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A DISEASE ON MYASTHENIA GRAVIS

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ABSTRACT

Substantial therapeutic progress has been made in myasthenia gravis (MG) even before the molecular medicine. In very mild cases and in some ocular forms of MG, treatment with acetyl cholinesterase inhibitors may be sufficient, at least temporarily, but commonly some kind of immunologically active treatment is needed. In generalized MG, a wide array of immunosuppressive treatments has been established through observational studies, some prospective, but most of them have never been tested in a randomized trial. Within the immunologically active drugs, corticosteroids and the immunosuppressive drug azathioprine (Aza) have been studied the longest. The several alternatives are available including cyclosporine A, cyclophosphamide, and methotrexate, all of them off-label in most western countries. Tacrolimus is under investigation. Serial measurements of anti-acetylcholine receptor antibodies, once these are elevated, are a useful adjunct for monitoring long-term treatment success and may help in weaning from higher to lower doses or to single drugs rather than combinations. For very severe and treatment-resistant cases, co-treatment with intravenous immunoglobulin. Including older children and adults up to the 5th decade, a complete transversal thymectomy is recommended based on available open trials and expert opinion, preferentially during the first year of disease.

INTRODUCTION

Patients with Myasthenia gravis (MG) or Lambert-Eaton syndrome (LES) may have worsening of symptoms upon exposure to a variety of medications. Underlying disorders of neuromuscular transmission may affect presynaptic release of acetylcholine (LES) or the postsynaptic muscle fiber membrane at the endplate (MG). Similarly, adverse drug effects can occur presynaptically. In a patient with a reduced safety factor for neuromuscular transmission, exposure to a drug or clinical state which further reduces the efficiency of neuromuscular transmission can result in significant clinical weakness[1].

Myasthenia gravis (MG) is one of the best-characterized human immune-mediated disorders. Infantile onset of MG is much more common in the Chinese pediatric population Many Caucasian patients present in adolescence or early adult life, and these are most often female. MG is caused by serum antibodies binding to the nicotinic acetylcholine receptor (nAChR) on the postsynaptic surface of the neuromuscular junction, and which is essential for neuromuscular transmission. The antibodies lead to loss of nAChR, resulting in progressive weakness and fatigue of voluntary muscles. But within an individual patient the level of antibodies correlates well with disease status, and they are very rare (1%) in healthy subjects. A small percentage of patients (10–15%) with a clinical diagnosis of MG do not have detectable anti-AChR in their serum this condition is probably due to antibodies directed at some other neuromuscular junction target The role of serum anti-AChR antibodies in MG was clearly demonstrated by passive transfer experiments in which injection of MG immunoglobulin (Igs) into experimental mice produced many of the symptoms and signs of MG. It was confirmed by a striking clinical response to plasma exchange and immunosuppressive treatment. The thymus gland is involved in MG. Many patients, particularly those with onset of disease during adolescence or early adult life (early-onset MG), respond well to thymectomy, and about 25% do not need further treatment[2].

MYASTHENIA GRAVIS

First used for myasthenia gravis in 1984 in Intravenous Immunoglobulin (IVIG). The prototype NMJ disease is myasthenia gravis (MG). Familiarity with this disorder assists the clinician in recognizing others involving defective neuromuscular transmission. Furthermore, since MG is the most common of the junction diseases, it represents the most common clinical setting in which use of specific drugs may lead to clinical worsening. Myasthenia gravis is an autoimmune disorder of neuromuscular transmission involving the production of auto antibodies directed against the nicotinic AChR. Receptor antibodies are detectable in the

sera of 80-90% of patients with MG. Women are affected about twice as often as men. Symptoms may begin at virtually any age with a peak in women in the second and third decades, while the peak in men occurs in the fifth and sixth decades. Associated autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosis, and pernicious anemia are present in about 5% of patients. Thyroid disease occurs in about 10%, often in association with anti thyroid antibodies (Conti-Fine BM et al., 2006) About 10-15% of MG patients have thymoma which is usually a benign tumor, and lymphoid hyperplasia with proliferation of germinal centers is present in 50-70% of patients[3].

