Review Article

Anaesthesia and myasthenia gravis

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Myasthenia gravis is an autoimmune disease, resulting from the production of antibodies against the acetylcholine receptors of the endplate. These antibodies reduce the number of active receptors, brought about either by functional block of the receptors, by increased rate of receptor degradation, or by complement-mediated lysis. In myasthenic muscles, the miniature endplate potential amplitude is decreased, and a large proportion of the endplate potentials are subthreshold. Repetitive nerve stimulation results in a decremental response. The disease is frequently associated with morphological abnormalities of the thymus. In young patients, thymic hyperplasia is common while thymoma is more frequent in elderly patients. Medical treatment of myasthenia gravis aims at improving of neuromuscular transmission by anticholinesterases, suppressing the immune system by corticosteroids and immunosuppressants, or by decreasing the circulating antibodies by plasmapheresis. Adults with generalized myasthenia should have a transsternal thymectomy. A balanced technique of general anaesthesia which includes the use of muscle relaxants can be safely used, provided neuromuscular transmission is monitored. Myasthenic patients are sensitive to nondepolarizing relaxants but intermediate-acting nondepolarizing relaxants such as atracurium and vecuronium are eliminated rapidly, and can be titrated to achieve the required neuro-

muscular block that can be completely reversed at the end of surgery. Postoperatively, ventilatory support may be required in high-risk patients. Also, medical treatment may be maintained, tapered or discontinued depending on the outcome of surgery. Thymectomy benefits nearly 96% of patients, 46% develop complete remission and 50% are asymptomatic or improve on therapy.

La myasthénie grave est une maladie auto-immune résultant de la production d'anticorps contre les récepteurs d'acétylcholine sur la plaque motrice. Ces anticorps réduisent le nombre de récepteurs actifs, soit par un bloc fonctionnel des récepteurs, par une augmentation de la vitesse de dégradation du récepteur ou par une lyse provoquée par les compléments. Avec les muscles myasthéniques, l'amplitude du potentiel miniature de la plaque motrice est diminuée et une grande proportion des potentiels est sous le seuil d'excitation. Une stimulation nerveuse répétitive produit une réponse qui diminue graduellement. La maladie est associée fréquemment à des anomalies morphologiques du thymus. L'hyperplasie du thymus est commune chez les jeunes patients, alors que le thymome est plus fréquent chez les patients plus âgés. Le traitement médical de la myasthénie grave vise l'amélioration de la transmission neuromusculaire à l'aide d'anticholinestérasiques, la suppression du système immunitaire à l'aide de corticostéroïdes et d'immunosuppresseurs, ou la diminution des anticorps circulant à l'aide de la plasmaphérèse. Les adultes qui présentent une myasthénie généralisée devraient subir une thymectomie trans-sternale. Une technique balancée d'anesthésie générale peut être utilisée avec sécurité, incluant l'utilisation des myorésolutifs, en autant que la transmission neuromusculaire est monitorée. Les patients myasthéniques sont sensibles aux myorésolutifs non-dépolarisants, mais les relaxants à action intermédiaire tel que l'atracurium et le vécuronium sont éliminés rapidement et peuvent être dosés pour obtenir un bloc neuromusculaire adéquat et complètement réversible à la fin de la chirurgie. Un support ventilatoire peut être requis dans la période post-opératoire chez les patients à haut risque. Le traitement médical peut être maintenu, diminué ou cessé selon l'issue de la chirurgie. Près de 96% des patients bénéficient de la thymectomie, 46% développent une rémission complète et 50% sont asymptomatiques ou s'améliorent avec le traitement.

Key words

COMPLICATIONS: myasthenia gravis;

NEUROMUSCULAR RELAXANTS: atracurium, vecuronium, succinylcholine;

NEUROMUSCULAR TRANSMISSION: myasthenia gravis;

SURGERY: thymectomy.

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Accepted for publication 12th January, 1992.

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The incidence of myasthenia gravis (MG) is about one in every 20,000 adults. The hallmark of the disease is weakness and rapid fatigability of voluntary skeletal muscles with repetitive use, followed by partial recovery with rest.¹

Pathophysiology

Myasthenia gravis (MG) is the prototype of antibody-mediated autoimmune disease. It may be associated with other disorders of autoimmune origin such as thyroid hypofunction, rheumatoid arthritis, and systemic lupus erythematosus. Myasthenia gravis results from the production of autoantibodies against the acetylcholine receptor (AChR) of the neuromuscular synapse.^{1–3} However, it is not yet known what triggers the autoimmune response or what permits it to be sustained. An immunoregulatory defect has been postulated,⁴ and there is evidence of genetic predisposition.⁵ Using the most sensitive assays, AChR antibodies are detected in the sera of 85–90% of myasthenic patients.³ The great majority of AChR antibodies belong to the IgG class. Antibody-negative patients are those with mild or localized myasthenia, and may represent merely one end of the spectrum of myasthenia gravis.² The available evidence suggests both that individ-

TABLE I Thymic morphology of eleven myasthenic patients who underwent thymectomy

Age (yr)	Sex	Thymus morphology
15	F	Hyperplasia
18	F	Hyperplasia
20	F	Hyperplasia
32	M	Thymoma
36	F	Normal
37	M	Thymoma
48	M	Malignant thymoma
56	M	Malignant thymoma
57	M	Normal
73	M	Malignant thymoma

ual myasthenic patients have heterogeneous populations of AChR antibodies, and that there is only limited sharing of idiotypes between patients.² Most of the antibodies bind to the main immunogenic region of the alpha subunit of the endplate receptors.² Thus, MG is largely a post-junctional disorder characterized by reduction of functional AChR.

