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EFNS/ENS GUIDELINES

EFNS/ENS Guidelines for the treatment of ocular myasthenia

E. Kerty[a,b*], A. Elsais[a,b*], Z. Argov[c], A. Evoli[d] and N. E. Gilhus[e,f]

[a]Department of Neurology, Oslo University Hospital, Oslo; [b]Faculty of Medicine, University of Oslo, Oslo, Norway; [c]Department of Neurology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [d]Institute of Neurology, Catholic University, Roma, Italy; [e]Department of Clinical Medicine, University of Bergen, Bergen; and [f]Department of Neurology, Haukeland University Hospital, Bergen, Norway

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Background and purpose: The symptoms of acquired autoimmune ocular myasthenia are restricted to the extrinsic eye muscles, causing double vision and drooping eyelids. These guidelines are designed to provide advice about best clinical practice based on the current state of clinical and scientific knowledge and the consensus of an expert panel.

Search strategy: Evidence for these guidelines was collected by searches in the MEDLINE and Cochrane databases. The task force working group reviewed evidence from original articles and systematic reviews. The evidence was classified (I, II, III, IV) and consensus recommendation graded (A, B or C) according to the EFNS guidance. Where there was a lack of evidence but clear consensus, good practice points are provided.

Conclusions: The treatment of ocular myasthenia should initially be started with pyridostigmine (good practice point). If this is not successful in relieving symptoms, oral corticosteroids should be used on an alternate-day regimen (recommendation level C). If steroid treatment does not result in good control of the symptoms or if it is necessary to use high steroid doses, steroid-sparing treatment with azathioprine should be started (recommendation level C). If ocular myasthenia gravis is associated with thymoma, thymectomy is indicated. Otherwise, the role of thymectomy in ocular myasthenia is controversial. Steroids and thymectomy may modify the course of ocular myasthenia and prevent myasthenia gravis generalization (good practice point).

Objectives

Myasthenia gravis (MG) is an autoimmune disorder affecting the postsynaptic neuromuscular junction membrane. Ocular manifestations at the onset of the disease are evident in a large majority of patients.

Whilst there are accepted guidelines with regard to the treatment of generalized myasthenia gravis (GMG) [1], this is not the case for ocular myasthenia where the treatment strategy is controversial. Although there are already EFNS guidelines for treatment of autoimmune neuromuscular transmission disorders, they do not deal specifically with ocular myasthenia [1].

Correspondence: E. Kerty, Department of Neurology, Oslo University Hospital, Rikshospitalet, Postbox 4950 Nydalen, 4 Oslo, Norway (tel.: +47 23071829; fax: +47 23070490; e-mail: emilia.kerty@medisin.uio.no).
*These two authors contributed equally to this paper.

The goal of therapy should be to minimize patients' symptoms and possibly prevent the generalization of the disease with minimal side effects.

Background

Myasthenia gravis (MG) is an acquired organospecific autoimmune disease. In most patients antibodies are directed against the nicotinic acetylcholine receptors (AChRs); in a few patients antibodies target postsynaptic AChR-associated proteins such as the muscle-specific tyrosine kinase (MuSK) and the low-density lipoprotein-related receptor 4 (Lrp4). Despite the progress in antibody detection, some patients still remain antibody negative ('sero-negative' myasthenia).

Almost all MG patients will have ocular manifestations at some point during the course of their disease. Although ocular symptoms are often the first to appear, most patients progress to GMG and only 15% continue to have isolated ocular complaints for

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the entire course of the disease [2]. In the majority of patients, disease progression will take place within the first year after onset and within 2 years in up to 80% of cases [2–4]. If patients have restricted ocular disease for 2 years without developing GMG, they are not likely to develop it later [5]. When weakness is limited to the extrinsic ocular muscles and levator palpebrae superioris (LPS), the disease is called ocular myasthenia [6]. All ages and both genders may be affected.

