Q J Med 2009; **102**:97–107
doi:10.1093/qjmed/hcn152 Advance Access publication 5 December 2008

Review

QJM

Myasthenic crisis

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Summary

Myasthenic crisis is a life-threatening medical emergency requiring early diagnosis and respiratory assistance. It can affect between one-fifth and one-third of all patients with generalized autoimmune myasthenia gravis. Myasthenic crisis is to be distinguished from other causes of acute neuromuscular paralysis which in most cases, can be achieved clinically. High dose corticosteroids in combination with plasma exchange or immunoglobulin are the cornerstone of treatment for this fully reversible cause of neuromuscular paralysis.

Introduction

Myasthenic crisis is a reversible cause of neuromuscular paralysis, which needs to be diagnosed and treated promptly. It is typically associated with autoimmune myasthenia gravis, which has an estimated population prevalence of 200–400 per million.[1] The commonest form of myasthenia gravis is characterized by acquired antibodies against postsynaptic acetylcholine receptors (AChR) in the motor end plate of skeletal muscles. Injury from immune complex deposition and complement activation reduce the contact area of the postsynaptic surface, which, together with the loss of functional AChR molecules, reduce the safety of neuromuscular transmission leading to impulse blockade at the motor end plate (Table 1). Here, we review the diagnosis and management of myasthenic crisis, a life-threatening medical emergency which may potentially challenge emergency physicians and neurologists.

Search criteria

The present review was based on our reading of the standard medical texts and a search of PubMed and Medline for articles on 'myasthenic crisis', 'myasthenia gravis' and 'respiratory failure' between 1966 and 2007. Only articles in English or with English translation were reviewed. In addition, we searched appropriate reference texts to support the discussion. The articles were selected on the basis of their relevance and originality.

Classification of myasthenia

Failure of transmission across neuromuscular junction may occur due to a variety of reasons, and the defining feature of any myasthenic syndrome is painless, fatigable weakness of voluntary muscles (Table 2). Congenital myasthenic syndromes represent a heterogeneous group of disorders caused by genetic defects in neuromuscular transmission. Congenital myasthenic syndromes do not weaken respiratory muscles and consequently are not implicated in myasthenic crisis. D-penicillamine-induced myasthenia gravis is caused by an autoimmune mechanism similar to anti-AChR antibody positive myasthenia gravis but the symptoms usually

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Table 1 Disease mechanisms of anti-AChR antibodies in myasthenia gravis

- Complement binding and activation at the post-synaptic junction of motor end plate;
- Destruction of synaptic membrane which becomes unfolded (simplified) with reduction of surface area of contact;
- Cross-linking of AChR molecules on the post-synaptic membrane leading to endocytosis and degradation of the linked receptor protein resulting in fewer receptors in the neuromuscular junction;
- Functional block of AChR resulting in fewer competing receptors available for binding of acetylcholine released during neuromuscular transmission.

Table 2 Classification of acquired myasthenic syndromes

Autoimmune
- Pre-synaptic: LEMS
- Post-synaptic: AChR-MG and MuSK-MG
- Neonatal (passive transfer of maternal antibodies in AChR-MG)
- Drug induced: D-penicillamine

Toxic
- Botulism
- Neuroparalytic envenomation (e.g. tick and snake bites)
- Organophosphate and carbamate poisoning
- Overdose of anti-cholinesterases

disappear after drug withdrawal. Acute toxic paralysis of neuromuscular junction transmission leading to severe muscle weakness and respiratory failure may also be caused by curare, snake venom, tick bite and botulism. Antibodies directed against voltage-gated calcium channels in the pre-synaptic side of motor end plate are responsible for Lambert Eaton myasthenic syndrome (LEMS). A few cases of LEMS have been associated with autoimmune myasthenia gravis and although some patients with LEMS may experience transient or mild involvement of bulbar muscles, respiratory failure due to LEMS alone is extremely rare.