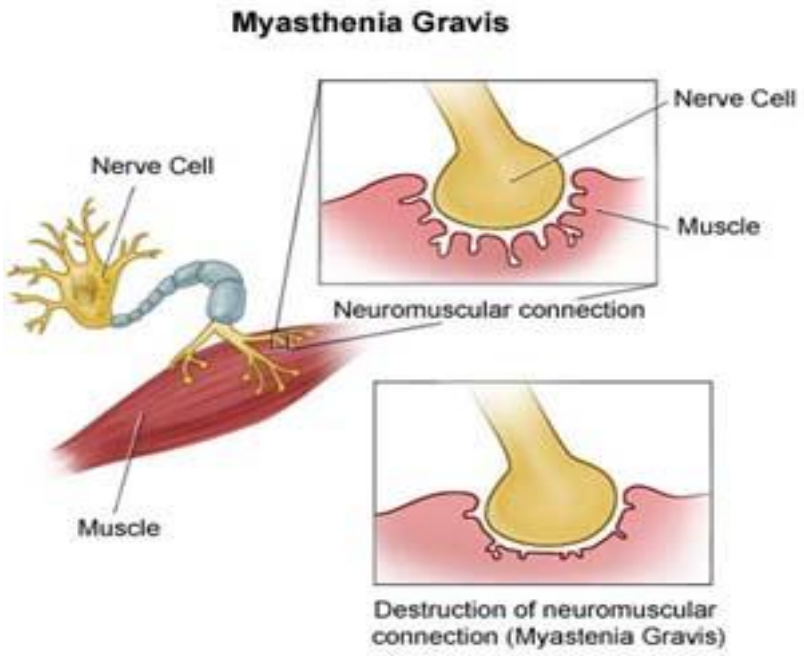

Fig. 1 Schematic diagram of Myasthenia Gravis

BACK GROUND

The aim of this review was to summarize the findings of all population-based epidemiological studies of myasthenia gravis (MG) paying attention to serological sub type-specific studies and age and sex specific incidence. Myasthenia gravis (MG) is an autoimmune disease usually caused by antibodies that block or destroy receptors for the neurotransmitter acetylcholine, leading to muscle weakness and fatigue. It is likely to occur as the result of a number of disease entities that result in an indistinguishable clinical picture. There are paraneoplastic forms (thymoma-associated) and non paraneoplastic forms and the disorder are immunologically heterogeneous - for example serum antibodies can be detected to muscle acetylcholine receptors (AChR-Ab) or the muscle-specific receptor tyrosine kinase but not both in the same patien. From case series and epidemiological studies, a bimodal

distribution of MG IR has been frequently described suggesting a hormonal or environmental influence on disease onset[4]. MG occurs in both sexes, at all ages and in all races. A large number of MG epidemiological studies have been performed worldwide over the last 60 years with marked variability in observed incidence and prevalence of the disease. Systematic review of MG epidemiology has been carried out in the past by Phillips but 28 further studies have been performed since and this review predates the discovery of Mu SK- Ab MG. In his review, Phillips commented upon apparent increasing IR and PR with time but without similar change in MR, and proposed that these trends were due to improved diagnosis and a changing natural history of disease related to better treatment.

In Old Days:

1934: Neostigmine introduced by "***Mary Walker***"

1935: ACTH administration shown to improve MG symptoms and shrink thymoma

1969: Azathiaprine administered

1971: First successful corticosteroid trial

DEFINITION:

Neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. Underlying defect is decrease in the available Acetylcholine receptors at NMJ, due to antibody mediated auto immune.

What causes MG

MG develops in adult life as the result of a defect in the immune system. The immune system's job is to produce antibodies against bacteria and viruses. Unfortunately, it sometimes produces antibodies against "self" proteins causing "auto" immune disease[5]. The majority of patients with MG produce antibodies against a self-protein called the acetylcholine receptor (AChR) . This is found at the junction between the nerve and the muscle (the neuromuscular junction (see figure 1 & 2). It acts as a "receiver" for the chemical signal, acetylcholine that is released from the nerve when we want to use a muscle. The antibodies bind to the acetylcholine receptors on the muscle membrane and greatly reduce their ability to receive the chemical signal. As a result the patient experiences muscle weakness which becomes worse as they repeatedly try to use the same muscle although we now understand how antibodies to the acetylcholine receptor cause muscle weakness, we do not know why patients with MG develop these particular antibodies. In some patients with MG, the thymus gland in the chest appears to be important in triggering the abnormal immune response.

