

Guidelines for treatment of autoimmune neuromuscular transmission disorders

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Background: Important progress has been made in our understanding of the autoimmune neuromuscular transmission (NMT) disorders; myasthenia gravis (MG), Lambert–Eaton myasthenic syndrome (LEMS) and neuromyotonia (Isaacs' syndrome).

Methods: To prepare consensus guidelines for the treatment of the autoimmune NMT disorders, references retrieved from MEDLINE, EMBASE and the Cochrane Library were considered and statements prepared and agreed on by disease experts.

Conclusions: Anticholinesterase drugs should be given first in the management of MG, but with some caution in patients with MuSK antibodies (good practice point). Plasma exchange is recommended in severe cases to induce remission and in preparation for surgery (recommendation level B). IvIg and plasma exchange are effective for the treatment of MG exacerbations (recommendation level A). For patients with non-thymomatous MG, thymectomy is recommended as an option to increase the probability of remission or improvement (recommendation level B). Once thymoma is diagnosed, thymectomy is indicated irrespective of MG severity (recommendation level A). Oral corticosteroids are first choice drugs when immunosuppressive drugs are necessary (good practice point). When long-term immunosuppression is necessary, azathioprine is recommended to allow tapering the steroids to the lowest possible dose whilst maintaining azathioprine (recommendation level A). 3,4-Diaminopyridine is recommended as symptomatic treatment and IvIG has a positive short-term effect in LEMS (good practice point). Neuromyotonia patients should be treated with an antiepileptic drug that reduces peripheral nerve hyperexcitability (good practice point). For paraneoplastic LEMS and neuromyotonia optimal treatment of the underlying tumour is essential (good practice point). Immunosuppressive treatment of LEMS and neuromyotonia should be similar to MG (good practice point).

Background and objectives

Autoimmune neuromuscular transmission (NMT) disorders are relatively rare, but often debilitating diseases.

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This is continuing Medical Education article, and can be found with corresponding questions on the internet at <http://www.efns.org/EFNSContinuing-Medical-Education-online.301.0.html>. Certificates for correctly answering the questions will be issued by the EFNS.

Myasthenia gravis (MG) is caused by autoantibodies against components of the post-synaptic neuromuscular junction. The autoimmune attack at the muscle endplate leads to NMT failure and muscle weakness. Lambert–Eaton myasthenic syndrome (LEMS) is caused by antibodies against the voltage-gated calcium channels (VGCC) at the pre-synaptic side of the muscle endplate. The antibodies inhibit acetylcholine release and cause NMT failure and muscle weakness. Neuro-myotonia (peripheral nerve hyperexcitability; Isaacs' syndrome) is caused by antibodies to nerve voltage-gated potassium channels (VGKC) that produce nerve hyperexcitability and spontaneous and continuous

skeletal muscle overactivity presenting as twitching and painful cramps and stiffness.

Our increased understanding of the basic mechanisms of neuromuscular transmission and autoimmunity has led to the development of novel treatment strategies. NMT disorders are now amenable to treatment and their prognoses are good. Treatment developed for other and more common antibody-mediated autoimmune disorders with similar pathogenetic processes have been applied also for NMT disorders. Although present treatment strategies are increasingly underpinned by scientific evidence, they are still based partly on clinical experience. In this article, we have evaluated the available literature and have given evidence-based treatment guidelines.

Materials and methods

Search strategy

MEDLINE 1966–2009 and EMBASE 1966–2004 were examined with appropriate MESH and free subject terms: 1. myasthenia, 2. myasthenia gravis, 3. Lambert–Eaton, 4. Lambert–Eaton myasthenic syndrome/LEMS, 5. neuromyotonia, 6. Isaacs' syndrome.

1–6 was combined with the terms: 7. treatment, 8. medication, 9. therapy, 10. controlled clinical trial, 11. randomized controlled trial, 12. clinical trial, 13. multicenter study, 14. meta-analysis, 15. cross-over studies, 16. thymectomy and 17. immunosuppression.