The term *myasthenic crisis* refers to respiratory weakness in patients with acquired, autoimmune form of myasthenia gravis. Neonatal myasthenia gravis results from passive transfer of maternal antibodies and is self-limiting. Autoimmune myasthenia gravis is currently divided into two groups, which are clinically and immunopathologically distinct. The commonest form of myasthenia gravis is associated with anti-AChR antibodies (AChR-MG) and the past literature of myasthenic crisis is largely based on this group. Since 2000, a second group of patients with myasthenia gravis has been identified who have autoantibodies directed against muscle specific tyrosine kinase (MuSK). Patients with MuSK-antibody associated myasthenia gravis (MuSK-MG) are usually younger women who present with predominant facial, bulbar and respiratory weakness, lingual atrophy and relatively mild limb weakness.[2] Up to 50% of anti-AChR antibody negative patients may segregate into the category of MuSK-MG.[3] Patients who do not have anti-AChR or MuSK-antibodies (antibody-negative MG), such as those with ocular myasthenia, have a clinical phenotype very similar to AChR-MG. The HLA-haplotypes of AChR-MG and MuSK-MG are also different and the immunopathogenesis of myasthenia in MuSK-MG is probably independent of thymus, which plays a pivotal role in the mechanism of disease in AChR-MG. A comparison of AChR-MG and MuSK-MG is shown in Table 3. There are only rare examples of acquired myasthenia gravis who have shared clinical features and antibodies against both AChR and MuSK.[4] Presence of non-AChR and MuSK antibodies, such as anti-titin and ryanodine receptor antibodies, are reported in patients with severe disease regardless of the clinical subgroup.[5]

By definition, all patients with myasthenic crisis are in respiratory failure due to muscle weakness and require ventilatory assistance. These cases fall in the categories 3 and 4 in the Osserman classification of myasthenia gravis,[6] and class V of the disease severity staging proposed by the Myasthenia Gravis Foundation of America.[7] These classifications are shown in Table 4. Myasthenic patients in whom post-operative extubation has been delayed beyond 24 h because of respiratory weakness are also considered to be in crisis. In the pre-immunotherapy era, myasthenic crisis had significant mortality (up to 75%), but it has fallen below 5% due to rapid access to respiratory support and immunotherapy in the recent years.[8]

Mechanism

Myasthenic crisis is caused by severe weakness of respiratory muscles, upper airway muscles (bulbar myasthenia) or both. It is typically precipitated by poor control of generalized disease, medical treatment for bulbar myasthenia (steroids and anticholinesterases); concomitant use of certain

Table 3 Comparison of AChR- and MuSK-antibody associated myasthenia gravis

Clinical features	AChR-MG	MuSK-MG
Pattern of muscle weakness	Limb>bulbar Neck extensor>neck flexor Ptosis and external ocular muscle weakness often conspicuous	Bulbar>limb Neck flexor>neck extensor Ptosis and external ocular muscle weakness usually mild
Muscle wasting	Loss of proximal limb and ocular muscles only in long-standing disease ('myasthenic myopathy')	Early wasting of facial and tongue muscles common
Thymus pathology	65% thymic hyperplasia; 15% thymoma	10% thymic hyperplasia
Risk of recurrent crisis	Low	High

Table 4 Clinical classifications (modified) of the severity of myasthenia gravis

Osserman's classification
(1) Localized, non-progressive disease (ocular myasthenia)
(2) Gradual onset generalized disease (involving more than one group of striated muscles, both skeletal and bulbar)
(3) Acute fulminant generalized disease with severe bulbar involvement
(4) Late severe disease (usually developing 2 years or more after symptoms in category 1 or 2)
(5) Muscle atrophy (not due to disuse) in late generalized disease, restricted to skeletal muscles and usually related to the duration of the disease and clinical severity (myasthenic myopathy)

