



Myasthenia Gravis: Current Review

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ABSTRACT

Myasthenia gravis (MG) is an acquired autoimmune disorder characterized clinically by weakness of skeletal muscles and fatigability on exercise. Weakness increases during the day and improves with rest. Extraocular muscle (EOM) weakness or ptosis is present initially in 50% of patients and 90% occurs during the course of illness. AChE inhibitors and immunomodulating therapies are the mainstays of treatment. In mild form, AChE inhibitors are used. Important risk factors for poor prognosis include age older than 40 years, a progressive disease, and thymoma.

Key words: myasthenia - immunology fi diagnosis fi treatment - prognosis

INTRODUCTION

Myasthenia gravis is an autoimmune disorder caused by the presence of autoantibodies specific to human nicotinic acetylcholine receptor (AChR), which is concentrated in the post synaptic region of the neuromuscular junction⁽¹⁾.

MG is uncommon. Estimated annual incidence is 2 per 1,000,000. The female-to-male ratio is said classically to be 6 : 4, but as the population aged, the ratio is now equal. MG can presents at any age⁽²⁾. Among children population in Hong Kong the estimated prevalence is 1: 4000⁽³⁾. Myasthenia gravis was the commonest type of non inherited NMJ disorders (62%), mostly ocular type (89%).

Epidemiological study in England⁽⁴⁾ found 100 cases in a population of 684 000 (prevalence 15 per 100 000 population, 95% CI: 12–18). The commonest presenting symptoms and signs were ptosis (64%) and diplopia (64%). A population-based study in Greece found the average annual incidence of seropositive myasthenia gravis was 7.40/million population/year (women 7.14; men 7.66). The point prevalence rate was 70.63/million (women 81.58; men 59.39)⁽⁵⁾. This review discusses the clinical aspect, treatment, and prognosis of MG based on previous current literature.

CASE ILLUSTRATION

A 22 year-old female presented with major complaints of ptosis and diplopia. Patient felt that the weakness became more severe in the afternoon and after activities (especially during daylight). The eyelids had the same width in the morning, but the left eyelid dropped as day progresses. Double vision became more severe in the afternoon and after activities like reading, causing letters look double after 15 minutes. The object become double in horizontal direction; more pronounced when looking upward.

The symptom improved after rest (nap), and relieved in the morning (after night sleep). She didn't have headache, blurred vision, speech disturbance, swallowing difficulties, extremities and/or general weakness. The symptoms was slowly progressed within months. There were no symptoms of malignancy, thyroid disease, and generalized weakness.

DISCUSSION

Pathophysiology

When an action potential travels down a motor nerve and reaches the nerve terminal, acetylcholine (ACh) molecules are released from the presynaptic vesicles and adhere to ACh receptors (AChRs) at the peaks of postsynaptic folds. Channels in the AChRs open, allowing Na⁺ and other cations to enter into the muscle fiber endplate and depolarize it. The multiple depolarizations will sum up, and if large enough, trigger an action potential, which travels along the muscle fiber to produce contraction⁽¹⁾.

In MG, there is a reduction of AChRs available at the muscle endplate and flattening of the postsynaptic folds causing reduction of available endplates; producing fewer endplate potentials that might fail to be translated into an action potential. The end result is an inefficient neuromuscular transmission⁽⁶⁾.

MG is Ab-mediated, producing loss of or compromised function of skeletal muscle nicotinic acetylcholine receptors (AChR's). Three mechanisms have been implicated: (a) autoantibodies against AChR cross-link surface AChR and induce their endocytosis, resulting in their depletion from the postjunctional membrane; (b) the autoantibodies themselves interfere directly with AChR function by blocking acetylcholine-binding sites; and (c) the autoantibodies contribute to destruction of endplates with consequent AChR loss.



Patients become symptomatic once the ACh receptors is reduced to approximately 30% of normal. The disease does not affect smooth and cardiac muscle because they have a different cholinergic receptors antigenicity⁽¹⁾.

