LEARNING OBJECTIVES
1. Participant will be aware of new literature regarding myasthenia gravis
2. Participant will be aware of scientific breakthroughs regarding myasthenia gravis
3. Participant will incorporate new information in patient care in the field of myasthenia gravis

CME QUESTIONS
1. Do statins cause myasthenia?
2. What is the latest blood test for myasthenia?
3. Do MuSK antibodies carry a higher or lower risk of thymoma?

KEYWORDS
1. Myasthenia gravis
2. Autoantibodies
3. Exacerbation
4. Thymoma
5. Immunomodulation

INTRODUCTION
What is the latest on Myasthenia?
Brief overview of major or interesting papers on the topic of Myasthenia Gravis in the last 2 years
Review of the conclusion of the two major studies of the use of mycophenolate mofetil in myasthenia

DIAGNOSIS
Abstract: Patients with myasthenia gravis (MG) are divided into three groups: (1) acetylcholine receptor antibody positive MG: 80%, (2) muscle-specific receptor tyrosine kinase (MuSK) antibody positive MG: 5-10%, and (3) double seronegative MG. In 2011, autoantibodies (Abs) against low-density lipoprotein receptor-related protein 4 (Lrp4) were identified in Japanese MG patients and thereafter have been reported in Germany and USA. In other Lrp4 Ab papers, Lrp4 Ab positive sera inhibited agrin-induced aggregation of AChRs in cultured myotubes, suggesting a pathogenic role regarding the dysfunction of the neuromuscular endplate. Anti-MuSK autoantibodies were revealed to block binding of collagen Q (ColQ) to MuSK. Anti-Kv1.4 antibodies targeting alpha-subunits (Kv1.4) of the voltage-gated potassium channel occurs frequently among MG patients with thymoma. Further understandings of neuromuscular junction structure and functions through newly discovered autoantibodies may provide more specific clinical information and treatments in MG.

Ann Neurol. 2011 Feb;69(2):418-22. doi: 10.1002/ana.22312. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Higuchi O, Hamuro J, Motomura M, Yamanashi Y. PMID: 21387385 Division of Genetics, Department of Cancer Biology, the Institute of Medical Science, the University of Tokyo, Japan.
Abstract: Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction, where acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density lipoprotein (LDL) receptor-related protein 4 (Lrp4) are essential. About 80% and 0% to 10% of patients with generalized MG have autoantibodies to AChR and MuSK, respectively, but pathogenic factors are elusive in others. Here we show that a proportion of AChR antibody-negative patients have autoantibodies to Lrp4. These antibodies inhibit binding of Lrp4 to its ligand and predominantly belong to the immunoglobulin G1 (IgG1) subclass, a complement activator. These findings together indicate the involvement of Lrp4 antibodies in the pathogenesis of AChR antibody-negative MG.

Abstract: Myasthenia gravis (MG) is an autoimmune disorder characterized by a defect in synaptic transmission at the neuromuscular junction causing fluctuating muscle weakness with a decremental response to
implications of the anti-LRP4 antibody positivity remain to be clarified.

COMMENT

Not yet commercially available, but we continue to whistle away at the seronegative myasthenia gravis cohort.

Do acetylcholine receptor and striated muscle antibodies predict the presence of thymoma in patients with myasthenia gravis? Decroos EC, Hobson-Webb LD, Juel VC, Massey JM, Sanders DB. Muscle Nerve. 2013 Apr 27. doi:10.1002/mus.23882. PMID: 23625360 Neuromuscular Section, Division of Neurology, Department of Medicine, Duke University Medical Center, DUMC 3403, Durham, North Carolina, 27710, USA.

Abstract Introduction: Acetylcholine receptor (AChR) and striated muscle antibodies (StrAbs) are found frequently in myasthenia gravis (MG) patients with thymoma. In this study we aimed to determine the positive predictive value (PPV) and negative predictive value (NPV) of these antibodies for thymoma in patients with MG. Methods: Antibody findings, thymic histology, and onset age were reviewed for 1141 patients with MG. PPV and NPV of these antibodies for thymoma were determined. Results: The PPV of AChR binding antibodies plus StrAbs was highest (50.0%) with onset before the age of 40 years. The PPV of all antibodies was low (<9%) after age 40. Higher StrAb levels did not increase the PPV. The NPV of AChR binding antibodies was high (99.7%) for all ages. Conclusions: Patients without AChR binding antibody are not likely to have a thymoma. StrAbs and AChR binding antibodies are not diagnostic for thymoma, but in early-onset MG their presence should raise the clinical suspicion for thymoma.

COMMENT

Antibodies predict thymoma in the under 40 population, and are not all that helpful after 40. Could help in decision making, but I think I will always order a CT chest in new myasthenia patients.

