

## Neuromuscular junction in health and disease

N. P. Hirsch\*

*The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK*

*\*E-mail: nicholas.hirsch@uclh.nhs.uk*

A number of illnesses and other factors can affect the function of the neuromuscular junction (NMJ). These may have an effect at pre- or post-junctional sites. This review outlines the anatomy and the physiology of the NMJ. It also describes the mechanisms and physiological basis of many of the disorders of the NMJ. Finally, the importance of these disorders in anaesthetic practice is discussed.

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The neuromuscular junction (NMJ), the most studied of all synapses, provides the link between myelinated motor nerves and skeletal muscle. In health, it is an integral part of an impressively efficient biological amplification system, which converts minute nerve action potentials into muscle contraction. A sound knowledge of the physiology of the NMJ is essential to the anaesthetist and intensivist because dysfunction of the synapse, whether because of disease or the administration of neuromuscular blocking agents, can result in respiratory and bulbar muscle failure. This review outlines the structure and function of the NMJ and discusses the anaesthetic implications of disease of the junction.

### Structure and function of the NMJ

Consideration of the structure and function of the mature NMJ can be conveniently divided into presynaptic, synaptic, and postsynaptic phases. The embryological development, maturation, and organization of the NMJ have recently been reviewed by Naguib and colleagues.<sup>30</sup>

#### *Presynaptic structure and function*

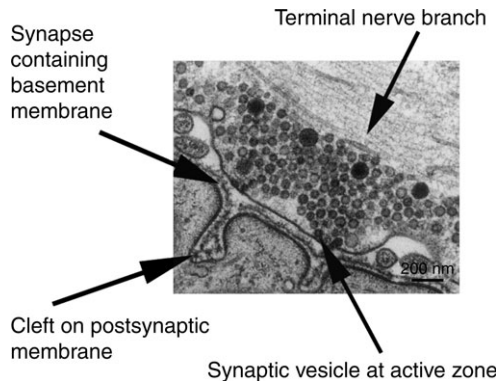
As each myelinated motor axon reaches its target muscle, it divides into 20–100 unmyelinated terminal fibres, each of which innervates a single muscle fibre. The combination of the terminal fibres from a motor axon and the muscle fibres they serve is called a motor unit (Fig. 1). The terminal fibres contain both potassium ( $K^+$ ) and sodium ( $Na^+$ ) channels, which control the duration and amplitude of the action potential.<sup>39</sup>

In contrast, the nerve terminal has a paucity of  $Na^+$  channels and the action potential continues passively into this area. The nerve terminal contains synaptic vesicles (SVs), each of which contains 5000–10 000 molecules of the neurotransmitter acetylcholine (ACh). The content of a

single vesicle is referred to as a 'quantum' of the transmitter. In the inactivated nerve terminal, the SVs are held in an actin framework close to the active zones from which they release their contents. Occasional spontaneous release of quanta of ACh results in the production of a so-called miniature endplate potential at the postsynaptic membrane. The arrival of the action potential at the nerve terminal results in opening of the voltage-gated calcium ( $Ca^{2+}$ ) (P/Q and possibly N-type) channels, which are arranged in regular parallel arrays at the active zones. The ensuing rapid increase in free  $Ca^{2+}$  within the nerve terminal initiates a train of events which result in mobilization of the SVs from their actin matrix, docking at the active zones, and release of their quanta of ACh into the synaptic cleft. The mobilization and docking processes involve the activation of the protein synapsin and the formation of the soluble N-ethylmaleimide sensitive factor attachment receptor (SNARE) complex (this involves presynaptic proteins, SV docking, and membrane fusion), respectively.<sup>9</sup> The extent of the  $Ca^{2+}$  influx into the nerve terminal (and therefore the amount of ACh released) is determined by the duration of the nerve depolarization and this appears to be limited by voltage-gated and  $Ca^{2+}$ -dependent  $K^+$  channel activation. In general, one action potential results in the exocytosis of 50–300 SVs; this represents approximately 10 times the necessary amount of ACh needed to reach the postsynaptic ACh receptor threshold.

