THE BARE ESSENTIALS

Myasthenia gravis and other neuromuscular junction disorders

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Myasthenia gravis is the most common autoimmune disease affecting the neuromuscular junction and is characterised by painless fatigable muscle weakness. It is caused by autoantibodies against neuromuscular junction proteins, either the nicotinic acetylcholine receptor (AChR) or the muscle specific tyrosine kinase (MuSK). Mutations in neuromuscular junction proteins cause congenital myasthenic syndromes. Other antibody mediated conditions affecting the neuromuscular junction include Lambert Eaton myasthenic syndrome and neuromyotonia.

EPIDEMIOLOGY OF MYASTHENIA GRAVIS

- Myasthenia gravis affects approximately 100 patients per million population.
- It has a bimodal age of onset—early and late onset myasthenia gravis.
- Early onset myasthenia gravis typically affects women less than 40 years of age whereas the later onset form is more common in older men.
- With improved diagnosis and survival, the prevalence is increasing, especially in the elderly.

NEUROMUSCULAR PHYSIOLOGY (FIG 1)

- Acetylcholine is the key neurotransmitter at the interface between the presynaptic nerve terminal and postsynaptic muscle membrane.
- Nerve impulses reaching the synapse open voltage gated calcium channels (VGCC) causing influx of calcium ions. This induces fusion of the acetylcholine (ACh) vesicles to the synaptic membrane and release of neurotransmitter.
- Binding of acetylcholine to nicotinic AChRs at the postsynaptic membrane leads to short lived openings of their intrinsic ion channels. The resulting cation entry depolarises the muscle membrane locally; if that reaches a critical threshold, it opens voltage gated sodium channels, generating an action potential that is propagated through the muscle fibre causing muscle contraction.
- ACh is broken down by acetylcholinesterase, anchored in the synaptic space by collagen-Q, thus terminating the signal.
- Rapid and efficient neuromuscular transmission depends on the tight clustering of AChRs at the neuromuscular junction, for which MuSK, Rapsyn and Dok-7 play key roles.
- Loss of approximately 60% of AChRs is necessary to cause myasthenic weakness, and is seen in both the acquired and congenital forms of the disease.

ANTIBODIES IN MYASTHENIA GRAVIS

- Approximately 80–85% of generalised and 50% of ocular myasthenia patients have antibodies against AChRs.
- 5–8% of generalised myasthenia gravis patients have antibodies against MuSK, which are rarely detected in pure ocular myasthenia gravis.
- 50% of the "seronegative" myasthenia gravis patients have low affinity antibodies against clustered AChRs in a newly developed cell based immunofluorescent assay, with the remaining 50% having no detectable antibody on the conventional radioimmunoassay or cell based assay.
- Comparison of the different subgroups of myasthenia is given in table 1.

CLINICAL FEATURES OF MYASTHENIA GRAVIS

- Typically, patients present with extraocular muscle weakness (ptosis or diplopia) and later develop limb and bulbar muscle weakness.
- Patients with MuSK antibodies have predominantly ocular, facial and bulbar muscle involvement.
- Worsening of weakness after prolonged and sustained muscle contraction (fatigability) is the hallmark of myasthenia.
- Patients are often tested before and after a brief amount of muscle exertion to test for fatigability—sustained up-gaze for a few seconds to elicit weakness of the eyelids, limb strength after repeated abduction/adduction at the shoulder, or neck flexion against sustained resistance, if the weakness is not apparent otherwise.
- Tendon reflexes and sensory examination are normal.

Exacerbating factors

Several physiological, pathological and iatrogenic factors exacerbate myasthenia and can occasionally lead to respiratory failure and myasthenic crisis. These are summarised in box 1. In many female myasthenic patients, worsening of symptoms may occur regularly around their menses. However, very often a clear trigger may not be identified. Infection is probably the most common trigger for exacerbation of myasthenic symptoms. It is crucial to obtain a detailed drug history in case any recent new drug introduction could be a