Myasthenia Gravis Foundation of America classification
Class I: ocular myasthenia, also may have weakness of eye closure
Class II: mild weakness of non-ocular muscles
Class III: moderate weakness of non-ocular muscles
Class IV: severe weakness of non-ocular muscles
Class V: requiring intubation, with or without mechanical ventilation
- Class II–IV are each divided into subgroups (a) (predominant limb and trunk muscle weakness) and (b) (predominant bulbar weakness); severity of ocular muscle weakness does not affect the staging.

antibiotics, muscle relaxants, benzodiazepines, β-blockers and iodinated radiocontrast agents (Table 5); systemic infections often involving the respiratory tract, aspiration and surgery. Other recognized triggers for crisis in refractory myasthenia are emotional stress, hot environment, sudden elevation of body temperature[9] and hyperthyroidism, with autoimmune thyroid disease being a common association of myasthenia gravis.

The life-time prevalence of myasthenic crisis in patients with myasthenia gravis is roughly between 20% and 30%[8,10,11] and it usually occurs during the course of first symptomatic presentation in the young and later in the course of the disease in the elderly (Table 6).[12,13] White patients with generalized myasthenia gravis are more likely to respond poorly to treatment than black patients.[14] Pregnancy is associated with an aggravation of myasthenia gravis in approximately a third of all women and myasthenic crisis in pregnancy carries high perinatal mortality.[15]

Differential diagnosis

Acute respiratory paralysis due to neuromuscular weakness may be a presenting feature of a number of disorders affecting motor neurons, peripheral nerve, neuromuscular junction and muscles (Table 8). Respiratory paralysis is a recognized feature of drug overdose and envenomation and may complicate central nervous system disorders due to brainstem (medullary) or high cervical spinal cord pathology. Weakness of eye muscles (ptosis and external ophthalmoplegia) is common in AChR-MG and patients may have any combination of weak eye movements, even simulating internuclear ophthalmoplegia. Myasthenia gravis is probably the

Table 5 Commonly used drugs which may worsen myasthenia gravis

Antimicrobials	Aminoglycosides (amikacin, gentamicin, streptomycin); Macrolides (doxycycline, erythromycin, minocycline, oxytetracycline, tetracycline, azithromycin, telithromycin) Quinolones (ciprofloxacin, ofloxacin, norfloxacin) Antimalarials (chloroquine, hydroxychloroquine, quinine) Urinary antiseptic: nalidixic acid
Anticonvulsants	Phenytoin and carbamazepine
Antipsychotics	Neuroleptics (phenothiazines, sulpiride, atypicals like clozapine)
Cardiovascular agents	β-blockers (all, including topical β-blocker, e.g. timolol eye drops and combined α and β-blocker, e.g. labetolol) Calcium channel blockers (verapamil, nifedipine) Class I anti-arrhythmic drugs (quinidine, procainamide)
Others	Neuromuscular-blocking agents Local anaesthetics (lignocaine) Muscle relaxants (long-acting bezodiazepines, baclofen) Iodinated radiocontrast agents Botulinum toxin

Table 6 Demographic features of early and late onset myasthenic crisis in adults[a]

Features	Early onset (before 50 years)	Late onset (after 50 years)
Sex ratio	F:M = 2:1	F:M = 1:1
Incidence of myasthenic crisis	15–20%	Up to 50%
Median duration from first symptom of myasthenia	8 months	Not known (probably longer)
Common trigger	Infection	Poorly controlled disease
Response to therapy	Usually rapid (75% recover by 4 weeks)	Relatively slow (50% recover by 4 weeks)
Relapse rate	Low (<10%)	May be high (upto 33%)

[a]Compiled from the literature.

