

The myasthenic patient in crisis: an update of the management in Neurointensive Care Unit

Pacientes miastênicos em crise: uma melhora de conduta na unidade de terapia intensiva

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular transmission leading to generalized or localized muscle weakness due most frequently to the presence of autoantibodies against acetylcholine receptors in the postsynaptic motor end-plate. Myasthenic crisis (MC) is a complication of MG characterized by worsening muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation. It also includes postsurgical patients, in whom exacerbation of muscle weakness from MG causes a delay in extubation. MC is a very important, serious, and reversible neurological emergency that affects 20–30% of the myasthenic patients, usually within the first year of illness and maybe the debut form of the disease. Most patients have a predisposing factor that triggers the crisis, generally an infection of the respiratory tract. Immunoglobulins, plasma exchange, and steroids are the cornerstones of immunotherapy. Today with the modern neurocritical care, mortality rate of MC is less than 5%.

Key words: myasthenic crisis, myasthenia gravis, respiratory failure, immunosuppressive therapy, thymectomy.

RESUMO

Miastenia grave (MG) é um distúrbio autoimune que afeta principalmente a transmissão neuromuscular, levando a fraqueza muscular generalizada ou localizada. É devida mais frequentemente à presença de auto-anticorpos anti-receptores de acetilcolina na fenda pós-sináptica da placa motora. A crise miastênica (CM) é uma complicação da MG caracterizada por piora da fraqueza muscular, resultando em falência respiratória, o que requer entubação endotraqueal e ventilação mecânica. Isto ocorre também em pacientes pós-cirúrgicos, em que há piora da fraqueza muscular devido à MG, causando um atraso na extubação. MC é uma emergência neurológica importante, séria e reversível que afeta 20–30% dos pacientes miastênicos, usualmente durante o primeiro ano de enfermidade, podendo a crise miastênica ser a manifestação inicial da MG. A maioria dos pacientes tem fatores predisponentes que desencadeiam a crise, geralmente uma infecção do trato respiratório. Imunoglobulina, plasmáfereze e esteróides são a pedra angular da imunoterapia. Hoje, dentro da terapia neurocrítica, a taxa de mortalidade na CM é menor que 5%.

Palavras-Chave: crise miastênica, miastenia grave, falência respiratória, terapia imunossupressiva, timectomia.

Myasthenic crisis (MC) is an uncommon life-threatening neurological emergency¹⁻³. It may occur in patients who have previously diagnosed myasthenia gravis (MG) or may be the onset of the disease, generally during the first year after diagnosis⁴⁻⁶. The hallmark of MC is the bulbar or respiratory failure^{1,2,5,7-12}. The management of these patients is challenging due to the fluctuating nature of the disease^{4,5,8-12}. Prevention and treatment of MC requires admission to intensive care unit

(ICU) — preferably a neuroscience ICU — close observation, and, when necessary, intubation for ventilatory and feeding support^{2,8-13}. In addition, acute care should be focused on reducing circulating antibody titers with immunologic therapy such as plasmapheresis (PE), immunoglobulin (IVIg), and corticosteroids^{2,8-13}. Despite the growing interest and newer treatment modalities, deficiencies in management still persist. Not all ICU physicians have experience in neurological aspects

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of MG. This paper reviews the available evidence in the detection and treatment of the MC from a multidisciplinary perspective, with the intention to help to correct management.

EPIDEMIOLOGICAL DATA

The annual incidence of MG is 1–2/100,000¹⁴, with an estimated prevalence of 5–15/100,000^{3,14}; 21% of patients had onset after 60 years¹⁵ and 30% of them will develop some degree of bulbar or respiratory muscle weakness¹⁵. About 15–20% of MG patients will develop MC, usually within the first year of illness^{4,6–11}. MC may be the initial presentation of MG in about 20% of patients and one-third of surviving may experience another crisis^{4,6–11}. Overall, women are twice as likely as men to be affected^{3,14}. The average age of admission with crisis is 59 years¹⁶. The occurrence of MG shows a bimodal distribution, with the following male:female ratios: 3:7 if aged <40 years, 1:1 if aged 40–49 years, 3:2 if aged >50 years^{14,17}. The outcome has improved significantly, and today the reported mortality rate is around 5%^{2,7,9,10,16}.

HOW WE DEFINED MYASTHENIC CRISIS?

By definition, all MG patients with acquired (neonatal) or autoimmune form showing a respiratory failure due to muscle weakness and requiring ventilatory assistance

should be considered in MC^{2,4–12,18}. Although there is no universally accepted definition, MC should be considered a true neurological emergency characterized by “Severe weakness of the bulbar (innervated by cranial nerves) and/or respiratory muscles, enough to cause inability to maintain adequate ventilation and/or permeability of upper airways, causing respiratory failure that requires artificial airway or ventilatory support”^{2,6}. Postoperative myasthenic patients in whom extubation has been delayed more than 24 hours also should be considered crisis⁷. Generally, patients with MC correspond to class 3 or 4 in Osserman and Genkins classification¹⁴ or class V according to Myasthenia Gravis Foundation¹⁴ (Table 1).

PREDISPOSING FACTORS

Patients who develop MC in their great majority have a precipitating factor, although, in 30–40% of cases, none is found^{2,5–7,9–12,19,21}. Respiratory infection (40%), emotional stresses, microaspirations (10%), changes in medication regimen (8%), surgery, or trauma are among the most common predisposing factors^{2,5–7,9–12,16,18}. Many drugs exacerbate MG and may determine MC¹⁹. They should be avoided or used with caution. Some examples have been listed in Table 2. It is important to note that telithromycin, a macrolide, is absolutely contraindicated in MG^{14,19–21}. Initial treatment with prednisone led to exacerbation of MG in almost half of

Table 1. Clinical classifications (with modifications) of the severity of myasthenia gravis.

Osserman and Genkins ¹⁴
Ocular myasthenia, localized nonprogressive
Generalized disease of gradual onset involving more than one muscle group (bulbar or skeletal)
Acute fulminant disease
Late severe disease (>2 years after symptoms onset)
Muscle atrophy related to duration and clinical severity of the disease
Myasthenia Gravis Foundation [†]
Class I: Ocular myasthenia (may have weakness of eye closure all other muscles have normal strength)
Class II*: Mild weakness (affecting muscles besides ocular muscles; may also have ocular muscle weakness of any degree)
Class IIa: mostly affecting extremities, axial muscles, or both; may also have involvement of oropharyngeal muscles to lesser degree
Class IIb: mostly involving oropharyngeal, respiratory muscles, or both; may also have involvement of extremities, axial muscles, or both to lesser or equal degree
Class III*: Moderate weakness (in muscles besides ocular muscles; may also have weakness of any degree of ocular muscles)
Class IIIa: involvement is mostly of extremities, axial muscles, or both; may also have involvement of oropharyngeal muscles to lesser degree
Class IIIb: mostly involving oropharyngeal, respiratory muscles, or both; may also have involvement of extremities, axial muscles, or both to lesser or equal degree
Class IV*: Severe weakness (in muscles besides ocular muscles; may also have weakness of any degree of ocular muscles)
Class IVa: involvement is mostly of extremities, axial muscles, or both; may also have involvement of oropharyngeal muscles to lesser degree
Class IVb: mostly involving oropharyngeal, respiratory muscles, or both; may also have involvement of extremities, axial muscles, or both to lesser or equal degree
Class V: Myasthenic crisis [intubation, with or without mechanical ventilation (except when intubated for routine postoperative management), quantitative myastheniagravis scoring system developed for determination of disease severity]

*Class II–IV are divided into subgroups according to predominance of muscle weakness: (a) limb and trunk; (b) bulbar.