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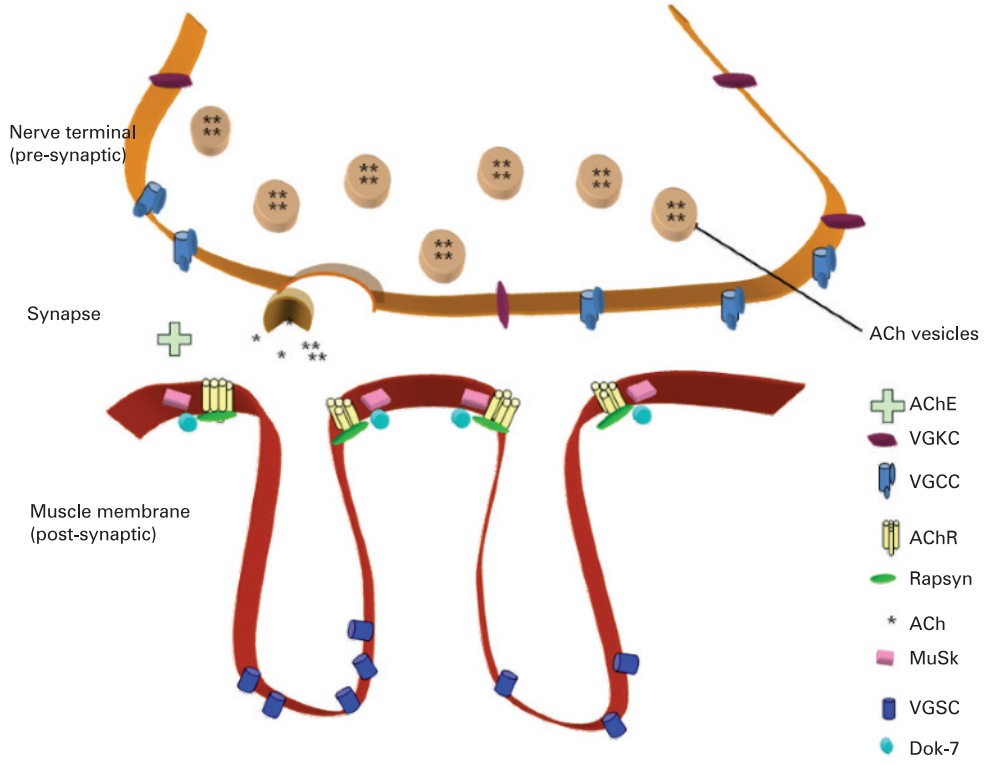

Figure 1 The neuromuscular junction and the proteins involved in neuromuscular transmission. Several of the proteins at the neuromuscular junction are targets for autoimmune disorders (AChR and MuSK in myasthenia gravis, VGCC in Lambert–Eaton myasthenic syndrome and VGKC in neuromyotonia). Genetic mutations can affect several of these proteins (AChR, Rapsyn, MuSK, Dok-7, etc) causing congenital myasthenic syndromes. ACh, acetylcholine; AChE, acetylcholinesterase; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase; VGCC, voltage gated calcium channel; VGKC, voltage gated potassium channel; VGSC voltage gated sodium channel.

potential culprit for a patient's presentation, or worsening of symptoms.

Myasthenic crisis

- A medical emergency that may progress to respiratory failure requiring ventilation.
- Affects approximately 10–15% of patients, usually within 2–3 years of diagnosis.
- MuSK antibody myasthenia patients are more likely to have myasthenic crises.
- Very occasionally, patients present in myasthenic crisis at the onset of disease.
- Increasing muscle weakness and double vision may be seen prior to the development of crisis.
- Quieter breath sounds, reduced chest expansion, tachycardia and rise in blood pressure indicate imminent deterioration.
- Since the ventilation–perfusion ratio is well maintained, oxygen saturation and arterial blood gases are normal until late in the crisis.
- Measurement of forced vital capacity is a useful predictor for impending respiratory failure.
- Typically forced vital capacity less than 1 l or 15 ml/kg requires intensive care treatment and respiratory support.
- Myasthenic crisis should be differentiated from other conditions causing respiratory failure (table 2).

Table 1 Comparison of different subgroups of myasthenia gravis

Subgroup	Proportion of all myasthenia gravis (%)	Age of onset (years)	Sex (M:F)	Clinical features	AChR antibodies	MuSK antibodies	Thymus
Ocular myasthenia gravis	15–25	4–90	3:2	Ptosis, ophthalmoplegia	Approx 50%	Very rare	Mild hyperplasia (30%)
Early onset AChR-myasthenia gravis	20–25	2–40	1:3	Ptosis, ophthalmoplegia, generalised weakness	Approx 85%	Absent	Hyperplasia (>80%)
Late onset AChR-myasthenia gravis	30–40	>40	3:2	Ptosis, ophthalmoplegia, generalised weakness	Approx 60%	Absent	Atrophy
MuSK-myasthenia gravis	5–8	2–70	1:3	Predominant ocular, facial and bulbar weakness	Absent	100%	Normal or atrophy
Seronegative myasthenia gravis	5–10	10–70	1:2	Ptosis, ophthalmoplegia, generalised weakness	Antibodies against clustered AChR in 50–60%	Absent	Mild hyperplasia

AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase.