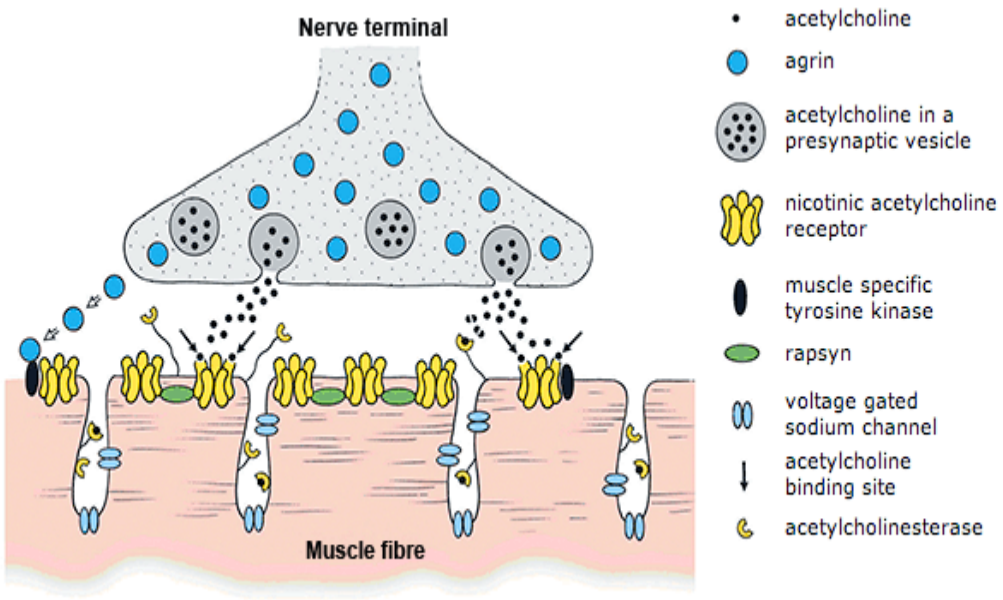

Fig. 2 Nerve terminal Position release acetylcholine to Muscle fiber

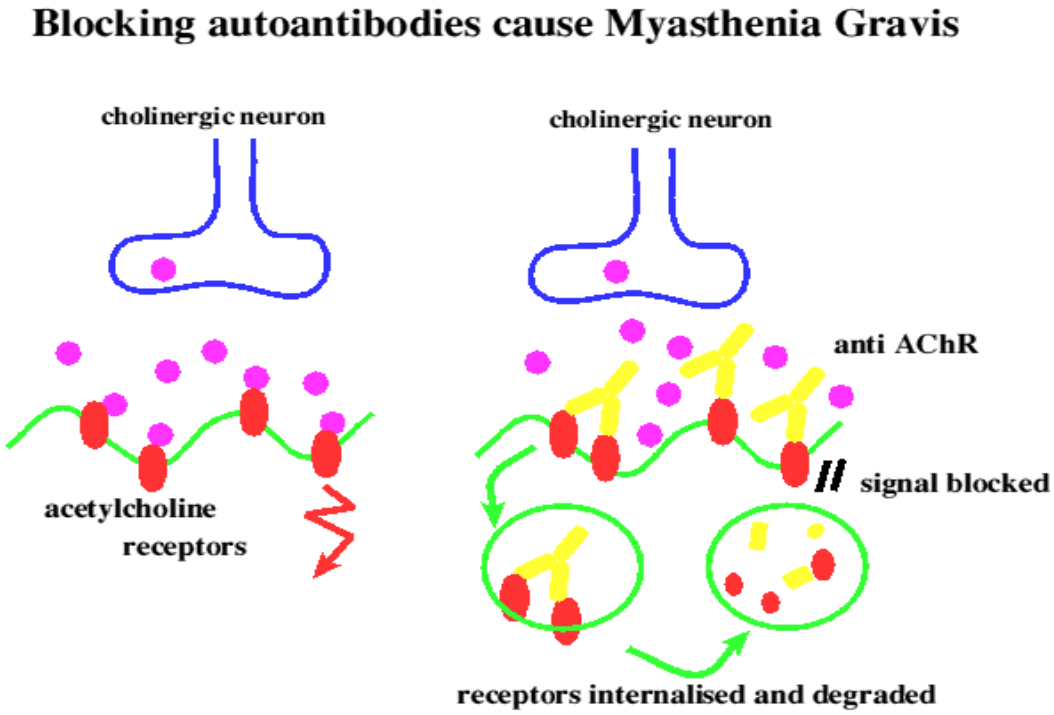

Fig. 3 Blocking auto antibodies causes Myasthenia Gravis

PATHOPHYSIOLOGY

Myasthenia gravis is a autoimmune disorder immune response creates acetylcholine receptor (AChR) antibodies that cause the following the binding and activation of complement at the neuromuscular junction that can lead to loss of AchR. Accelerated internalization and degradation of AChR molecules cross linked by antibody, resulting in loss of AChR