[†]Myasthenia Gravis Foundation of America (MGFA) clinical classification based on neurologic examination limitations of clinical classification fluctuating weakness examiner's subjective classification of mild, moderate, severe classification should be based on most severely affected muscles.

Table 2. Medication and drugs that may provoke myasthenia crisis.

Drug Class	Medication
Antipsychotics	Phenothiazines, sulpiride, atypicals (clozapine)
Neuromuscular-blocking drugs	Succinylcholine, Vecuronium
Anticholinergic drugs	Including ocular proparacaine
Cardiovascular medications	Cibenzoline Lidocaine (systemic dosing) Procainamide Propranolol (and other beta blockers) Quinidine Verapamil Bretylium Statins
Neurologic and psychoactive medications	Chlorpromazine Lithium Phenytoin Carbamazepin Trihexyphenidyl Trimethadione
Antibiotics	All aminoglycosides Ciprofloxacin Colistin Lincomycins (includes clindamycin) Macrolides Erythromycin Clarithromycin Telithromycin (has risk of exacerbation of MG, including rapid onset of life-threatening acute aespriatory failure Penicillins (include ampicillin and imipenem-cilastatin) Polymyxins Tetracyclines
Other antimicrobial drugs	Emetine Imiquimod Ritonavir
Antirheumatologic and immunosuppressive medications	Chloroquine Penicillamine Prednisone (and other glucocorticosteroids) Interferons
Other medication	Aprotinin Iodinated-contrast agents Levonorgestrel Magnesium (including magnesium sulfate) Methoxyflurane Pyrantel pamoate Propafenone Dextro carnitine-levocarnitine but not levocarnitine alone Interferon alfa Methocarbamol Transdermal nicotine Acetazolamide

patients, whereas 9–18% of them develop MC^{19,22}. Therefore, initiation of corticosteroids should always occur in a hospital setting, where respiratory function can be monitored^{19,22}. Predictors of exacerbation from prednisone include older age, lower score on Myasthenia Severity Scale (Table 3), and bulbar symptoms²². Live vaccines should be avoided in

MG patients receiving immunosuppression^{2,7,19}. Contrast agents²⁰ and electrolyte alterations (hypokalemia, hypophosphatemia) may exacerbate muscle weakness^{2,7}. Thyroid disease, which can coexist with MG, can exacerbate or unmask MG weakness when untreated, while over-replacement with levothyroxine may also cause MC^{2,7,19}. If a MG patient requires general anaesthesia, neuromuscular-blocking agents should be used cautiously since they are particularly sensitive to non-depolarizing agents and the response to depolarizing drugs is variable^{2,7,21}. The association of MG with thymic pathology is well known. MC is almost as twice more frequent in patients with thymoma^{2,7,14,23–25}. Pregnancy aggravates MG in 33% of the cases, and MC in pregnancy carries high perinatal mortality^{2,7,26}.

PATHOPHYSIOLOGY OF MYASTHENIC GRAVIS AND MYASTHENIC CRISIS

MG is an autoimmune disorder resulting from antibody-complement-mediated and T-cell-dependent immunologic attack on the postsynaptic membrane of the neuromuscular junction, mainly against acetylcholine receptor (AChR)^{14,27,28} (Fig 1). The antibodies that bind to epitopes of the skeletal muscle end-plate region result in abnormal neuromuscular transmission and clinical weakness^{14,27,28}. There are different antibodies directed at the neuromuscular junction and detectable in the plasma (Table 4)^{14,27,28}. AChR antibodies bind to the main immunogenic region of alpha subunit of AChR of postsynaptic membrane resulting in decreased numbers and density of AChR^{14,27,28}. They are present in 70–90% of patients with generalized MG and between 30 and 70% of patients with ocular form^{14,27,28}.

About 10% of patients show antibodies to muscle-specific tyrosine kinase (Anti MuSK)^{14,27,28}. Patients with MuSK typically are female and have characteristic weakness pattern involving principally bulbar, neck, shoulder, and respiratory muscles^{14,27,28}. MuSK is a protein located at the postsynaptic membrane, which is responsible for clustering the AChR at the muscle membrane surface during development, but the function in mature skeletal muscle and its role in pathophysiology of MG is unknown^{14,27,28}. Other muscle autoantibodies reacting with striated muscle titin and ryanodin receptor (RyR) antigens are found in up to 95% of MG patients with thymoma and in 50% of late-onset MG patients²⁹ (>50 years). Thymomas are present in <2% of patients without antistriated antibodies³⁰. Following thymectomy, rise in antistriated muscle antibody titer may be a sign of recurrent tumor³⁰. These antibodies are usually associated with more severe MG³⁰. Titin is a protein, providing a direct link between mechanical muscle strain and muscle gene activation^{14,28,28}. Antititin antibodies may also be detected in 50% of patients with late-onset generalized MG without thymoma^{28,29}. The RyR is the calcium channel of the sarcoplasmic reticulum

Table 3. Quantitative myasthenia gravis score for disease severity.