The Cochrane Central Register of Controlled Trials (CENTRAL) was also sought.

Articles in English that contained data which could be rated according to the guidance statement for neurological management guidelines of EFNS were included [1].

Information from patient and other voluntary organizations and existing guidelines including those from the American Academy of Neurology was reviewed and validated according to the above-mentioned criteria. Finished and ongoing Cochrane data based projects on LEMS treatment, immunosuppressive MG treatment, IvIg for MG, plasmapheresis for MG and corticosteroids for MG in addition to thymectomy for MG were reviewed.

Methods for reaching consensus

Four members of the task force prepared parts of the manuscript and draft statements about the treatment of MG, LEMS and neuromyotonia. Evidence was classified as classes I to IV and recommendations as levels A to C according to the scheme agreed for EFNS guidelines (1). When only class IV evidence was available but

consensus could be reached, the task force has offered advice as good practice points (1). The statements were revised and collated into a single document, which was then revised iteratively until consensus was reached.

Myasthenia gravis (MG)

MG is characterized by a fluctuating weakness of skeletal muscle with remissions and exacerbations [2]. In 85% of patients with MG, the disease is caused by antibodies against the AChR at the post-synaptic side of the neuromuscular junction that cause transmission failure and produce destruction of the endplate. Of the 15% of generalized MG patients without AChR antibodies, 20–50% have antibodies against another synaptic antigen, muscle-specific tyrosine kinase [MuSK] [3]. The remaining patients probably have antibodies against unknown antigens at the neuromuscular junction or low level/affinity antibodies against AChR or MuSK that are not detectable by standard assays. MG is closely associated with thymic pathology. Fifteen per cent of patients with MG have a thymoma and often have antibodies against additional striated muscle antigens such as titin [4] and ryanodine receptors [5]. These antibodies are more common in thymoma and severe MG and are considered as useful markers [6,7]. A hypertrophic thymus is found in 60% of patients with MG, typically young women, whilst most patients with debut after 50 years of age have a normal or atrophic thymus.

MG often used to cause chronic, severe disability and had a high mortality. However, improved treatment allied with advances in critical care have transformed the long-term prognosis and life expectancy is now near normal [8–11].

Symptomatic treatment

Acetylcholine esterase inhibitors (of which pyridostigmine is the most widely used) inhibit the breakdown of ACh at the neuromuscular junction. This increases the availability of ACh to stimulate AChR and facilitates muscle activation and contraction. These drugs are most helpful as initial therapy in newly diagnosed patients with MG, and as sole long-term treatment of milder disease.

These drugs are usually well tolerated at standard doses of up to 60 mg five times per day. Adverse effects are caused by the increased concentration of ACh at both nicotinic and muscarinic synapses. The common muscarinic effects are gut hypermotility (stomach cramps, diarrhoea), increased sweating, excessive respiratory and gastrointestinal secretions [12,13], and

bradycardia. The main nicotinic adverse effects are muscle fasciculations and cramps.

There are no placebo-controlled randomized studies of these drugs, but case reports, case series and daily clinical experience demonstrate an objective and marked clinical effect (class IV evidence). Although there is inadequate evidence for a formal recommendation, the task force agreed that an anticholinesterase drug should be the first-line treatment for all forms of MG (class IV evidence, good practice point). Although its use should be cautious in patients with anti-MuSK antibodies who often show Ach hypersensitivity [14].

The optimal dose is determined by the balance between clinical improvement and adverse effects and can vary over time and with concomitant treatment. There is one report of additional effect of intranasally administered pyridostigmine, although this is not commercially available [15] (class III evidence).

3,4-Diaminopyridine releases ACh from nerve terminals. In a double-blind, placebo-controlled trial, the drug seemed effective in congenital (hereditary and non-immune) myasthenia patients. Juvenile patients with MG did not respond [16] (class III evidence). The drug is not recommended in autoimmune MG, although it may prove useful in some forms of congenital myasthenia (level C recommendation).