most frequent cause of bulbar palsy presenting as dysphonia, dysarthria and dysphagia in conjunction with ptosis and ocular palsy. Atrophy of tongue is a typical feature of MuSK-MG,[16] but presence of both wasting and fasciculations of tongue muscle clearly point away from myasthenic crisis and are more likely to be the result of motor neuron disease (progressive bulbar palsy), bulbospinal muscular atrophy (Kennedy's disease, Fazio-Londe and Brown-Vialetto syndromes), syringobulbia or skull base pathology. Bulbar palsy and respiratory muscle weakness is also a feature of acute inflammatory demyelinating polyneuropathy (Guillain Barre syndrome), which may occasionally be associated with bilateral ptosis. Although tendon reflexes may be retained early in the course of evolving Guillain Barre syndrome, presence of normal tendon reflexes in an established case with severe muscle weakness and respiratory failure would be most unusual. Marked autonomic symptoms, poorly reactive, dilated pupils with loss of accommodation and diminished tendon reflexes are suggestive of botulism. Paralytic poliomyelitis and acute diphtheritic paralysis, both extremely rare in the Western world, may also present with bulbar weakness and respiratory failure.

Weakness of facial muscles is a feature which is common to myasthenia gravis, Guillain Barre syndrome and acute polymyositis. AChR-MG patients have weakness of both neck flexors and extensors, *occasionally* selectively affecting the extensor muscles (the hanging or dropped head sign). Patients with MuSK-MG and acute polymyositis have marked weakness of neck flexors. Weak neck flexors are also a feature of Guillain Barre syndrome and often correlate with respiratory muscle weakness. Disproportionate weakness of anterior neck muscles is a feature shared by

Table 7 Neurological causes of respiratory muscle or bulbar weakness

Primary muscle disease
- Acid maltase deficiency
- Acute rhabdomyolysis
- Distal myopathy with vocal cord palsy
- Dystrophic muscle disease (Duchenne's, oculopharyngeal muscle dystrophy and type 1 myotonic dystrophy)
- Hypothyroid myopathy
- Hyphophosphaemic myopathy
- Polymyositis

Neuromuscular junction disorders
- AChR-MG and MuSK-MG
- LEMS
- Toxic myasthenic syndromes (Table 2)

Critical illness myoneurpathy

Peripheral nerve disorders
- Acute intermittent porphyria
- Diphtheritic polyneuropathy
- Guillain-Barre syndrome
- Vascultic neuropathy (mononeuritis multiplex and brachial plexopathy)

Motor neuronopathy
- Bulbospinal muscular atrophy (Kennedy's disease, Brown-Vialetto, Fazio-Londe syndromes)
- Motor neuron disease
- Poliomyelitis
- Spinal muscular atrophy

Central nervous system disorders
- Cervical spinal cord transection (secondary to trauma, compression or inflammation)
- Brainstem lesions (vascular, inflammatory or compressive)
- Head injury
- Neurotropic infections (e.g. tetanus and rabies)
- Overdose of alcohol, sedatives and recreational drugs

progressive muscular dystrophies (such as type 1 myotonic dystrophy), motor neuron disease, spinomuscular atrophy and syringomyelia. Limb weakness is usually most obvious in proximal muscles in myasthenia gravis and acute polymyositis, and both proximal and distal in Guillain Barre syndrome. Primary disorders of muscle and neuromuscular junction do not generally weaken arm muscles disproportionately and respiratory muscle weakness in conjunction with paralysis of arms and shoulders would be more typical of anterior horn cell disease (motor neuron disease or poliomyelitis) and peripheral neuropathy. Guillain Barre syndrome and spinal cord pathology are the two likely causes of respiratory failure associated with severe leg weakness. Adult-onset acid maltase deficiency may present with respiratory muscle weakness and these patients often have contracture of calf muscles. Features of marked and symptomatic autonomic disturbance are typical of botulism, less commonly observed in Guillain Barre syndrome and rarely reported in myasthenic crisis.

Previously, it was customary to differentiate between cholinergic crisis and myasthenic crisis in patients with a known diagnosis of myasthenia gravis taking high doses of oral anticholinesterases as the mainstay of therapy. Cholinergic crisis in myasthenic patients is uncommon in today's practice as most symptomatic patients with generalized disease receive immunotherapy as preferred treatment and anticholinesterases are largely restricted to short-term symptom control. More commonly, cases of respiratory paralysis due to cholinergic crisis are associated with toxic exposure to organophosphate insecticides. In occasional patients with myasthenia gravis on higher doses of oral anticholinesterases (pyridostigmine or neostigmine), the clinical features are sufficiently distinct from myasthenic crisis (no ptosis, small pupils, muscle fasciculations, hypersalivation, bradycardia, diarrhoea, bowel and bladder incontinence).