(correlates most closely with clinical severity of disease), Functional AChR block that impairs binding of acetylcholine to receptor, leading to poor muscle contraction[6]. Postsynaptic membrane is destroyed and decreases available binding sites for acetylcholine, leading to muscle weakness H.

MYASTHENIA GRAVIS: SIGNS & SYMPTOMS

1. Fluctuating weakness increased with exertion Fluctuating exertion
2. Eyes: ptosisptosis, diploplia, proptosis, EOM , weakness
3. Facial muscle weakness: mask face, horizontal smile, myasthenia sneer.
4. Dysarthria, Dysarthria, dysphasia, open jaw, jaw.
5. Respiratory muscle weakness Respiratory weakness.
6. Limb muscle weakness (upper > lower).
7. Normal reflexes and sensation normal sensation (F. E. Somnier et al., 1997).

Fig. 4 THE "MORNING ROUNDS POST CALL SIGN"

Pharmacologic Challenge: Tensilon Test

- ✓ Give AchE acetyl cholinesterase inhibitor
- ✓ Edrophonium Tensilon is short acting
- ✓ Evaluate pre/post weakness

Fig. 5 Tensilon test difference in Face (Man)

CLINICAL PRESENTATION

- ➢ Characteristic sporadic muscle weakness that worsens after affected muscles are used (fatigable weakness)
- ➢ Usually presents first in the extrinsic ocular muscles and progresses to muscles in the extremities

- Bulbar symptoms – dysphasia, dysarthria
- Extra ocular muscle (EOM) weakness – diplopic
- ✓ Symptoms are present in 2/3 of patients
- ✓ Disease is considered ocular MG if symptoms remain limited to EOM (10% of patients)
- Respiratory – respiratory failure in small percent of patients
- ✓ Death in severe cases
- ✓ May be associated with thymoma
- Commonly associated autoimmune disorders (50% of patients)
- ✓ Rheumatoid arthritis
- ✓ Systemic lupus erythematosus
- ✓ Pernicious anemia

TREATMENT & MANAGEMENT[7]

1. Acetyl cholinesterase inhibitor treatment for myasthenia gravis

- ✓ Myasthenia gravis is a disease in which antibodies directed against acetylcholine receptors block the transmission of nerve impulses to muscles, causing fluctuating muscle weakness and fatigability.
- ✓ Acetyl cholinesterase inhibitors, including pyridostigmine, inhibit the breakdown of acetylcholine, the neurotransmitter at the neuromuscular junction (NMJ).
- ✓ The inhibition produced by these drugs increases the availability of acetylcholine to stimulate the acetylcholine receptors and so facilitates muscle activation and contraction.
- ✓ Other treatments proposed for myasthenia gravis include drugs that suppress the immune system, including corticosteroids and azathioprine, and thymectomy (surgical removal of the thymus gland).
- ✓ Only one small randomized controlled cross-over trial relevant to the treatment of myasthenia gravis was identified. It included three participants with ocular myasthenia gravis and seven with generalized myasthenia gravis who received intranasal neostigmine (an acetyl cholinesterase inhibitor) or placebo.
- ✓ This varies over time and depends on other types of treatment given at the same time to inhibit the underlying autoimmune response.