Immunological background

The thymus and its cellular products, the T cells, are involved in many aspects of autoimmune diseases. It could represent an unique site of autosensitization against AChR antigenic determinants and myoid cells bearing AChR are present in the normal thymus.⁶ In myasthenia gravis,⁷ one may assume that T cells become sensitized against the myoid AChR when they are present in the thymus at a critical stage of maturation. The immunoregulatory T cells play a key role in the pathogenesis of MG. The macrophage-associated AChR interacts with AChR helper T cells, which proliferate and produce factors that promote anti-AChR antibody production by B cells.

According to the network theory, antidiotypic antibodies can initiate or modify the immune response. Anti-idiotypes to AChR antibodies have been reported in MG.² However, their role in the initiation and perpetuation of MG remains to be proven. Several arguments suggest the existence of a close relationship between MG and thymus function.⁸ The disease is frequently associated with morphological abnormalities of the thymus gland (hyperplasia or thymoma), and thymectomy has been reported to improve the symptoms of the disease. Fifteen to 20% of patients with MG have thymomas. Thymomas are more likely in patients older than thirty years of age, whereas thymic hyperplasia frequently occurs in younger patients.⁸ Table I shows the different thymic morphology which was observed in 11 myasthenic patients operated upon in our hospital. All patients <30 yr were women having thymic hyperplasia. In contrast, patients >30 yr were predominantly males with the frequent occurrence of benign or

malignant (locally invasive) thymomas. Only two of the patients had normal thymic morphology.

Neuromuscular junction

Under normal conditions, only 25–30% of the endplate receptors are required to maintain neuromuscular transmission. The remaining 70–75% of the receptor pool constitutes a “safety margin.”⁹ In MG, there is a decrease in the number of functional AChR available, with a subsequent decrease of the “safety margin.” Reduction in the number of active receptors at the endplate is brought about either by functional block, by an increased rate of receptor degradation, or by complement-mediated lysis of the postsynaptic membrane.²

Further support for the concept of postsynaptic abnormality in myasthenia gravis comes from electron microscopic studies of neuromuscular junctions of myasthenic muscles. The postsynaptic membrane shows sparse, shallow folds with markedly simplified geometric patterns.^{10,11}

Recently, it has been reported that the AChRs at normally innervated neuromuscular junctions are composed of two subpopulations with strikingly different rates of turnover.¹² The majority of junctional AChRs are stable with a half-life of over 12 days. The remainder, estimated to be about 20% of the total, are rapidly turned over (RTOs), with a half-life of approximately one day. It has been postulated that the RTOs may be the precursors of the stable AChRs. In MG, the AChR antibodies may decrease the number of receptors, not only as a direct action on the stable receptors but also by depletion of the RTOs.¹⁰ When the AChR antibodies are removed by plasmapheresis, rapid resynthesis of RTOs may account for the speedy clinical recovery.

It is tempting to speculate that the fatigue and the decremental response observed in the myasthenic patient are not only due to a decrease of the functional postjunctional AChR, but also may be secondary to dysfunction of the presynaptic autofacilitation cholinergic receptors.^{13,14} In MG, autoantibodies may decrease the presynaptic nicotinic autofacilitation leading to a preferential decline of the neuromuscular response evoked at high stimulation rate, with less reduction of response at normal rates of stimulation. However, the morphological and electrophysiological studies indicate that the neuromuscular defect of myasthenia gravis is postsynaptic.^{10,11,15,16}

Electrophysiological studies^{15,16}

Early single microelectrode studies indicated that the miniature endplate potential (MEPP) frequency is normal but the MEPP amplitude is reduced in myasthenia gravis, suggesting that the neuromuscular transmission defect is due to reduction in the postsynaptic response. The pre-

synaptic synthesis, packaging and release of ACh are normal.

In MG, a large proportion of the EPPs are subthreshold, i.e., do not trigger an action potential, while the remainder are barely threshold. Repetitive nerve stimuli evoke successively smaller muscle action potentials indicating an increasing block of neuromuscular transmission.

The most commonly used electrodiagnostic test of neuromuscular transmission is repetitive stimulation of a motor nerve while recording compound muscle action potentials (CMAPs) from an appropriate muscle. In MG, nerve conduction velocity measurements are normal. The amplitude of the initial CMAP is normal, though the average value of this measurement is less than the normal average. Repetitive stimulation at frequencies between one and five per second results in a decremental response. The decrement usually increases with increasing stimulation rate. The tested muscle must be warmed and the decrement must be measured after exhaustion to obtain the maximum diagnostic yield.

Clinical presentations of MG¹⁷

Transient neonatal myasthenia

Fifteen to 20% of neonates born to myasthenic mothers have transient myasthenia. Pregnancy may produce either exacerbation or remission of the disease. There seems to be no correlation between the occurrence of neonatal myasthenia and the severity or duration of the mother's myasthenia. Signs are usually present at birth,¹⁸ but occasionally may be delayed for 12–48 hr. Commonly associated features include difficulty in sucking and swallowing, difficulty with breathing, ptosis and facial weakness.

The most likely explanation of neonatal myasthenia is the passage of AChRA across the placenta, but no correlation has been found between the presence or degree of neonatal myasthenia and the concentration of the antibodies in the infant's serum.

The condition has a tendency to spontaneous remission, usually within two to four weeks, and once therapy has been tapered and stopped there is no risk of relapse. In severely affected infants, treatment should be commenced immediately by oral neostigmine, 1–5 mg, depending on the severity of response.