The role of thymus in the pathogenesis of MG is not entirely clear, but 75% of MG patients have some degree of thymus abnormality (eg, hyperplasia in 85% of cases, thymoma in 15% of cases). Given the immunologic function of thymus and clinical improvement following thymectomy, thymus is suspected to be the site of autoantibody formation. However, the stimulus that initiates the autoimmune process has not been identified⁽¹⁾. Why the disease afflicts first and predominantly the extraocular muscles remains unanswered. It probably has to do with the physiology and antigenicity of the muscles⁽⁶⁾.

Symptoms and Signs

The usual initial complaint is specific muscle weakness rather than generalized. The severity typically fluctuates over hours; least severe in the morning and worse as the day progresses. It also varies over the course of weeks or months, with exacerbations and remissions⁽¹⁾.

• Ophthalmic symptoms

Among patients, 75% initially complain of ocular disturbance, mainly ptosis and diplopia. Eventually, 90% of patients with MG develop ocular symptoms. Ptosis may be unilateral or bilateral, and may shift from eye to eye⁽⁶⁾.

Ptosis is usually most prominent upon sustained upward gaze or repeated eyelid closure (blinking). In cases of unilateral ptosis, the contralateral lid may assume a ptotic position upon occluding the ptotic eye or lifting the ptotic lid with a finger (Hering phenomenon)⁽¹⁾. Extraocular muscle involvement does not follow a certain pattern. Any acquired ocular motility disturbance with ptosis, but normally reacting pupils, should raise the clinical suspicion of MG⁽²⁾.

• General symptoms and signs

Weakness occur in facial, oropharyngeal, limb, and trunk muscles, without any other sign of neurologic deficit, such as sensory loss, change in deep tendon reflexes, or muscle atrophy⁽⁶⁾. Weakness may involve limb musculature with myopathic-like proximal weakness greater than distal muscle weakness. Isolated limb muscle weakness as the presenting symptom is rare and occurs in fewer than 10% of patients⁽²⁾.

Supporting additional examination

• Fatiguability test

In ocular MG, fatiguability test can be done by asking the patient to blink repeatedly or gaze upward for an extended time

(Simpson test). Increased drooping is a sign of fatigue. The phenomenon of 'enhanced' ptosis can be demonstrated in patients with bilateral ptosis by elevating and maintaining the more ptotic eyelid in a fixed position. The opposite eyelid slowly falls and may close completely⁽⁷⁾.

The lid-twitch sign is another way to test for fatiguability. The patient is directed to look down for 10-15 seconds and then to refixate quickly in the primary position. Observation of an upward overshoot of the lid with several twitches, followed by repositioning of the lid to the original ptotic state, identifies the easy fatiguability and rapid recovery of the muscle. The 'peek' sign occurs when the palpebral fissure widens after a period of voluntary eyelid closure^(1,7).

• Anti-acetylcholine receptor antibody

This test is reliable for diagnosing autoimmune MG. The anti-AChR antibody (Ab) is positive in 74% of patients. Results are positive in about 80% of patients with generalized myasthenia and in 50% of those with pure ocular myasthenia⁽²⁾.

• Antistriated muscle (anti-SM)

Antistriated muscle (anti-SM) Ab is another important test in patients with MG. It is present in about 84% of patients with thymoma younger than 40 years and less often in patients without thymoma⁽²⁾.

• Tensilon or Prostigmin test

In ocular myasthenia without systemic manifestations, up to 95% of patients will have a positive Tensilon or Prostigmin test⁽⁷⁾.

• Neurophysiological test

Electromyography is used to confirm the diagnosis of MG, but usually are not available on an emergency basis⁽¹⁾. Repetitive nerve stimulation (RNS) should lead to a decremental response in compound action potentials on EMG. A stimulation rate of 1-5 per second should result in a ° 10% decrease in amplitude by the fourth action potential. RNS results are less likely to be positive in patients with ocular MG.

Single fiber electromyography (SFEMG) records action potentials from single muscle fibers in a motor unit. SFEMG is a substitute for the RNS in patients with ocular MG, being much more sensitive. This test is technically demanding and operator dependent. It has a lower specificity, and can give positive results in other neuromuscular disorders⁽⁶⁾.

Other test for diagnosis exclusion

Thyroid function tests are indicated to rule out associated Graves disease or hyperthyroidism. This is essential especially in patients with ocular MG where concomitant hyperthyroidism is most frequent. MRI or CT of mediastinum (thin slices) is indicated to rule out a thymoma or thymic enlargement⁽⁶⁾.



