectomy

The benefit of thymectomy for patients with nonthymomatous MG is supported by the results of multicenter, assessor-blinded trials. The benefit of thymectomy is not immediate. The 1-year remission rate was $<20\%$; however, during 7–10 years, the remission rate increased to up to 50% ³⁶⁾. Remission rate were higher in children of generalized MG after thymectomy than the rate of spontaneous remission^{5,6,8,37)}. Thymectomy performed within the first year after onset is associated with higher remission rates^{37,38)}. Therefore, thymectomy is recommended as early as possible in case of generalized weakness.

Thymectomy is recommended by most centers for the following patients²⁰⁾: (a) those with thymomatous, generalized MG; (b) those aged <60 years with nonthymomatous, generalized AChR-Ab-positive MG; and (c) those aged <60 years with nonthymomatous, generalized MG and seronegative MG. However, for patients with nonthymomatous, generalized MuSK-Ab-positive MG, those with ocular MG, and for most patients aged ≥ 60 years, we suggest not performing thymectomy^{20,36)}.

Therapeutic approach

The treatment of MG is highly individualized and depends on the age of the patient, the type and severity of the disease, and the pace of progression.

1. Generalized MG in adult (Fig. 2)

The initial step in most adult patients with mild or moderate

disease is symptomatic therapy in the form of pyridostigmine³⁴⁾. Those with severe disease, or rapidly worsening disease, should be treated much like patients with myasthenic crisis, by using rapid therapies (i.e., IVIG or plasmapheresis) followed by longer-acting immunotherapies such as glucocorticoids, azathioprine, mycophenolate mofetil, or cyclosporine. For those patients receiving pyridostigmine alone and whose symptoms are under good control or in remission, we simply follow their clinical course. Thymectomy should also be considered in all adult patients aged <60 years²⁰⁾.

An immunotherapeutic agent is required for patients who remain significantly symptomatic with pyridostigmine treatment, or who became symptomatic again after a temporary response to pyridostigmine³⁴⁾. In young adult patients, we favor the use of glucocorticoids. Often, a good response can be obtained with high doses initially, and that response can be maintained after tapering to low doses. For patients who cannot achieve a clinical improvement on prednisone, another immunomodulating agent is substituted. These include patients with relative contraindications to glucocorticoids (such as diabetes or advanced age), liver disease (precludes azathioprine), renal disease (precludes cyclosporine), or leukopenia (problematic for both azathioprine and mycophenolate)³⁴⁾.

Thymectomy should be considered because of its potential longer-term benefit. Patients with thymoma clearly need surgical treatment. Although the need for thymectomy is less certain in patients with nonthymomatous tissue, there is evidence showing that thymectomy improves clinical outcomes.

2. Juvenile MG

Pyridostigmine is the first-line therapy in children. Steroids are generally used for severe disease that is unresponsive to anticholinesterase agents. Steroids retard bone growth, increase the risk of adult osteoporosis, and are especially problematic for chronic use in children³²⁾. Azathioprine, mycophenolate mofetil, and cyclosporine have been used successfully in JMG^{4,7)}; however, concerns about serious adverse effects, including impaired fertility and late development of malignancy, are of even greater concern in children than in adults.

As a long-term treatment for MG, thymectomy has been performed successfully and with low morbidity in children³⁷⁾. Thymectomy is a widely accepted option for peripubertal and postpubertal children with generalized MG who have positive AChR-Abs or who are seronegative^{7,32,33,37)}. The rates of improvement and remission seen in an uncontrolled series seem to be similar to that reported in adults after thymectomy³⁷⁾. No significant deleterious consequences of removing the thymus in childhood have been reported⁴⁾. However, children with pure ocular MG or MuSK-positive MG have not been shown to benefit from thymectomy. The role of thymectomy in prepubertal children remains controversial. This group has a higher incidence of spontaneous remission^{4,33)}.

요약

중증 근무력증은 근육의 빠른 피로와 악화를 특징으로 하는 만성 자가 면역 질환으로 골격근의 신경-근 접합부의 차단이 원인이다. 근

Fig. 2. Treatment of generalized myasthenia gravis. AZA, azathioprine; MMF, mycophenolate mofetil.

신경 접합부에서 아세틸콜린 수용체에 부착하는 자가 항체로 인한 신경 근육 전달 장애가 원인이다. 또한, MuSK, LRP4 및 그 외 운동종말판 단백질에 대한 자가 항체들이 관련되어 있다. 중증 근무력증은 침범된 근부위 (안구형 및 전신형), 발생 연령 및 흉선의 병리 소견에 따라 분류될 수 있다. 혈청 항체 및 임상 증상에 따라 조기발병형, 후기발병형, 흉선중, MuSK 혹은 LRP4 양성형, 혈청 항체 음성형, 및 안구형의 소집단 분류가 가능해지고, 각 소집단별 치료 계획 수립과 예후 예측을 용이하게 할 수 있다. Pyridostigmine 은 증상 치료를 위한 1차 선택 약물이다. 여기에 치료 반응이 부족한 경우에, 우선적인 면역억제치료로서, 스테로이드, 다른 면역조절약물들, 그리고 흉선절제술을 고려하게 된다. 중증 근무력증의 치료는 환자 개인의 특성, 연령, 임상 증상 및 심한 정도 등에 따라 치료 형태를 결정하게 된다.

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