Congenital or infantile myasthenia

The congenital myasthenias comprise a number of genetically determined diseases showing variable muscle weakness from birth. One of these syndromes is referred to as “congenital endplate acetylcholine-receptor-deficiency.”¹⁹ A structural malformation of the postsynaptic membrane, with almost complete absence of functional

TABLE II Summary of the different clinical presentations of myasthenia gravis

	<i>Aetiology</i>	<i>Onset</i>	<i>Sex</i>	<i>Thymus</i>	<i>Course</i>
Neonatal myasthenia	Passage of antibodies from myasthenic mothers across the placenta	Neonatal	Both sexes	Normal	Transient
Congenital myasthenia	Congenital endplate pathology genetic, autosomal recessive pattern of inheritance	0–2 yr	Male>female	Normal	Non-fluctuating, compatible with long survival
Juvenile myasthenia	Auto-immune disorder	2–20 yr	Female>males (4:1)	Hyperplasia	Slowly progressive, tendency to relapse and remission
Adult myasthenia	Auto-immune disorder	20–40 yr	Female>males	Hyperplasia>thymoma	Maximum severity within 3–5 yr
Elderly myasthenia	Auto-immune disorder	>40 yr	Males>females	Thymoma (benign or locally invasive)	Rapid progress, higher mortality

folds, may lack the fine structural specialization with a consequent reduction in ACh receptor insertion sites.

Congenital myasthenia presenting in infants of non-myasthenic mothers is rare. More commonly, the onset of symptoms is after the neonatal period within the first one to two years of life. The course tends to be non-fluctuating, compatible with long survival and little need for medication. Congenital myasthenia may occur in siblings, suggesting an autosomal recessive pattern of inheritance. The condition is not autoimmune in nature, and hence therapy primarily depends on anticholinesterase therapy.

Juvenile myasthenia

About four percent of all cases of myasthenia have onset of symptoms before the age of ten and about 24% before the age of 20. There is a marked preponderance of female cases (c. 4:1). In contrast to the infantile form, genetic factors appear to play a relatively small role in the juvenile cases and, like adult MG, autoimmune mechanisms play a role in the pathogenesis. The distinction of juvenile MG may be artificial; these cases undoubtedly merge with the adult variety. However, thymoma is not a feature of the juvenile cases. The course tends to be slowly progressive with marked fluctuation and tendency to relapse and remissions.

Adult MG

The incidence is about 1 in every 20,000 adults. There is a preponderance of women, 2:1 in patients <50 yr, but >50 yr it is equally distributed between the sexes. Hyperplasia of the thymus gland is present in over 70% of patients, and 10–15% have thymomas. Thymic hyperplasia is more frequent in young patients, while thymoma is more frequent in elderly patients. Male patients tend to have more rapid progress of the disease, higher mortality, and

lower rates of remission and improvement than women.

The clinical course of MG is marked by periods of exacerbations and remissions. The extraocular muscles are involved at some time in the course of the disease in almost every patient during the first year. However, in three-quarters of patients whose initial symptom is ptosis or diplopia, the disease becomes clinically generalized within the first one to three years when the severity of the disease reaches or approaches a maximum for each patient. Weakness of pharyngeal and laryngeal muscles (bulbar muscles) results in dysphagia, dysarthria and difficulty in eliminating oral reaction. Arm, leg, or truncal weakness can occur in any combination and is usually asymmetrical in distribution. After the disease reaches its maximum severity, most patients who survive continue with a chronic form of the disease with fewer and less severe episodes of exacerbation. Table II summarizes the different clinical presentations of myasthenia gravis.

Myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LES)^{20–22}

Lambert-Eaton syndrome is an acquired disorder of the motor nerve terminal in which quantal release of ACh is reduced. Typically the patient is a 50- to 70-yr-old man who complains of weakness of the limb-girdle muscles which may be erroneously confused with MG. It frequently occurs in association with cancer, especially small-cell carcinoma of the lung.

There is some evidence for an autoimmune basis to LES. It has been suggested that pathogenic IgG antibodies cross-react with the pre-synaptic voltage-dependent calcium channels which are essential for the quantal release of ACh. In the myasthenic syndrome, MEPP frequency is decreased. The ACh content and acetyltrans-

ferase activity in diseased nerve endings are normal, suggesting that the synthesis and packaging of ACh are normal and that the defect is an abnormality in vesicular release. The decreased quantal release of ACh will manifest as a neuromuscular disorder. Also, dysautonomia can occur secondary to impaired ACh release at cholinergic autonomic sites, and manifest by dry mouth, impaired accommodation, urinary hesitance and constipation.

A classical electromyographic finding in LES is the incremental response. In contrast to MG, exercise or tetanic stimulation improves rather than reduces muscle strength. Clinically, the patient usually has a marked EMG defect in the face of relatively good muscle strength, while the MG patient usually has a modest abnormality of the EMG in the face of marked muscular fatigability and weakness. Also, the skeletal muscle weakness of LES is not reliably reversed with anticholinesterase, while 3,4-diaminopyridine has been shown to cause an increase of transmitter release and can effectively antagonize the neuromuscular and autonomic nervous system disorders.

In contrast to MG patients who are sensitive to nondepolarizing muscle relaxants and resistant to depolarizing relaxants, patients suffering from LES are sensitive to both depolarizing and nondepolarizing relaxants. The syndrome should be considered in those patients undergoing diagnostic procedures such as bronchoscopy, mediastinoscopy, or thoracotomy for the suspected diagnosis of carcinoma of the lung.

Classification of myasthenia gravis

Myasthenia gravis may be classified on the basis of the skeletal muscles involved and the severity of the symptoms. The various stages of the disease have been classified by Ossermann and Genkins (1971):²³

- I Ocular signs and symptoms only
- IIA Generalized mild muscle weakness
- IIB Generalized moderate weakness, and/or bulbar dysfunction
- III Acute fulminating presentation, and/or respiratory dysfunction
- IV Late severe generalized myasthenia gravis

Type I is limited to involvement of the extraocular muscles. Type IIA is a slowly progressive and mild form of skeletal muscle weakness, which spares the muscles of respiration. Type IIB is a more severe and rapidly progressive form of skeletal muscle weakness. Type III is characterized by an acute onset and rapid deterioration that is associated with a high mortality. Type IV is a severe form that results from progression of Type I and II.