Ephedrine increases ACh release. It has probably less effect and more severe side effects including sudden death and myocardial infarction, compared with pyridostigmine [17] (class III evidence). Terbutalin, a B₂-adrenergic agonist has also been tried and seems promising as an adjunct for a subgroup of patients with MG [18]. Pyridostigmine should be preferred to ephedrine in the symptomatic treatment of MG (level C recommendation).

Immune-directed treatment

Definitive MG treatments target the autoimmune response by suppressing the production of pathogenic antibodies or the damage induced by the antibodies. The aim of immunotherapy is to induce and then maintain remission. MG patients with a thymoma and other patients with anti-titin and anti-RyR antibodies usually have a severe disease [6,19] (class III evidence), thus suggesting more aggressive treatment strategies should be considered in these patients (level C recommendation).

Most MG treatment studies are insufficient. There is no consideration of whether patients have had thymectomy. In non-operated patients, it is unknown how many of them had thymoma. In studies conducted before 1980, the percentage of patients with and without

AChR antibodies is not known, and the MuSK antibodies were detected recently. There are no controlled and prospective trials of immunosuppressive treatment in children and adolescents. Evidence suggests that each immunological subtype of MG may be associated with a different spectrum of clinical phenotypes and thymus pathologies that should be considered when designing optimum treatment strategies [20].

Plasma exchange

Antibodies are removed from patient sera by membrane filtration or centrifugation. The onset of improvement is within the first week and the effect lasts for 1–3 months. From unrandomized reports, semi-selective immunoabsorption to tryptophan-linked polyvinylalcohol gels or protein-A columns appears to be as effective as plasmapheresis, with the advantage that protein substitution is not required.

Short-term benefits of plasma exchange have been reviewed by Gajdos *et al.* (Cochrane review) [21] who conclude: 'There are no adequate randomized controlled trials, but many case series report short-term benefit from plasma exchange in myasthenia gravis, especially in myasthenic crisis'. The NIH consensus of 1986 states: 'the panel is persuaded that plasma exchange can be useful in strengthening patients with myasthenia gravis before thymectomy and during the post-operative period. It can also be valuable in lessening symptoms during initiation of immunosuppressive drug therapy and during an acute crisis.' (class IV evidence). Plasma exchange is recommended as a short-term treatment in MG, especially in severe cases to induce remission and in preparation for surgery (level B recommendation).

There is one report on the use of repeated plasma exchange over a long period in refractory MG. It failed to show any cumulative long-term benefit in combination with immunosuppressive drugs [22] (class II evidence) [21] (class I evidence). Repeated plasma exchange is not recommended as a treatment to obtain a continuous and lasting immunosuppression in MG (level B recommendation).

Intravenous immunoglobulin (IvIg)

IvIg had a positive effect in several open studies especially in the acute phase of MG [23,24] (class IV evidence). It has been used for the same indications as plasma exchange; rapidly progressive disease, preparation of weak patients for surgery including thymectomy and as an adjuvant to minimize long-term side effects of oral immunosuppressive therapy [25]. A recent Cochrane review compared the efficacy of IvIg compared

to plasma exchange, other treatments or placebo. It concluded: 'the only randomized controlled trial examining early treatment effects did not show a significant difference between IvIg and plasma exchange for the treatment of myasthenia gravis exacerbations'. Non-randomized evidence consistently favours the interpretation that they are equally effective in this situation [26,27] (class I evidence) (level A recommendation). Two multicentre randomized controlled studies suggest that although efficacy is equal, side effects of IvIg may be fewer and less severe. Thus, IvIg may be the preferred option [28] (class I evidence). However, the controlled study by Gajdos *et al.* (1997) used a lower volume of plasma exchange than usual for the treatment of MG crisis, and the end-point was improvement at a time-point set too late to allow proper assessment of whether one therapy worked quicker than the other. There are published abstracts but no articles suggest that plasma exchange work faster in MG crisis.