#### *Synaptic cleft structure and function*

The synaptic cleft is the space between the nerve terminal and the postsynaptic membrane and measures ~50 nm. After release from the nerve terminal, ACh diffuses within a few microseconds across the synaptic cleft to the postsynaptic membrane. However, ~50% of the released ACh is either hydrolysed by acetylcholinesterase (AChE) contained within the cleft or diffuses out of the cleft before it



**Fig 1** Transmission electron micrograph of the NMJ.

reaches its target. The high concentration of AChE within the cleft terminates the action of ACh preventing it from activating the postsynaptic nicotinic acetylcholine receptors (nAChRs) more than once. Also contained within the cleft are a number of complex proteins that maintain the integrity, the formation, and the clustering of the postsynaptic ACh receptors.<sup>30</sup>

*Postsynaptic membrane structure and function*

The postsynaptic membrane is folded into secondary synaptic folds at the top of which are clustered the nAChRs<sup>24</sup> at a concentration of  $\sim 20\,000$  receptors  $\mu\text{m}^{-1}$  (Fig. 2). The high density of receptors ensures the safety factor for neuromuscular transmission.<sup>38</sup> Away from the endplate, the concentration of nAChRs is one thousand times lower. The

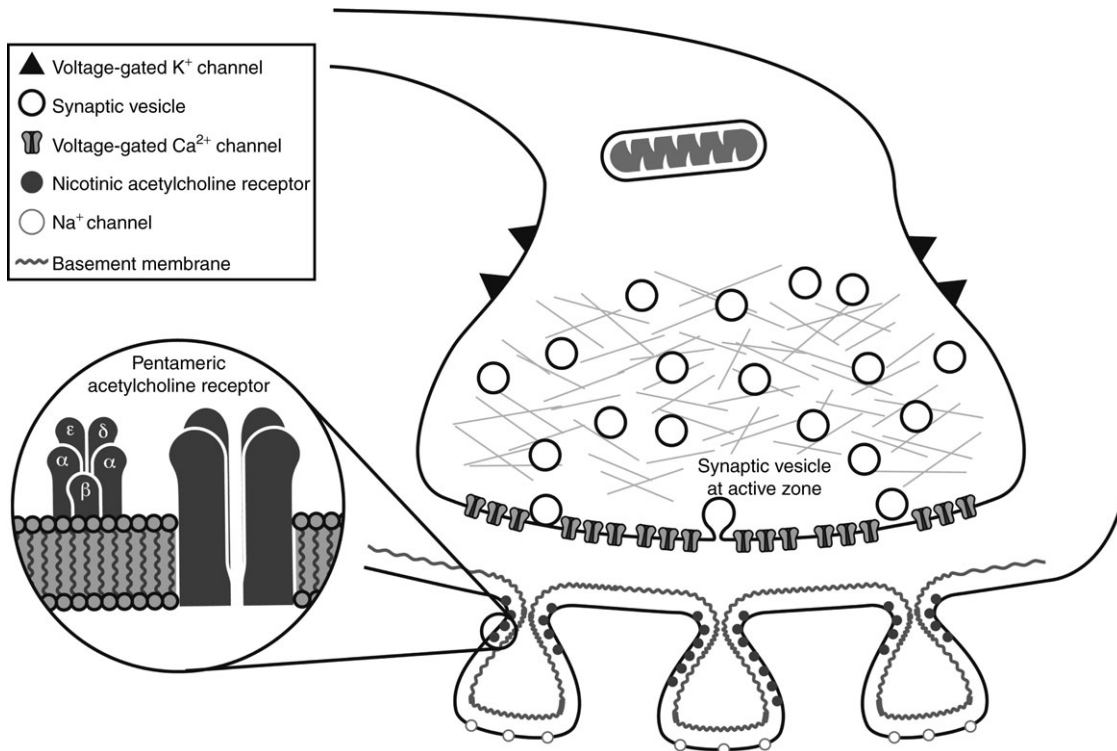
nAChR is a transmembrane protein consisting of five subunits arranged in a pentameric unit. In the adult mammal, these are designated  $\alpha_2\beta\delta\epsilon$ . The subunits are spaced like the staves of a barrel surrounding a central transmembrane pore, while on their synaptic surface they provide the binding sites for ACh. In the absence of ACh, the central pore remains impermeable to the flow of cations. The pore opens in response to two molecules of ACh binding to the N-terminal domain of the junctions of the  $\alpha\delta$  and  $\alpha\epsilon$  subunits. This allows sodium to enter and depolarize the muscle cell membrane, which initiates the propagation of action potentials across the surface of the muscle, which through a number of steps results in muscle contraction.