Course of myasthenia gravis²⁴

The distribution, severity, and outcome of the disease are determined during the first one to three years after the

onset, suggesting that injury to ACh receptors occurs mainly during this time. In 14%, the disease remains clinically localized to extraocular muscles and in the remaining 86% becomes generalized. It is likely that the final severity of muscle weakness is influenced by:²

- (a) The safety margin of neuromuscular transmission.
- (b) The ability of the muscle to compensate for the receptor deficit by rapid resynthesis of AChRs.
- (c) Differences in the AChR molecule in different muscles, and perhaps in different patients.

Medical treatment

Current medical treatment of myasthenia gravis is aimed at (1) enhancing neuromuscular transmission by anticholinesterases, (2) suppressing the immune system by corticosteroids and azathioprine, (3) decreasing the circulating antibody level by plasmapheresis.²⁵ However, there are differences in opinion about the selection, sequence and timing of these options.

Cholinesterase Inhibitors (ChEI) such as neostigmine and pyridostigmine were the mainstay of therapy for MG since 1934 until ten years ago. Because ChEI represent only symptomatic therapy, they are of little aid in most cases of severe, or progressive MG, particularly if there is oropharyngeal or respiratory muscle involvement. Also, evidence in experimental animals indicates that the long-term administration of anticholinesterases results in changes in the configuration of the AChR similar to those seen in patients with MG.²⁶ ChEI are indicated in mild or localized MG. Treatment schedules are individualized on a sliding daily schedule with maximum patient participation. Patients' understanding of the pharmacokinetic behaviour of the drug used is important, with detailed description of underdose (myasthenic) and overdose (cholinergic) states.²⁷

*Plasma Exchange (Plasmapheresis)*²⁸⁻³⁰ will lead to marked improvement of remission in 45% of cases. Myasthenia gravis patients with circulating antiacetylcholine receptor antibodies usually show a dramatic decrease in the levels of these antibodies following the first few treatments. Improvement usually begins between the first and the fourth exchange (with a regimen of three exchanges weekly). A "course" of plasmapheresis usually lasts from one to two weeks and involves the performance of four to eight individual exchanges. Exchange volumes range from one to four litres and replacement fluids commonly used are albumin, plasma protein fraction and saline. Fresh frozen plasma is not often used because of hypersensitivity reactions and transmission of hepatitis and HIV virus. However, improvement lasts for only four days to 12 weeks. Plasmapheresis may be used on an urgent

basis in a myasthenic crisis with respiratory embarrassment. Also, it may be used together with or after corticosteroids of other immunosuppressants. Recent reports show that plasmapheresis may be used alone as a preparation to thymectomy.^{31,32}

*Corticosteroids*³³ such as prednisone will lead to marked improvement or remission in about 80% of cases, with improvement beginning between 12 hr to 30 days. Improvement may be maintained with decreasing dosage or discontinuation of therapy.

*Immunosuppressive drugs*³⁴ such as azathioprine produce some degree of improvement in 45% of patients. Excellent results will be seen in type II, rapidly progressive MG, in old people, or in the thymoma-associated MG. Improvement begins at between three to twelve months, and is only maintained when the drug therapy is maintained. About one third of patients with type II MG proceed to a complete but azathioprine-dependent remission, and the remaining two thirds to a marked improvement. In type I MG, azathioprine is less effective but will help reduce the need for corticosteroids or plasmapheresis. Cyclosporin A is more selective and requires less time to act than azathioprine. It suppresses the activation and proliferation of T-helper lymphocytes. However, because of its adverse reactions including nephrotoxicity and hepatic dysfunction, cyclosporin A is only used in patients with severe MG whenever azathioprine is not effective or results in idiosyncratic reactions.³²

Corticosteroids or plasmapheresis are preferable to immunosuppressive drugs when one considers the rapid improvement. This is particularly the case in acute severe MG with respiratory failure. In less acute cases, azathioprine is advantageous.

Experimental strategies of therapy

New experimental strategies have been designed for the management of myasthenia (Table III) and are being tested in animals with experimental autoimmune myasthenia gravis.

Thymectomy

There is a consensus that all adults with generalized MG should have a thymectomy.^{31,32,35,36} This has been propagated by evidence of the safety of the procedure and excellent outcome. Thymectomy is the preferred form of treatment of MG with generalized weakness, particularly for patients <55 yr. However, age is no contraindication for thymectomy, and older patients >50 yr can benefit from surgery.³⁷ There is also unanimity about excision of thymomas, although remission of myasthenia is less frequent than in patients without tumour. Thymectomy

TABLE III Experimental strategies in myasthenia gravis

-
1	Inhibit endocytosis of AChRs
2	"Hot antigen suicide" of AChR-specific B cells
3	Novel immunosuppressive agents
	(a) cyclosporin A
	(b) total lymphoid irradiation
4	Induction of tolerance
5	Anti-idiotypic approaches:
	(a) antibodies
	(b) T-cell "vaccination"
6	Suppressor cells for AChR
7	Knowledge of AChR molecular structure
-

may be less indicated in children because of unsubstantiated fears that early thymectomy might lead to immunodeficiency. However, there is no evidence of adverse effects and there have been many reports of improvement in children.³⁸ The operation is usually recommended for patients with ocular myasthenia. As the operation becomes safer, clinicians refer patients with milder symptoms, which may be partly responsible for the improved outcome.

