

China guidelines for the diagnosis and treatment of myasthenia gravis

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Myasthenia gravis (MG) is neuromuscular disorder induced neurotransmission defects at the neuromuscular junctions. MG is an autoimmune disease in which the autologous immune system, including the corresponding antibodies, immune cells and complement systems, attacks the cholinergic receptor (AChRs) of the postsynaptic membrane, resulting in weakness of skeletal muscle. A rare portion of MG cases is mediated with antibodies specific to muscle specific kinase (MuSK) and low-density lipoprotein receptor related protein 4 (LRP4). The major clinical symptoms of MG are presented as weakness of skeletal muscle, fatigue prone, which are worsened after exercise. Adequate rest and treatment with cholinesterase inhibitors could significantly relieve and reduce the symptoms. The average onset rate is about 8-20 cases per 100,000 people.^[1] MG is not age specific but there is a higher onset rate in females than males at the population before 40 of age. Such

gender preference is reversed after 50-year-old. At the age category of 40-50, there is no gender preference.

CLINICAL SYMPTOMS AND CLASSIFICATIONS

Clinical symptoms

Systemic skeletal muscle may be affected. However, at the early stage of MG, there may be firstly the muscle weakness of extraocular, throat and limbs. Seemingly, the skeletal muscles innervated by the cranial nerves are more susceptible than those innervated by spinal nerves. The weakness of skeletal muscles initiates at a group of muscles first and gradually spreads to other groups of muscles and eventually the whole system. For some patients of MG, they may rapidly experience weakness of all skeletal muscles and even myasthenic crisis.

The skeletal muscle weakness of MG is volatile with ease of fatigue, which are worsening towards the end of the day. The weakness and fatigability is progressively worsening during physical activity,

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which is improved after adequate rest. The initial symptom is the ptosis either symmetrically or asymmetrically and diplopia which are observed in more than 80% of patients.^[2] In certain cases, alternative or bilateral ptosis and nystagmus are also observed. Patients suffer also from lagophthalmos. However, pupil size remains normal.

Due to the weakness of the muscles involved in swallowing, there is dysphagia, difficulty of chewing and velopharyngeal insufficiency. For the symptoms of vocality, patients of MG have dysarthria and hypophonia, some of who may also have nasality. Weakness of facial muscle leads to hanging jaw sign, shallow nasolabial fold, leaky cheek blowing, snarling expression when smiling and sleepy or sad expression. Weakness of cervical muscle, patients could not hold their upright easily. Although it is usually not the primary symptoms of MG, limb movement is highly affected spreading from the proximal ends. In certain cases, the respiratory muscle is under myasthenic crisis which leads to dyspnea. Assisted ventilation is necessarily needed to sustain life.^[3,4,5]

Classification: modified Osserman scale

Class I: ptosis and diplopia without other muscle weakness elsewhere for 2 years.

Class II: generalized symptoms with more than one set of weak muscle: (1) mild generalized form; Weakness in limbs with or without ocular signs, but without prominent bulbar signs. Patients could live independently; (2) moderate generalized or faciopharyngeal form; symptoms as in II A but with bulbar signs. Patients could live independently.

Class III: severe acute generalized form; acute onset and rapid development. Faciopharyngeal symptoms were observed in the first few weeks to months followed by respiratory insufficiency with or without ocular signs. Patients could live independently.

Class IV: severe chronic generalized form; unapparent signs at early stage due to the slow pathological progress. All symptoms stated in Class I, II and III are developing within 2 years.

Class V: muscle atrophy form; severe development with also muscle atrophy within 6 months.

EXAMINATION

Methyl sulfate neostigmine test

Intramuscular administration of 1.0-1.5 mg methyl sulfate neostigmine for adult. Atropine (0.5 mg) could

be applied intramuscularly if there are any muscarinic cholinergic receptor-mediated side effects. For children, neostigmine should be reduced to 0.02-0.03 mg/kg, while total amount should not be more than 1.0 mg. Test should be performed at the muscle with significant symptoms and referred to the clinical absolute score for MG. The baseline of muscle tone should be firstly recorded, which is repeated every 10 min for 1 h. The relative score, as the diagnostic value, should hence be pooled by the absolute score of the trial with most significant improvement according to the following formula:

Relative score = (Baseline-absolute score of each trial)/Baseline × 100%

There is usually less than 25% of negative diagnosis while more than 60% for positive diagnosis, and 25-60% are as suspicious positive cases. Further tests are needed to confirm the negative diagnosis.