Box 1 Factors exacerbating weakness in myasthenia gravis and potentially triggering myasthenic crisis

- Infections
- Stress—trauma, postoperative
- Withdrawal of cholinesterase inhibitors (when symptoms not fully controlled)
- Rapid introduction or increase of steroids
- Electrolyte imbalance—hypokalaemia, hypophosphataemia
- Anaemia
- Medications: most are rarely implicated, except those highlighted
  - Antibiotics
    - Aminoglycosides: **gentamicin**, amikacin, **telithromycin**, etc
    - Quinolones: ciprofloxacin, norfloxacin, etc
    - Tetracyclines: doxycycline, minocycline, etc
    - Antimalarials: **chloroquine**
  - Antirheumatic drugs: **penicillamine**
  - Anaesthetic agents: **succinylcholine**
  - Antiarrhythmic drugs: quinidine, procainamide
  - Antihypertensives: β blockers and calcium channel blockers
  - Neuropsychiatric drugs: lithium, chlorpromazine, phenytoin
  - Chemotherapy: cisplatin
  - **Botulinum toxin**

DIAGNOSIS

- If myasthenia gravis is suspected, AChR antibody should be checked first. In generalised myasthenia, this is positive in 80–85% of patients. If the AChR antibodies are negative, MuSK antibodies should be tested as these are present in 5–8% of patients.
- Neurophysiology with repetitive nerve stimulation shows decremental response. Single fibre electromyography shows increased jitter and blocking, indicating a neuromuscular transmission defect. These neurophysiological abnormalities may be confined to the facial muscles in MuSK antibody positive cases.
- Edrophonium (Tensilon), a short acting acetyl cholinesterase inhibitor, is injected intravenously to assess objective improvement in muscle strength (especially ptosis or ophthalmoplegia). Subjective improvement is more difficult to interpret and the test is vulnerable to false positives and negatives. The test is best performed in a double blind fashion for more convincing results. In view of the bradycardic tendency of edrophonium, cardiac monitoring, a prepared dose of atropine and resuscitation equipment should be available. The test should be avoided altogether in the elderly.
- 10–15% of myasthenia gravis patients have an associated thymoma and hence a CT scan of the chest should be performed in all patients, with or without serum antibodies.

Table 2 Differential diagnosis of myasthenic crisis

Diagnosis	Principle signs	Investigations
Guillain–Barré syndrome	Initial proximal weakness, some distal sensory symptoms, absent reflexes	Lumbar puncture, nerve conduction studies
Myopathies (eg, acid maltase)	Proximal weakness, no sensory changes	Raised serum creatine kinase, electromyography, muscle biopsy
Cervical myelopathy (structural or inflammatory)	Usually subacute onset, sensory level, urinary retention	MR scan, lumbar puncture
Motor neuron disease	Usually with clear preceding history, muscle fasciculation and wasting, brisk reflexes	Electromyography
Brainstem stroke/inflammation	Cranial nerve signs, altered consciousness, brisk reflexes, sensory signs	MR scan, lumbar puncture
Botulism	History of intravenous drug abuse, weakness spreading caudally, autonomic disturbances (sluggish pupillary responses, dry eyes)	Electromyography
Lambert–Eaton myasthenic syndrome	Rare; subacute proximal leg weakness, autonomic symptoms	Electromyography, voltage gated calcium channel antibodies
Organophosphate poisoning	History of pesticide use, chemical warfare, symptoms similar to cholinergic crisis	Red cell acetylcholinesterase levels
Cholinergic crisis	Salivation, lacrimation, diarrhoea, urinary incontinence, bradycardia, miosis, bronchospasm (in addition to muscle weakness and respiratory failure)	Drug history and clinical signs

TREATMENT

Symptomatic treatment (table 3)