Removal of as much thymic tissue as possible (anterior mediastinal exenteration) via transsternal approach is the logical goal of thymectomy in the treatment of myasthenia gravis;³⁶ even small remnants of thymic tissue seem to affect outcome adversely. Complete thymectomy cannot be achieved by the trans-cervical approach.³⁶

Anaesthetic management

The anaesthetic management of the myasthenic patient must be individualized to the severity of the disease and the type of surgery. The use of regional or local anaesthesia seems warranted whenever possible. Whenever local or regional anaesthesia is used, the dose of the local anaesthetic may be reduced in patients to decrease the possible effects of anaesthetics on neuromuscular transmission. This may be particularly important when ester local anaesthetics are administered to patients receiving anticholinesterase therapy. General anaesthesia can be performed safely, provided the patient is optimally prepared and neuromuscular transmission is adequately monitored during and after surgery.³⁹⁻⁴¹

Preoperative preparation

Adequate preoperative evaluation of the myasthenic patient must be carried out carefully. Age, sex, onset and duration of the disease as well as the presence of thymoma may determine the response to thymectomy. Also, the severity of myasthenia and the involvement of bulbar or respiratory muscles must be evaluated. Preoperative respiratory function tests must be performed since chronic respiratory disease and/or a preoperative vital capacity

TABLE IV Algorithm for preoperative preparation of a myasthenic patient scheduled for thymectomy

<2.9 L are two of the predictive criteria for postoperative respiratory support.

Optimization of the condition of the myasthenic patients can markedly decrease the risk of surgery and improve the outcome.³² Many regimens have been recommended for preoperative treatment. Table IV depicts one of these regimens which may be used for preoperative preparations of the myasthenic patient scheduled for thymectomy.³²

It is controversial whether anticholinesterase therapy should be maintained or discontinued before and after surgery.⁴⁰ Anticholinesterases potentiate the vagal responses and hence adequate atropinization must be ensured. Also, anticholinesterases can inhibit plasma cholinesterase activity with a subsequent decrease in the metabolism of ester local anaesthetics, and the hydrolysis of succinylcholine will be decreased. As in nonmyasthenic patients, the duration of succinylcholine block in myasthenic patients is inversely related to the plasma cholinesterase activity. In contrast with succinylcholine, the inhibition of acetylcholinesterase by anticholinesterases may increase the need for nondepolarizing muscle relaxants in the myasthenic patient, although this has not been documented.

Recently, plasmapheresis alone without immunosuppression has been used to optimize the medical status of the myasthenic patient prior to surgery. Anticholinesterase agents are discontinued, while corticosteroid medications are maintained to be tapered and discontinued postoperatively.³¹

Premedication

Myasthenic patients may have little respiratory reserve,

FIGURE 1 Succinylcholine dose-response curves in normal and myasthenic patients (Reproduced, with permission from Eisenkraft et al. Resistance to succinylcholine in myasthenia gravis: a dose-response study. *Anesthesiology* 1988; 69: 670-3.)

and hence depressant drugs for preoperative premedication should be used with caution, and avoided in patients with bulbar symptoms. We usually premedicate myasthenic patients with atropine 0.6 mg *im*, and only use diazepam, 5 mg *po*, for sedation. It is advisable to inform patients that postoperative tracheal intubation and respiratory support may be required.

Anaesthetic techniques

Two techniques have been recommended for general anaesthesia in the myasthenic patient. Because of the unpredictable response to succinylcholine and the marked sensitivity to nondepolarizing muscle relaxants, some anaesthetists avoid muscle relaxants and depend on deep inhalational anaesthesia, such as halothane, for tracheal intubation and maintenance of anaesthesia.^{42,43} However, others utilize a balanced technique which includes the use of muscle relaxants, without the need for deep inhalational anaesthesia with its concomitant respiratory and cardiovascular side effects.

Response to muscle relaxants

Adequate understanding of the response of the myasthenic patient to both depolarizing and nondepolarizing relaxants is necessary for their safe administration. In MG, there is a decrease in the number of functional AChRs available, with a subsequent decrease of the "safety margin" which is why the myasthenic patient may demonstrate an abnormal neuromuscular response to both depolarizing and nondepolarizing muscle relaxants.⁴⁴ The decrease of functional endplate receptors in MG can decrease the response to the chemical transmitter, as well as to other depolarizing agents such as decamethonium and succinylcholine. In contrast, the decreased "safety margin" results in a marked sensitivity to nondepolarizing relaxants.

The abnormal response of the myasthenic patients to

FIGURE 2 Electromyographic response to ulnar nerve stimulation by a train-of-four every 20 sec, showing the effect of succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ in three myasthenic patients with different plasma cholinesterase activity. Upper tracing: plasma cholinesterase $5.16 \text{ U} \cdot \text{ml}^{-1}$. Middle tracing: plasma cholinesterase $1.45 \text{ U} \cdot \text{ml}^{-1}$. Lower tracing: plasma cholinesterase $0.73 \text{ U} \cdot \text{ml}^{-1}$. (Reproduced, with permission, from Baraka A. Suxamethonium block in the myasthenic patient – correlation with plasma cholinesterase. *Anaesthesia* 1992; 47 in press.)

muscle relaxants is encountered even in patients with localized ocular myasthenia⁴⁵ and during remission⁴⁶ who may have circulating antibodies and decreased receptor population sufficient to maintain neuromuscular transmission, but without the normal “safety margin” provided by an excess of receptor sites.