Neuromuscular weakness in critically ill patients is commoner than anticipated, with reports estimating 33–82% of patients being affected after receiving ventilation for >4 days.[17] Diaphragmatic weakness is common and there may be superimposed neuromuscular junction transmission defect ('critical illness neuromuscular junction abnormality').

However, review of the patient's primary illness, drug chart (therapeutic use of neuromuscular blocking agents, corticosteroids), absence of eye signs and poor reflexes on examination and electrophysiology findings (myopathic EMG and/or nerve conduction abnormality) easily distinguish critical illness myoneuropathy from myasthenic crisis.

Investigations

An experienced clinician should be able to suspect the diagnosis of myasthenic crisis at bedside after neurological examination and basic investigations (Tables 8 and 9). Peripheral nerve electrophysiology (repetitive motor nerve stimulation and single fibre EMG) is the preferred investigation to confirm the diagnosis. Edrophonium (Tensilon) test is not to be recommended in any patient who is suspected to be in crisis because of false positive and negative results, and the risk of worsening muscle weakness in patients with anticholinesterase overdose. In addition, worsening of bulbar and respiratory symptoms in MuSK-MG after anticholinesterase administration is known and could confound the clinical diagnosis.

Management

The management of myasthenic crisis does not differ between patients with AChR-MG, MuSK-MG and seronegative patients. Prompt recognition of impending respiratory paralysis is the key to successful management of myasthenic crisis. The evolution of respiratory muscle weakness in AChR-MG often follows a pattern where the intercostals and accessory muscles for respiration weaken first, followed by the diaphragm. In MuSK-MG, bulbar weakness always precedes respiratory failure. Respiratory muscle weakness may be precipitated by steroid therapy and presence of bulbar symptoms and older age were risk factors associated with steroid-induced exacerbation in myasthenia gravis.[18] The most important threat to life in myasthenic crisis is respiratory failure and patients must be offered elective ventilation on clinical diagnosis without waiting for blood gas changes to show hypoxemia. Careful observation and bedside measurements (vital capacity, peak flow measurement, pulse rate and blood pressure) are more important than repeated monitoring of blood gases.

The standard 20/30/40 rule (vital capacity <20ml/kg; peak inspiratory pressure <−30 cm H_2O and peak expiratory pressure <40 cm H_20) is probably the most helpful guide to decide when intubation

Table 8 Common differential diagnosis of myasthenic crisis

Clinical assessment	Myasthenic crisis	Cholinergic crisis	Guillain Barre syndrome	Poly myositis	Botulism	Motor neuron disease	Spinal cord disease
Eye							
External Ophthalmoplegia	+++	−	+[a]	−	++	−	−
Pupils	Normal and reactive	Small and reactive	Normal, but may not react[a]	Normal and reactive	Dilated and sluggish	Normal and reactive	May be small but reactive[b]
Face							
Ptosis	+++	−	±	−	±	−	±[b]
Facial weakness	++	±	+++	++	+	−	−
Limb muscles							
Weakness	++	++	+++	+++	+++	+++	+++
Fasciculations	−	+++	±	−	−	+++	±
Tendon reflexes	++	++	−	+	−	+++ and/−	+++ or −
Plantar reflex	Flexor	Flexor	Flexor/ absent	Flexor	Flexor/ absent	Extensor	Extensor
Sensations	Normal	Normal	Symptoms/ signs	Normal	Symptoms	Normal	Sensory level
Sphincter control	Normal	Normal	Sometimes lost	Normal	Lost	Normal	Lost
Autonomic symptoms	±	+++	+	−	+++	−	+