Diagnosis

Myasthenia gravis diagnosed from clinical characteristics. An array of biological, pharmacological, and instruments test can assist diagnosis. A negative result does not definitely exclude MG⁽⁸⁾.

Table 1. Myasthenia gravis classification (Osserman and Gerkins)

Degree	Symptoms and signs
I	Purely ocular (ptosis and diplopia)
II A	Mild generalized (ocular and extremities, no prominent bulbar signs)
II B	Moderate generalized (ocular and/ or bulbar signs, variable limb muscle involvement, no crises)
III	Acute fulminating generalized signs with prominent bulbar involvement and crises
IV	Late severe generalized and prominent bulbar signs and crises

Differential diagnosis

Disorders of neuromuscular junction [NMJ] are clinically heterogeneous. The clinical expressions of these disorders are myasthenic features in the form of variable muscle weakness and fatigability. The name myasthenic syndromes [MS] is given to a group of disorder of NMT with different pathophysiology from acquired autoimmune myasthenia gravis^(9,10).

• Lambert-Eaton myasthenic syndrome (LEMS)

Lambert-Eaton myasthenic syndrome (LEMS) is a rare condition caused by abnormality of acetylcholine (ACh) release at the neuromuscular junction. Cancer is eventually found in 40% of patients with LEMS; usually small cell lung cancer (SCLC), although LEMS also has been associated with other cancers⁽¹¹⁾. A comparative study of clinical pattern between MG and LEMS from 101 patients showed that LEMS do not affect ocular weakness in all cases⁽¹²⁾.

• Botulism

The effects of the toxin are limited to blockade of peripheral cholinergic nerve terminals, including those at neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. This blockade produces a characteristic bilateral descending paralysis of the muscles innervated by cranial, spinal, and cholinergic autonomic nerves but no impairment of adrenergic or sensory nerves. Botulism has severe, progressive, and symmetric pattern⁽¹³⁾.

Treatment

The aim of MG treatment is to achieve three essential objectives : (1) Optimise neuromuscular transmission, (2) Reduce or neutralise the consequences of the autoimmune reaction, and (3) modify the natural history of MG by inducing remission, defined as permanent condition of absence of symptoms without treatment⁽⁸⁾. AChE inhibitors and immunomodulating therapies are the mainstays of treatment. In the mild form of the disease, AChE

inhibitors are initially used. Most patients with generalized MG require additional immunomodulating therapy⁽²⁾.

Other novel treatments for MG are Plasma Exchange, Immunoglobulin, and thymectomy. Plasmapheresis or plasma exchange is effective, especially in preparation for surgery or as short-term management of an exacerbation.

A consensus meeting on IVIg concluded that IVIg treatment (2g/kgBW) was most useful in acute deteriorating disease, minimising the risk of bulbar or respiratory weakness requiring intensive care support. It was also useful temporarily in patients with severe condition when other treatments had not yet effective. Use in chronic condition and as a primary treatment was not recommended. No significant difference was found in a randomised controlled trial comparing plasmapheresis and IVIg treatment. Mechanism of Immunoglobulin Therapy are: (1) Microbial and toxin inhibition, (2) Complement "deactivation", (3) Receptor Blockade, (4) Anti Idiotypes, and (5) Modulating Cytokine Production⁽¹⁴⁾.

Thymectomy is an important treatment option in MG, especially if a thymoma is present. It has been proposed as a first-line therapy in most patients with generalized myasthenia. Thymectomy may induce remission. American Association of Neurology recommended thymectomy for nonthymomatous autoimmune MG patients. Thymectomy is recommended as an option to increase the probability of remission or improvement⁽¹⁵⁾.

Prognosis

In ocular MG, >50% of cases evolve to generalised MG within a year, spontaneous remission in < 10%(8). Approximately 15-17% of patients will remain having strictly ocular symptoms over a mean follow-up period of 17 years. Those patients are referred as ocular MG. The rest develop a generalized weakness and are referred as generalized MG⁽⁶⁾. A study of 37 patients MG showed that the presence of thymoma associated with poorer outcome.

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