Because of the decreased number of AChR and/or their functional blockade by AChR antibodies, succinylcholine may not effectively depolarize the endplate resulting in “resistance.” The ED_{50} and ED_{95} in myasthenic patients is 2.0 and 2.6 times normal, respectively (Figure 1).⁴⁷ Thus, high doses of succinylcholine may be required for rapid sequence tracheal intubation in a patient with MG. The endplate potential may not reach the threshold required for inducing depolarizing “phase I” block, and hence succinylcholine may readily induce phase II block.⁴⁰ Also, it is possible that the phase II block seen in some cases is due to the decreased plasma cholinesterase activity induced by the preoperative anticholinesterase administration. Anticholinesterase can decrease the plasma cholinesterase activity,⁴⁸ with a subsequent delayed hydrolysis of succinylcholine and potentiation of neuromuscular block.⁴⁹ Recently, we have shown an inverse relationship between the duration of succinylcholine block in the myasthenic patient and plasma cholinesterase activity (Figure 2).⁵⁰

The reduction of the number of ACh receptors at the neuromuscular junction, and the consequent reduction of the “safety margin”⁵¹ makes myasthenic patients extremely sensitive to nondepolarizing muscle relaxants. There is a large spectrum in the severity of the disease in patients with myasthenia gravis, and thus muscle relaxant requirements are also extremely variable. One tenth of the normal paralyzing dose may be sufficient to paralyse a patient

FIGURE 3 Dose-response relationship for atracurium in patients with myasthenia gravis versus normal individuals. (Reproduced, with permission, from Smith CE, Donati F, Bevan DR. Cumulative dose-response curve for atracurium in patients with myasthenia gravis. *Can J Anaesth* 1989; 36: 402–6.)

FIGURE 4 Mean log dose-logit response curves for vecuronium in myasthenic versus control normal patients. (Reproduced, with permission, from Eisenkraft JB, Book WJ, Papatestas AE. Sensitivity to vecuronium in myasthenia gravis: a dose-response study. *Can J Anaesth* 1990; 37: 301–6.)

with MG which is why many anaesthetists avoid the administration of nondepolarizing relaxants. However, this policy may not apply to intermediate-acting relaxants such as atracurium and vecuronium. Both atracurium^{52,53} and vecuronium^{54–57} are rapidly eliminated, and their dose can be titrated to achieve the required neuromuscular blockade that can be completely reversed at the termination of the surgical procedure. Figures 3 and 4 depict the mean dose-

response curve of atracurium and vecuronium in the myasthenic versus the normal patients.

Monitoring of neuromuscular transmission

Neuromuscular transmission must be monitored carefully during surgery by peripheral nerve stimulation to titrate the necessary dose of muscle relaxants, and to ensure complete reversal of neuromuscular block at the termination of surgery.⁵²⁻⁵⁷ Monitoring should be continued postoperatively for early detection of neuromuscular dysfunction.

Postoperative management

Ventilatory function must be monitored carefully after surgery. Despite the enormous number of studies in the literature, few correlate tests of neuromuscular function with adequate ventilation. It has been shown recently in normal patients that many of the recommended tests such as maintained response to tetanic stimulation of a peripheral nerve can return to normal, while the pharyngeal and neck muscles necessary to protect the airway can still be partially paralysed.⁵⁸ The different response of peripheral versus bulbar muscles may be more evident in myasthenic patients, particularly those suffering from bulbar and/or respiratory muscle weakness. It is essential that sustained respiratory muscle strength be confirmed before extubation of the trachea and resumption of spontaneous ventilation. Patients should be considered partially paralysed until they wake up and can lift their head for five seconds. An inspiratory force exceeding -25 cm H₂O may be used as a criterium of adequate respiratory function.

Myasthenic patients may be at increased risk of developing postoperative respiratory failure. Several authors have proposed criteria for predicting which patients will require prolonged postoperative mechanical ventilation. Following transsternal thymectomy, up to 50% of patients require prolonged postoperative ventilation.

Four risk factors have been identified:

- 1 Duration of myasthenia gravis for longer than six years (12 points). Duration of MG proved to have the greatest value in predicting the need for ventilatory support.
- 2 A history of chronic respiratory disease other than respiratory dysfunction directly due to MG (10 points).
- 3 A dose of pyridostigmine greater than 750 mg per day, 48 hr before operation (8 points).
- 4 A preoperative vital capacity < 2.9 L (4 points).

These risk factors were weighted according to their significance as predictors; a total score of $\geq$ ten points identified those patients likely to need postoperative pulmonary ventilation for more than three hours.

Following transcervical thymectomy, only 7.4% of patients required prolonged ($>$ three hours) postoperative ventilation. Positive predictors of prolonged ventilation

are: clinical classification of MG (Ossermann classes 3 and 4), a previous history of respiratory failure due to MG, and associated steroid therapy.⁶⁰ However, transcervical thymectomy is not as effective as transsternal thymectomy by the criteria of incidence and degree of remission.³⁶

Outcome

Thymectomy benefits nearly 96% of patients regardless of preoperative characteristics: 46% develop complete remission, 50% are asymptomatic or improve on therapy, and 4% remain the same.³⁶ However, thymectomy does not always induce a decrease in anti-AChR antibody titer, and when it does, the antibody titer decrease is slow, occurring after the catabolism of the already present antibodies. Also, the anti-AChR auto-sensitized T cells survive long after thymectomy.⁸ These reservations do not question the role of the thymus in the pathogenesis of MG or the value of thymectomy.