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), seconds	61	11–60	1–10	Spontaneous	
Ptosis (upward gaze), seconds	61	11–60	1–10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30–49	Dysarthria at 10–29	Dysarthria at 9	
Right arm outstretched (90° sitting), 240 seconds	240 seconds	90–239	10–89	0–9	
Left arm outstretched (90 degrees sitting), 240 seconds	240 seconds	90–239	10–89	0–9	
Vital capacity, % predicted	≥80	65–79	50–64	<50	
Right-hand grip, kgW					
Men	≥45	15–44	5–14	0–4	
Women	≥30	10–29	5–9	0–4	
Light-hand grip, kgW					
Men	≥35	15–34	5–14	0–4	
Women	≥25	10–24	5–9	0–4	
Head lifted (45° supine), seconds	120	30–119	1–29	0	
Right leg outstretched (45° supine), seconds	100	31–99	1–30	0	
Right leg outstretched (45° supine), seconds	100	31–99	1–30	0	

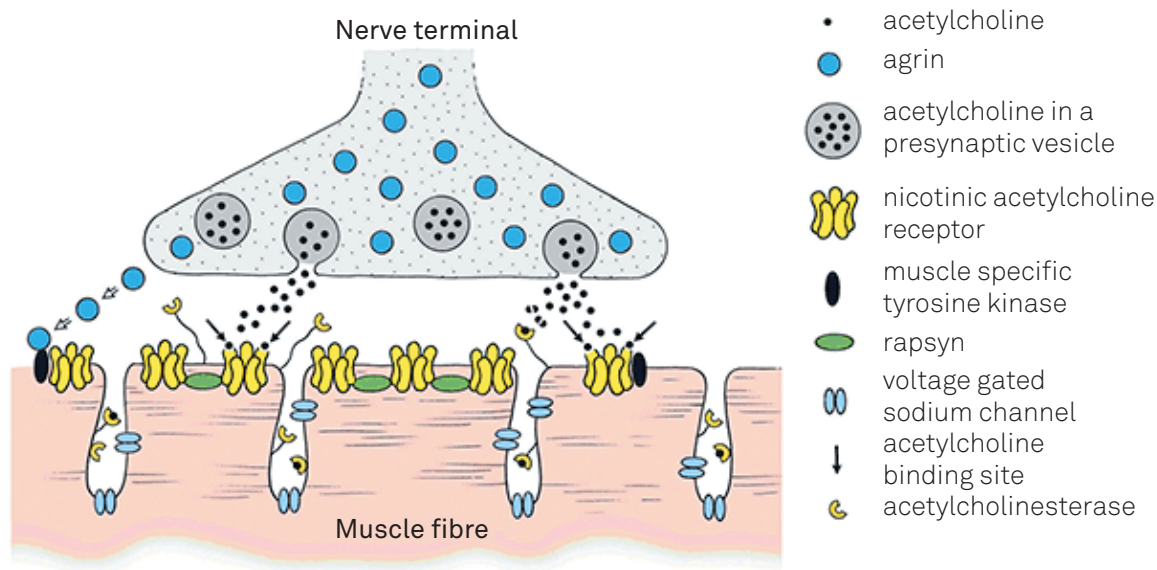


Fig 1. Normal neuromuscular junction and pathophysiology of myasthenia gravis. In the normal neuromuscular junction, acetylcholine (ACh) released from the nerve terminal following a nerve action potential binds to the acetylcholine receptor (AChRs) on the postsynaptic muscle, triggering a muscle action potential propagated by the voltage-gated sodium channel. Acetylcholinesterase scavenges and breaks down unbound ACh. In a separate pathway, neural agrin binds muscle-specific tyrosine kinase (MuSK) initiating clustering of phosphorylated rapsyn and AChRs, stabilizing the postsynaptic structure opposite the nerve. MuSK initiates clustering of the cytoplasmic protein rapsyn and AChRs and is believed to maintain normal postsynaptic architecture. In myasthenia gravis caused by antibodies to the AChRs, there is blockade of the binding site for ACh, cross-linking of the AChR with subsequent internalization and reduction in its surface expression, and initiation of complement and cellular inflammatory cascades with damage to the post- and presynaptic structures. The molecular physiology of myasthenia gravis mediated by antibodies to MuSK has not been established.

Table 4. Clinical subtypes and the occurrence of the various muscle autoantibodies in the different subgroups of myasthenia gravis.

MG subgroups	Age of onset	Thymic histology	HLA associations	Muscle autoantibodies (percentage of patients)				Clinical findings
				AChR	MuSK	Titin	RyR	
Early-onset non-MuSK nonthymoma	<40	Hyperplasia	DR3-B8 DR9 (in Asians)	+ (100%)	– (100%)	+ (10%)	– (100%)	These patients are more often female. In addition to anti-AChR antibodies, other organ-specific autoantibodies might be present, and patients might be affected by other autoimmune diseases, most commonly autoimmune thyroid disease. Antibodies to non-AChR muscle components are not typically seen in early-onset MG
Late-onset non-MuSK non-thymoma	>40	Normal/ thymic atrophy	DR2-B7	+ (100%)	– (100%)	+ (58%)	+ (14%)	These patients are more often male and usually have normal thymic histology or thymic atrophy. They can present with ocular or generalized weakness, but typically have a more severe disease course compared with early-onset MG, and spontaneous remissions are rare. The presence of anti-ryanodine receptor antibodies has been associated with more severe, generalized, or predominantly oropharyngeal weakness, and frequent myasthenic crises
MuSK positive (regardless of onset age)	<40 (most patients)	Normal	DR14-DQ5	– (100%)	+ (100%)	NA	NA	Whereas patients with anti-MuSK antibodies can have presentations similar to anti-AChR-positive MG, they commonly have atypical clinical features, such as selective facial, bulbar, neck, and respiratory muscle weakness and marked muscle atrophy, occasionally with relative sparing of ocular muscles. Respiratory crises are more common than in generalized anti-AChR-positive disease. Weakness can involve muscles that are not usually symptomatic in MG, such as paraspinal and upper esophageal muscles. Enhanced sensitivity, nonresponsiveness, and even clinical worsening in response to anticholinesterase agents have also been reported. Disease onset in patients with anti-MuSK MG tends to be earlier, and patients are predominantly female
Seronegative (regardless of onset age)				– (100%)	– (100%)	– (100%)	– (100%)	Patients with MG who lack both anti-AChR and anti-MuSK antibodies (so-called seronegative MG) are clinically heterogeneous and can have purely ocular, mild generalized, or severe generalized disease. The true prevalence of seronegative MG might be quite low, because some patients might have low-affinity anti-AChR antibodies that are not detected with currently available assays. Not surprisingly, these patients are essentially indistinguishable from patients with anti-AChR-positive MG in terms of clinical features, pharmacological treatment response, and even thymic abnormalities in some cases

Continue...