[a]In Miller Fisher syndrome (a variant of Guillain Barre syndrome).
[b]Only if Horner's syndrome is associated.

is necessary.[19] Other clinical rules for predicting impending ventilator failure and need for airways protection are inability to raise the head due to neck muscle weakness and paradoxical breathing. As in any other condition with neuromuscular paralysis, an experienced clinician should anticipate the need for respiratory assistance in myasthenic crisis rather than deal with emergency intubation ('when in doubt, intubate'). Non-invasive ventilation (NIV) has been used as an alternative to intubation and mechanical ventilation for patients in myasthenic crisis,[20] but the experience of NIV in acute neuromuscular paralysis is still relatively limited. NIV has the potential, however, to reduce the incidence of prolonged intubation and tracheostomy in neuromuscular paralysis.

There have been few randomized controlled treatment trials in myasthenic crisis and both plasma exchange and human intravenous immunoglobulin (IVIg) are comparable in terms of efficacy on the basis of clinical evidence,[21–23] only one of which[21] was a prospective study. However, response to plasma exchange may be more predictable and we take the view that plasma exchange is probably more effective than IVIg in myasthenic crisis. In one retrospective multi-centre review of 54 episodes of myasthenic crisis,[24] plasma exchange had a superior outcome for ventilatory status at 2 weeks ($P = 0.02$) and functional outcome at 1 month ($P = 0.04$). The recommended therapeutic dose of IVIg is 2 g/kg but a randomized double-blind clinical trial found no significant superiority of 2 g/kg dose over 1 g/kg dose in patients with exacerbation of myasthenia gravis.[25] A randomized trial of daily versus alternate day plasma exchange in severe myasthenia gravis found no superiority of one over the other in terms of outcome.[26] The clearance of MuSK-antibody during serial sessions of plasmapheresis for MuSK-MG[27] was comparable to the experience in AChR-MG. IgA-deficient myasthenic patients should not receive IVIg; plasmapheresis is not recommended in patients with cardiac failure, sepsis, hypotension and pregnancy; it is also not considered to be a suitable procedure in paediatric patients. The wider availability and ease of administration of IVIg makes it an automatic choice as the first-line therapy for myasthenic crisis since access to plasmapheresis, particularly during out-of-hours, is restricted to selected centres and major teaching hospitals only.

The use of continuous anticholinesterase (intravenous pyridostigmine) as a therapy for myasthenic crisis[22] remains controversial, especially because of the risk of cardiac complications (arrhythmia and myocardial infarction). Coronary vasospasm form excessive anticholinergic treatment is known to be an iatrogenic cause of myocardial infarction in myasthenia gravis.[28] Besides the risk of cardiac complication, large doses of anticholinesterases promote excessive salivary and gastric secretions, which may increase the risk of aspiration pneumonia. Immunoadsorption therapy was used to treat

Table 9 Investigations for suspected neuromuscular paralysis

Baseline

Blood:

- 'The 3 Cs': cell count, culture and CRP
- Urea, creatinine and electrolytes (Na, K)
- Creatine kinase (CK)
- TSH
- Liver enzymes (ALT, GGT)
- Calcium profile

ECG

Chest X-ray

Specific (as appropriate for the individual case)

- Serum antibody (AChR, MuSK, voltage-gated calcium channels)
- Toxic screen (suspected poisoning/overdose)
- Metabolic screen (porphyria)
- Neurophysiology (EMG, single fibre EMG for orbicularis oculi, nerve conduction and repetitive motor nerve stimulation of limb and facial muscles)
- Cerebrospinal fluid analysis by lumbar puncture (Guillain Barre syndrome, poliomyelitis)
- Muscle biopsy (polymyositis, acid maltase deficiency)
- MR imaging (spinal cord/brain)
- Gene mutation analysis (muscular dystrophy and spinal muscular atrophy)

Table 10 Principles of management of myasthenic crisis

General
Airway assistance and ventilation
Discontinue anticholinesterases and any offending drug (e.g. antibiotic, β-blocker)
Cardiac monitoring
Identify and treat infection
Prophylaxis for deep vein thrombosis
Initiate specific treatment (see below)
Specific
Plasma exchange (removal of 1–1.5 times plasma volume on each session × 5)
Alternatively, human intravenous immunoglobulin (0.4 mg/kg/day × 5); and
High dose corticosteroids (prednisolone 1 mg/kg/day)

a case of post-operative myasthenic crisis successfully,[29] but experience with this procedure is very limited.