Following thymectomy, different therapeutic regimens have been recommended depending on the outcome of surgery. Most early-onset myasthenics can be treated effectively with thymectomy alone, while late-onset myasthenia as well as myasthenia associated with thymoma needs additional postoperative immunosuppression.⁶¹

References

- 1 Drachman DB. Myasthenia gravis. *N Engl J Med* 1978; 298: 136-42.
- 2 Drachman DB, De Silva S, Ramsay D, Pestronk A. Humoral pathogenesis of myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 90-105.
- 3 Lindstrom JM, Seybold ME, Lenon VA, et al. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. *Neurology* 1976; 26: 1054-9.
- 4 Shinomiya N, Segawa M, Yata I. In vitro study of T-cells regulating anti-acetylcholine receptor antibody formation in myasthenia gravis. *Ann N Y Acad Sci* 1981; 377: 882-3.
- 5 Behan PO, Shields J. Genetics. In: Lisak R, Barchi R (Eds.) *Myasthenia Gravis*. W. B. Saunders, Philadelphia, 1982; Chapter 3: 37-50.
- 6 Raimond F, Morel E, Bach JF. Evidence for the presence of immunoreactive acetylcholine receptors on human thymus cells. *J Neuroimmunol* 1984; 6: 31-40.
- 7 Müller-Hermelink HK, Kirchner T, Hoppe F, Demel S. Thymic myoid cells - stimulants and/or targets of autoimmune myasthenia gravis. In: De Baets MH, Dosterhufs HJGH, Toyka KV. *Monographs in Allergy, Myasthenia Gravis*, Krager, New York, 1988; 25: 68-74.
- 8 Berrih-Aknin S, Morel E, Raimond F, et al. The role of the thymus in myasthenia gravis: immunohistological and

- immunological studies in 115 cases. *Ann N Y Acad Sci* 1987; 505: 50–70.
- 9 Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. *J Physiol* 1967; 191: 59–90.
 - 10 Woolf AL. Morphology of the myasthenic neuromuscular junction. *Ann N Y Acad Sci* 1966; 135: 33–58.
 - 11 Engel AG, Santa T. Histometric analysis of the ultrastructure of the neuromuscular junction in myasthenia gravis and in the myasthenic syndrome. *Ann N Y Acad Sci* 1971; 183: 46–63.
 - 12 Stanley EF, Drachman DB. Stabilization of acetylcholine receptors at neuromuscular junctions: analysis by specific antibodies. *Ann N Y Acad Sci* 1987; 505: 121–32.
 - 13 Wessler I. Control of transmitter release from the motor nerve by presynaptic nicotinic and muscarinic autoreceptors. *Trends in Pharmacol Sci (TiPS)* 1989; 10: 110–4.
 - 14 Bowman WC. Prejunctional and postjunctional cholinergic receptors at the neuromuscular junction. *Anesth Analg* 1980; 59: 935–43.
 - 15 Elmqvist D, Hofmann WW, Kugelberg J, Quastel DMJ. An electrophysiological investigation of neuromuscular transmission in myasthenia gravis. *J Physiol* 1964; 174: 417–34.
 - 16 Sanders DB. The electrodiagnosis of myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 539–55.
 - 17 Dubowitz V. Myasthenia gravis. In: Dubowitz V (Ed.). *Muscle Disorders in Childhood*. W.B. Saunders Company Ltd., Philadelphia 1978; 191–201.
 - 18 Usta N, Baraka A. Undiagnosed myasthenia gravis in a parturient undergoing cesarean section – maternal and neonatal complications. *Middle East Journal of Anesthesiology* 1984; 7: 277–81.
 - 19 Smit LME, Veldman H, Jennekens FGI, Molenaar PC, Siu Oen B. A congenital myasthenic disorder with paucity of secondary synaptic clefts: deficiency and altered distribution of acetylcholine receptors. *Ann N Y Acad Sci* 1987; 505: 346–56.
 - 20 Elmqvist D, Lambert EH. Detailed analysis of neuromuscular transmission in a patient with the myasthenic syndrome sometimes associated with bronchogenic carcinoma. *Mayo Clin Proc* 1968; 43: 689–713.
 - 21 Lambert EH, Rooke EK, Eaton LM, Hodgson CH. Myasthenic syndrome occasionally associated with bronchial neoplasms. *Neurophysiologic studies*. In: HR Viets (Ed.). *Myasthenia Gravis*. Springfield IL, Charles C Thomas, 1961: 362–410.
 - 22 Kim YI. Lambert-Eaton myasthenic syndrome: evidence for calcium channel blockade. *Ann N Y Acad Sci* 1987; 505: 377–81.
 - 23 Osserman KE, Jenkins G. Studies on myasthenia gravis. Review of a twenty-year experience in over 1200 patients. *M Sinai J M* 1971; 38: 497–537.
 - 24 Grob D, Arsura EL, Brunner NG, Namba T. The course of myasthenia gravis and therapies affecting outcome. *Ann N Y Acad Sci* 1987; 505: 472–99.
 - 25 Drachman DB, McIntosh KR, De Silva S, et al. Strategies for the treatment of myasthenia gravis. *Ann N Y Acad Sci* 1988; 540: 176–86.
 - 26 Engel AG, Lambert EH, Santa T. Study of long-term anticholinesterase therapy. Effects on neuro-muscular transmission and on motor endplate line structure. *Neurology* 1973; 23: 1273–81.
 - 27 Jenkins G, Kornfeld P, Papatestas AE, Bender AN, Matta RJ. Clinical experience in more than 2000 patients with myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 500–14.
 - 28 Reimann PM, Mason PD. Plasmapheresis: technique and complications. *Intensive Care Med* 1990; 16: 3–10.
 - 29 Seybold ME. Plasmapheresis in myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 584–7.
 - 30 Dau PC, Lindstrom JM, Cassel CK, Denys EH, Shev EE, Spitler LE. Plasmapheresis and immunosuppressive drug therapy in myasthenia gravis. *N Engl J Med* 1977; 297: 1134–40.
 - 31 Olanow CW, Wechsler AS, Sirotkin-Roses M, Stajich J, Roses AD. Thymectomy as primary therapy in myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 595–606.
 - 32 Toyka KV. Myasthenia gravis. In: Richard T Johnson (Ed.). *Current Therapy in Neurologic Disease – 3*, Philadelphia; BC Decker Inc 1990; 385–91.
 - 33 Johns TR. Long-term corticosteroid treatment of myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 568–83.
 - 34 Matell G. Immunosuppressive drugs: azathioprine in the treatment of myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 588–94.
 - 35 Taha AM, Haddad R, Allam C, Baraka A. The thymus and myasthenia gravis. *Middle East Journal of Anesthesiology* 1981; 6: 99–112.
 - 36 Younger DS, Jaretzki III A, Penn AS, et al. Maximum thymectomy for myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 832–5.
 - 37 Olanow CW, Lane RJM, Roses AD. Thymectomy in late-onset myasthenia gravis. *Arch Neurol* 1982; 39: 82–3.
 - 38 Rowland LP. Therapy in myasthenia gravis. *Ann N Y Acad Sci* 1987; 505: 566–7.
 - 39 Stoelting RK, Dierdorf SF, McCommon RL. Myasthenia Gravis. In: *Anesthesia and Co-Existing Disease*, 2nd ed, New York: Churchill Livingstone, 1988; 626–30.
 - 40 Miller J, Lee C. Muscle diseases. In: Katz J, Benumof J, Kadis LB (Eds.). *Anesthesia and Uncommon Diseases*. Philadelphia: W.B. Saunders Company, 1981; 530–61.
 - 41 Dierdorf SF. Rare co-existing diseases. In: Barash PG, Cullen BF, Stoelting RK (Eds.). *Clinical Anesthesia*, Philadelphia: J. B. Lipincott Company, 1989; 441–2.
 - 42 Churchill-Davidson HC. Myasthenia gravis. *A Practice of Anaesthesia*. 5th ed. London: Lloyd-Luke (Medical Books) Ltd, 1984; 739–40.