Although many central nervous system diseases (e.g. stroke, spinal cord injury, and multiple sclerosis) and peripheral nerve diseases (e.g. Guillain–Barré syndrome) result in a secondary up-regulation of nAChR because of a decrease in the exposure of the nAChR to ACh, this review will be restricted to a discussion of conditions that primarily affect the NMJ.

**Diseases affecting the presynaptic NMJ complex (Table 1)**

*Autoimmune neuromyotonia (Isaacs’ syndrome)*

Isaacs’ syndrome is characterized by focal or generalized myokymia (visible muscular rippling movements), muscle cramps, and stiffness. It is caused by antibodies directed



**Fig 2** Diagram showing components of the NMJ.

**Table 1** Diseases of the presynaptic NMJ

Disease	Mechanism of disease
Autoimmune neuromyotonia (Isaacs' disease)	Antibodies directed towards delayed rectifier potassium channels in terminal nerve fibres. Results in inefficient repolarization after action potential
LEMS	IgG antibodies directed towards presynaptic voltage-gated calcium channels. Results in decreased mobilization and, therefore, decreased release of ACh vesicles
Botulism	Botulinum toxins inhibit SV exocytosis by proteolysis of components of the SNARE complex
Congenital MG	May be a result of deficiency of choline acetyltransferase leading to a defect of presynaptic ACh resynthesis, or a result of paucity of SVs

towards the delayed rectifier  $K^+$  channels in terminal nerve fibres resulting in their down-regulation.<sup>42</sup> This results in repeated action potentials and hence hyperexcitability of peripheral motor nerves. Approximately 20% of patients have an associated thymoma. Patients are often treated with sodium channel-blocking drugs such as phenytoin and carbamazepine.

Owing to its rarity, few reports have appeared regarding anaesthesia for neuromyotonia. However, anaesthetists should be aware that there is a possible association of the condition with myasthenia gravis (MG),<sup>31</sup> rheumatoid disease,<sup>32</sup> and the Lambert–Eaton myasthenic syndrome (LEMS).<sup>22</sup> It appears that the abnormal muscle activity that characterizes the condition persists during general anaesthesia, but may be abolished during epidural and spinal anaesthesia; peripheral nerve blockade appears to have a variable effect. Successful epidural analgesia for labour in an asymptomatic patient has been reported.<sup>29</sup>

### Lambert–Eaton myasthenic syndrome

LEMS is a rare autoimmune condition, in which divalent IgG antibodies cross-link the presynaptic voltage-gated  $Ca^{2+}$  channels, disrupting the normal parallel architecture of the channels, and reducing the number of active zone complexes.<sup>16</sup> This results in a reduction in the mobilization and fusion of SVs and subsequently the amount of ACh released into the synapse. It usually occurs in middle-aged patients although it has been reported rarely in children. Fifty per cent of cases are associated with small cell carcinoma of the bronchus (C-LEMS).<sup>36</sup> The clinical picture of LEMS is one of weak (and often tender) proximal limb muscles in the presence of depressed tendon reflexes. Although oro-pharyngeal and ocular muscles are usually spared, respiratory muscle weakness can result in respiratory failure.<sup>44</sup> Autonomic function is