- Pyridostigmine improves neuromuscular transmission by inhibiting acetylcholinesterase and so increasing the availability of acetylcholine at the motor endplate.
- Maximum daily dose of pyridostigmine is 360 mg; higher doses are unlikely to give additional benefit. Most patients require around 180 mg/day.
- Cholinergic adverse effects such as abdominal cramps, diarrhoea, increased salivation and sweating are counteracted by giving oral propantheline (15 mg usually 15–30 min before the pyridostigmine dose is due).
- For fixed deficits such as ptosis and diplopia, ophthalmic surgical intervention may be helpful

Immunosuppression (table 3)

- Corticosteroids are the definitive therapy.
- Prednisolone is usually initiated slowly (eg, starting dose of 10 mg, daily or on alternate days and increasing by 10 mg every week until target dose is achieved or symptoms and signs resolve). This is to minimise the possibility of exacerbation and crisis, especially in patients with bulbar symptoms. Faster titrations (eg, increasing by 10 mg daily, if a daily regimen is prescribed, or when steroid dose is due if alternate day regimen is used) can be achieved if steroids are initiated in hospital.
- The target dose of prednisolone is 1–1.5 mg/kg on alternate days (maximum 100 mg) for generalised myasthenia gravis and 0.75 mg/kg on alternate days (maximum 60 mg) for ocular myasthenia gravis.
- Alternate day steroid regimen is recommended from initiation of treatment since there is some suggestion that there are fewer adverse effects than with daily steroid regimens. However, a few patients feel significantly worse on the

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Table 3 Drugs used in myasthenic disorders, their usual doses, adverse effects and monitoring required

Therapy	Usual adult oral dose	Common adverse effects	Cautions/monitoring
Pyridostigmine	60–360 mg/day in 3–6 divided doses (up to 450 mg, rarely)	Diarrhoea, abdominal cramps, nausea, increased salivation, bladder or bowel urgency	Asthma, recent myocardial infarction, bradycardias
Corticosteroids	For generalised myasthenia gravis 10 mg on alternate days increasing by 10 mg every week up to 1.5 mg/kg (maximum 100 mg) or until symptoms and signs resolve; for ocular myasthenia 5 mg on alternate days increasing by 5 mg every week up to 0.75 mg/kg (maximum 60 mg) on alternate days or until clinical remission, whichever is earlier.	Short term: sleep disturbance, mood changes, acne, weight gain, blurred vision, dyspepsia. Long term: peptic ulceration, osteoporosis, proximal myopathy, fluid retention, weight gain, diabetes mellitus, hypertension and increased susceptibility to infections	Periodic bone density scans (add bisphosphonates, vitamin D and calcium for bone protection, and proton pump inhibitors for gastric protection) (Bisphosphonates may be avoided prior to and during pregnancy)
3,4 diaminopyridine	10 mg four times/day increasing to a maximum of 20 mg 4–5 times/day depending on response	Peri-oral and distal paraesthesia (common), insomnia, gastrointestinal disturbances (high doses occasionally cause seizures)	Used only under specialist prescription
Azathioprine	Usually started at 25 mg/day gradually increasing by 25–50 mg every week up to 2.5 mg/kg daily (requires up to 12 months for therapeutic effect)	Nausea, vomiting, bone marrow suppression and liver dysfunction, warts. Long term risk of non-melanoma skin cancer.	Regular monitoring of full blood count and liver function (weekly for first 2 months and 3 monthly if blood results are stable). TPMT assay if available.
Mycophenolate mofetil	1 g twice daily	Dyspepsia and bone marrow suppression.	Regular monitoring of blood pressure, full blood count, creatinine and liver function. (weekly for first month, fortnightly for next 2 months and monthly thereafter).
Ciclosporin	Start at 25 mg twice daily increased by 50 mg every 3 days. Typically 2.5 mg/kg/day	Nausea, vomiting, excess body hair, hypertension and renal dysfunction.	Monitor renal function and blood pressure. Some centres monitor blood levels.
Tacrolimus	50 μg/kg/day (trough level to be maintained at 5–10 ng/ml)	Nausea, vomiting, hypertension, bone marrow suppression, glucose intolerance, renal and hepatic dysfunction.	Regular monitoring of full blood count, blood pressure, renal and liver function. Blood tacrolimus levels to be monitored regularly to adjust the dose.
Methotrexate	7.5 mg/week titrated up to a maximum of 20 mg/week as per response and adverse effects	Nausea, vomiting, mouth ulcers, bone marrow suppression, respiratory and hepatic complications	Chest *x* ray prior to starting treatment. Regular monitoring of full blood count and liver function (weekly for first 2 months and then 3 monthly). Add folic acid 5 mg weekly to prevent bone marrow suppression and gastrointestinal adverse effects
Cyclophosphamide	1–3 mg/kg/day	Nausea, vomiting, diarrhoea, fatigue, cystitis, haematuria, bone marrow suppression	Regular monitoring of full blood count, liver function and urine dipstick for haematuria (weekly for first month, fortnightly for next 2 months and monthly thereafter).

