24.18 Disorders of the neuromuscular junction 6295

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ESSENTIALS Two fundamentally different pathological processes are associated with disease at the neuromuscular junction: (1) acquired disorders in which autoantibodies are directed against nerve or muscle receptor or ion channels; (2) rare inherited conditions in which the defect may be pre- or postsynaptic. Myasthenia gravis Aetiology and epidemiology—the fundamental disorder is loss of func- tional acetylcholine receptors most frequently as a result of binding of antiacetylcholine receptor (anti-AChR) antibodies. Incidence is about 10 per million population and prevalence about 8 per 100 000, with a marked female bias in cases aged under 40 years and male preponderance in those over 50 years. Thymomas occur in about 10% of cases. Clinical features and diagnosis—the most characteristic feature is fatiguability, meaning demonstrable weakness (without muscle pain) precipitated by repeated or sustained muscular activity. In more than 50% cases this first manifests as diplopia and ptosis. For prac- tical purposes, a positive anti-AChR or anti-MuSK antibody test is confirmatory and no further diagnostic investigations are required; electromyography and the intravenous edrophonium test are helpful in seronegative patients. The presence of a thymoma can only be as- sessed by CT or MRI of the thorax. Treatment and prognosis—thymomas require excision, but this in it- self will not improve myasthenia. Anticholinesterase drugs (e.g. pyri- dostigmine) give symptomatic improvement in most patients, and may be sufficient in those with very mild disease. Other manage- ment is determined by the

type of disease: (1) ocular myasthenia— alternate-day prednisolone with/without steroid-sparing agents (e.g. azathioprine); (2) early-onset seropositive disease—some patients benefit from thymectomy, with prednisolone and azathioprine in- dicated for those who do not, and other immunosuppressants in those who are refractory; (3) late-onset, anti-MuSK, and seronega- tive diseases—most respond to immunosuppression; (4) myasthenic crisis—supportive care with intubation and assisted ventilation may be required; plasma exchange and intravenous immunoglobulin may both lead to rapid improvement. Overall prognosis is good, with over 90% achieving near-normal functional recovery. Lambert–Eaton myasthenic syndrome A presynaptic disorder, associated with small-cell lung cancer in c.60% of cases, caused by the presence of antibodies that reduce the number of functional presynaptic P/Q-type voltage-gated cal- cium channels. The condition is characterized by limb-girdle weak- ness and symptoms of autonomic dysfunction. Pyridostigmine may offer some symptomatic benefit, but 3,4-diaminopyridine is more effective and the drug of choice. For those with inadequate symp- tomatic benefit, immunosuppression, as for myasthenia gravis, is in- dicated. In cancer-associated disease, removal of the tumour often leads to improvement; immunosuppression can be effective when an associated cancer is unlikely. Other conditions These include (1) congenital myasthenic syndromes—usually auto- somal recessive; various forms include presynaptic, endplate acetyl- cholinesterase deficiency, and postsynaptic; (2) neuromyotonia—may be idiopathic, but recognized associations include tumour and ac- quired demyelinating polyneuropathies; the main clinical features are muscle stiffness, cramps, and twitching; electromyography shows highly characteristic features; most patients gain symptomatic relief from carbamazepine, phenytoin, or lamotrigine. Neuromuscular transmission Anatomically there are three main components to the neuro- muscular junction (Fig. 24.18.1). The presynaptic component is the motor nerve terminal, which contains packages (quanta) of acetylcholine, each of which contains several thousand molecules of acetylcholine. This is separated from the postsynaptic acetyl- choline receptors, which sit atop the terminal expansions of the junctional folds of the muscle fibre membrane, by the synaptic space. The nerve fibre membrane contains voltage-gated sodium, potassium, and calcium channels. Voltage-gated sodium channels are also present postsynaptically, at the base of the clefts of the junctional folds. The nicotinic acetylcholine receptor is a pentameric structure composed of four different subunits—α, β, γ, and δ in fetal muscle, 24.18 Disorders of the neuromuscular junction David Hilton-Jones and Jacqueline Palace

section 24 Neurological disorders 6296 and α, β, ε, and δ in adult muscle. It is configured to produce a cen- tral ion channel. Depolarization of the motor nerve terminal is dependent on voltage-gated sodium channels. Repolarization is the result of in- activation of these sodium channels and opening of voltage-gated potassium channels. During depolarization, voltage-gated calcium channels open—the influx of calcium ions into the nerve terminal triggers release (by exocytosis) of quanta of acetylcholine. The acetylcholine binds to the interfaces between the α and γ and α and ε subunits of the acetylcholine receptors. This alters the conformation of the channel, allowing cations (mainly sodium) to enter the muscle fibre. This influx generates the endplate poten- tial, which in turn activates voltage-gated sodium channels. These trigger the action potential that is propagated away from the neuro- muscular junction, along the muscle fibre, and initiates contraction. Spontaneous release of individual quanta of acetylcholine, as op- posed to the multiple release triggered by a nerve action potential, gives rise to miniature endplate potentials, which can be recorded by a microelectrode inserted into the muscle fibre. These are of insufficient amplitude to trigger an action potential in the muscle fibre membrane. The action of acetylcholine