2. Short-term immune therapies[8]

Plasma exchange and intravenous immunoglobulin are used for short-term treatment of MG exacerbations and when it is desirable to achieve a rapid clinical response. Plasma exchange temporarily reduces the concentrations of circulating anti-AChR antibodies and produces

improvement in a matter of days in most patients with acquired MG. Typically one exchange, removing one to two plasma volumes, is done every other day, up to a total of four to six times. Published reports indicate that plasma exchange effectively improves strength in most patients with severe MG. Common side-effects include hypotension and paresthesias from citrate induced hypocalcaemia (G. Harcourt et al., 1995) the standard dosing regimen for intravenous immunoglobulin (1–2 g/kg) involves the infusion of large volumes and is very expensive. Although rare, severe complications do occur, some of which are related to the large volume and high viscosity of the infused preparation

3. Long-term immune therapies

Most therapeutic recommendations on the use of chronic immunosuppressive agents for MG are based on evidence from either small, randomized controlled trials.

a. Corticosteroids:

Corticosteroids were the first immunosuppressant medications to be used in MG, and remain the most commonly used immune-directed therapy. In four large retrospective series of steroid treatment for generalized MG, administered at various doses, more than 73% of the 422 patients treated achieved either marked improvement or remission. Oral prednisone at relatively low doses (20 mg/day, increased by 5–10 mg/day every 3 days until symptoms resolve) might be more effective than anticholinesterase drugs in ocular MG .

Prednisone should therefore be considered in all patients with ocular MG who do not achieve full control of symptoms with anti cholinesterase medications. Although not definitive, evidence suggests that corticosteroid treatment might delay or reduce the frequency of progression of ocular MG to generalized disease.

b. Non-steroidal immunosuppressive agents

I) Azathioprine is a purine anti metabolite that interferes with T-cell and B-cell proliferation. Retrospective studies indicate that azathioprine is effective in 70–90% of patients with MG, but the onset of benefit might be delayed for as long as 12 months. Azathioprine (initiated at 50 mg daily) can be used alone or as a steroid-sparing agent in MG, but when used in combination with prednisone it might be more effective and better tolerated than prednisone alone.

II) Cyclosporine inhibits T-cell proliferation via disruption of calcineurin signaling, which blocks the synthesis of interleukin 2 and other proteins essential to the function of CD4 T cells. Its effi cacy in MG has been suggested by a small, randomized, placebo-controlled clinical trial, and retrospective studies have supported its use as a steroid-sparing agent[9] .

III) Tacrolimus (FK506) has a similar mechanism of action as cyclosporine, and potential benefit in MG.

c. Other immunosuppressive agents

A small percentage of patients with MG are refractory or develop intolerable side effects to treatment with corticosteroids in combination with one or more of the immunosuppressive agents described above. Agents that can be considered in these refractory patients include cyclophosphamide and rituximab. In a recent randomized controlled trial, pulsed doses of intravenous cyclophosphamide (500 mg/m2) given to patients with refractory MG improved muscle strength and reduced steroid requirement. Rituximab is a chronic monoclonal antibody directed against the B-cell surface marker CD20 (S. P. Luckman et al., 2006) It effectively reduces circulating B-cell counts, and on the basis of its potential for targeting auto reactive B-cell clones, might have a therapeutic role in antibody-mediated autoimmune diseases.

DIAGNOSTIC TESTS FOR MYASTHENIA GRAVIS[10]:

a. Ameliorative test: Edorphonium 2-10 mg injected slowly i.v. improves muscle strength only in myasthenia gravis and not in other muscular dystrophies.

b. Provocative test: Myasthenia are highly sensitive to d-tubocurarine, 0.5 mg i.v. causes marketed weakness in them but is effective in non-myasthenics. This best in hazardous facilities for positive pressure respiration must be at hand before performing. Demonstrated of anti-NR antibodies in plasma or muscle biopsy specimen is a more reliable test.

Laboratory Testing

- Serum antibody testing: Positive test is diagnostic of MG
  - ✓ Anti-AChR measurement
    - Positive in 85-90% of patients
    - Specificity approaches 100%
  - Negative AChR does not exclude disease
  - Approximately 50% of ocular MG patients are negative for this antibody
- **Anti-Musk:** MUSK is a trans membrane endplate polypeptide involved in a signaling pathway that maintains the normal functional integrity of the NMJ.
- Maintenance of AChR clustering at the muscle endplate,
  - ✓ Detectable in 30-40% of anti-AChR negative patients
  - ✓ Do not order if clinically, patient has isolated ocular MG

- ✓ Bulbar symptoms more common if this antibody is present

- Anti-striation protein:
  - ✓ Detectable in 70-80% of thymomatous MG and 20-30% of non thymomatous MG patients
  - ✓ Rare in ocular MG