In mild or moderate MG, no significant difference in efficacy of IvIg and placebo was found after 6 weeks. In moderate exacerbations of MG, no statistically significant difference in efficacy was found between IvIg and methylprednisolone. Randomized controlled trials have not shown evidence of improved functional outcome or steroid-sparing effect with the repeated use of IvIg in moderate or severe stable MG [26,27] (class I evidence). However, a randomized placebo-controlled study showed a significant response in patients treated with IvIg, the greatest improvement occurring in subjects with more severe disease [29].

Thymectomy (TE)

There are several surgical approaches to TE: full or partial sternotomy, transcervical and thoracoscopic. There are no randomized controlled studies for TE in MG.

It is difficult to compare the outcomes of the different operative techniques (confounding factors influenced both the controlled and the uncontrolled studies) but outcomes are probably similar [30] (Meyer *et al.*, 2009) (class III evidence).

Despite the absence of randomized, well-controlled studies, TE in MG patients with and without thymoma is widely practised. Post-operative improvement can take months or years to appear, making it difficult to distinguish TE effects from those of immunosuppressive drugs, which are often used concomitantly. In a controlled study, a 34% remission and a 32% improvement rate were achieved after TE compared with 8% and 16% for matched patients without the operation [31] (class III evidence). The patient should be in a clinically

stable condition before this elective intervention. The perioperative morbidity is very low and consists in wound healing disorders, bronchopneumonia, phrenic nerve damage and sternum instability.

The Quality Standard Subcommittee of the American Academy of Neurology [32,33] analysed 28 articles written 1953–1998 describing outcomes in 21 MG cohorts with or without TE (class II evidence). Most series used the trans-sternal approach, and the follow-up ranged from 3 to 28 years. There are a number of methodological problems in the studies including the definition of remission, the selection criteria, the medical therapy applied in both groups and data on antibody status. However, 18 of the 21 cohorts showed improvement in patients with MG who underwent TE. Patients with MG undergoing TE were twice as likely to attain medication-free remission, 1.6 times as likely to become asymptomatic, and 1.7 times as likely to improve. No study found a significant negative influence of TE. Patients with purely ocular manifestations did not benefit from TE. The outcome for younger TE patients was not significantly different from the total MG group. Mild MG (Ossermann grade 1–2) did not profit from surgery, whilst more severe cases (Ossermann grade 2b–4) were 3.7 times as likely to achieve remission after TE than those without surgery ($P < 0.0077$).

Gronseth *et al.* asserted unequivocally that 'for patients with non-thymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement'. Their recommendation is supported by this task force with the specification that patients with generalized MG and AChR antibodies are the group most likely to benefit (level B recommendation).

The widespread opinion that an early TE in the course of MG improves the chance of a quick remission is based on observations that lack detailed information and cannot be verified by meta-analysis. However, from pathogenic considerations it is tempting to assume that early TE should be preferred to TE after many years.

The indication for TE in AChR antibody-negative patients with MG is controversial. This group is heterogeneous. Some patients are false negative as they have low affinity AChR antibodies not detected by standard assays [34], whilst others have MuSK and possible other still undetected antibodies. A retrospective cohort study displayed a similar post-operative course in AChR antibody-negative and AChR antibody-positive patients with a follow-up of at least 3 years [35]. Remission or improvement after TE occurred in 57% of AChR antibody-negative patients and in 51% of AChR antibody-positive patients. One study [36] could not

prove any effect of TE in 15 MuSK antibody-positive patients, whilst MuSK antibodies predicted a poor outcome of TE in another study [37]. Available evidence suggests that TE should not be recommended in MuSK antibody-positive patients. Early onset generalized MG without AChR and MuSK antibodies should have TE in the same way as MG with AChR antibodies.

In MG patients with a thymoma, the main aim of TE is to treat the tumour rather than for any effect on the MG. Once thymoma is diagnosed, TE is indicated irrespective of the severity of MG (good practice point). Thymoma is a slow-growing tumour, and TE should be performed only after stabilization of the MG. After TE, the AChR antibody titre usually falls less in patients with thymoma than in those with thymic hyperplasia [38]. The prognosis depends on early and complete tumour resection [39].