on acetylcholine receptors is termin- ated by the hydrolysis of acetylcholine by the enzyme acetylcholin- esterase, which is anchored to the basal lamina by a collagen-like molecule, ColQ (see Fig. 24.18.1). The acquired neuromuscular junction disorders are associated with antibodies directed against one of the ion channels (Table 24.18.1). The fact that there are three autoimmune disorders known to affect such a small region may be explained by the neuromuscular junction, unlike the peripheral nerve, not being contained within the blood– nerve barrier, which stops just short of the nerve terminal, and thus being potentially exposed to circulating humoral attack. The inherited disorders may affect presynaptic processes (acetylcholine resynthesis, packaging, or release), acetylcholinesterase binding, or postsynaptic function (acetylcholine receptor numbers or localization). Pathogenic mechanisms are considered in more detail when discussing individual disorders. Myasthenia gravis This is by far the most common of the conditions discussed in this chapter and it responds favourably to treatment. In general, over 90% of patients can be returned to normal function, although in most this represents a pharmacological remission and the patient remains dependent on treatment. Epidemiology All ethnic groups are affected. The annual incidence is about 10 per million population, and the prevalence about 8 per 100 000. All ages may be affected. There is a marked female bias in patients below age 40 years, who are often HLA B8-DR3, whereas over the age of 50 years men predominate, and myasthenia is increasingly recognized in very elderly people. A rather different pattern is seen in people of Asian origin; prepubertal onset is very common, the disease is often purely ocular, and there is a strong association with HLA DRw9. Pathogenesis The fundamental disorder in myasthenia gravis is loss of functional acetylcholine receptors, which in most cases is a result of binding of anti-acetylcholine receptor (anti-AChR) antibodies. High- affinity immunoglobulin IgG class antibodies can be detected, by the standard assay used for diagnostic purposes, in 85% of patients with generalized myasthenia and about half of those with purely ocular myasthenia (so-called seropositive cases). Antibodies bind to the main immunogenic region of the α subunits of the acetylcho- line receptor, and also to other sites on the surface of the receptor. δ α ε α β (b) Muscle fibre Acetylcholine receptors Nerve terminal Voltage-gated sodium channels Axon Voltage-gated potassium channels Acetylcholine Voltage-gated calcium channels (a) Fig. 24.18.1 (a) Diagrammatic representation of the neuromuscular junction demonstrating the molecules that are targets for autoimmune and genetic diseases. (b) Cartoon of the organization of the subunits of the nicotinic acetylcholine receptor. These subunits form a channel in the membrane (central hole), which opens when acetylcholine (ACh) binds. The adult form differs from the fetal form by substitution of the γ subunit with an ε subunit. Antibodies in myasthenia bind to both forms, often to the main immunogenic region on the α subunits. Antibodies in rare cases of fetal arthrogryposis bind to the γ subunit close to the ACh-binding site. Table 24.18.1 Ion channels responsible for the different clinical disorders Ion channel Clinical disorder Acetylcholine receptor Myasthenia gravis Voltage-gated calcium channel Lambert–Eaton myasthenic syndrome Voltage-gated potassium channel Acquired neuromyotonia

 Patients who do not have antibodies detected by this assay are clas- sified as seronegative. However, there is overwhelming evidence even in these patients that their disease is immune mediated: their clinical characteristics are similar to those of seropositive patients, they respond to plasma exchange and immunosuppressant therapy, their plasma can induce neuromuscular transmission dysfunction when injected into animals, and the infants of such mothers may be born with neonatal myasthenia (see next), indicating transplacental transfer of a humoral component. The last decade has seen the iden- tification of