Other Testing

- Consider anti cholinesterase testing (Tensilon test using edrophonium) in AChR-negative patients improvement in muscle strength is diagnostic of MG.
- Repetitive stimulation or single-fiber electro myogram
  - ✓ Positive in 90% of MG patients – demonstrates a primary postsynaptic neuromuscular junctional disorder

Differential Diagnosis

- Guillain-Barré syndrome
- Amyotrophic lateral sclerosis (Lou Gehrig disease)
- Eaton-Lambert syndrome
- Botulism
- Brainstem/cavernous sinus lesions
- Enterovirus (poliomyelitis)
- Polymyositis
- Acute intermittent porphyria
- Drug-related myopathy
- Corticosteroids

THYMECTOMY

Since the thymus can be abnormal in-patients with MG, surgical removal of the thymus (thymectomy) is recommended for some patients. Following thymectomy, MG symptoms do not usually improve in-patients with a thymoma, but may improve in young patients with an enlarged thymus. In these patients, approximately 1 in 4 is cured by thymectomy, 2 in 4 have significant improvement, but 1 in 4 does not improve. Improvement following thymectomy is usually apparent in the first year, but may take up to 3 years to occur (Bergtraum MP, et al. 2002). If the patient recovers, or improves significantly following thymectomy, then they may not need any additional therapy. But many patients will need further treatments[11].

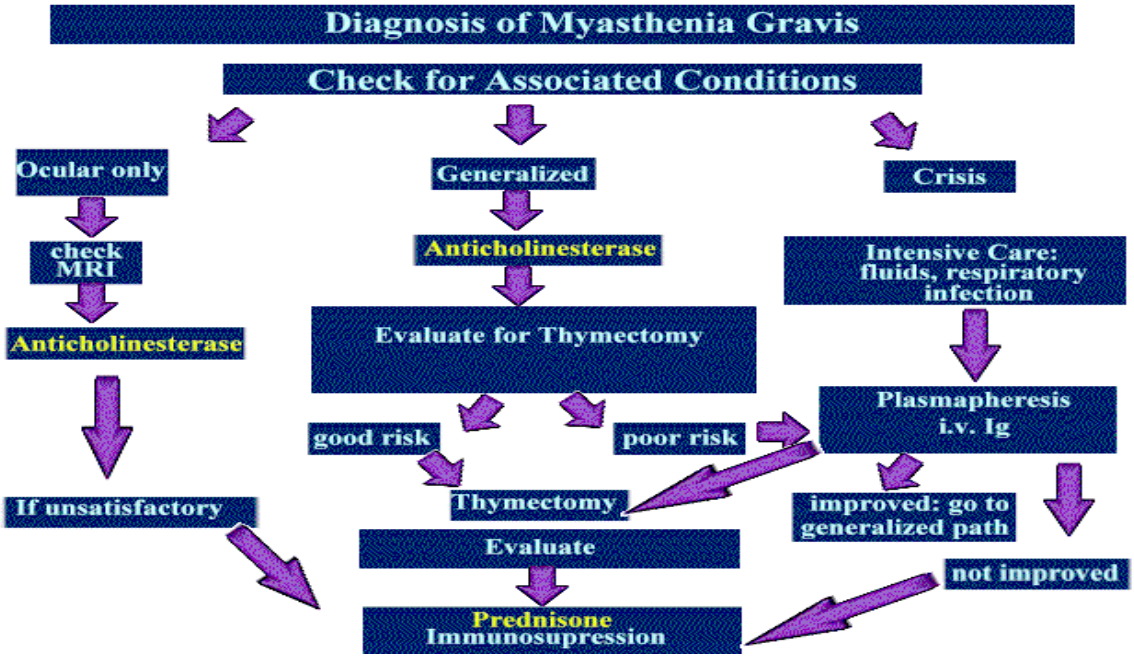

Fig. 5 Schematic representation diagnosis of Myasthenia Gravis

CONCLUSION

Myasthenia gravis is a potentially fatal condition that should be considered in elderly patients with bulbar symptoms. Statin medication should be introduced cautiously and considered as a potential cause or precipitant of worsening muscle strength in patients with myasthenia gravis. The diagnosis is often difficult to ascertain because of the frequent absence of a family history of the disease, and because of the pre-eminence of the myopathic signs compared with myasthenia signs. The early onset of the first symptoms, the presence of fluctuations, the demonstration of a neuromuscular block, repetitive CMAP after single stimulation, and the cholinesterase.

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