Corticosteroids

In observational studies, remission or marked improvement is seen in 70–80% of patients with MG treated with oral corticosteroids, usually prednisolone [40] (class IV evidence), but the efficacy has not been studied in double-blind, placebo-controlled trials. Steroids have side effects including weight gain, fluid retention, hypertension, diabetes, anxiety/depression/insomnia/psychosis, glaucoma, cataract, gastrointestinal haemorrhage and perforations, myopathy, increased susceptibility to infections and avascular joint necrosis. The risk of osteoporosis is reduced by giving bisphosphonate [41] (class IV evidence), and antacids may prevent gastrointestinal complications. The task force agreed that oral prednisolone should be a first choice drug when immunosuppressive drugs are necessary in MG (good practice point). Some patients have a temporary worsening of MG if prednisolone is started at high dose. This steroid dip occurs after 4–10 days and sometimes can precipitate a MG crisis. Thus, we recommend starting treatment at low dose, 10–25 mg on alternate days increasing the dose gradually (10 mg per dose) to 60–80 mg on alternate days. If the patient is critically ill, one should start on a high dose every day and use additional short-time treatments to overcome the temporary worsening. When remission occurs, usually after 4–16 weeks, the dose should be slowly reduced to the minimum effective dose given on alternate days (good practice point).

Azathioprine

Azathioprine is in extensive use as an immunosuppressant. It is metabolized to 6-mercaptopurine, which

inhibits DNA and RNA synthesis and interferes with T-cell function. The onset of therapeutic response may be delayed for 4–12 months, and maximal effect is obtained after 6–24 months. Azathioprine is usually well tolerated but idiosyncratic flu-like symptoms or gastrointestinal disturbances including pancreatitis occur in 10%, usually within the first few days of treatment. Some patients develop hepatitis with elevations of liver enzymes. Leucopenia, anaemia, thrombocytopenia or pancytopenia usually respond to drug withdrawal. Blood cell effects and hepatitis often do not recur after cautious reintroduction of the drug. Careful monitoring of full blood cell count and liver enzymes is mandatory and the dosage should be adjusted according to the results. About 11% of the population are heterozygous and 0.3% homozygous for mutations of the thiopurine methyltransferase gene (which can be monitored in blood) and have an increased risk of azathioprine-induced myelosuppression.

One large double-blind randomized study has demonstrated the efficacy of azathioprine as a steroid-sparing agent with a better outcome in patients on a combination of azathioprine and steroids than in patients treated with steroids alone [42] (class I evidence). It has an immunosuppressive effect when used alone without steroids [43] (class III evidence). In a small randomized study, prednisone was associated with better and more predictable early improvement in muscle strength than azathioprine [44] (class III evidence). In patients where long-term immunosuppression is necessary, we recommend starting azathioprine together with steroids to allow tapering the steroids to the lowest dose possible, whilst maintaining azathioprine (level A recommendation).

Methotrexate

Methotrexate should be used in selected patients with MG who do not respond to first choice immunosuppressive drugs (good practice point). It is well studied in other autoimmune disorders, but there is no evidence of sufficient quality published for MG.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with immunosuppressive properties. It is a strong suppressor of B-lymphocyte activity and antibody synthesis and at high doses it also affects T-cells. In a randomized, double-blind, placebo-controlled study including 23 patients with MG, those on treatment had significantly improved muscle strength and a lower steroid dose compared with the placebo group. Intravenous pulses of cyclophosphamide allowed reduction of systemic

steroids without deterioration of muscle strength or serious side effects [45] (class II evidence). However, the relative high risk of toxicity including bone marrow suppression, opportunistic infections, bladder toxicity, sterility and neoplasms, limits the use of this medication to patients with MG intolerant or unresponsive to steroids plus azathioprine, methotrexate, cyclosporin or mycophenolate mofetil (level B recommendation).