other causative antibodies. In up to one-half of so-called seronegative cases there is an anti- body directed against muscle-specific tyrosine kinase (MuSK) which has a role in receptor clustering (see Fig. 24.18.1). The exact pathogenic mechanism in these anti-MuSK cases remains uncertain but, as noted next, such patients have a rather characteristic clin- ical presentation. It has been shown that low-affinity anti-AChR or MuSK antibodies, detectable with a cell-based assay, may be present in those patients with neither AChR nor MuSK antibodies detect- able by the standard assay. The most recent antibody to be recog- nised, although its pathogenic significance is not yet established, is directed against low-density lipoprotein 4 (Lrp4). Loss of functional acetylcholine receptors by antibody binding is due to complement-mediated lysis, acceleration of internal- ization and degradation, and blocking of acetylcholine binding. Morphological consequences include widening of the synaptic cleft and a marked reduction of the postsynaptic folds of the muscle fibre membrane. Although the efferent limb of the immune response, described next, has been reasonably well characterized, numerous questions remain to be answered about the afferent limb. Susceptibility to my- asthenia gravis is associated with particular immune response genes with correlation to different haplotypes relating to the age of onset of the disease (particularly HLA B8-DR3 in younger patients). These observations are not of immediate relevance to routine clinical prac- tice. In contrast, knowledge about involvement of the thymus is rele- vant to classification and management. The thymus has a key role in the process of inducing immune tol- erance, by removal of self-antigen T-cell clones, and it is not nor- mally a source of autoantibodies. The acetylcholine receptor is, however, expressed on thymic myoid cells and in early onset, anti- AChR antibody-positive patients there is hyperplasia of the thymic medulla, with germinal centres surrounded by a T-cell zone. In the germinal centres there is enrichment of acetylcholine receptor-specific T cells and B/plasma cells. On the basis of these observa- tions, and the beneficial response to thymectomy, there seems little doubt that the thymus is involved in the pathogenesis of myasthenia gravis, but exactly how has yet to be elucidated. Identification of the mechanism may well be important in developing immune-specific treatment. In late-onset cases and anti-AChR antibody-negative patients, the thymus is typically much less abnormal or atrophic (which is normal in later life), although some pathological changes have been noted. In such cases there is no good evidence of benefit from thymectomy. Patients with anti-MuSK antibodies show very little thymic path- ology and probably do not benefit from the operation. Thymomas occur in about 10% of cases. They are locally inva- sive (notably affecting the pleura and pericardium) and may seed within the pleural cavity. These patients are almost invariably anti- AChR antibody positive. Surgical excision is required because of local tumour invasiveness, but, in contrast to those patients with thymic hyperplasia, this does not usually ameliorate the myasthenic symptoms. Based on the presence or absence of antibodies detected by the routine clinical assay and the state of the thymus gland, five main subgroups of patients can be identified (Table 24.18.2)–the fifth group being MuSK positive patient. Penicillamine-induced myas- thenia, which generally recovers after drug withdrawal, is clinically similar to the idiopathic disease and the patients are anti-AChR anti- body positive. Clinical features Myasthenia gravis causes skeletal muscle weakness, but the most characteristic feature is fatigability. The term ‘fatigue’ causes some confusion because it may have different meanings to a clinician, physiologist, and layperson. Thus, the fatigue of chronic fatigue syndrome is quite different from that of myasthenia. Simply put, fatigue in myasthenia gravis manifests itself by increasing demon- strable weakness, without muscle pain, precipitated by repeated or sustained muscular activity. Symptoms fluctuate from day to day and week to week, which may in part explain the common delay in diagnosis and suspicions as to its genuineness. Other factors that can exacerbate the weakness include heat, emotional factors,

menstruation, intercurrent infections, and drugs that interfere with neuromuscular transmission (aminoglycoside antibiotics, quinine, quinidine, β-blockers, procainamide, and neuromuscular-blocking drugs related to anaesthesia). In over half of patients, the presenting symptoms relate to extraocular muscle weakness (diplopia and ptosis); these muscles will be involved in over 90% of patients at some stage during the disease. The next most frequent presentation is with limb-girdle weakness. Typically, as the disease worsens, the weakness spreads from the extraocular muscles to the lower facial and bulbar muscles (causing dysarthria and dysphagia), to the neck, and then to the limbs. However, there are many variations on this theme. A rela- tively common presentation in older patients, typically men, is with selective weakness of neck extension—as they walk the head drops forwards and they arrive in the clinic holding up the head with a hand under the chin. Relatively selective weakness of finger extension Table 24.18.2 The four main subgroups of myasthenia gravis Age of onset (years) Thymoma Sero-negative <40

> 40 Thymus Hyperplasia Atrophy Thymoma ?Normal/atrophy Anti-AChR antibody titre High Low Intermediate Absent

section 24 Neurological disorders 6298 and abduction is common. In patients with anti-MuSK antibodies there is a female preponderance, prevalent oculobulbar involvement sometimes with facial muscle and tongue atrophy, often very limited limb involvement, and a high frequency of ventilatory insufficiency. On examination, weakness may or may not be evident—fatigue can be demonstrated in limb muscles, but is often most striking around the eyes and with respect to bulbar muscles. Fatigable ptosis is a striking sign (Fig. 24.18.2). As the patients give their history, the fatigue of bulbar muscles may be revealed by increasing dys- arthria. A potentially misleading sign is ‘pseudo-internuclear oph- thalmoplegia’, which may be bilateral—failure of adduction due to weakness of the medial recti. Eye movements may show striking fatigue. With increasing severity, the weakness at rest may be so marked that it is difficult to demonstrate fatigue. Respiratory muscle weakness may be out of proportion to limb weakness; it is best as- sessed by measuring the forced vital capacity (not peak flow). A fall in blood oxygen saturation is a late sign and should not be used alone to monitor ventilatory function. Muscle wasting is seen only in undertreated patients with long-established disease, although it is more common in patients with anti-MuSK antibodies. The tendon reflexes are normal, and indeed often rather brisk. There are no ab- normal sensory signs. There is an increased incidence of other autoimmune diseases, particularly thyroid disease (about 3% of patients) and less fre- quently rheumatoid arthritis, systemic lupus erythematosus, poly- myositis, and acquired neuromyotonia. Coexistence of myasthenia and Lambert–Eaton myasthenic syndrome has been reported. Natural course This is very variable. In some patients the disorder remains con- fined to the extraocular muscles (ocular myasthenia gravis). If that is the case for more than 2 years, and particularly if the patient is seronegative, the development of generalized disease is unlikely. Older studies, before the introduction of immunosuppressive ther- apies, suggest that the disease reaches maximum severity within 7 years. In one study, the interval between onset and the first episode of maximal weakness (‘myasthenic crisis’) was less than 36 months in over 80% of patients. Permanent spontaneous remis- sion occurs, but is rare—of the order of 1% per annum. On the other hand, particularly early in the course of the disease, there may be protracted periods of spontaneous remission, sometimes lasting several years. Diagnosis This is based on the clinical picture, supported by appropriate la-