TPMT, thiopurine methyltransferase.

Red flags during immunosuppressive therapy

If the following is observed during immunosuppressive therapy, the drug should be withdrawn and the tests repeated at weekly intervals. If blood tests are normalising, the drug may be restarted at a lower dose or an alternative immunosuppressant used.

- Progressive anaemia
- Total white cell count $<3.0\times10^9$/l
- Neutrophil count $<1.5\times10^9$/l
- Platelet count $<100\times10^9$/l
- Progressively abnormal liver function
- Serum creatinine increases by >30% from baseline (especially for mycophenolate and ciclosporin)
- Haematuria (for cyclophosphamide)

non-steroid day, in which case changing over to a daily regimen is sensible. Also, daily regimens are recommended in diabetics to avoid fluctuations in blood glucose levels.

- The dose should be increased until the target dose is achieved or until symptoms and signs resolve if this occurs at a lower dose. Once remission is achieved (which may take several months), the dose should be reduced gradually to the minimum maintenance dose.
- In generalised myasthenia gravis, a second line immunosuppressant ("steroid sparing agent") is started at the same time as prednisolone; azathioprine takes at least 12 months to become effective. Other immunosuppressants probably act more rapidly.

Myasthenia gravis: conclusions

- Myasthenia gravis causes fatigable muscle weakness and often presents with ptosis and ophthalmoplegia.
- Early onset (<40 years) myasthenia more commonly affects women, late onset is more common in men.
- AChR antibodies are found in 80–85% of generalised and 50% of ocular myasthenia patients, MuSK antibodies in 5–8% of generalised myasthenia gravis.
- Decremental response to repetitive nerve stimulation and prolonged jitter or blocking on single fibre EMG are the neurophysiological hallmarks of myasthenia gravis.
- Monitoring of forced vital capacity is vital in patients with severe bulbar weakness.
- Myasthenic weakness is often exacerbated by infections and can lead to myasthenic crisis.
- Pyridostigmine, steroids and immunosuppressants are the mainstay of treatment.
- All patients with myasthenia gravis should be screened for thymoma.
- Thymectomy is often advised in mild to moderate AChR antibody positive generalised myasthenia gravis with onset less than 45 years of age.

- Azathioprine is the preferred first line steroid sparing drug; target dose 2.5 mg/kg/day.
- Thiopurine methyltransferase blood levels, if available, can be checked before starting azathioprine, but whatever the result the patient should still be closely monitored for bone marrow suppression and liver dysfunction.
- Macrocytosis and lymphopenia while on azathioprine are to be expected and are possibly desirable responses; the drug should not be withdrawn because of these.
- If remission is not achieved after 18 months of an adequate dose of azathioprine, other immunosuppressants may be considered; methotrexate, ciclosporin and mycophenolate mofetil.
- Once remission is achieved with corticosteroids with or without immunosuppressants, patients should not require pyridostigmine and it should be withdrawn.
- Any increased long term risk of malignancy in patients with myasthenia taking second line immunosuppressant drugs is uncertain, but the possibility should be discussed. Skin lesions (warts and non-melanomatous cancers) are relatively common with azathioprine and advice should be given about sun exposure

Further information

The Myasthenia Gravis Association,
The College Business Centre, Uttoxeter New Road, Derby DE22 3WZ, UK
Freephone: 0800 919922; Telephone: +44 (0)1332-290219; Fax +44 (0)1332-293641
Email: mg@mga-charity.org; Website: http://www.mga-charity.org/ or http://www.mgauk.org/
Official website of the Myasthenia Gravis Association. Contains a very comprehensive information pack about myasthenia gravis, Lambert–Eaton myasthenic syndrome and congenital myasthenic syndromes. Also general information leaflets about nutrition, fatigue, psychosocial aspects, driving, accessing benefits, plasma exchange, etc.