Cyclosporin

Cyclosporin has an immunosuppressive effect in both organ transplantation and autoimmune disorders. It is an inhibitor of T-cell function through inhibition of calcineurin signalling [46]. Tindall *et al.* [47] conducted a placebo-controlled double-blind randomized study in 20 patients for 6 months with an open extension (class II evidence) [48,49] (class III evidence). The cyclosporin group had significantly improved strength and reduction in AChR antibody titre compared with the placebo group. Two open trials of 1 and 2 years treatment and one retrospective study all support the beneficial effect of cyclosporin [10,50–52] (class III evidence). Cyclosporin is effective in MG, has significant side effects of nephrotoxicity and hypertension and should be considered only in patients intolerant or unresponsive to azathioprine (level B recommendation).

Mycophenolate mofetil

Mycophenolate mofetil's active metabolite, mycophenolic acid, is an inhibitor of purine nucleotide synthesis and impairs lymphocyte proliferation selectively. A few studies including a small double-blind, placebo-controlled study of 14 patients have shown that mycophenolate mofetil is effective in patients with poorly controlled MG and as a steroid-sparing medication [53–59] (class III, class IV evidence). These findings could not be reproduced in a recent placebo-controlled study over 9 months [60] (class II evidence). Therefore, the effect of mycophenolate mofetil in MG is not unequivocally documented, but it may be tried in patients intolerant or unresponsive to azathioprine (recommendation level B).

FK506 (tacrolimus)

Tacrolimus (FK506) is a macrolide molecule of the same immunosuppressant class as cyclosporin. It inhibits the proliferation of activated T-cells via the calcium–calcineurin pathway. FK506 also acts on ryanodine receptor-mediated calcium release from sarcoplasmic reticulum to potentiate excitation–contraction coupling in skeletal muscle [61]. Case reports

and a small open trial all showed a useful improvement of MG with minor side effects [9,62–66] (class III evidence). Interestingly, patients with anti-RyR antibodies (and potential excitation–contraction coupling dysfunction) had a rapid response to treatment indicating a symptomatic effect on muscle strength in addition to the immunosuppression (53). FK506 should be tried in MG patients with poorly controlled disease, especially in RyR antibody-positive patients (level C recommendation).

Antibodies against leucocyte antigens

There are case reports of improvement of refractory MG with monoclonal antibodies against different lymphocyte subsets such as anti-CD20 (rituximab) (B-cell inhibitor) [67–70] (class IV evidence) and anti-CD4 (T-cell inhibitor) [71] (class IV evidence), both reporting good clinical outcome. These treatment strategies are promising, but more evidence is needed before any recommendations can be given.

Training, weight control and lifestyle modifications

The importance of reducing weight and modification of activities of daily living has been suggested, but there is no hard scientific evidence to this. There are reports that show some benefit of respiratory muscle training in MG [72,73] (class III evidence) and strength training in mild MG [74] (class III evidence). Physical training can be carried out safely in mild MG and produces some improvement in muscle force (level C recommendation). Seasonal flu vaccination should be recommended in patients with MG (good practice point).

MG is associated with a slightly increased rate of complications during birth and more frequent need of operative interventions [75,76] (class II evidence). Transient neonatal MG occurs in 10–20% of children born to MG mothers. Maternal MG is also a rare cause of arthrogyphosis congenita and of recurrent miscarriages [77]. Acetylcholine esterase inhibitors and immunosuppressive drugs should be continued during pregnancy when necessary for the MG, except for methotrexate which is damaging to ova and sperm and should be stopped at least 3 months before attempting conception. Mycophenolate mofetil and other new drugs where no safety data are available should also be stopped 3 months before conception [78] (good practice point). Effective immunosuppression can improve severe foetal MG-related conditions (class III evidence). Women with MG should not be discouraged from conceiving, and pregnancy does not worsen the long-term outcome of MG [79] (class II evidence).