Electromyography

Repetitive nerve stimulation

Repetitive nerve stimulation (RNS) is an electrical stimulation to nerves, such as facial, accessory, axillary and ulnar nerves, for MG diagnosis, with repetitive and high-powered low frequency (2-5 Hz) signal. Compound muscle action potential (CMAP) over the testing muscles will be recorded.

The duration of stimulation is about 3 s. The decrement of CMAP of MG is measured by comparing the CMAP value of the fourth or fifth stimuli to that of the first stimulus. Diagnosis will be concluded as positive when there is more than 10% reduction. MG patients on acetylcholinesterase inhibitor medication should not receive this test until 12-18 h of washing out. For diagnosing presynaptic lesions, frequency of RNS should be increased to 10-20 Hz. Increment with more than 100% should be classified as abnormal.

Single fiber EMG

Single fiber EMG (SFEMG) is to measure the variable latency of the single axon innervation to the muscle fibers, known as Jitter. The variable latency is usually about 15-35 s, of which more than 55 ms will be classified as increased variability of latency. Two or more variable latency in every 20 Jitters of a single set of muscle will be classified as abnormal. Any block during SFEMG should also be classified as abnormal. Despite of the significant sensitivity, SFEMG is not specific for MG, which is mainly for Class I MG and those cases without positive outcomes in RNS test. Furthermore, SFEMG is not affected by any acetylcholinesterase inhibitors.

Serum antibody tests

AChR

For diagnosing MG with the specific antibodies, positive results could be detected in about 50-60% patients with ptosis and other ocular sign, while about 85-90% patients with generalized sign would have positive outcomes. Based on also the medical history of muscle weakness, positive diagnosis is enough to confirm MG. Further tests are needed if it is a negative outcome.

Anti-MuSK

Anti-MuSK could be detected in some patients with generalized sign of muscle weakness who have negative outcomes in the test of AChR antibody, while other patients may present positive outcomes of low-density LRP-4 antibody or other antibodies without known antigens at the neuromuscular junctions. Negative outcomes could be due to the low levels or weak affinity of these antibodies, resulting in undetectable outcome. It should also be noted that the ratio of anti-MuSK positive result in Western population is usually higher than that in Asian population.

Anti-striated muscle antibodies

Anti-striated muscle antibodies include anti-titin, anti-RyR and *etc.* This type of antibodies is usually detected in those MG patients with severe signs, desensitization of conventional therapies of MG and with also thymoma. This test is not for MG diagnosis but it strongly indicates the opportunity of thymoma and other related transformations.

Thymus imaging

There are approximately 20-25% MG patients who suffer also from thymic tumors while 80% have abnormal condition of thymus. Amongst the MG patients with thymic tumors, 20-25% of them present MG symptoms.^[7] Ninety-four percent thymic tumors could be positive diagnosed by mediastinal CT. However, some cases are only diagnosed by advanced CT scan or MRIs.

DIAGNOSIS

Bases of diagnosis

Clinical symptoms

There is patchy distribution of weakness on certain particular striated muscle, exhibiting volatility and

ease of fatigue. These MG symptoms are usually worsened across the day and after activities, which would be relieved after rest. In majority, ocular muscle is the common and first victim.

Pharmacological response

Positive outcome in neostigmine test.

EMG tests

Ten percent decrement of CMAP and 2 or more variable latency (> 55 ms) in SFEMG with or without any blocks.

Antibody tests

Test of anti-AChR in blood sample of generalized form of MG is positive. Anti-MuSK and LRP-4 would only be detected in some rare cases of MG.

With all clinical symptoms, and positive outcomes of pharmacological and electrophysiological tests, it can be diagnosed as MG. When it is available, blood test of anti-AChR or other related antibodies could be adopted for further confirmation. Furthermore, other unknown diseases may interfere the diagnosis.

Differential diagnoses

Ocular MG

Miller-Fisher syndrome: it is a derivative of Guillain-Barré syndrome, which is with acute paralysis of extraocular muscle, ataxia and loss of tendon reflexes. EMG results indicate there is delay of neurotransmission. Furthermore, in the analysis of cerebrospinal fluid, there is protein-cell separation. In some cases, GQ1b antibody is detectable.

Chronic progressive external ophthalmoplegia (CPEO): CPEO is one of the mitochondrial myopathies, patients of which experienced symmetrical, bilateral and progressive ptosis, paralysis of extraocular muscle, myogenic lesions and lactic acidosis. Some patients may experience also weakness of proximal limbs and delay of peripheral nerve transmission. Muscle biopsy and gene tests are needed for further confirmation.