boratory results. For practical purposes, a positive anti-AChR or anti-MuSK antibody test is confirmatory and no further diagnostic investigations are required. In seronegative patients, electromyog- raphy (EMG) and the intravenous edrophonium (Tensilon) test are helpful. Although the edrophonium test (demonstration of im- provement with a short-acting cholinesterase inhibitor) has a long pedigree and sound pharmacological basis, there are concerns about its use, particularly by doctors who are inexperienced. The patient is given 600 µg atropine intravenously; this blocks the po- tentially unpleasant muscarinic effects of the edrophonium and also acts as a single-blind placebo for the patient. The test dose of 2 mg edrophonium follows, which in some patients is sufficient to give a diagnostic response. If not, a further 8 mg edrophonium is given. There must be an easily assessable measure of improvement—most commonly degree of ptosis. The test is therefore likely to be of most use in patients with purely ocular symptoms and signs. Rarely, car- diorespiratory collapse may occur. False-negative and false-positive results are not uncommon. The conventional EMG measure for diagnosing myasthenia gravis is the demonstration of a decremental response of the compound muscle action potential in response to repetitive nerve stimulation at 3 Hz. More sensitive, but not specific and only available in specialist centres, is the presence of increased jitter and blocking, as assessed by single-fibre EMG. The presence of a thymoma can be assessed only by CT or MRI of the thorax. Differential diagnosis There are few difficulties in the presence of extraocular muscle in- volvement and readily demonstrable fatigue, although there can be confusion with Lambert–Eaton myasthenic syndrome and con- genital myasthenic syndromes. Diagnostic difficulties can occur when, as occasionally happens, eye signs and fatigue are absent. Amyotrophic lateral sclerosis with little wasting may be suspected. Conversely, in long-established myasthenia, muscle wasting may be misleading. More difficult is seronegative, purely ocular myas- thenia; the most important differential diagnosis is mitochondrial cytopathy, in which increased jitter may also occur. Other diagnoses to consider include oculopharyngeal muscular dystrophy and thy- roid ophthalmopathy. (a) (b) Fig. 24.18.2 (a, b) Fatigable ptosis in myasthenia gravis.

 Botulism, caused by food poisoning, an infected wound, or clos- tridial overgrowth in the gastrointestinal tract in infants, may need to be considered. Features of autonomic malfunction are usually present. Treatment There is no universally agreed approach to treatment, but basic guidelines to help clinicians without extensive experience of managing myasthenia have been published recently. As noted, thymomas require excision, but this in itself will not im- prove the myasthenia. Subsequent management of the myasthenia in patients with thymic tumours is as for those with myasthenia without a thymoma. Anticholinesterase drugs, by reducing acetylcholine breakdown, give symptomatic improvement in most patients, and may be suffi- cient in those with very mild disease. Pyridostigmine is the drug of choice, given orally four or five times daily, starting at 30 mg/dose and increasing if required to 60 mg/dose with a maximum dose of 360 mg/day. Abdominal cramping is a common side effect, relating to muscarinic overstimulation, and responds to propantheline, ideally taken 30 min before each dose of pyridostigmine. If an ad- equate response is not obtained at this dose of pyridostigmine, further increases should not be made and other forms of therapy should be considered. The management of ocular myasthenia differs somewhat from the generalized form of the disease, the latter also depending on age of onset and antibody status. Ocular myasthenia If anticholinesterase drugs have given an inadequate response, alternate-day prednisolone therapy should be introduced. A suit- able starting daily dose is 5 mg, increasing by 5 mg every fourth dose (or weekly) until an adequate response has been obtained (often, for an adult, a dose of around 30