Table 4. Continuation

Thymoma (regardless of onset age)	+ (100%)	May occur in some patients	+ (95%)	+ (70%)	About 10–15% of patients with MG have a thymic epithelial tumor – a thymoma. Thymoma-associated MG is equally common in men and women and can occur at any age, with peak onset at the age of 50 years ^{23,24} . Clinical presentations tend to be more severe than in nonthymomatous patients with early-onset MG, commonly with progressive generalized and oropharyngeal weakness. However, long-term prognosis is similar to that of late onset, nonthymomatous MG. With rare exceptions, MG patients with thymoma have high titers of anti-AChR antibodies, and they usually also have antibodies against titin. Additional paraneoplasia-associated antibodies (and their related syndromes) might occur in thymomatous MG, including anti-voltage-gated K ⁺ and Ca ²⁺ channel, anti-Hu (antineuronal nuclear autoantibody 1), antidihydropyrimidinase-related protein 5 (formerly anticollapsin response mediator protein 5), and antiglutamic acid decarboxylase antibodies. The presence of autoantibodies to a voltage-gated K ⁺ channel, KCNA4 (formerly Kv1.4), has been recently reported in Japanese patients with severe MG, thymoma, and concomitant myocarditis and/or myositis. In patients with thymoma, surgery (thymohymectomy) often completely and permanently removes the tumor, but symptoms of MG usually persist and require chronic immunotherapy
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HLA: histocompatibility antigen; AChR: acetylcholine receptor; MuSK: muscle-specific tyrosine kinase; RyR: ryanodin receptor.

involved in excitation-contraction coupling of striated muscle^{14,28-30}. It is found in 50% of patients with MG and thymoma^{14,28-30}. Higher RyR antibody levels are associated with severity^{14,28-30}. Patients with RyR antibodies are characterized by frequent involvement of bulbar, respiratory, and neck muscles^{14,28-30}. Neck weakness at onset is a distinctive feature of patients with RyR antibodies, while respiratory symptoms are found in patients with titin antibodies with and without RyR antibodies^{14,28-30}. Limb involvement with few or no bulbar signs is typical in RyR-antibody-negative MG²⁸⁻³⁰. Since many thymoma patients have RyR antibodies, neck weakness and nonlimb bulbar distribution of symptoms are initial characteristic features. Such symptom distribution should raise the suspicion of thymoma²⁸⁻³⁰. Thymoma and late-onset MG share similar serological profile with high prevalence of titin and RyR antibodies and lower AChR antibody concentrations compared with early-onset MG^{29,30}.

Finally, there is a remaining group of patients who do not have either AChR or MuSK antibodies and they actually

are considered seronegative^{14,27}. Clinically they are similar to patients with AChR antibodies.

During MC, the respiratory failure can be hypoxemic, hypercapnic, or both and result from poor airway protection, inadequate secretions clearance, and hypoventilation. Bulbar (oropharyngeal) muscle dysfunction may be the predominant feature in some patients³¹. In MuSK-MG, bulbar weakness always precedes respiratory failure⁷. The dysfunction of bulbar muscles alters cough, swallowing reflexes, as well as sigh mechanisms^{2,5,7,9-11,31,32}. Signs of bulbar weakness include dysphagia, nasal regurgitation, nasal and staccato speech, jaw and tongue weakness, and bifacial paresis³². It is difficult to handle secretions that accumulate in the oropharynx. Upper airway patent is lost^{2,5,7,9-11,31,32}. These alterations increase the likelihood of microaspiration, atelectasis, upper airway resistance, dead space, and work of breathing^{2,5,7,9-11,31,32}. Muscle weakness in AchR-MG tends to initially affect intercostals and accessory muscles and then the diaphragm⁷. The recruitment of accessory muscles indicates significant inspiratory weakness³². Weak

cough or difficulty in counting notes weakness of expiratory muscles³². Anxiety, accompanied by tachycardia and tachypnea, may be the first sign of air hunger³². Respiratory muscles are unable to maintain adequate tidal volume. Ventilation becomes rapid and shallow, decreasing pulmonary functional residual capacity, resulting in atelectasis, closing a vicious circle that increases work of breathing with exacerbation of muscle weakness that culminates altering the ventilation/perfusion relationship causing hypoxia and hypercapnia^{2,5,7,9-11,31,32} (Fig 2).

The signs of MC should be sought in all patients with MG, even when they do not complain weakness because central ventilatory drive usually remains intact during crisis; so, even when minute ventilation response to CO₂ is poor, the generalized weakness can mask the usual signs of respiratory distress. Respiratory muscles may suddenly fatigue, producing precipitous respiratory collapse³². In addition, some patients may present with respiratory insufficiency out of proportion to limb or bulbar weakness^{2,5,7,9-11,31-33}. In rare cases of MC, ventilatory failure is the only clinically overt manifestation^{34,35}.

HOW TO MAKE A CORRECT DIAGNOSIS?

MC is an acute respiratory failure due to worsening MG, characterized by forced vital capacity (FVC) below 1 L, negative inspiratory force (NIF) of 20 cm H₂O or less, and the need for ventilatory support^{2,5,7,9-11,31-33}. Arterial blood gas analysis commonly shows hypercarbia before hypoxia. There should be a low threshold for endotracheal intubation due to rapid

deterioration of bulbar and respiratory muscles. For these reasons, a strict monitoring of respiratory status with regular bedside pulmonary function testing is appropriate^{2,5,7,9-11,31-33}.

Patients with previous diagnosed Myasthenia gravis

The presence or worsening of clinical features, such as progressive muscle weakness (arms, limbs), palpebral ptosis, bulbar muscle involvement, and dysphagia together with the presence of respiratory distress (dyspnea, shortness of breath, tachypnea, use of accessory muscles) may help to identify patients at risk for MC^{2,5,7,9-11,31-33}.

Patients without a previous diagnosis of Myasthenia gravis

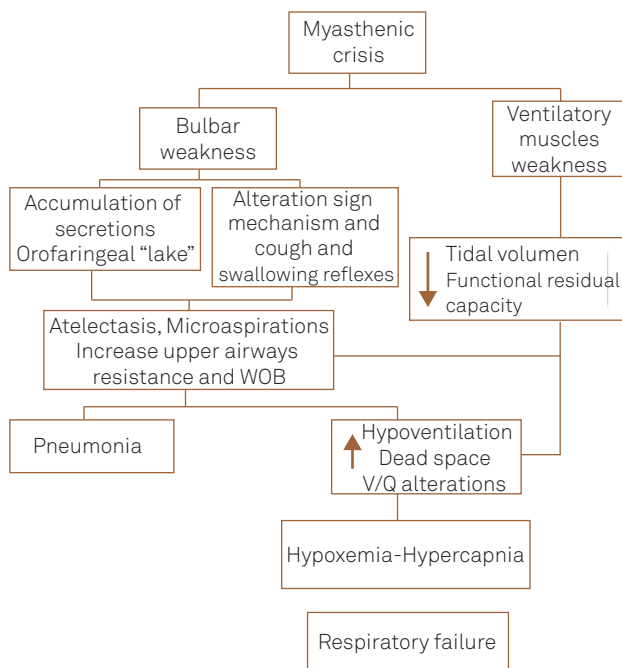
If MC is the first presentation of the disease, the specific clinical features of the myasthenic state cannot be evident. These patients quite suddenly show a severe respiratory distress, facial weakness, airway collapse, and muscle failure. Initially, oxygenation is preserved³². A suspected clinical diagnosis should be confirmed using electrophysiological, pharmacological, and laboratory testing^{2,7,14,17,36}, usually not available on an emergent basis³⁶.