Oculopharyngeal muscular dystrophy (OPMD): OPMD is a progressive muscular dystrophy, the patients of which experience progressive ptosis and weakness of the extraocular muscles. There is also a slight elevation of the serum level of creatine kinase. EMG diagnosis of OPMD shows myogenic lesion. Muscle biopsy and gene tests are needed for further confirmation.

deficient should be performed to reduce the risk of irreversible marrow lesion.

Cyclosporin A: this is an immunosuppressant for generalized and ocular MG, which starts to effect 3-6 months after administration. This is mainly used when glucocorticoid and azathioprine are not effective. Cyclosporin A could also be used with glucocorticoid for improving the MG with a decreasing blood level of AchR antibody. Cyclosporin A could be used in long term with a similar effect as azathioprine but with lesser side effect. Usually cyclosporin A was taken in orally in 2-4 mg/kg/day. The blood level of cyclosporin A was monitored in order to adjust the dose. The main side effect includes hypertension, tremor, renal dysfunction, muscle ache, gingival hyperplasia and flu-like symptoms. Blood test, hepatic and renal functions are regularly checked every month.

Tacrolimus (FK-506): This is also a potent immunosuppressant used for those patients not susceptible to glucocorticoid and other immunosuppressant, particularly those RyR antibody positive. This is also used with glucocorticoid at the early stage of treatment to reduce the usage of glucocorticoid and corresponding side effect. The therapeutic effect of FK-506 onset rapidly and significant effect should be observed around 2 weeks after administration. FK-506 is usually prescribed at 3.0 mg/day for oral dose. Blood level of FK-506 should be monitored in order to adjust the dose. MG patients with rapid metabolism should receive large dose till a significant effect observed. Side effects include alimentary symptoms, numbness, tremor, headache, hypertension, hyperglycemia, hyperkalemia, hypomagnesemia and renal failure. If no significant side effect, FK-506 could be chronically used. Blood glucose, hepatic and renal functions should be monitored every month.

Cyclophosphamide: this agent will be used when other immunosuppressants fail to provide any therapeutic effect on to severe cases MG or MG with thymus tumor. Cyclophosphamide should also be administered with glucocorticoid, which could be reduced in dose 6-12 months after treatment started. For adult, 400-800 mg cyclophosphamide per week should be intravenously perfused. Patients could also receive 100 mg/day in two oral doses till the total amount reaches 10-20 g (for some cases, patients need 30 g). For children, 3-5 mg/kg/day (totally amount should not exceed 100 mg) in two oral doses was administered. When there is improvement of symptoms, dose could be reduced to 2 mg/kg/day. Extra caution should be paid for children patient receiving cyclophosphamide. Side effects

includes reduction of white blood cells count, loss of hair, nausea, vomit, diarrhea, hemorrhagic cystitis and long term suppression of bone marrow mediated cancer risk.

Mycophenolate mofetil (MMF): MMF is not the first line agents for MG but it is also used with glucocorticoid at the early stage of treatment but not azathioprine. Usually, it will be administered at rate of 0.5-1 g and twice a day. When compared to azathioprine and cyclosporine, MMF is safer and with less hepatic and renal side effect. Common side effect includes alimentary symptoms, nausea, vomit and diarrhea. For MG patients taken MMF, their whole blood count will be performed once a week at the first month, twice a month at the second and third months and once a month after 3 months. If there is a reduction of neutrophils, patients should stop taking any MMF.

Anti-human CD20 monoclonal antibody (Rituximab): Rituximab is proven to be effective in treatment of autoimmune diseases.^[10] In treatment of MG, rituximab is suitable for patients, particularly those with MuSK positive, who have no significant improvement in treatment of glucocorticoid and traditional immunosuppressants. As single agent of MG treatment, recommended dose for adult is in rate of 375 mg/m² (i.v.) once a week. The treatment course is 22 days and agent is totally administered for 4 times.

Treatment with rituximab should be performed with facility of resuscitation. When there are any respiratory symptoms or hypotension, patients receiving this treatment should be monitored for 24 hours. Treatment has to be terminated when there are any adverse effects such as dyspnea, bronchospasm and hypoxemia. Other side effects include fever, chills, bronchospasm, leukopenia, thrombocytopenia and progressive multifocal leukoencephalopathy. It is also crucial to monitor any syndromes of cytokines release.