mg) or a maximum acceptable dose (around 0.75 mg/kg body weight) has been reached. Once remis- sion has been achieved, the pyridostigmine can be withdrawn, and then the prednisolone reduced slowly—initially by 5 mg/month, but when down to 20 mg by as little as 1 mg/month). Azathioprine (see next) may be added if there is an inadequate response or the min- imal effective dose of prednisolone is deemed to be unacceptably high. Ocular muscle surgery can be beneficial if there is a poor or in- complete response to treatment and if the defect appears to be fixed. Early-onset seropositive myasthenia Many, but not all, of these patients benefit from thymectomy, as con- firmed in the recent international thymectomy trial. Up to one-third enter remission, and a further one-half improve if given immunosup- pressive treatments. These benefits are occasionally rapid, but more typically develop over the following 1–2 years, possibly longer. The conventional approach was through a sternal split, but among the population most likely to be considered for surgery, young women, the cosmetic implications meant that many would not consider it. In most major centres, the preferred approach is now through video- assisted surgery, with or without a robot, including in some cases removal of a thymoma. The limited available evidence, but also con-siderable anecdotal experience, suggests that this ‘keyhole’ approach is as effective as the conventional approach, despite theoretical con- cerns that aberrant thymic tissue may be left behind by the less in- vasive approach. Thymectomy should only be performed in centres experienced in such surgery and with the support of appropriately trained anaesthetists and neurologists. For those patients who do not respond adequately to anticholinesterase drugs and thymectomy, immunosuppression is indicated. Introduction of prednisolone may exacerbate myasthenic weakness and should generally be done in hospital. The starting dose is 10 mg on alternate days, increasing by 10 mg/dose until the patient reaches the target dose of 1.5 mg/kg body weight per dose, or in an adult, a maximum dose of 100 mg on alternate days. When remission has been achieved the dose is slowly reduced, as for ocular myas- thenia, until the minimal effective dose has been established. A con- trolled trial has shown the benefits of the addition of azathioprine (2.5 mg/kg body weight per day); the starting dose is 25 or 50 mg daily, increased by 25 or 50 mg daily, each week (or more rapidly as an inpatient) until the target dose is reached. During introduc- tion, weekly tests of full blood count and liver function are required. When established, testing can be reduced gradually to 3 monthly. When available, thiopurine methyltransferase (TPMT) activity ana- lysis may be used to identify those at risk of azathioprine toxicity, but even in low-risk patients there should be regular haematological monitoring. Azathioprine takes more than 6 months to take max- imal effect, after which time it may be possible to reduce prednis- olone to a minimum. Some specialists introduce azathioprine at the same time as starting prednisolone in all patients with generalized disease, whereas others add it later if it is clear that the dose of pred- nisolone required to achieve admission is unacceptably high. For those who do not respond to, or are intolerant of, prednis- olone and/or azathioprine, other immunosuppressant drugs, such as ciclosporin, methotrexate, mycophenolate mofetil, and cyclophos- phamide, may be used. Despite many anecdotal reports of benefit, the role of rituximab remains uncertain. Late-onset myasthenia This form of myasthenia is increasingly recognized with many cases, of both sexes, presenting over the age of 70 years. Although not for-mally assessed, it appears that these patients do not benefit signifi- cantly from thymectomy. Most respond to the immunosuppressant regimen described earlier. Anti-MuSK and seronegative myasthenia Patients with such a myasthenia do not appear to respond to thym- ectomy. Seronegative myasthenia generally responds well to the immunosuppressant regimen outlined earlier. Patients with anti- MuSK antibodies may be more resistant to anticholinesterases and immunosuppression than anti-AChR-positive patients, and other immunosuppressant drugs may be

required. Treatment–resistant myasthenia Some patients prove to be very resistant to prednisolone and con- ventional immunosuppressant drugs. Recent evidence has shown that some, but certainly not all, will respond to rituximab. This may be particularly true for anti-MuSK myasthenia. There remains con- cern about possible long-term side-effects, including progressive multifocal leucoencephalopathy. Myasthenic crisis Intubation and assisted ventilation may be required. Plasma ex- change and intravenous immunoglobulin may both lead to a rapid