Recommendations for MG

After the diagnosis of MG is established, an acetylcholine esterase inhibitor should be introduced. Thymoma patients should have thymectomy. AChR antibody-positive early-onset patients with generalized MG and insufficient response to pyridostigmine therapy should be considered for thymectomy, ideally within 1 year of disease onset. Immunosuppressive medication should be considered in all patients with progressive MG symptoms. We recommend starting with prednisolone covered by bisphosphonate and antacid and azathioprine. Non-responders or patients intolerant to this regime should be considered for treatment with one of the other recommended immunosuppressive drugs. Recommendation levels are B, C or good practice points.

Lambert Eaton myasthenic syndrome (LEMS)

Antibodies to peripheral nerve P/Q-type VGCC antibodies are present in the serum of at least 85% of LEMS patients [80]. The disease is characterized by ascending muscle weakness that usually starts in the proximal lower limb muscles and is associated with autonomic dysfunction. Ptosis and ophthalmoplegia tend to be milder than in MG [81]. LEMS rarely causes respiratory failure [81]. In half of the patients, LEMS is a paraneoplastic disease and a small cell lung carcinoma (SCLC) will be found [82].

Symptomatic and immune-directed treatment

Evidence from small, randomized, controlled trials showed that both 3,4-diaminopyridine and IvIg improved muscle strength scores and compound muscle action potential amplitudes in LEMS patients [83] (Cochrane review) (class I evidence).

First-line treatment is 3,4-diaminopyridine [84]. An additional therapeutic effect may be obtained if combined with pyridostigmine. If symptomatic treatment is insufficient, immunosuppressive therapy should be started, usually with a combination of prednisone and azathioprine. Other drugs like cyclosporin or mycophenolate can be used, although evidence of benefit is limited to case series reports (class IV evidence) (level C recommendation).

For patients with a paraneoplastic LEMS, it is essential to treat the tumour. Chemotherapy is the first choice in SCLC, and this will have an additional immunosuppressive effect. In LEMS patients with a possible underlying SCLC corticosteroids, when required for the disease treatment, can be used; immunosuppressants should be avoided before the tumour is

ruled out. This does not apply to thymoma that has a slow growth.

The presence of LEMS in a patient with SCLC improves tumour survival [85]. For a more detailed description of LEMS, consult the Guidelines for the management of paraneoplastic disorders [86].

Neuromyotonia (peripheral nerve hyperexcitability)/ISAACS syndrome

This commonest acquired form of generalized peripheral nerve hyperexcitability is autoimmune and caused by antibodies to nerve voltage-gated potassium channels (VGKC). [87], although the only generally available assay detects these antibodies in only 30–50% of all patients [87]. Neuromyotonia is paraneoplastic in up to 25% of patients and can predate the detection of neoplasia, usually thymus or lung, by up to 4 years [88]. The clinical hallmark is spontaneous and continuous skeletal muscle overactivity presenting as twitching and painful cramps and often accompanied by stiffness, pseudomyotonia, pseudotetany and weakness [89]. One third of patients also have sensory features and up to 50% have hyperhidrosis suggesting autonomic involvement. Central nervous system features can occur (Morvan's syndrome). [88,90]

Symptomatic and immune-directed treatment

Neuromyotonia usually improves with symptomatic treatment [89], although evidence is case reports and case series (class IV evidence). Carbamazepine, phenytoin, lamotrigine and sodium valproate can be used, if necessary in combination.

Neuromyotonia often improves and can remit after treatment of an underlying cancer [89]. In patients whose symptoms are debilitating or refractory to symptomatic therapy, immunomodulatory therapies should be tried [89,91]. Plasma exchange often produces useful clinical improvement lasting about 6 weeks accompanied by a reduction in electromyography activity [89] and a fall in VGKC antibody titres [92]. Single case studies suggest that IvIg can also help [93]. There are no good trials of long-term oral immunosuppression. However, prednisolone, with or without azathioprine or methotrexate, has been useful in selected patients 86 [94] (class IV evidence) (good practice point).

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