During this treatment, hepatic and renal functions, blood and urine biochemistries have to be monitored regularly. Treatment should be immediately terminated if there is any immunosuppression mediated side effects. For patients with HBsAg positive and compromised hepatic function, nucleotides (NAs) should be administered 2-4 weeks before treatment.

Intravenous administration of g-globulin

This is for acute situation and pre-operative treatment for MG patients, usually combined with immunosuppressants and glucocorticoid.^[11] g-globulin will be intravenously perfused at rate of

400 mg/kg/day for 5 days. Effect of this treatment will onset in 5-10 days and last for 2 months. As similar as the plasmapheresis discussed below, side effects are less but both procedures cannot be combined. For moderate and severe MG patients, repetitive treatment of this could not maximize the therapeutic effect. Side effects include headache, aseptic meningitis, flu signs and renal dysfunction.

Plasmapheresis

This is mainly for acute cases of MG, myasthenic crisis and pre-operative treatment for thymectomy.^[12] This is also used for cases without further improvement after chronic treatment with immunosuppressants. Plasmapheresis should be performed every other day in the first week, totally 3 times. If there is no significant improvement, procedure should be continued once a week for 5-7 weeks. Each treatment introduces 1,500 mL health human plasma and 500 mL 706 supplement. Significant effect will onset 2 days after the first or second treatment lasting for 1-2 months. Side effects include hypotension, low blood calcium, infection and hemorrhage. Plasmapheresis should be performed in aseptic environment. Termination should be used if there is any complication. MG patients with infection and receiving perfusion of g-globulin should not receive this procedure.

Thymectomy

It is crucial to perform thymectomy for the MG patients with thymus tumor, which could eliminate risks of invasion and proliferation.^[7] Thymectomy could also improve the MG signs of patients. However, in certain cases, the MG condition would be worsened. For mild MG (Osserman class I), thymectomy could not have any improvement. However, for Osserman class II to IV, particularly those with AChR antibody positive, thymectomy provides a significant improvement. MG signs would be usually reduced 2-24 months after the operation and medication could be also reduced. Although some MG patients will recover totally after thymectomy, some will experience MG reoccurrence in a few years. Generally thymectomy is beneficial for MG with abnormal thymus glands. Such operation is suitable for patients older than 18 year-old. For severe cases with non-malignant thymus tumor, treatments, such as perfusion of g-globulin, will be firstly recommended than surgery when MG signs have been slightly improved, which could also prevent post-operation myasthenic crisis.

Thymus radiotherapy

The sophistication of radiological techniques makes

Table 1: Differential diagnoses of myasthenic and cholinergic crises

	Myasthenic crisis	Cholinergic crisis
Heart rate	Tachycardia	Bradycardia
Muscle	Weak	Weak and fasciculation
Pupil	Normal or dilated	Constricted
Skin	Faint and cold	Warm and flushing
Secretion	Normal	Increase
Neostigmine test	MG improved	MG aggravated weakness

MG: myasthenia gravis

this as a popular therapy for MG.^[13] This approach is suitable for those MG patients who experience invasive thymus hyperplasia, reoccurrence of MG and not sensitive to other medication. Daily treatment dose is 1 to 2 Gy and 5 times per week. The total amount is 50-60 Gy.

Others

Respiratory muscle training and other strength training in mild case of MG could improve the muscle strength. It is highly recommended that patients should control weight and limit the daytime activity. Seasonal flu shot is also beneficial in therapy.

Therapies for different types of MG

Ocular MG: although it is more prevalent in children under 10 year old and adult above 40, this could be seen in any age groups. 80% patients of MG experience first with ocular MG which could be controlled by individualized doses of AChE inhibitors. For better treatment, AChE inhibitors could be combined with glucocorticoid and methylprednisolone. In recent review literatures, oral dose of glucocorticoid, e.g. prednisone, is better in treat of ocular MG than only AChE inhibitors and more effective in preventing the transformation to generalized forms of MG. However, randomized and blinded clinical trials are needed to confirm this. In order to have better treatment, it is also recommended to apply immunosuppressants and glucocorticoid. Thus, glucocorticoid induced side effect could be reduced.

Generalized form: as AChE inhibitors are not effective enough to control the MG symptoms, treatment should combine with glucocorticoid and other immunosuppressants, e.g. azathioprine, cyclosporine, tacrolimus and MMF. Some cases of generalized MG need methylprednisolone, 40-50% of which may be worsened during treatment and needed endotracheal intubation or tracheotomy. High dose of g-globulin could be used when methylprednisolone fails to provide any effect. Thymectomy should be performed early for those with abnormalities of thymus glands, such as thymus tumor and thymus hyperplasia.