section 24 Neurological disorders 6300 improvement (within 1–2 weeks) in strength, but the beneficial effects start to wear off within about 8 weeks. However, this gives useful time in which to establish an immunosuppressant regimen, as discussed earlier. Plasma exchange and intravenous immunoglobulin are also useful in preparing myasthenic patients for thymectomy and may reduce the likelihood of deterioration consequent upon the intro- duction of prednisolone. Osteoporosis is an important concern in patients receiving long-term, high-dose prednisolone. Management guidelines differ depending upon age, sex, and coexistent morbidity. Local guidelines should be followed with respect to bone density scanning and use of calcium, vitamin D, and bisphosphonates and related drugs. Prognosis The outlook for most patients with myasthenia is good, with over 90% achieving near-normal functional recovery. Death is most likely to occur during a myasthenic crisis early on in the course of the disease. The response to thymectomy has been noted. Unwanted effects relating to the immunosuppressant drugs may have an im- portant influence on the outcome. Myasthenia in pregnancy Recent ‘best practice’ guidelines have been published and should be of help to both clinicians and patients. Pregnancy has no significant long-term effect on myasthenia, but relapse may be more common in the puerperium. Some 10% of infants born to myasthenic mothers have transient neonatal myasthenia due to transplacental passage of maternal anti-AChR antibodies. Symptoms include feeding and respiratory difficulties, generalized weakness, and, less commonly, ptosis. They resolve within a few weeks. Immunosuppressive treatment with prednisolone or azathioprine, and probably ciclosporin, should be maintained during pregnancy to ensure good control of the mother’s myasthenia and to reduce the likelihood of neonatal weakness. There is no evidence of sig- nificant teratogenicity or other harmful effects on the fetus from these drugs, although appropriate preconception counselling is es- sential. Similarly, breastfeeding is not contraindicated for women taking these drugs. Methotrexate is contraindicated for women and men attempting to conceive. Recent evidence suggests that mycophenolate mofetil may be associated with a specific fetal malformations. Much more rarely, the infant is born with arthrogryposis multi- plex congenita, secondary to profound intrauterine weakness and lack of movement. This relates to maternal antibodies that target the fetal form of the acetylcholine receptor, which is present at the neuromuscular junction until the last weeks of pregnancy, and in some cases the mother herself has been asymptomatic. Future research This may provide a better understanding of the immune processes involved, and thus lead to the development of selective treat- ments that avoid generalized immune suppression or other un- wanted effects of the currently available drugs. Recently there have been many reports that rituximab may be of benefit in patients with myasthenia, including those resistant to more conventional immunosuppressant regimes and particularly those with MuSK myasthenia. However, on current evidence it cannot be recom- mended as first-line treatment and further studies are required. Lambert–Eaton myasthenic syndrome Lambert–Eaton myasthenic syndrome is a presynaptic disorder, characterized by limb-girdle weakness and symptoms of autonomic dysfunction, which is often associated with small-cell lung cancer. Delayed diagnosis is common. Symptomatic and immunosuppres- sant therapies are available. Epidemiology Some 60% of patients have cancer-associated Lambert–Eaton myasthenic

syndrome, usually caused by small-cell lung cancer and much more rarely by other tumours; in these cases the peak pres- entation is in the fourth to sixth decades. The other 40% have non-cancer-associated Lambert–Eaton myasthenic syndrome and may present from childhood onwards. It is estimated that 3% of patients with small-cell lung cancer develop Lambert–Eaton myasthenic syn- drome, but that the diagnosis is frequently not made. The weakness is often attributed to nonspecific cachectic effects and the disorder is neither suspected nor investigated. Lambert–Eaton myasthenic syndrome, similar to many other paraneoplastic disorders (see Chapter 24.23), may predate the appearance of the cancer by as much as 5 years. Pathogenesis Both forms are associated with IgG class antibodies, which reduce the number of functional presynaptic P-/Q-type voltage-gated cal- cium channels by cross-linking adjacent channels. This causes re- duced calcium influx and therefore reduced quantal release of acetylcholine. As in myasthenia, patients with Lambert–Eaton myasthenic syndrome have an increased incidence of other forms of autoimmune disease, including a rare association with acquired myasthenia gravis. Small-cell lung cancers express voltage-gated calcium channelss and it is proposed that the tumour triggers an antibody response to those channels; the antibodies then cross-react with the calcium channels at the neuromuscular junction, causing Lambert–Eaton myasthenic syndrome. Clinical features Most patients present with an abnormality of gait and complain that their legs feel heavy or weak. Symptomatic upper limb weakness tends to present later. Autonomic dysfunction is common, but infre- quently volunteered, and includes dryness of the mouth and consti- pation. In men, impotence may predate limb weakness. Compared with myasthenia gravis, ocular symptoms are rarely severe or par- ticularly troublesome, and bulbar weakness is rare. On examination, mild ptosis and diplopia may be evident. The ab- normality of gait is often more striking than demonstrable weakness when testing on the examination couch. This is partly because of the phenomenon of postexertional potentiation. Physiologically, with sustained effort, there is mobilization of nerve calcium stores and consequently increased quantal release of acetylcholine. Clinically, this augmentation is apparent in two ways: first, strength increases after a few seconds of maximal effort; second, the tendon reflexes,

 which are reduced or absent, increase or appear following 10–15 s of maximal contraction of the relevant muscle. Sensory testing is normal. Diagnosis Single-fibre electromyography, as in myasthenia gravis, shows in- creased jitter and blocking, and repetitive nerve stimulation studies show decrement at certain frequencies. However, the characteristic neurophysiological finding, which reflects the clinical observa- tions made earlier, is of a small-amplitude compound muscle ac- tion potential that shows potentiation, sometimes enormous, 15 s after voluntary maximal contraction. Diagnosis is confirmed by demonstrating the presence of anti-voltage-gated calcium channels antibodies, which are detectable in up to 90% of cases. Treatment Pyridostigmine may offer some symptomatic benefit, but 3,4- diaminopyridine is generally more effective. 3,4-Diaminopyridine blocks the voltage-gated potassium channels (see Fig. 24.18.1), thereby prolonging the duration of the nerve action potential, re- sulting in a greater influx of calcium. The maximum dose of 3,4- diaminopyridine is 100 mg daily. If the symptomatic response is inadequate then treatment with alternate-day prednisolone (up to 1.5 mg/kg body weight per dose) and azathioprine (2.5 mg/kg body weight per day), as in myasthenia gravis, can be highly effective cancer-associated and noncancer- associated Lambert–Eaton myasthenic syndrome, but in the former group use of such drugs must be discussed with the oncologists. In a smoker in whom a cancer is not identified at presentation, it is prudent to repeat chest imaging (CT or MRI) yearly for 5 years. In cancer-associated Lambert–Eaton