Emerging therapies for myasthenia gravis

- Rituximab, an anti-CD20 B cell monoclonal antibody, has been used in several refractory patients, especially MuSK cases. This depletes the antibody producing B cells and is given as an infusion once every 4 weeks.
- Genetic modification of cholinesterase using Monarsen has completed early clinical trials with good results without cholinergic adverse effects.
- Etanercept and infliximab, anti-tumour necrosis factor α monoclonal antibodies have been trialled on a limited basis, with mixed results.
- Complement inhibitors such as eculizimab are currently undergoing clinical trials.

Treatment of exacerbations of myasthenic weakness

- Intravenous immunoglobulin (IVIg) is the most commonly used therapy for acute worsening of myasthenia; 0.4 g/kg/day for 5 days. Improvement occurs within 1–2 weeks and lasts up to 12 weeks.
- Plasma exchange usually involves exchanging a plasma volume of 2–3 l daily for 5 days. Improvement is probably more rapid than with IVIg but they have similar efficacy.
- Respiratory crisis requires ventilatory support in addition to the above.
- It is crucial to recognise significant bulbar weakness even without enough respiratory muscle weakness to require ventilation. The patient should be kept nil by mouth and fed via a nasogastric tube until bulbar function recovers with no risk of aspiration.

Thymectomy in myasthenic syndromes

- 10–15% of myasthenia gravis patients have an associated thymoma.
- Conversely, 50% of patients with thymoma have myasthenia.
- The characteristic pathological change in the thymus of young patients with AChR antibodies is hyperplasia, comprising lymphoid follicles with or without germinal centres extending around perivascular spaces.
- The thymus is usually normal in MuSK myasthenia but screening is recommended to exclude a neoplasm which has been reported, albeit rarely.
- Thymomas can be seen in neuromyotonia but only very rarely in the Lambert–Eaton myasthenic syndrome.
- The role of thymectomy is uncertain and is currently the subject of an international multicentre trial. Currently, younger (less than 45 years) patients with AChR antibodies and generalised, rather than purely ocular, myasthenia gravis are often offered thymectomy
- Myasthenic control should be optimised preoperatively. However, high dose immunosuppression (especially steroids) immediately prior

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Lambert–Eaton myasthenic syndrome: conclusions

- Over 50% of cases are associated with an underlying cancer, usually small cell lung cancer.
- It typically presents with proximal weakness of the lower limbs, dry mouth and areflexia; rapid progression strongly suggests an associated cancer.
- Approximately 90% of cases have voltage gated calcium channel antibodies.
- Neurophysiology shows reduced compound muscle action potential amplitude which typically increases by >100% following voluntary contraction.
- Symptomatic treatment is 3,4-DAP. Pyridostigmine may offer some additional benefit; immunosuppression may be required if symptomatic treatment is ineffective.
- Screening for cancer should be undertaken for at least 5 years, especially in smokers.

to surgery leads to greater postoperative complications.

- Histologically confirmed thymoma patients need surveillance with CT or MRI of the chest at a minimum of 1, 3 and 7 years to detect recurrence. Depending on the histological diagnosis and extent of spread, some thymoma patients require postoperative radiotherapy and/or chemotherapy.

LAMBERT–EATON MYASTHENIC SYNDROME (LEMS)

This rare autoimmune disorder affects synaptic transmission at both the neuromuscular junction and autonomic ganglia.

- It is caused by antibodies against P/Q type voltage gated calcium channels.
- It is about 20 times less common than myasthenia gravis.
- 50–60% of patients have an underlying neoplasm, usually small cell lung cancer, and rarely adenocarcinomas and lymphoproliferative disorders.

Box 2: Disorders associated with peripheral nerve hyperexcitability syndromes

- Neoplasms
- Thymoma
  - Small cell lung cancer
  - Lymphoma
- Myasthenia gravis
- Acquired neuropathies (Guillain–Barré and chronic inflammatory demyelinating polyneuropathy)
- Inherited neuropathies (hereditary motor and sensory neuropathy)
- Drugs: gold, oxiplatin
- Toxins: insecticide, insect bite, rattle snake toxin
- Genetic causes
  - KCNA1 (potassium channel) mutation
  - Schwartz–Jampel syndrome

- Non-cancer cases may be associated with other autoimmune diseases, such as insulin dependent diabetes mellitus and thyroid disease.