The protocol that we have generally followed with success in our patients with myasthenic crisis is shown in Table 10. There is no significant advantage of an initial pulse of intravenous methylprednisolone over regular prednisolone, which is given by nasogastric tube at a pharmacological dose (1 mg/kg) and must be continued by mouth for several months after recovery from the crisis until alterative immunosuppressive or steroid-sparing agents (such as azathioprine or ciclosporin) become effective. Cause of death in treated myasthenic crisis is usually cardiac (arrhythmia) or infection (sepsis).[12]

Thymus and myasthenic crisis

Nearly 65% of young patients AChR-MG, mostly women, will have thymic hyperplasia and about 15% of all patients may have thymic tumour (thymoma). Thymectomy is always recommended in patients with thymoma. Early thymectomy within the first 2 years of symptom onset is an option in adults with non-thymomatous AChR-MG and generalized disease.[30] Thymectomy is usually carried out after symptom stabilization with plasmapheresis, which is considered to improve outcome from thymic surgery in myasthenic patients.[31] In our experience, thymectomy is the only intervention in myasthenia gravis which offers the realistic prospect of complete remission (defined as no need for medication or only requiring low-dose single drug). The 5-year outcome of both transsternal and extended transcervical thymectomies appear to be comparable.[32] Pre-operative history of myasthenic crisis and presence of bulbar symptoms are risk factors associated with post-operative myasthenic crisis after thymectomy[33] and a higher daily dose of pyridostigmine (>270 mg) and body mass index (BMI >25.6) predicted worse outcome after videothoracoscopic thymectomy in one study.[34]

In our practice, we saw the best benefit of thymectomy in younger AChR-MG patients (<60 years) with thymic hyperplasia. The role of thymectomy in non-thymomatous patients with myasthenia gravis is currently being evaluated in a randomized controlled clinical trial.[35] There is some evidence that non-thymectomized patients may have a higher risk of myasthenic crisis ($P = 0.001$, odds ratio 2.8 with CI of 1.5–5.2).[36] In addition, attacks may be more severe in non-thymectomized patients who may require longer duration of ventilatory support and hospital admission.[36] In MuSK-MG, role of thymectomy is less clear as thymus is not considered to be a major player in the disease pathogenesis. The unpredictable effect of thymectomy on disease remission in some cases of non-thymomatous, generalized AChR-MG may reflect inadequate immunosuppressive therapy during post-thymectomy period and presence of residual thymic tissue, but there are few systematic studies to address these issues. Since true seronegative myasthenic patients are considered to have same disease as seropositive cases, the indication of thymectomy would be very similar as in AChR-MG (younger patients, generalized disease and thymic hyperplasia).

Post-crisis follow up

The risk of spontaneous relapse of myasthenic crisis is low in early-onset disease, but a third of late onset severe disease may experience recurrent crisis (Table 6). It is estimated that the rate of extubation failure in myasthenic crisis is around 27% and the risks of failure are higher in older people, in patients with pneumonia or atelectasis or in those who required prolonged care in intensive care unit.[37] We practice a mandatory period of close observation for 72 h in the high dependence care unit for extubated patients before transfer to the general ward and the duration of observation may have to be longer for less stable patients. Unless contraindicated, all patients should be treated with low molecular weight heparin to prevent deep vein thrombosis and pulmonary embolism.