**Table 2** Autoimmune diseases associated with the LEMS and MG

Hyper/hypothyroidism
Rheumatoid disease
Systemic lupus erythematosus
Pernicious anaemia
Polymyositis
Diabetes mellitus
Coeliac disease

abnormal in most patients,<sup>41</sup> and this often results in a dry mouth, erectile dysfunction, gastrointestinal (GI) slowing, and postural hypotension. Diagnosis of LEMS consists of the detection of antibodies directed towards the voltage-gated  $Ca^+$  channels and characteristic electromyographic (EMG) findings. Tetanic stimulation of the muscle results in an increment of the compound muscle action potential as a result of increased  $Ca^{2+}$  mobilization in the presynaptic terminal.<sup>45</sup>

The majority of patients with both C-LEMS and non-C-LEMS respond to oral 3,4-diaminopyridine (3,4-DAP). This increases ACh release at the NMJ by blocking voltage-gated  $K^+$  channels, thus prolonging the action potential and increasing quantal release. Treatment of the underlying malignancy with surgery, radiotherapy, or chemotherapy can lead to improvement or remission. Those with non-C-LEMS often require immunosuppression, often with a combination of prednisolone and azathioprine.

Patients with C-LEMS often have the associated features of malignancy and smoking-related diseases. In addition, all patients with LEMS may have associated autoimmune disease (Table 2). Many will be receiving corticosteroids, and hydrocortisone 'cover' will be needed on induction of anaesthesia. Severe weakness may require a course of plasma exchange or intravenous human immunoglobulin (IvIg) before operation.<sup>8</sup> The autonomic features, and especially postural hypotension, may be exacerbated by anaesthetic induction agents and positive pressure mechanical ventilation. Patients with LEMS show extreme sensitivity to both depolarizing and non-depolarizing neuromuscular blocking drugs<sup>43</sup> and these should be avoided if possible. Other non-anaesthetic medication may worsen the muscular weakness by inhibiting neuromuscular transmission (Table 5).

### Botulism

Botulism is the clinical syndrome caused by neurotoxins produced by the anaerobic Gram-positive organism *Clostridium botulinum*. Seven different serotypes of the organism are recognized, and each produces antigenically distinct neurotoxins. Neurotoxins A, B, and E account for nearly all of the human cases.<sup>11</sup> Although the toxins target different proteins at the presynaptic region of the NMJ (e.g. toxin types A and E target the SNAP-25 protein of the SNARE complex), all cause failure of release of ACh from the terminal.<sup>26</sup>

**Table 3** Clinical botulism syndromes

Syndrome	Comments
Foodborne botulism	Caused by ingestion of food contaminated by <i>Clostridium</i> spores or with toxin produced under anaerobic conditions (e.g. home canning). Nausea, vomiting, and abdominal pain occur within ~36 h. Autonomic dysfunction (blurred vision, diplopia, bradycardia, and hypotension) followed by descending flaccid paralysis occur
Wound botulism	Results from contamination of surgical or other wounds. Recently commonly seen in drug abusers injecting 'black tar' heroin subcutaneously ('skin-popping'). Incubation period 4–14 days. Similar presentation to foodborne botulism without GI symptoms
Infant botulism	Result of absorption of toxin produced within GI tract of children >1 yr old. Classically <i>Clostridium</i> spores ingested in infected honey
Adult infectious botulism	Similar aetiology to infant botulism. Usually seen after GI tract surgery or antimicrobial therapy
Inadvertent botulism	Follows accidental overdose or accidental i.v. injection of botulinum toxin during the treatment of movement disorders (e.g. focal dystonia)

The condition is classified according to the source of the infection (Table 3).

The diagnosis of botulism depends on the detection of *botulinum* toxin and the presence of *C. botulinum* from serum, faeces, gastric content, or wound exudates, depending on the category of botulism suspected. The mouse inoculation test remains the most sensitive and specific assay for the toxin. However, although EMG may help in reaching the diagnosis<sup>27</sup> while results of the inoculation test are awaited, the diagnosis mainly relies on clinical suspicion.