ICE TEST


Abstract Introduction: Several studies have reported high diagnostic sensitivity and specificity for the ice test in myasthenia gravis. All of the studies employed a case-control design, in which the diagnosis was already known at the time of the test for both patients and controls, leading to case selection bias. This suggests that the available literature substantially overestimates the diagnostic utility of these tests. Methods: A retrospective cohort study.
without selection bias was performed to examine the sensitivity and specificity of the ice test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the ice test were determined by means of a 2 × 2 table. Results: The ice test has a sensitivity of 0.92 (95% CI 0.62-1.00), specificity of 0.79 (95% CI 0.56-1.00), PPV of 0.73 (95% CI 0.48-0.90), and NPV of 0.94 (95% CI 0.70-1.00). Conclusion: Due to its high negative predictive value the ice test is still a reliable and useful bedside test.

J Neuroophthalmol. 2013 Jun;33(2):169-71. doi: 10.1097/WNO.0b013e31828bb19b. Variable ptosis after botulinum toxin type A injection with positive ice test mimicking ocular myasthenia gravis. Alaraj AM, Oystreck DT, Bosley TM. Department of Ophthalmology (AMA), College of Medicine, Qassim University, Buraidah, Saudi Arabia; Department of Ophthalmology (DTO, TM), College of Medicine, King Saud University, Riyadh, Saudi Arabia; and Division of Ophthalmology (DTO), Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa.

Abstract: We describe a patient who received cosmetic botulinum toxin type A injections to the brow and subsequently developed unilateral ptosis that was variable during examination and was transiently improved after the ice pack test. Ptosis gradually resolved spontaneously over approximately 3 months. This is the third patient to have variable ptosis documented after botulinum toxin type A injection to the brow and the second to have a positive ice test. The ice test is not completely specific for myasthenia gravis but may, at times, improve ptosis resulting from other defects at the neuromuscular junction. Wound botulism now is much more common because of illicit drug use, and the ice test also might be positive in this setting.

COMMENT

Ice test is becoming much more common than tensilon test in clinical practice. It is fast, accurate and safe. However, like any test, there are pitfalls. Take a good history!

TREATMENT


COMMENT

Letter to the editor describing prompt and sustained benefit from treatment with rituximab for MuSK positive generalized MG patients. Interesting that there was sustained post-treatment benefit lasting 1-3 years after last treatment.


COMMENT

Letter to Editor - Report of 4 patients with ocular MG, successfully treated with tacrolimus, without steroids.

CLINICAL


Abstract BACKGROUND: The use of neuromuscular blocking agents is still controversial in myasthenic patients but rocuronium could be useful after the introduction of sugammadex as a selective antagonist. The aim of the study was to evaluate the use of rocuronium-sugammadex in myasthenic patients undergoing thoracoscopic thymectomy. METHODS: After ethical approval, 10 myasthenic patients undergoing videothoracoscopic-assisted thymectomy were enrolled in the study. Neuromuscular block was achieved with 0.3 mg/kg rocuronium and additional doses were given according to train-of-four (TOF) monitoring or movement of the diaphragm. Sugammadex 2 mg/kg was given after surgery. Recovery time (time to obtain a TOF value > 0.9) was recorded for all subjects. RESULT: All patients were extubated in the operating room after administration of sugammadex. Mean rocuronium dose was 48 mg and the average operation time was 62 min. Recovery time after sugammadex administration was 111 s (min 35; max 240). CONCLUSIONS: A rapid recovery of neuromuscular function was found in myasthenic patients receiving rocuronium when sugammadex was used for reversal. This combination could be a rational alternative for myasthenic patients for whom neuromuscular blockade is mandatory during surgery.

COMMENT

Sugammadex is a modified gamma-cyclodextrin. Is a selective relaxant binding agent indicated to reverse the neuromuscular blockade induced during general anaesthesia. The mechanism of action of sugammadex differs from that of other commonly used reversal agents, such as neostigmine and edrophonium. It binds the rocuronium by encapsulating it, and preventing binding with the acetylcholine receptor. Sugammadex is approved in the EU, Australia, Iceland, New Zealand and Norway.

Abstract: We describe a patient with stable generalized myasthenia gravis who presented with new onset severe ophthalmoplegia and ptosis after initiation of voriconazole for aspergillosis. METHODS: Ligand-protein docking software was used to simulate the interaction of voriconazole with the acetylcholine receptor (AChR). We tested voriconazole binding to AChR in comparison to high affinity and neutral compounds. RESULTS: There was no clinical improvement after intravenous immunoglobulin infusion and plasmapheresis. However, the patient improved slowly after withdrawal of voriconazole. Based on our results, voriconazole binds favorably to AChR and may putatively block muscle nicotinic AChRs. Other theoretical explanations include blocking potassium channels and reducing their intracellular trafficking. CONCLUSIONS: The mechanisms involved in ocular exacerbation may be multi-factorial, reflecting the intricate dynamics of the neuromuscular junction. It is important to consider medications that harbor pyridine or pyrimidine moieties as potential causes of exacerbation in myasthenic patients, especially those who present with ocular symptoms.

COMMENT

Another drug to put on the list? Very complicated case, but it was generalized MG, with big exacerbation with pulmonary (not CNS) aspergillosis.