Clinical features

- Non-paraneoplastic patients can present in any age group.
- Paraneoplastic patients are generally >50 years old and are usually smokers.
- Typically presents with proximal muscle weakness, predominantly affecting the lower limbs.
- In contrast with myasthenia gravis, strength may improve after sustained exercise.
- The tendon reflexes are commonly reduced or absent but strong contraction of the relevant muscle against resistance often allows the reflex to be elicited; this ''potentiation'' of absent or hypoactive tendon reflexes is virtually diagnostic.
- In addition to the muscle weakness, almost all patients have some autonomic involvement; dry mouth, postural lightheadedness, sphincter disturbance or impotence. In comparison with myasthenia gravis, ocular, facial and bulbar muscle involvement is less common.

Pointers for paraneoplastic Lambert–Eaton myasthenic syndrome

- Rapid progression of symptoms
- Early involvement (within 6 months) of distal muscles
- Dysarthria
- Impotence

Diagnosis

- VGCC antibodies are detected in approximately 90% of cases.
- VGCC antibody is almost always positive in patients with an underlying small cell lung cancer.
- Neurophysiological assessment classically demonstrates reduction in compound muscle action potential amplitude with a subsequent increase in amplitude of >100% following voluntary maximal activation or repetitive nerve stimulation at 40 Hz.
- A comprehensive work-up for an underlying neoplasm should be undertaken. If initially negative, chest imaging should be repeated annually for at least 5 years, especially in a smoker. Positron emission tomography scanning is likely to play an important role to detect occult malignancy in these patients.

Treatment

- Symptomatic treatment with 3,4-diaminopyridine (3,4-DAP), typically 10–20 mg four times daily. This drug blocks potassium channels in the nerve terminal, prolonging the nerve action

Table 4 Summary of clinical features of the more commonly encountered congenital myasthenic syndromes

	Responsible genes	% of UK cases	Pathology	Differentiating clinical features	Treatment
AChR deficiency	*CHRNE, CHRNA, CHRNB, CHRND*	20	Low expression of AChR	Early onset, severe ophthalmoplegia	Pyridostigmine + 3,4-DAP
Rapsyn deficiency	*RAPSN*	15	Deficiency of AChR clustering protein	Arthrogryposis multiplex congenita, apnoeic episodes, congenital strabismus, syndrome improves with age	Pyridostigmine + 3,4-DAP
Dok-7 synaptopathy	*DOK7*	15	Incomplete synaptogenesis	Congenital stridor, late appearance of motor weakness, limb girdle pattern of weakness, tongue wasting	Ephedrine or salbutamol + 3,4-DAP
Slow channel syndrome	*CHRNA, CHRNE, CHRNB, CHRND*	7	Prolonged channel opening in response to ACh	Variable severity and age at onset, distal arm weakness predominant, moderate ophthalmoplegia, prominent muscle wasting. Autosomal dominant inheritance	Fluoxetine or quinidine
Fast channel syndrome	*CHRNA, CHRNE, CHRND*	5	Shortened channel opening in response to ACh	Respiratory insufficiency at birth, sudden and severe crises throughout childhood, severe ophthalmoplegia	Pyridostigmine + 3,4-DAP
Acetylcholinesterase deficiency	*COLQ*	5	Failure to anchor AChE in synaptic cleft	Axial and respiratory weakness from early infancy, slowed pupillary light response.	Ephedrine
Choline acetyltransferase deficiency	*CHAT*	2	Failure of ACh synthesis	Apnoeic episodes in infancy, EMG decrement often only at 10 Hz stimulation	Pyridostigmine
Other congenital myasthenic syndromes	Unknown	30	Unknown		

3,4-DAP, 3,4-diaminopyridine; ACh, acetylcholine; AChE, acetylcholinesterase; AChR, acetylcholine receptor.

potential and enhancing calcium ion entry at the presynaptic nerve terminal, which in turn allows more calcium dependent release of acetylcholine.

- Pyridostigmine provides less benefit than in myasthenia gravis although in conjunction with 3,4-DAP it can allow a lower dose of the latter.
- Immunosupression with corticosteroids is used in both forms of the Lambert–Eaton myasthenic syndrome.
- Additional treatment with azathioprine, ciclosporin and mycophenolate mofetil is used in non-paraneoplastic cases although the evidence is limited to case reports/series and is certainly less robust than for myasthenia gravis.
- In severe disease, plasma exchange and IVIg are probably equally effective but the effect of each is short lived (and generally less effective than in myasthenia gravis), lasting up to 8 weeks.
- In paraneoplastic cases, treatment of the small cell lung cancer improves both the prognosis and the neurological outcome.