myasthenic syndrome, re- moval of the tumour often leads to symptomatic improvement. Plasma exchange and intravenous immunoglobulin both give short-term benefit and can be used in cancer-associated and non- cancer-associated Lambert–Eaton myasthenic syndrome. Prognosis In cancer-associated Lambert–Eaton myasthenic syndrome, the prognosis is largely determined by the tumour. In noncancer- associated Lambert–Eaton myasthenic syndrome many patients can be rendered asymptomatic, but some prove very resistant to treatment. Congenital myasthenic syndromes This is a rare group of conditions with an overall prevalence in the United Kingdom of around 1 in 200 000 people. However, some areas have a prevalence as high as 1 in 70 000, reflecting diagnostic variation as well as the effects of racial composition and familial clustering. Congenital myasthenic syndrome (CMS) is a genetic- ally determined (usually autosomal recessive—so a history of con- sanguinity is common), non-autoimmune disorder. Major clinical features include onset in infancy, fatigable weakness, a decremental response to repetitive nerve stimulation, and absence of AChR or MuSK antibodies. A significant exception to this generalization is the classic slow-channel syndrome, which may present in infancy or adult life, and is inherited as an autosomal dominant trait. The syndromes may be classified on the basis of the site of the defect of neuromuscular transmission, but this is not always certain. A re- vised classification is evolving based on the molecular mechanisms identified. Diagnosis depends on electrophysiological tests, the clin- ical phenotype and response to treatment, and in around 80–90% cases on identification of the specific genetic defect. Presynaptic disorders These are the least well characterized of the myasthenic disorders. They include disorders of acetylcholine resynthesis caused by cho- line acetyltransferase (ChAT) mutations resulting in reduced ACh release. ChAT CMS is characterized by episodic apnoeas in early life and symptoms respond to anticholinesterase drugs. Endplate acetylcholinesterase deficiency Mutations in the acetylcholinesterase collagen-like tail subunit gene (COLQ), which is responsible for anchoring acetylcholinesterase to the basal lamina, affects the normal termination of neuromuscular transmission. The consequent prolonged endplate potentials lead to a desensitization of the AChRs and depolarization blockade and an additional secondary excitotoxic myopathy. Characteristic features such as a repetitive compound muscle action potential in response to a single stimulus and a slow pupillary response to light are re-ported in a minority. Severe and progressive muscle weakness is usually evident from birth or early infancy although milder pheno- types are reported. Anticholinesterase drugs, not surprisingly, are ineffective but ephedrine or oral salbutamol can improve symptoms. Postsynaptic disorders These disorders are associated with mutations in the genes that en- code the AChR subunits or associated AChR-clustering proteins. They may affect the number of receptors, the receptor-presenting area, or the kinetic properties of the central ion channel. The most common disorder in the United Kingdom is acetylcho- line receptor deficiency, which is most frequently caused by muta- tions in the ε-subunit gene. Presentation is at birth or within the first few years of life. There is generalized weakness, delayed motor milestones, feeding difficulties, and extraocular muscle involve- ment. There is a good response to anticholinesterase drugs and 3,4-diaminopyridine. The fast-channel syndrome is phenotypically similar to acetyl- choline receptor deficiency and may be associated with α-, δ-, or ε-subunit mutations. The mechanism is altered kinetics of the re- ceptor ion channel. The slow-channel syndrome is also a kinetic disorder that can be associated with mutations in any of the adult AChR subunits. As in endplate acetylcholinesterase deficiency it causes a desensitiza-tion blockade and electromyography may show a repetitive response to a single nerve stimulus. This overstimulation of muscle and the prolonged endplate potentials lead to a secondary excitotoxic my- opathy. Slow-channel disorder is an autosomal dominant condition with variable penetrance and may remain subclinical. In adult life it may present with progressive weakness,

characteristically affecting finger extensors and thumb abductors. Anticholinesterase drugs are unhelpful, but quinidine or fluoxetine may be beneficial. Mutations in rapsyn, an AChR-clustering protein, is associ- ated with a common mutation (N88K), thus aiding screening. The rapsyn defect leads to reduced numbers of clustered AChRs. This