Ptosis may be unilateral or bilateral, and it is usually asymmetric [7]; the degree of LPS weakness varies from slight drop of one eyelid to nearly complete paralysis. Ophthalmoparesis is also variable and can mimic almost any pattern of ocular misalignment. Nearly all patients with diplopia have associated ptosis [8]. The pupil is not affected. If ocular myasthenia is suspected on the basis of history and clinical findings, the same diagnostic tests should be performed as for GMG in order to confirm the diagnosis, i.e. response to the edrophonium test, the ice pack test or the rest test, antibody assays, and neurophysiological tests. 40%–70% of ocular myasthenia patients have anti-AChR antibodies on the conventional assay [9,10]; the use of a cell-based assay with clustered AChRs appears to significantly increase the sensitivity of anti-AChR antibody detection [11]. On the other hand, high antibody levels and the presence of thymoma are uncommon in ocular myasthenia and when present are associated with an increased risk of secondary generalization [12]. Only a few ocular myasthenia cases have antibodies to MuSK [13–15], whilst there are no data on the frequency of anti-Lrp4 antibodies in this patient population [16–18]. Antibody detection confirms the diagnosis of autoimmune myasthenia. In patients without detectable antibodies the suspicion of sero-negative MG must be confirmed by the pharmacological and/or electromyography test.

Antibodies to voltage-gated potassium channel Kv1.4 are relatively frequent in Japanese GMG patients and indicate a more severe disease. Such antibodies have recently been found in mild or predominantly ocular myasthenia in a Caucasian cohort [19]. The diagnostic relevance of these antibodies is currently unclear.

Low-rate repetitive nerve stimulation shows low sensitivity (11%–39%) but high specificity (89%–98%) for the diagnosis of ocular myasthenia [20]. Examination of the orbicularis oculi, orbicularis oris or nasalis will increase the percentage of abnormalities identified, but these studies are not well tolerated.

Single-fibre electromyography, which is the most sensitive test for neuromuscular transmission, when performed in facial muscles has a high sensitivity for detecting MG in these subjects [21,22], false positives being described in ocular neuropathies and myopathies [23].

The diagnosis of ocular myasthenia can be difficult in patients with no detectable antibodies and with atypical signs (i.e. fluctuations may be absent in long-standing disease). Thyroid dysfunction is a common comorbidity and endocrine orbitopathy can lead to diagnostic confusion, whilst treatment of thyroid dysfunction may improve myasthenic weakness.

Ocular myasthenia is usually regarded as a mild disease, although it can significantly impair patients' daily activities and can progress to GMG. Ptosis and diplopia are often disabling symptoms that require treatment. Evidence based clinical data derived from randomized, prospective, placebo-controlled clinical trials are lacking. Therapies are generally based on observational studies, case series, case reports and clinical experience.

Search strategy and method for reaching consensus

A literature search was performed using the reference databases MEDLINE and the Cochrane Library: the keywords used were myasthenia gravis and ocular myasthenia and these were combined with the terms treatment, medication, therapy, immunosuppression, clinical trial and thymectomy. Articles in English that contained data which could be rated according to the guidance statement for neurological management guidelines of EFNS were included [24]. Scientific evidence for treatment was sorted into classes I– IV and recommendations were rated at levels A–C according to current EFNS guidance [24]. When sufficient evidence for recommendations A–C was not available, the task force offered advice as 'good practice points' provided there was consensus amongst all members of the task force.

Consensus was reached after several rounds of circulating drafts to the task force members.

Recommendations

Acetylcholinesterase-inhibitor drugs

Acetylcholinesterase (AChE) inhibitors improve neuromuscular transmission by enhancing the availability of acetylcholine to the remaining AChRs. Pyridostigmine is the agent most widely used. It is usually started at 30 mg three to four times per day and can be increased up to 60 mg four to five times per day according to clinical effect and the patient's tolerance. The standard

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paediatric dose is 7 mg/kg/day [1]. The maximum dose is generally determined by the occurrence of adverse effects.

Neostigmine is a short-acting AChE inhibitor that is usually started at 15 mg orally every 4 h or at 0.5–2.5 mg iv, im or sc every 1–3 h, not to exceed 10 mg/day. The standard paediatric dose is 2 mg/kg/day, divided into doses administered every 3–4 h.

The advantage of AChE inhibitors is that they are fast-acting, safe and free of long-term side effects.

Short-term side effects are common and are caused by the increased concentration of acetylcholine at the nicotinic and muscarinic synapses. The most common muscarinic adverse effects are increased secretions, abdominal cramps, diarrhoea, sweating, nausea and bradycardia; nicotinic effects mostly consist of muscle fasciculations and cramps.

AChE inhibitors have a better effect on ptosis than on diplopia. Long-term follow-up suggests that most patients ultimately move to other treatment options [25,26]. AChE inhibitors do not influence the development of generalization [12,27].

There are no placebo-controlled randomized studies of AChE inhibitors. However, case series, case reports and daily clinical experience demonstrate an objective clinical effect (Class IV evidence). The task force agreed that an AChE inhibitor drug should be the first-line symptomatic treatment for ocular myasthenia (good practice point).