Electrophysiological testing

In MG, repetitive nerve stimulation (RNS) shows a significant decremental response (>9%) between the first and fourth or fifth compound muscle action potential (CMAP) at low rates (2–5 Hz)^{14,17,36}. RNS depletes Ach stores at neuromuscular junction, reducing the safety factor and the probability of successful neuromuscular transmission CMAP becomes reduced in amplitude and area^{14,17,36}. In patients with respiratory involvement, phrenic and long thoracic nerves should also be tested³⁷. The results of repetitive long thoracic nerve and phrenic stimulation show a good correlation with respiratory symptoms and management requirements³⁷. Single-fiber electromyography (SFEMG)³⁸ is the most sensitive test for abnormal neuromuscular transmission detection; however, it is time consuming and requires special expertise³⁸.

Pharmacologic testing: edrophonium (Tensilon)

The Tensilon (edrophonium) test is useful in diagnosing MG and in distinguishing MC from cholinergic crisis^{2,7,14,17}. Edrophonium is an acetylcholinesterase inhibitor with rapid onset (30 seconds), and effects lasting 5 minutes reported a sensitivity of 86% for ocular MG and 95% for generalized MG^{14,17}. Edrophonium temporarily improves the safety factor of neuromuscular transmission and may elicit improved muscle strength^{2,7,14,17}. Once airway and ventilation are secured, give an initial dose of 1–2 mg and watch for 1 minute, then give 3 mg, and another 3 mg if necessary^{14,17}. Typical side effects of sweating, tearing, fasciculations, and abdominal cramping may indicate peak edrophonium effect. Observe for possible serious adverse effects such as hypotension or arrhythmias and have always atropine available as antidote^{14,17}.



WOB indicates work of breathing; V/Q: ventilation/perfusion relationship.

Fig 2. Pathophysiology of myasthenic crisis.

If muscle strength improves within 1 minute of any dose increment, test is positive and no further edrophonium needs to be administered^{14,17}. Edrophonium test is not recommended in patient in crisis because of likelihood of false-positive or false-negative results, and the risk of worsening muscle weakness above all in patients with anticholinesterase overdose^{2,7,14,17}. Patients with a cholinergic crisis may respond to edrophonium challenge by increasing salivation and bronchopulmonary secretions, diaphoresis, and gastric motility^{2,5,7,14,17}. These changes should be managed expectantly, as the half-life of edrophonium is short (10 min). In addition, worsening of bulbar and respiratory symptoms in MuSK-MG after anticholinesterase administration is known and could confound the clinical diagnosis¹⁷. If the patient requires ventilatory support there is no need to distinguish the two crisis entities¹⁷. False-positives have been also reported in lower motor neuron diseases and brainstem tumors¹⁷.

Serological testing

If MG is suspected, the patients should be tested for AChR antibodies^{14,17,39}. If these are negative, MuSK antibodies should also be tested^{14,17,39}. Antibodies should be sent for analysis before the institution of any immunotherapy. Anti-AChR antibodies are elevated in 85–90% of patients with generalized MG^{14,17,28,39}. MuSK-related autoimmune-acquired MG presents with slightly different phenotype^{14,17,28,39}.

Other testing

Chest computerized tomography (CT) should be performed in patients with MG to exclude thymoma^{14,17}. Chest CT is more sensitive than plain chest radiographs for delineating anterior mediastinal masses. MRI does not improve diagnostic sensitivity. Iodinated contrast agents may precipitate worsening of myasthenic weakness²⁰. Although this is an uncommon phenomenon, we do not routinely use iodinated contrast agents during chest CT to assess for thymoma. These examination should be made in a stable patient. Since MG often coexists with other autoimmune disorders, particularly thyroid disease, patients should undergo thyroid and other autoimmune testing when clinically appropriate^{14,17,39}.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes other disorders of the neuromuscular junction including Lambert–Eaton syndrome, botulism, congenital myasthenic syndromes, and tick paralysis^{2,5,7,9–11,14,17}. In addition, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and variants, particularly those featuring external ophthalmoplegia and ptosis, may simulate MG^{2,5,7,9–11,14,17}. Motor neuron disease and brainstem ischemia involving oropharyngeal weakness may appear in MG^{14,17}.

A number of disorders that cause respiratory failure due to muscle weakness should be considered in the differential diagnosis (Table 5).

ACUTE MANAGEMENT

General evaluation

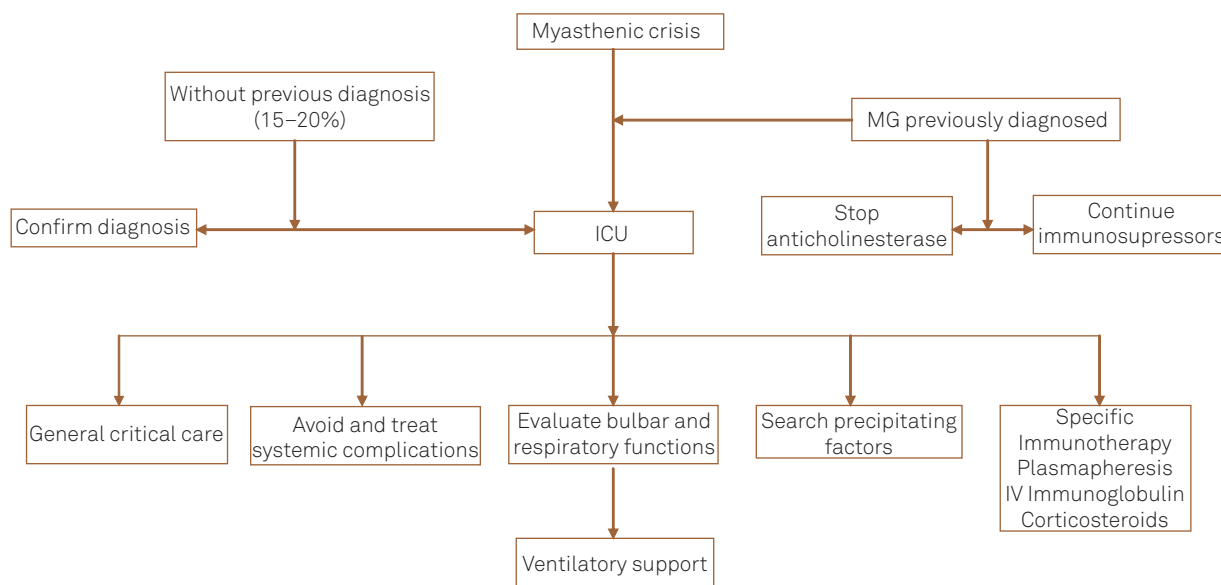
The management of MC should follow a step by step, sequential, and multidisciplinary protocol (Fig 3), based on guidelines of the European Federation of Neurological Societies⁴⁰. Prompt recognition of impending respiratory paralysis is the key to successful management^{31–33}. The evolution of respiratory muscle weakness in AChR-MG often follows a pattern where the intercostals and accessory muscles weaken first, followed by the diaphragm^{31–33}. In MuSK-MG, bulbar weakness always precedes respiratory failure⁷.