Treatment of botulism requires careful co-ordination of intensive care treatment and microbiological advice. Although mild cases of botulism may not require ventilatory support, the onset of respiratory and bulbar failure may be rapid. All patients with botulism must therefore be nursed in a high-dependency area with immediate access to mechanical ventilation. Patients with foodborne botulism may require prolonged periods of ventilation.<sup>12</sup> In addition to the neuromuscular effects, botulinum toxin causes blockade of cholinergic synapses in the autonomic nervous system leading to cardiovascular instability, GI dysfunction, and urinary retention. Patients with recent onset foodborne wound or adult infectious botulism should receive equine ABE antitoxin. If given early in the disease, it lowers mortality and shortens the course of the illness. However, it must be preceded by a cutaneous sensitivity test to help identify the allergy to the preparation, which occurs in 9% of patients. A human botulinum immunoglobulin is available for treatment of infant botulism<sup>2</sup> and for those with allergy to the antitoxin. Antibacterial drugs and debridement may have a role in wound botulism.

## Diseases affecting the postsynaptic apparatus (Table 4)

### Acquired MG

MG is the most common disorder affecting the postsynaptic membrane.<sup>47</sup> This autoimmune disease has an annual incidence of 0.25–2.0 per 100 000 population and a bimodal distribution, tending to affect young women and older men. It appears that the incidence in the latter group is increasing. In the majority of cases (85%), MG is associated with an IgG antibody raised against the postsynaptic AChR. The anti-AChR antibodies reduce the number of effective receptors to approximately one-third of the normal number by a number of mechanisms.<sup>23</sup> Cross-linking of the AChRs by the antibody results in increased degradation of the receptors, and the resultant decrease in receptor half-life to ~3 days (from a normal of 10 days) leads to a decrease in the total number of AChRs. In addition, the antibody–AChR complex binds complement resulting in damage to the postsynaptic membrane, which typically has fewer secondary synaptic folds and a widened synaptic cleft. Both mechanisms reduce neuromuscular transmission and result in decreased generation of postsynaptic action potentials and therefore decreased muscle contraction. It appears that in acquired autoimmune MG, blocking of the AChR sites to ACh is not a prominent feature. Of those MG patients without anti-AChR antibodies (so-called seronegative MG), 70% are found to have antibodies directed towards the muscle-specific receptor kinase (MuSK) at the NMJ.<sup>17</sup> This has an essential role in directing the agrin-dependent clustering of AChRs during development.

The cause of MG remains elusive. However, the majority of seropositive patients have an abnormality of

**Table 4** Diseases affecting the postsynaptic NMJ

Disease	Mechanism of disease
Acquired MG	Autoimmune disease in which IgG autoantibodies (Abs) are directed towards the postsynaptic nAChR (in 85% of patients). Others have Abs directed towards the MuSK receptor
Neonatal MG	Seen in babies born to mother with MG. A result of placental transfer of anti-AChR Abs
Drug-induced MG	Most commonly seen after treatment with penicillamine. Reverses after withdrawal of drug
Congenital MG	Most commonly due to genetic defects in the AChR subunit morphology. Rare and complex group of diseases. Slow channel syndromes are because of a defect producing prolonged opening of AChR channels. Results in varying degrees of myopathy. Fast channel syndromes result in a decreased affinity of the AChR for ACh

the thymus gland, either thymic hyperplasia (60%) or a thymoma (10%), although the exact relationship between the gland and MG largely remains obscure.

Acquired MG is characterized by weakness and fatigability of voluntary muscles. In 15% of patients, the disease is confined to the eyes (ocular MG), but often becomes generalized later. Ptosis, usually asymmetric and fluctuant, is the most common sign, and diplopia or blurred vision the most common symptom. Bulbar muscle weakness is often prominent resulting in dysarthria, difficulty with chewing, and dysphagia. Proximal limb weakness is more prominent than distal limb weakness. Respiratory muscle weakness rarely occurs in isolation but can affect some 20% of patients with MG. Severe MG, especially when accompanied by bulbar weakness, may require tracheal intubation and mechanical ventilation of the lungs. This is known as a myasthenic crisis.

Generally, anti-AChR antibody-positive MG patients can be assigned to one of four groups:

- Those who have an associated thymoma (10%). Patients are usually 40–60-yr-old and many have antibodies to other muscle proteins (e.g. ryanodine receptors).
- Early onset MG (<40 yr) is more common in women and associated with thymic hyperplasia. Antibodies to other muscle antigens are unusual.
- Late onset MG (>40 yr) is more common in men and usually associated with an atrophic thymus gland.
- Ocular myasthenia is confined to the eyes but may become generalized later. In this group, only ~50% are positive for anti-AChR antibodies.