section 24 Neurological disorders 6302 condition usually presents in infancy and is characterized by squint without limitation of eye movements and mild resolving joint con- tractures. Such children often have unexplained and acute crises in muscle weakness, and bulbar and respiratory function, and the diagnosis is crucial because this phenotype responds so well to anticholinesterases. Occasionally adulthood-onset cases are de- scribed with a very mild phenotype. DOK7 mutations have been recently described in cases of CMS with a limb-girdle phenotype, and normal eye movements in most cases. DOK7 is a postsynaptic protein that interacts with MuSK. This disorder generally responds poorly to anticholinesterases, but over months often improves markedly when ephedrine or oral sal- butamol is given. Recently, mutations in glutamine-fructose-6-phosphate transaminase 1 (GFPT1) and dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosaminephosphotransferase 1 (DPAGT1) genes have been identified in patients with a limb-girdle CMS associated with tubular aggregates on muscle biopsy. These have relative sparing of ocular, facial, and bulbar muscles, tend to present after infancy (in early childhood), respond to anticholinesterases and 3,4-DAP may give additional benefit. AChR deficiency syndromes caused by AChR ε-subunit or rapsyn mutations and DOK7 mutations make up more than 75% of all gen- etically confirmed cases of CMS in the United Kingdom and thus initial diagnostic screening focuses on these three genes. Neuromyotonia This term describes a condition in which peripheral nerve over- activity leads to spontaneous muscle activity. It is thus quite different from classic myotonia, which relates to an abnormality of muscle fibre membrane activity. Neuromyotonia may be seen in association with a variety of inherited disorders (notably neuropathies and spinal muscular atrophy), but the most common form is acquired; this form may be idiopathic, but recognized associations include tumour (thymoma—sometimes also in association with myas- thenia gravis; bronchial carcinoma) and acquired demyelinating polyneuropathies. Most acquired cases are autoimmune in origin and about 50% have antibodies directed against voltage-gated potas- sium channels in the peripheral nerve (see Fig. 24.18.1), for which an assay is now available. As noted earlier, activation of these chan- nels is an important factor in nerve repolarization—the symptoms of neuromyotonia can be understood in terms of reduced numbers of potassium channels, prolonged depolarization, and excessive re- lease of acetylcholine. The main clinical features are muscle stiffness, cramps, and twitching (myokymia), which may be localized or generalized. Voluntary muscle contraction may precipitate or exacerbate the abnormal activity. The myokymia persists during sleep and gen- eral anaesthesia. Additional symptoms include peripheral paraes- thesias and excess sweating, and, rarely, mood change, disturbed sleep, and hallucinations. These central symptoms are part of a con- dition called Morvan’s syndrome which is discussed elsewhere (see Chapter 24.24). Apart from the muscle twitching (which may be confused with the fasciculation of denervation), physical examination may be normal. Mild weakness may be evident, proximally or distally. In long-standing cases, muscle hypertrophy (simply a form of work hypertrophy) may be present. Tendon reflexes may be reduced. Electromyography shows highly characteristic, and diagnostic, doublet, triplet, or multiplet motor unit discharges, or periods of continuous motor unit discharge, with a high (up to 300 Hz) intraburst frequency. Fibrillation and fasciculation potentials may also be seen. Further confirmation of the diagnosis comes from anti- voltage-gated potassium channels antibody assay,

which is positive in about 50% of cases using the currently available assay. Chest imaging should be considered to exclude thymoma and bronchial carcinoma. Most patients gain symptomatic relief from carbamazepine, phenytoin, or lamotrigine. If the benefit is insufficient, immunosup- pression with prednisolone and azathioprine is often helpful. FURTHER READING Neurobiology of myasthenic syndromes Vincent A (2007). Myasthenia gravis and myasthenic syndromes. In: Gilman S (ed) Neurobiology of disease. Elsevier Academic Press, Burlington, MA. Myasthenia gravis Benveniste O, Hilton-Jones D (2010). The role of rituximab in the treatment of myasthenia gravis. European Neurological Review, 5, 95–100. Evoli A, et al. (2003). Clinical correlates with anti-MuSK anti- bodies in generalized seronegative myasthenia gravis. Brain, 126, 2304–11. Evoli A, et al. (2010). Autoimmune and inherited disorders of neuro- muscular transmission. In: Karpati G, et al. (eds) Disorders of volun- tary muscle. Cambridge University Press, Cambridge. Higuchi O, et al. (2011). Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol, 69, 418–22. Norwood F, et al. (2014). Myasthenia in pregnancy: Best practice guidelines from a UK multispeciality working group. J Neurol Neurosurg and Psych, 85, 538–43. Sussman J, et al. (2015). Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol, 15, 199–206. Lambert–Eaton syndrome Maddison P, Newsom-Davis J (2005). Treatment for Lambert–Eaton myasthenic syndrome. Cochrane Database Syst Rev, 2, CD003279. Titulaer MJ, et al. (2011). Clinical Dutch–English Lambert–Eaton myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. J Clin Oncol, 29, 902–8. Wirtz PW, et al. (2002). Differences in clinical features between the Lambert–Eaton myasthenic syndrome with and without cancer: an analysis of 227 published cases. Clin Neurol Neurosurg, 104, 359–63. Wirtz PW, et al. (2005). Lambert–Eaton myasthenic syndrome has a more progressive course in patients with lung cancer. Muscle Nerve, 32, 226–9. Congenital myasthenic syndromes Burke G, et al. (2003). Rapsyn mutations in hereditary myasthenia: distinct early- and late-onset phenotypes. Neurology, 61, 826–8.

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