Immune-directed treatment

Corticosteroids

Corticosteroids act on the immune system in different ways, e.g. by modulating cytokine production [28], inducing T lymphocyte apoptosis [29] and repressing the transcription of inflammatory cytokines [30]. Based on several retrospective series, corticosteroids lead to significant improvement in ocular myasthenia [12,31]. The question of whether early treatment with steroids reduces the risk of generalization is controversial [32,33]. Retrospective studies suggest a reduced rate of generalization in patients treated with corticosteroids for ocular MG [12,34,35]. Some GMG patients have a temporary worsening of the disease if corticosteroids are started at high dose. Some patients may have unrecognized GMG, and therefore 10–20 mg prednisolone or prednisone every other day as an initial dose is recommended, increasing by 5–10 mg every 5 days until the symptoms improve significantly. A lower peak dose than in GMG (50–60 mg on alternate days) can often control the symptoms. After the symptoms have been resolved – usually after 4–6 weeks – a slow tapering off of steroids can lead to a minimum effective dose or to complete withdrawal [12,35]. About one-third of the patients require long-term treatment [2,35–37] owing to disease relapses. Due to the potential long-term side effects of corticosteroid therapy, some experts recommend its use for the treatment of ocular myasthenia only with severe ocular disease [32]. Side effects from corticosteroids include obesity (including 'moon face'), hypertension, diabetes, opportunistic infections, osteoporosis, glaucoma, cataracts, increased facial hair (women) and gastric ulcer. These side effects are generally contingent on dose and treatment duration. A low carbohydrate, low sodium diet can prevent or minimize weight gain; vitamin D supplementation and bisphosphonates are useful to prevent osteoporosis.

Observational studies have reported good effects of oral corticosteroids in controlling ocular symptoms (Class III evidence), but the efficacy has not been studied in double-blind, placebo-controlled trials. Six of the eight studies that examined the effects of oral corticosteroids showed a benefit in terms of reducing the risk of progression to GMG [2,12,27,38–42] (Class III).

AChE treatment alone usually will not solve the ocular problems and the task force agreed that oral prednisolone/prednisone should be the drug of choice when immunosuppressive treatment is necessary for ocular myasthenia (recommendation level C).

Azathioprine

Azathioprine is a purine analogue functioning as purine antagonist and inhibits DNA synthesis and cell proliferation [43]. Azathioprine is the most frequently used non-steroidal immunosuppressant for the treatment of MG. Treatment with azathioprine, as a steroid-sparing agent, should be started when steroids cannot be lowered to a safe level or at the same time as steroids are initiated in patients at risk for steroid adverse effects (glucose intolerance, overweight, osteoporosis). The onset of therapeutic response may be delayed for several months, and often occurs after 3–10 months of continuous therapy. The dosage is usually 2.5–3 mg/kg/day at the start of treatment and 1 mg/kg/day as maintenance. Azathioprine-related side effects (e.g. leukopenia, thrombocytopenia, nausea, vomiting, hepatotoxicity and risk of neoplasia) generally occur at higher doses [44]. Blood counts and liver function analyses should be performed at baseline and rechecked weekly for 4 weeks and then every 3 months in the first year and every 6 months after that. About 11% of the population are hetero-

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zygous and 0.3% homozygous for mutations of the thiopurine methyltransferase gene and have an increased risk of azathioprine-induced myelosuppression.

Two studies have examined the effects of azathioprine and both indicated a beneficial effect on the risk of progression from ocular to generalized MG [12,40] (Class III evidence). Azathioprine, usually administered concomitantly with prednisolone, significantly reduced the development of GMG (12% compared with 64% for patients without immunosuppressive treatment) [12] (Class III evidence). A placebo-controlled randomized study showed that the combination of prednisolone and azathioprine is more effective than prednisolone alone in the treatment of GMG [45] (Class I evidence). Testing for thiopurine methyltransferase deficiency before start of treatment with azathioprine is recommended.

The task force has agreed that when steroid treatment does not result in good control of the symptoms and/or if it is necessary to use high steroid doses, azathioprine should be started in order to reduce steroids to the lowest effective dose (recommendation level C).