Although corticosteroids have never been evaluated in any double-blind, placebo controlled clinical trials, the collective experience is that

Table 11 Key points about myasthenic crisis

- Myasthenic crisis is a rare but potentially life-threatening medical emergency and the diagnosis should be clinically suspected.
- Patients in myasthenic crisis require ventilatory assistance and usually respond to a combination of high-dose corticosteroids and plasma exchange or human intravenous immunoglobulin.
- There is some evidence to suggest that pre-emptive thymectomy in anti-AChR-MG may prevent prolonged or severe myasthenic crisis.
- Pharmacological management of myasthenic crisis is largely based on observational studies as there have been very few randomized controlled trials of treatment, a situation which is unlikely to change in the near future.

prednisolone is highly effective in symptom control. Patients already receiving high-dose steroids during recovery from myasthenic crisis require to be treated for several weeks (usually 18–24 weeks). We start biphosphonate therapy for bone protection against steroid-induced osteoporosis at the same time when steroids are instituted. It is our practice to introduce azathioprine when the patient is ready to go home. The reason for initiating azathioprine nearer the time of discharge is primarily to ensure that an appropriate steroid dose has been established to stabilize myasthenic symptoms. The onset of therapeutic effect of azathioprine is usually delayed for at least 6 months by which time steroids are tapered off to an alternate daily maintenance dose. Our practice is to continue treatment with oral prednisolone at a dose of 1 mg/kg for first 8–10 weeks before tapering it by 5 mg every week, which minimizes the risk of steroid-induced myopathy. Azathioprine is considered to be relatively safe as an immunosuppressant during pregnancy, but treatment should not be initiated during pregnancy. It is metabolized to mercaptopurine by the enzyme thiopurine methyltransferase (TPMT). It is a good practice point to measure TPMT enzyme activity in the blood before commencing azathioprine treatment in order to identify individuals who are homozygous for low TPMT activity and consequently carry a higher risk of myelosuppression. There is also a small increase in the life-time risk of cancer on long-term use.

Ciclosporin, methotrexate or mycophenolate is an alternative when patients are intolerant or unresponsive to azathioprine and tacrolimus is only chosen if symptoms are poorly controlled. Rituximab, an anti-CD20 monoclonal antibody, may become an option for treatment-refractory myasthenia gravis, but there is insufficient evidence at present to make a recommendation[38] and the potential risk of progressive multifocal leucoencephalopathy from immunosuppression makes rituximab an unlikely choice. A recent Cochrane review concluded that use of ciclosporin and cyclophosphamide, with or without steroids, was associated with improved outcome after 6 months of treatment and treatment benefit remained unproven for azathioprine, tacrolimus or mycophenolate.[39] Ciclosporin may be the preferred immunosuppressive agent in myasthenia gravis in the shorter term as azathioprine effect does takes longer than 6 months, and sometimes up to 18 months during which period alternative immunotherapy (corticosteroids, intermittent plasma exchange or IVIg) would be required.

A neglected issue in the care of myasthenic patients is the need for psychological support. It has been long recognized that sudden emotional stress, feelings of anxiety, aggression and envy may increase myasthenic weakness and chronic weakness may influence the personality of the sufferer.[6] Some of these symptoms may relate to the medications (steroids and anticholinesterases), but psychological support of a patient recovering from myasthenic crisis is no less important than drug therapy. Home-based inspiratory muscle training and breathing exercises are helpful for patients with generalized myasthenia gravis and may improve respiratory muscle strength and endurance.[40]

Conclusion

Diagnosis of myasthenic crisis should be suspected clinically and patients with impending crisis must be admitted to an intensive care unit for respiratory support. The key issues regarding the management of myasthenia gravis are summarized in Table 11. The condition is fully reversible and carries no long-term disability if treated quickly and appropriately. Thymectomy soon after first symptomatic presentation of generalized AChR-MG may prevent prolonged myasthenic crisis. Patients with MuSK-MG have a higher risk of myasthenic crisis because of bulbar weakness and may require prolonged therapy.

Conflict of interest: None declared.

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