Medication could usually be reduced after operation. For some cases, no more MG signs will be seen post-operation. For children, AChE inhibitors, glucocorticoid and g-globulin are beneficial for generalized form of MG. Otherwise, with cautions, patients could be treated by immunosuppressants and thymectomy.

MG crisis:^[14,15] it is the compromised respiratory muscle leading to severe difficulty in breathing, which has to be supported by artificial respiration, such as positive pressure respiration, endotracheal intubation and tracheotomy, and monitoring the oxygen saturation and partial pressure of carbon dioxide. MG crisis could be classified as in Table 1. For myasthenic crisis, dose of AChE could be increased within the safe window till there is any improvement. Overdose of AChE could be reversed by atropine or methylprednisolone. For some cases, it is also practical to apply high dose of g-globulin and plasmapheresis. For cholinergic crisis, treatment with AChE inhibitors should be reduced or terminated and should not resume and increase gradually until 5-7 days. Atropine or combined with methylprednisolone, plasmapheresis and g-globulin could also be adopted. Nowadays, AChE inhibitors should be limited at not more than 480 mg per day. Thus, cholinergic crisis is uncommon. If respiratory failure is found in blood gas analysis (in both type I and II), endotracheal intubation and positive pressure respiration should be immediately applied. Artificial respiration of MG patients should have extra care to prevent lung infection and adjustment of the auxiliary breathing mode for earlier independent breathing.

MG at pregnancy:^[16] it is still not very clear that how pregnancy affects MG. For most cases, pregnancy will not aggravate MG and affect the labor time and route. AChE inhibitors and glucocorticoid are relatively safe for fetuses but other immunosuppressants may affect the embryonic development which should be terminated if pregnant. Teratogenic drugs, e.g. methotrexate and MMF, should not be used. It is also recommended for MG patients to take caution of contraception.

MG with MuSK antibody positive: generally, AChE, glucocorticoid and immunosuppressants are not effective for MG with AChR antibody negative but MuSK positive. Up to date, there is no special and effective treatment for this type of MG. plasmapheresis could relieve the MG signs for short term. There is a case report that anti-CD20 monoclonal antibody is therapeutic potent to this type of MG.^[9] Multiple thymectomy is also beneficial for this type of MG.

MG with other complications

Some MG patients could suffer from also other

disorders, such as Graves diseases, polymyositis, multiple sclerosis, Sjogren's syndrome, periodic paralysis, Hashimoto 's disease, rheumatoid arthritis, systemic lupus erythematosus, Guillain-Barré syndrome, aplastic anemia. In some MG cases, cardiac muscle is also the victim, presenting abnormal EEG and arrhythmia. Therefore, it is recommended to pay also attention to such conditions other than MG.

Precautions for MG treatment

There are certain contraindication for MG patients, including steroids, antibiotics (e.g. Aminoglycoside), antifungal drugs (e.g. amphotericin), cardiovascular drugs (e.g. lidocaine, quinidine, β -blockers, verapamil and *etc.*), antiepileptic drugs (e.g. Phenytoin, ethosuximide), antipsychotics (e.g. chlorpromazine, lithium carbonate, diazepam, clonazepam), anesthesia (e.g. morphine and meperidine) and anti-rheumatic drugs (e.g. penicillamine and chloroquine).

It is also not recommended to do soapsuds enema. Plenty of rest, staying warm, steady emotion are also important for recovery from MG.

Prognosis

Ten-twenty percent of MG patients in ocular form will spontaneously heal, while 20-30% only experience extraocular MG. For the rest, more than 85% will gradually spread the signs to medulla oblongata and skeletal muscle, developing generalized form in 3 years. The pathogenesis of MG in about two-third of patients will develop to severe level within one year. 20% of MG patients will develop MG crisis within 1 year. MG signs and symptoms will be aggravated in certain conditions such as upper respiratory tract infection, diarrhea, thyroid disease, pregnancy, fever, trauma and medications affect the neuromuscular junctions.

Before the prevalent use of immunosuppressants for MG treatment, the mortality rate of MG is 30%. With also the development of mechanical ventilation and intensive care technique, nowadays the mortality (due to directly MG or indirectly other complication) decreases to below 5%.

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Conflicts of interest

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