Trigger detection and assessment of the respiratory and bulbar functions

It is essential to evaluate bulbar and respiratory functions together with ensure life support and detecting trigger conditions (precipitating factors)^{1,2,5,7–13,16,33}. Habitually, bulbar and respiratory dysfunction occurs simultaneously with

Table 5. Neurologic and systemic causes of muscle/respiratory weakness/failure.

Central nervous system (CNS)
Head trauma
Spinal cord Injury (traumatica, vascular, compressive, inflammatory)
Infections (tetanus, rabies)
Brainstem stroke (hemorrhagic, ischemic)
Drugs (barbiturates, alcohol)
Motor neuronopathy
Amyotrophic lateral sclerosis
Poliomyelitis
Infections (West Nile virus)
Peripheral nerve disorders
Guillain Barré syndrome
Acute intermittent porphyria
Vasculitis neuropathy
Diphtheric polyneuropathy
Neuromuscular junction disorders
Lambert-Eaton myasthenic syndrome
Cholinergic crisis
Botulism
Organophosphate overdose
Poisons (spider, snake)
Primary muscle disease
Acid maltase deficiency
Rhabdomyolysis
Polymyositis
Dystrophic muscle disease (Duchenne's)
Systemic diseases
Hypothyroidism
Hyphosphatemic myopathy
Hyper/hypokalemic periodic paralysis
Electrolyte disturbances



ICU: intensive care unit; IV: intravenous; MG: myasthenia gravis.

Fig 3. Algorithm for myasthenic crisis management.

generalized muscle weakness characteristic of myasthenic patients. Typical clinical features include shortness of breath, tachypnea, orthopnea, discomfort, tachycardia, sweating, use of accessory muscles of respiration, or paradoxical ventilation³¹⁻³³. The collapse of the airway is marked by coughing and swallowing disability, leading to accumulation of secretions in the pharynx³¹⁻³³. Patients are unable to swallow 5 cc of water or count until 20 in a single respiratory cycle^{7,31-33}.

Intubation and mechanical ventilation

The decision of the mode of ventilatory support should be based on clinical judgement. Careful observation and bedside measurements (vital capacity, peak flow measurement, pulse rate, and blood pressure) are more important than repeated monitoring of blood gases^{1,2,5,7-13,16,33}. Nevertheless, certain ventilatory tests can be performed, including forced vital capacity (FVC), negative inspiratory pressure (NIP), positive expiratory pressure (PEP), and arterial blood gases^{1,2,5,7-13,16,33}. The 20/30/40 rule (FVC < 20 mL/kg; NIP < 30 cmH₂O; and PEP < 40 cmH₂O) is probably the most helpful guide to decide intubation (Table 6). FVC < 30 mL/kg is associated with ineffective cough, poor handling of secretions, atelectasis, and hypoxemia. NIP < 20 cmH₂O signals marked weakness of the inspiratory muscles and diaphragm, while PEP < 40 cmH₂O indicates involvement of expiratory muscle function closely linked with the ability to cough and clear secretions^{1,2,5,7-13,16,33}. These determinations require training, depending on the patients' effort, and require proper closure of the mouth — all conditions are difficult to obtain during the crisis. Furthermore, these threshold values have not been established through prospective studies. In addition, muscle weakness often fluctuates,

Table 6. Ventilatory test in patients with myasthenic crisis.

	Normal	Intubation criteria	Weaning criteria	Extubation criteria
FVC (mL/kg)	>60	<20	>15	>25
NIP (cmH ₂ O)	>-70	<-30	>20	>40
PEP (cmH ₂ O)	>100	<40	>40	>50

FVC: indicates forced vital capacity; NIP: negative inspiratory pressure; PEP: positive expiratory pressures.

and patients can develop apnea suddenly, or may precipitously fatigue with the rapid development of respiratory failure before a downward trend in these parameters is noted^{1,2,5,7-13,16,31-33}. Moreover, none of them have been shown to be reliable predictors of the need for mechanical ventilation. Life-threatening hypoxemia (PaO₂ < 60 mmHg) occurs late in neuromuscular respiratory failure and generally improves with supplemental oxygen^{1,2,5,7-13,16,31-33}. In this situation, we can attempt the use of bilevel positive airway pressure (BiPAP), since the application of positive pressure helps to endure increased resistance of the upper airways in addition to preventing alveolar collapse and atelectasis^{2,5,7,31-33}. Severe hypercapnia (PaCO₂ > 50 mmHg) predicts BiPAP failure and indicates that muscle fatigue is imminent³⁶. The absolute indications for intubation may include cardiac or respiratory arrest, impaired consciousness, shock, life-threatening arrhythmias, severe blood-gas alterations, and bulbar dysfunction with confirmed aspiration^{1,2,5,7-13,16,50}. Much more difficult is the decision to intubate when such strict criteria are not met. If doubt exists, it is recommended to intubate and ventilate immediately^{2,7-13,33}. Endotracheal intubation

can often be performed electively rather than as an emergent response^{32,33}. The initial ventilatory support should be directed to improve muscle fatigue and to maintain lung expansion^{1,2,5,7-13,16,33}. We suggest as initial mode assist-control ventilation, with low tidal volumes (6–8 mL/kg), respiratory rate 12–16/min, and positive end-expiratory pressure (PEEP) of 5 cmH₂O. FiO₂ should be adjusted to achieve a SaO₂ >92% or PaO₂ >70 mmHg^{7-13,16,33}. Pressure support ventilation between 5 and 15 cmH₂O is another option^{7-13,16,33}. In case of atelectasis, we consider recruitment manoeuvres or the utilization of sighs (1.5 × tidal volume) 3 to 4 times per hour¹⁰. The degree of support is patient dependent and should be adjusted and based on arterial blood analysis. In patients with chronic hypercarbia, PaO₂ should be kept above 45 mm Hg to avoid alkalosis and bicarbonate wasting, which make weaning more difficult^{2,5,7-13,16,33}.

Bronchodilators may be useful in maintaining airway patency and overcoming bronchospasm. Inhaled ipratropium bromide may be of choice because it is safe and can decrease bronchial secretions⁴¹. Terbutaline, a β₂ adrenergic agonist, may be an effective adjunct therapy in these patients, although confirmation with larger trials will be required⁴². Meticulous attention to pulmonary toilet is required due to ineffective cough. Aggressive chest physiotherapy (percussion, vibration, and postural drainage) and airway clearance (regular suctioning and therapeutic fiberoptic bronchoscopy in severe cases) should be implemented⁴³. Inspired gas humidity should be around 80% at 37°C. Patients with a peak cough flow <180 L/min can augment cough response with manual physiotherapy and with insufflation-exsufflation devices. Cough response increases and is associated with improved prognosis independent of FVC or breathing pattern⁴⁴.