Peripheral nerve hyperexcitability: conclusions

- Acquired disorders of peripheral nerve hyperexcitability include neuromyotonia and cramp fasciculation syndrome.
- Neuromyotonia may be associated with thymoma or autoimmune disorders.
- A variable proportion (approximately 50%) of patients have voltage gated potassium channel antibodies.
- Symptomatic treatment with antiepileptic drugs is often helpful.
- Immunosuppressive treatment may be required.

DISORDERS OF PERIPHERAL NERVE HYPEREXCITABILITY

The two main disorders of peripheral nerve hyperexcitability are neuromyotonia and cramp fasciculation syndrome. There is considerable clinical and neurophysiological overlap between them, which also merge with frequent simple cramps without associated features. Some authors lump them all together and use the term "peripheral nerve hyperexcitability syndrome". A proportion of these patients have antibodies to the voltage gated potassium channels at the presynaptic nerve terminal of the neuromuscular junction.

Peripheral nerve hyperexcitability, however, can occur in other autoimmune processes, such as paraneoplastic syndromes, and is also seen in association with inherited neuropathies. Toxins may produce a similar clinical picture. Relevant conditions to be considered are shown in box 2.

Clinical features

- The clinical features of cramp fasciculation syndrome are muscle cramps, stiffness and fasciculations which often occur following exercise.
- In neuromyotonia there is additional myokymia (undulating rippling of muscles) and pseudomyotonia (excessively slow relaxation of muscles but without percussion myotonia); this may lead to muscle hypertrophy.
- Limb and trunk muscles are commonly affected, extraocular muscles more rarely.
- Hyperhidrosis is common.

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Congenital myasthenic syndromes: conclusions

- Patients have fatigable weakness similar to myasthenia gravis but do not have antibodies or respond to immunosuppressive therapy.
- Most patients present at birth or in childhood, but adult onset cases are well described.
- Infections often exacerbate symptoms and may precipitate crisis, particularly in infants.
- Delayed milestones, joint contractures and apnoeic episodes may be observed.
- Variable response to cholinesterase inhibitors.
- Neurophysiological abnormalities are similar to those seen in myasthenia gravis, with a decremental response to repetitive nerve stimulation and prolonged jitter on single fibre EMG.

- Neuromyotonia may also be seen in the context of Morvan's syndrome, a limbic encephalitis associated with voltage gated potassium channel antibodies. The patients may present with insomnia, seizures and psychiatric disturbances. However, there may also be peripheral (including neuromyotonia) and autonomic features.

Diagnosis

- Voltage gated potassium channel antibodies are identified in about 50% of neuromyotonia cases, less in cramp fasciculation syndrome.
- Electromyography in neuromyotonia demonstrates spontaneous motor unit discharges (myokymia or neurmyotonia) consisting of doublet, triplet or multiplet discharges in addition to fasciculations and fibrillations.
- In cramp fasciculation syndrome, the electromyographic features are milder—single motor unit discharges and fasciculations.
- CT scan of the chest is usually recommended to exclude an underlying thymoma, especially with positive voltage gated potassium channel antibodies.

Treatment

- Peripheral nerve hyperexcitability is treated symptomatically with carbamazepine, phenytoin, sodium valproate, gabapentin, pregabalin or lamotrigine.
- In severe cases with voltage gated potassium channel antibodies, plasma exchange or IVIg provide short term benefit, typically 6 weeks.
- Further maintenance immunosuppressive therapy with corticosteroids (plus azathioprine or methotrexate) is occasionally given.

CONGENITAL MYASTHENIC SYNDROMES

These are rare, approximately 5 per million in the UK, although the true prevalence is likely to be higher. Two-thirds have identifiable genetic mutations in proteins of the neuromuscular junction. There are several distinct syndromes, with clinical features varying with the nature of the mutation and the gene. Crucially, several of the syndromes deteriorate with pyridostigmine, despite sometimes an initially positive response, and alternatives are required. Immunosuppression is ineffective but frequently given inappropriately because of incorrect initial diagnosis (table 4).

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