- 43 Nilsson E, Paloheimo M, Muller K, Heinonen J. Halothane-induced variability in the neuromuscular transmission of patients with myasthenia gravis. *Acta Anaesthesiol Scand* 1989; 33: 395–401.
- 44 Churchill-Davidson HC, Richardson AT. Neuromuscular transmission in myasthenia gravis. *J Physiol* 1953; 122: 252–63.
- 45 Baraka A, Afifi A, Muallem M, Kachachi R, Frayha F. Neuromuscular effects of halothane, suxamethonium and tubocurarine in a myasthenic undergoing thymectomy. *Br J Anaesth* 1971; 43: 91–5.
- 46 Abel M, Eisenkraft JB, Patel N. Response to suxamethonium in a myasthenic patient during remission. *Anaesthesia* 1991; 46: 30–2.
- 47 Eisenkraft JB, Book J, Mann SM, Papatestas AE, Hubbard M. Resistance to succinylcholine in myasthenia gravis: a dose-response study. *Anesthesiology* 1988; 69: 760–3.
- 48 Baraka A, Wakid N, Mansour R, Haddad W. Effect of neostigmine and pyridostigmine on the plasma cholinesterase activity. *Br J Anaesth* 1981; 53: 849–51.
- 49 Baraka A. Suxamethonium-neostigmine interaction in patients with normal or atypical cholinesterase. *Br J Anaesth* 1977; 49: 479–84.
- 50 Baraka A. Suxamethonium block in the myasthenic patient – correlation with plasma cholinesterase. *Anaesthesia* 1992; 47 (in press).
- 51 Waud BE, Waud DR. The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. *Anesthesiology* 1971; 35: 456–64.
- 52 Baraka A, Dajani A. Atracurium in myasthenics undergoing thymectomy. *Anesth Analg* 1984; 63: 1127–30.
- 53 Smith CE, Donati F, Bevan DR. Cumulative dose-response curves for atracurium in patients with myasthenia gravis. *Can J Anaesth* 1989; 36: 402–6.
- 54 Hunter JM, Bell CF, Florence AM, Jones RS, Utting JE. Vecuronium in the myasthenic patient. *Anaesthesia* 1985; 40: 848–53.
- 55 Buzello W, Noeldge G, Krieg N, Brobmann GF. Vecuronium for muscle relaxation in patients with myasthenia gravis. *Anesthesiology* 1986; 64: 507–9.
- 56 Eisenkraft JB, Book WJ, Papatestas AE. Sensitivity to vecuronium in myasthenia gravis: a dose-response study. *Can J Anaesth* 1990; 37: 301–6.
- 57 Baraka A, Tabboush Z. Neuromuscular response to succinylcholine-vecuronium sequence in three myasthenic patients undergoing thymectomy. *Anesth Analg* 1991; 72: 827–30.
- 58 Pavlin EG, Holle RH, Schoene RB. Recovery of airway protection compared with ventilation in humans after paralysis with curare. *Anesthesiology* 1989; 70: 381–5.
- 59 Leventhal SR, Orkin FK, Hirsh RA. Prediction of the need for postoperative mechanical ventilation in myasthenia gravis. *Anesthesiology* 1980; 53: 26–30.
- 60 Eisenkraft JB, Papatestas AE, Pozner JN, Fagerstrom R, Jenkins G. Predictors of respiratory failure following transcervical thymectomy. *Ann N Y Acad Sci* 1987; 505: 888–90.
- 61 Oosterhuis HJGH. Long-term effects of treatment in 374 patients with myasthenia gravis. In: De Baeks MH, Oosterhuis HJGH, Toyka KV (Eds.). *Myasthenia gravis*. Monographs in Allergy, New York, 1988; 25: 75–85.