Adequate nutrition is important to avoid negative energy balance and worsening of muscle strength¹². All patients should receive adequate nutritional support (25–35 calories/kg) via enteral route whenever possible. In patients with hypercarbia and difficulty weaning, low carbohydrate feeds are the preferred solution⁴³. Potassium, magnesium, and phosphate depletion can exacerbate MC and should be repleted. Anemia can also increase weakness, and several experts recommend transfusions when hematocrit values are under 30%¹². Additionally, deep-vein thrombosis prophylaxis, hemodynamic stability, and glycemia control are strongly recommended^{2,7-13,16}.

Weaning from ventilation should start when the patient regains muscular strength; is hemodynamically stable without electrolyte disturbances, fever, infections, or systemic complications; and the reason for mechanical ventilation has been resolved or is in the process of frank resolution^{2,5,7-13,16,33}. Improvement in the strength of neck flexors and other adjunct muscles usually is associated with improvement in bulbar and respiratory muscle strength and can be a useful tool for assessing clinical improvement^{7-13,16,33}. Current recommendations about managing the weaning process emphasize the daily determination of simple criteria

such as a satisfactory oxygenation, PaO₂/FIO₂ ≥200 mmHg, PEEP ≤5 cmH₂O; hemodynamic stability, and a good consciousness status able to cough effectively^{2,5,7-13,16,33}. Patients should be transitioned to a spontaneous mode of ventilation (e.g., pressure support ventilation) previous to T-tube trial. Pressure support can then gradually be decreased to minimal settings^{33,43}. If the patient does not tolerate weaning, assisted ventilation should be reinstated.

It remains unclear when to attempt extubation after MC. Prolonged intubation in myasthenic patients may lead to several complications such as atelectasis, anemia, urinary tract infection, congestive heart failure, and ventilator-associated pneumonia^{11,45}. To prevent atelectasis, aggressive chest physiotherapy and frequent suctioning should be implemented together with continuous positive airway pressure (CPAP). Age >50 years, peak VC <25 mL/kg on postintubation days 1 to 6, and a serum bicarbonate ≥30 mmol/L are independent risk factors for prolonged intubation (>14 days)⁷. Extubation failure is most commonly associated with a weak cough and inadequate airway clearance^{33,45-47}. Tracheostomy is generally not needed in MC because the duration of intubation is often less than 2 weeks^{2,5,7-13,16,33,46}.

One rare condition that often requires tracheostomy is severe upper airway obstruction due to bilateral vocal cord paralysis. Furthermore, patients with a prolonged intubation are usually hospitalized three times longer and are less likely to be functionally independent upon discharge⁷.

A maximal expiratory pressure has been demonstrated to independently predict extubation success. However, there are no good clinical criteria for when and how to extubate safely. Fluctuating weakness and pulmonary complications often confound the decision to extubate⁴⁷. Patients are typically extubated if VC, P_{Imax}, and P_{E_{max}} are ≥15 mL/kg, ≤-20 cmH₂O, and >40 cmH₂O respectively, and tidal volume ≥5 mL/kg^{2,5,12,45,48}. If the patient complains of fatigue or shortness of breath, extubation should not be performed even if the criteria of these indices are met and blood gases are normal.

Noninvasive positive pressure ventilation

Noninvasive ventilation may be used to prevent intubation or reintubation in MC⁴⁹⁻⁵². With BiPAP, positive pressure is applied during both phases of respiratory cycle, enhancing airflow, alleviating the work of breathing during inspiration, and preventing airway collapse and atelectasis during expiration⁴⁹⁻⁵². There are studies of Noninvasive positive pressure ventilation (NIPPV) during MC⁴⁹⁻⁵². In 2002, Rabinstein and Wijdicks first reported their experience⁴⁹. All patients have had bulbar compromise. NIPPV was well tolerated and the length of hospital stay was significantly reduced compared with those who were intubated (mean 7±5 days *versus* 23±16 days; p=0.03). paCO₂ >50 mmHg portends BiPAP inefficiency⁴⁹. Subsequent reports suggest that NIPPV may be useful in preventing intubation or reintubation in these patients⁴⁷⁻⁵¹. A recent prospective study suggests that NIPPV, combined with assisted coughing after extubation, avoids the need for

reintubation or tracheostomy in patients with neuromuscular diseases, besides shortening their stay in the ICU^{50,51}. Early application of NIPPV after extubation can reduce the risk of respiratory failure and lowered mortality in hypercapnic patients with chronic respiratory disorders⁵¹. Use of NIPPV to avoid reintubation in MC is well established but is a relatively uncommon practice⁵¹. Some studies reported that NIPPV prevented reintubation in 70% of patients^{49,50}. It should be included in the routine approach to these patients at high risk for postextubation respiratory failure.

COMPLICATIONS IN THE MANAGEMENT OF MYASTHENIC CRISIS

Fever is the most common complication associated with MC^{2,5,7-13,16}. Infectious complications include pneumonia, bronchitis, urinary tract infections, *Clostridium difficile* colitis, bacteremia, and sepsis^{2,5,7-13,16}. When compared with patients admitted for noncrisis, patients admitted with MC are more likely to experience sepsis, deep-vein thrombosis, and cardiac complications including congestive heart failure, acute myocardial infarction, arrhythmias, and cardiac arrest. These complications, however, are not independent predictors of mortality^{2,5,7-13,16}.

STOP ANTICHOLINESTERASE DRUGS

Anticholinesterase therapy should be temporarily withdrawn immediately after establishing mechanical ventilatory support because they are unnecessary in this situation and may complicate pulmonary management^{2,5,7-13,16}. In addition, the continued use of these medications may promote cholinergic crisis by overdose¹¹. Although cholinergic crisis is an important consideration in the evaluation of the patient in MC, it is uncommon^{2,5,7-13,16}. Cholinergic crisis may cause increase of pulmonary secretions (muscarinic effects) and fasciculations (nicotinic effects), both of which contribute to exacerbate muscle weakness and respiratory failure^{2,5,7-13,16}. Furthermore, acetylcholinesterase inhibitors may promote cardiac arrhythmias and myocardial infarction^{2,5,7-13,16}. The time to start cholinergic agents (pyridostigmine) preferably orally or by nasogastric tube is not well established, but is recommended when the patient shows clinical improvement before weaning of mechanical ventilation^{2,5,7-13,16,18}.