Mycophenolate mofetil

Mycophenolate mofetil inhibits nucleic acid synthesis and the replication of B and T lymphocytes [46]. A prospective observational study was performed on 31 ocular myasthenia patients. Eighty-seven per cent of those who were on corticosteroids and then switched to mycophenolate mofetil remained as purely ocular MG over a mean period of 4.2 years. Four patients discontinued mycophenolate mofetil owing to side effects and all four progressed to GMG [47]. Symptom relapse, including ptosis and/or diplopia, occurred in 23% and was treated with pyridostigmine. Because these patients were initially treated with corticosteroids, it is difficult to determine whether mycophenolate mofetil or prednisolone *per se* modified the natural history of disease progression. However, this study showed that mycophenolate mofetil can be used as a steroid-sparing agent for the long-term treatment of ocular myasthenia (Class IV evidence, good practice point). The average dose of mycophenolate mofetil was 1 g/day, which is lower than in generalized MG. Effects are usually seen after a few weeks [48]. Mycophenolate mofetil side effects are usually mild and infections, myelosuppression and hepatotoxicity rarely occur. Blood count analyses should be performed at baseline and rechecked weekly for 4 weeks, then bimonthly for 2 months, then monthly for the first year and every 6 months after that.

Cyclosporine A and tacrolimus

Cyclosporine A and tacrolimus are calcineurin inhibitors, causing blockade of the nuclear factor of activated T cells [49]. Cyclosporine has been used to treat ocular myasthenia in isolated cases, with a good clinical response (Class IV, good practice point). Potential side effects, especially nephrotoxicity and hypertension, are significant.

Tacrolimus as monotherapy was described in a retrospective study for treatment of ocular myasthenia with good effect in four patients [50] (Class IV evidence). A randomized, double-blind, placebo-controlled study that also included ocular myasthenia patients showed that tacrolimus had a moderate steroid-sparing effect [51] (Class III evidence, good practice point).

Methotrexate

A small, single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in GMG showed that methotrexate has similar efficacy and tolerability to azathioprine and is an effective steroid-sparing agent [52] (Class III evidence, good practice point).

Other immunosuppressive drugs

Other immunosuppressant drugs, e.g. cyclophosphamide, etanercept and rituximab, have not been reported systematically for the treatment of ocular myasthenia.

Short-term treatments

High doses of immunoglobulin and plasma exchange represent short-term treatments, are recommended in severe cases of GMG and are not indicated for patients with purely ocular symptoms (good practice point).

Thymectomy

Despite the absence of randomized studies, thymectomy is recommended for patients with non-thymomatous GMG to increase the probability of remission or improvement [53]. Postoperative improvement can take a long time, making it difficult to distinguish the effect of surgery from the immunosuppressive drug treatment.

Thymectomy has been used to a limited extent and in highly selected populations with ocular myasthenia considered to be unresponsive to other therapies [20]. Remission rates were reported as 6%–50% [2,12,54,55] (Class III evidence). Some studies reported

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that thymectomized patients were less likely to progress to GMG and more likely to undergo full remission [56–58] (Class III evidence). A retrospective review of 110 patients with ocular myasthenia who underwent extended trans-sternal thymectomy demonstrated that 84.6% of patients experienced symptomatic improvement after a median follow-up of 33.5 months [59].

The task force has agreed that thymectomy is not recommended for ocular myasthenia as first-line treatment but should be considered if drug treatment has failed (good practice point).

Assistive devices

Mechanical lid elevation for eyelid droop with eyelid crutches or tape is effective and well tolerated for a short time [60] (Class IV evidence). Prolonged use can result in exposure keratopathy. In the case of fixed ptosis eyelid, lift surgery may be beneficial [61] (Class IV evidence). Prisms can be helpful for patients with stable ocular misalignment when the deviation is mild to moderate. Eye muscle surgery may be beneficial in rare cases when fixed strabismus persists for long term (good practice point). Occlusive devices and contact lenses will resolve diplopia through monocular vision but reduce the visual field [62] (Class IV evidence). The possibility of assistive devices should be discussed with the patient as an alternative to pharmacological treatment, even for a short time.

Recommendation

The treatment of ocular myasthenia should be started with pyridostigmine. If this is not successful in relieving symptoms, oral corticosteroids should be used on an alternate-day regimen. If steroid treatment does not result in good symptom control and/or if it is necessary to use high steroid doses, steroid-sparing treatment with azathioprine should be started. In thymomatous MG, thymectomy is indicated. A few reports suggest that thymectomy can prevent MG generalization. Recommendation levels are generally C or good practice points. Well designed, randomized, placebo-controlled multicentre trials with a sufficiently long follow-up period are needed to determine the efficacy of different immunosuppressive therapies in ocular myasthenia. Future studies should measure the improvement of ocular symptoms, risk of progression to generalized disease, and side effects.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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