The seronegative MG patients with anti-MuSK antibodies tend to present with bulbar and respiratory weakness rather than limb involvement.

Diagnosis of MG requires a high index of clinical suspicion, the use of edrophonium (Tensilon<sup>®</sup>), EMG examination, and the detection of the anti-AChR antibody. The Tensilon<sup>®</sup> test consists of the administration of up to 10 mg of the short-acting anti-AChE drug edrophonium. If positive, an improvement in muscle strength will be apparent within 45 s; the effects last ~5 min. Unfortunately, the test has a low sensitivity and specificity. The characteristic finding in EMG studies in MG is a decremental response of >10% in the compound muscle action potential on 2–3 Hz stimulation of an affected muscle. Single-fibre EMG, in which the response to stimulation of a single axon is recorded, is a more sensitive investigation. However, the abnormalities seen in MG on EMG examinations are not specific for MG and may occur in LEMS, motor neurone disease, and certain myopathies. In contrast, detection of the anti-AChR antibody is pathognomic for MG.

The treatment of MG falls into four categories:<sup>47</sup>

- Enhancement of neuromuscular transmission by the use of anti-AChE drugs (e.g. pyridostigmine or neostigmine).
- Immunosuppression, often with a combination of corticosteroids and azathioprine.
- Short-term improvement of MG can be gained with plasma exchange or IvIg, but this tends to be reserved for patients in myasthenic crisis or those requiring relatively rapid preoperative improvement.

#### *Anaesthetic management of MG*

Meticulous preoperative optimization of the MG patient should be carried out well in advance of surgery and can markedly decrease postoperative complications.<sup>3</sup>

Preoperative evaluation includes careful assessment of respiratory and bulbar function. The former is most reproducibly monitored at the bedside by serial measurements of forced vital capacity (FVC). A consistently reduced FVC and poor bulbar function are strong indicators of the need for postoperative mechanical ventilation.<sup>13</sup> Preoperative physiotherapy, including incentive spirometry, may benefit those with poor pulmonary reserve. Preoperative optimization of anticholinesterase and immunosuppressant drug therapy is essential and patients with poorly controlled MG often benefit from a preoperative course of plasma exchange or IvIg.

It is important that the anaesthetist is aware of the association of MG with other autoimmune conditions, especially thyroid disease (Table 2).

Premedication is acceptable if the patient has reasonable respiratory reserve. Traditionally, anticholinesterase drugs are omitted on the morning of surgery as they interfere with the metabolism of both depolarizing and non-depolarizing neuromuscular blocking drugs.<sup>46</sup> Patients receiving corticosteroid therapy require hydrocortisone 'cover' on induction of anaesthesia.

#### *Neuromuscular blocking drugs*

Owing to the decreased number of nAChRs, MG patients show a relative resistance to the action of suxamethonium and generally adults require twice the normal dose for effective NMJ blockade.<sup>14</sup> Children require up to four times the normal dose.<sup>10</sup> Furthermore, a Phase II block readily occurs.<sup>4</sup> In addition, if preoperative oral anticholinesterases have been administered or plasma exchange performed, the duration of action of suxamethonium may be prolonged. For these reasons, suxamethonium is avoided in MG patients if possible.