IMMUNOTHERAPY

Immunomodulatory treatment is considered standard of care for patients with MC^{2,5,7-13,16,18,40}. Specific immunotherapy consists in plasma exchange (PE), immunoadsorption (IA), and human IVIg. All of them have demonstrated similar

efficacy, so they can be chosen by availability, adverse effects, costs, experience, and patients' profile^{2,5,7-13,16,18,40}.

IVIg is a IgG-purified blood deriviate. The mechanism of action is unknown. It needs about 5 days to exert maximum therapeutic effects. The usual regimen is 0.4 g/kg/day for 3–5 days^{2,5,7-13,16,18,40}. One study did not find a difference between 1 or 2 g as total dose⁵². Patients should be screened for IgA deficiency to avoid anaphylaxis^{2,5,7-13,16}. More prevalent side effects are fever, overload of fluids, nausea, and headache. Less frequent and more serious complications are aseptic meningitis, pulmonary edema, anaphylaxis, renal dysfunction, cardiac arrhythmia, thrombocytopenia, stroke, myocardial infarction, and pulmonary embolism^{2,7-13,14,16}.

PE and IA are most effective when we need a fast response, particularly in patients who do not improve, are worsening, or are having severe complications^{2,5,7-13,16,18,40,53}. Response to treatment generally occurs after 2 days. The optimal response of PE and IA occurs in both AChR-Ac- and MuSK-positive patients. The proposed mechanism of action is rapid depletion of pathogenic antibodies from plasma, which causes an osmotic equilibration between extra- and intravascular spaces leading to reduction of antibodies in neuromuscular junction^{2,5,7-13,16,18,40}. Both apheresis procedures, PE and IA, must be performed at low-dose regimen; it is 1.5 L of plasma (20–25 mL/kg), per session, with an exchange rate of 10–20 mL/min. The procedure needs central venous access and anticoagulation. PE should be made in a course of five exchanges every other day over 10 days. Replacement fluid is generally normal saline/5% albumin^{2,5,7-13,16,18,40}. A series of nonrandomized studies have demonstrated beneficial short-term efficacy of this therapy in acute setting and during preparation for thymectomy^{2,5,7-13,16,18,40}.

PLASMAPHERESIS OR IMMUNOGLOBULIN?

This question does not have a response. IVIg may be better tolerated than PE; however PE showed similar short-term effects in comparison with IVIg in one RCT⁵⁴ but was more effective than IVIg in a retrospective study⁵⁵. PE may probably have a more predictable response than IVIg during crisis. IVIg and PE are equally effective in preparation for surgery⁵⁶. In conclusion, until now there is not enough evidence of high quality to support one therapy over another during MC. If there is insufficient or no response to treatment, PE can be given after IVIg, and IVIg can be administered after PE.

STEROIDS AND OTHER IMMUNOSUPPRESSIVE AGENTS

Patients who are taking steroids should not stop them^{2,5,7-13,16,18,40}. Possibly after crisis, the dose should be increased. If we need to start steroids after PE or IVIg, oral prednisone is preferred at 1 mg/kg/day (60–100 mg daily)^{2,7-13,16,40}.

The timing of initiation is controversial, but usually it is indicated when the patients cannot be extubated 2 weeks after specific immunotherapy^{2,7-13,16,40}. It may be initiated concurrently with IVIg or PE, since prednisone begins to work after 2 weeks. Enteral administration is preferred, and initiation of prednisone may be deferred until after extubation if the patient improves with IVIg or PE treatment^{2,5,7-13,16,18,40}. The mean time to improvement with prednisone is around 13 days. Worsening of symptoms with the initiation of corticosteroids is not predictive of overall response to corticosteroids²². Once the patient has begun to show improvement, dose can be decreased and gradually converted to alternate-day dosing. It is important to have in mind that steroids can exacerbate muscle weakness or may increase the risk of critical illness myopathy^{2,7-13,18,22}. In septic patients, it is preferable to delay steroids until infection is under control. Relative contraindications are diabetes with poor metabolic control or severe osteoporosis. Other immunosuppressive drugs, necessary to long-term management of MG, such as cyclosporine, azathioprine, or mycophenolate, are not useful during MC principally due to the delayed onset of action^{2,5,7-13,16,40}.

ROLE OF THYMUS: SURGICAL CONSIDERATIONS

Thymectomy plays a central role in management of MG^{14,17,40}. About 65% of the patients in seropositive group have thymic hyperplasia and 15% thymoma^{14,17}. Thymectomy is the only treatment in MG that offers possibilities of complete remission^{14,17}. Indications for thymectomy include: (a) failure of long-term conservative therapy, (b) thymoma, and (c) new onset of generalized MG^{14,17,40}. Patients with more benefits after thymectomy are those <60 years, seropositives, and with thymic hyperplasia^{14,17,40}. The role of a thymectomy in MuSK patients is not clear. Chu et al.⁵⁷ suggested that thymectomy seems to have a preventive effect in both incidence and severity of MC, but the frequency of postoperative crisis varied from 6% to 21.9%²³ defined as respiratory failure or delayed postoperative extubation (>24 hours)⁵⁷. Postoperative crisis has been related to age (onset of the disease more than 50 years)⁵⁸, severity (type

IIA, IIB, and III according to clinical grade of Osserman classification)^{57,58}, a history of MC²³, preoperative presence of bulbar weakness²³, serum AChR antibody levels >100 nmol/L, and intraoperative blood loss of >1 L. Other predisposing factors are obesity (BMI >25.6), higher doses of pyridostigmine (>270 mg) and immunosuppressants, FVC <2 L, and history of infection 1 month before surgery²⁵. Type and technique of surgery may affect the occurrence of MC after thymectomy⁵⁸⁻⁶⁰. The presence of thymoma is the more important isolated postoperative factor to develop MC together with radiation therapy, delayed ventilator weaning, and upper or lower pulmonary tract infections^{23-25,57}. The risk of MC has decreased with less invasive surgical techniques such as cervicotomy, partial sternotomy, or video-assisted thoracoscopic^{57,59,60}. In a study of 218 thymectomies with different techniques and approaches, no significant differences were found in terms of incidence or severity of MC or in the final outcome²⁵.

CONCLUSIONS

MC is a severe and life-threatening neurological condition characterized by generalized muscle weakness with respiratory or bulbar compromise that require ventilatory support. It can be the debut form of MG, so the diagnosis should be confirmed following a standardized protocol. Evaluation of bulbar and respiratory functions is imperative. The cornerstones of the treatment are correct ventilatory management, search and correction of predisposing factors, specific immunotherapy (PE, IVIg), avoiding systemic complications, and planification of long-term treatment (immunosuppressors). The majority of patients with MC require endotracheal intubation and mechanical ventilation. Thymectomy should be evaluated. With modern intensive care, the outcomes are excellent with mortality near to 5% attributed principally to comorbidities, cardiac complications, or pulmonary embolism.

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