Similarly, MG patients have abnormal responses to non-depolarizing neuromuscular blocking agents. These have a faster onset and a more prolonged action in MG.<sup>5</sup> The dose required depends on the affinity of the neuromuscular blocking drug for the nAChR and on the severity of the myasthenia. Sensitivity has been reported in a case of 'cured' MG.<sup>25</sup> Atracurium<sup>7</sup> and vecuronium<sup>18 19</sup> have been

studied in MG patients and, because of the former drug's metabolism, it is probably the neuromuscular blocking agent of choice. Again, the continued use of oral anticholinesterase drugs in the perioperative period may complicate the picture. This applies particularly to the use of mivacurium, which relies on normal hydrolysis by plasma cholinesterase.<sup>37</sup> Generally, tracheal intubation can be achieved without the use of relaxants but if they are used there should be careful monitoring of neuromuscular function. This is especially important as the action of anticholinesterase drugs to reverse neuromuscular block may be modified in MG.<sup>6</sup>

#### *Volatile anaesthetic agents*

The neuromuscular-blocking properties of volatile anaesthetic agents are exaggerated in MG and often provide adequate relaxation for tracheal intubation and subsequent surgery. These agents have the additional benefit that residual neuromuscular block after the discontinuation of the agent does not occur. The choice of agent does not seem to be critical as adequate muscle relaxation has been reported with the use of halothane,<sup>33</sup> enflurane,<sup>40</sup> isoflurane,<sup>34</sup> and sevoflurane.<sup>20</sup>

#### *Postoperative care*

Most patients can have their tracheal tube safely removed at the end of the procedure but those with severe MG may benefit from a period of elective mechanical ventilation. All patients require careful nursing in an intensive care setting with close co-operation among anaesthetists, intensivists, and neurologists. Adequate analgesia is essential, especially after thymectomy, and thoracic epidural analgesia has been used successfully.<sup>1</sup> Anticholinesterase therapy should be restarted in the immediate postoperative period and titrated against effect. However, many patients have a decreased requirement in the first 48 h. As with LEMS, certain drugs should be avoided as they may exacerbate neuromuscular weakness (Table 5).

#### *Neonatal MG*

This occurs in ~10% of babies born to mothers with MG and is caused by placental transfer of maternal anti-AChR antibodies. Spontaneous recovery tends to occur within 6 weeks although anticholinesterase therapy and occasionally mechanical ventilation of the lungs may be needed.

**Table 5** Drugs to be avoided or used with caution in myasthenic conditions

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Neuromuscular blocking drugs
Antibacterial drugs—aminoglycosides, polymyxins, ciprofloxacin
Prednisolone
Chloroquine
β-Adrenergic receptor antagonists
Magnesium
Calcium channel antagonists
Intravenous iodinated contrast agents

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#### *Drug induced myasthenia*

This may be associated with penicillamine therapy; it usually resolves when the drug is withdrawn.

#### *Congenital myasthenic syndromes*

Congenital myasthenic syndromes (CMS) are a rare, heterogeneous group of genetic diseases that can affect all components of the NMJ.<sup>15</sup> The presynaptic CMS defects include deficiency of choline acetyltransferase necessary for resynthesis of ACh after release and a decrease in the number of SVs and reduced quantal release; considerable genetic and phenotypic heterogeneity exists.

A synaptic form of CMS results in deficiency of AChE in the synaptic space.<sup>35</sup> The subsequent prolonged exposure of nAChRs to ACh leads to prolonged depolarization at the nAChR, loss of AChRs, and myopathy. Often the clinical features are of generalized, often life-threatening weakness from birth.

Postsynaptic CMS are caused by genetic defects in the AChR subunits and are generally divided into slow- and fast-channel syndromes.<sup>15</sup> The former are usually a result of an autosomal dominant  $\alpha$  subunit mutation, which results in prolonged channel opening. It often presents in early adolescence with facial, limb, and respiratory muscle weakness but ocular muscles are unaffected. Quinidine, an open-channel blocker, is the treatment of choice. The fast-channel syndromes involve mutations of the  $\alpha$ ,  $\delta$ , or  $\epsilon$  subunits, and cause a decreased affinity for ACh at the AChR. The clinical picture is similar to that of autoimmune MG, but the condition is treated with 3,4-DAP (which increases presynaptic release of ACh) and with anti-AChE drugs (which increase the number of AChRs stimulated by each quantum of ACh released).

Owing to their rarity, little anaesthetic literature exists about anaesthesia and the CMS. Sedation of a 3-yr-old child with CMS with isoflurane was uneventful<sup>28</sup> and successful spinal anaesthesia for Caesarean section has also been reported.<sup>21</sup>

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