STATINS AND MYASTHENIA


Abstract: Statin-induced myopathy is well-known, but the effect of cholesterol-lowering agents on myasthenia gravis (MG) has not been studied in detail. We investigated statin use and its effects on MG among patients with this disease. Statin information was systematically obtained from 170 patients being treated at the Neuromuscular Disease Clinic at the University of Alabama at Birmingham. When a new myalgic syndrome or worsening of MG developed within 4 months after statin treatment, no other likely cause was found, and clinical improvement occurred either with or without discontinuation of the statin, we considered these symptoms to be statin-induced. Fifty-four patients (31%) were on statins. The statin group had proportionally more males, and older patients compared with the non-statin group. A myalgic syndrome was noted in 7 (13%) patients, but it resolved without any sequelae after withdrawal of the statin. MG worsening occurred in 6 (11%) patients without regard to type of MG or brand of statin. MG worsening occurred independently of myalgic syndrome and involved predominantly oculobulbar symptoms within 1-16 weeks of statin treatment. In 4 patients, additional treatment was needed to reverse MG worsening. Statins are safe in the majority of MG patients, but their use must be accompanied by close observation for possible MG worsening.


Abstract: A few recent individual case reports have suggested that a myasthenic syndrome may be associated with statin treatment, but this association is not well described. We report 4 patients who developed symptoms of myasthenia gravis within 2 weeks of starting treatment with a statin drug. In 1 case the drug appears to have exacerbated underlying myasthenic weakness, whereas in the other 3 cases, de novo antibody formation appears to be most likely. In each case, some degree of recovery followed discontinuation of the statin medication.

COMMENT

Consensus is growing that statins are potential trigger or aggravator of myasthenia.

REVIEW


Abstract: Background: A subset of myasthenia gravis (MG) patients is refractory to standard therapies. Identifying the characteristics of this population is essential as newer treatment strategies emerge that may be more effective in this group. Objective: The aim of our study is to describe the clinical features of refractory MG patients and compare them to those of non-refractory patients. Methods: A retrospective chart review was completed of 128 MG patients referred to a tertiary neuromuscular clinic from 2003 to 2011. Patients were classified as refractory or non-refractory based on predefined criteria, and clinical features were compared. Results: Nineteen out of 128 patients were classified as refractory (14.8 percent). Compared to the non-refractory patients, the refractory patients were more likely to be younger at onset, female, thymomatous, and MuSK-antibody positive. Conclusion: Refractory MG patients represent a small but distinct group for whom exploring newer therapeutic approaches and immunopathologic differences is warranted.
COMMENT
Retrospective review that confirms the impression that it is the young women who have refractory disease.

PREGNANCY

Abstract: A national UK workshop to discuss practical clinical management issues related to pregnancy in women with myasthenia gravis was held in May 2011. The purpose was to develop recommendations to guide general neurologists and obstetricians and facilitate best practice before, during and after pregnancy. The main conclusions were (1) planning should be instituted well in advance of any potential pregnancy to allow time for myasthenic status and drug optimisation; (2) multidisciplinary liaison through the involvement of relevant specialists should occur throughout pregnancy, during delivery and in the neonatal period; (3) provided that their myasthenia is under good control before pregnancy, the majority of women can be reassured that it will remain stable throughout pregnancy and the postpartum months; (4) spontaneous vaginal delivery should be the aim and actively encouraged; (5) those with severe myasthenic weakness need careful, multidisciplinary management with prompt access to specialist advice and facilities; (6) newborn babies born to myasthenic mothers are at risk of transient myasthenic weakness, even if the mother’s myasthenia is well-controlled, and should have rapid access to neonatal high-dependency support.

COMMENT
Nice thorough review – keep a copy for patients to take to their high risk OB/GYN.

MUSK

Abstract: BACKGROUND AND PURPOSE: The differences in the characteristics of thymus histology, coexisting autoimmune diseases and related autoantibodies between anti-muscle-specific receptor tyrosine kinase (MuSK)-antibody (Ab)-positive myasthenia gravis (MG) patients, and anti-acetylcholine receptor (AChR)-Ab-positive MG patients are not clearly defined. METHODS: The types of thymus histology, coexisting autoimmune diseases and associated Abs in 83 MuSK-Ab-positive patients nationwide were investigated and were compared with those in AChR-Ab-positive patients followed at our institute (n = 83). As for the autoantibodies associated with thymoma, titin Abs were measured. RESULTS: Thymoma was not present in any of the MuSK-Ab-positive patients but presented in 21 patients (25.3%) amongst the AChR-Ab-positive patients. Titin Abs were absent in MuSK-Ab-positive patients but positive in 25 (30.1%) of the AChR-Ab-positive patients. Concomitant autoimmune diseases were present in eight MuSK-Ab-positive patients (9.6%) amongst whom Hashimoto’s thyroiditis and rheumatoid arthritis predominated, whereas 22 AChR-Ab-positive patients (26.5%) had one or more concomitant autoimmune diseases of which Graves’ disease predominated. CONCLUSIONS: Differences in frequency of thymoma and thymic hyperplasia, coexisting autoimmune diseases and autoantibody positivity between MuSK-Ab-positive and AChR-Ab-positive MG were indicated, suggesting that, in contrast with AChR-Ab-positive MG, thymus does not seem to be involved in the pathogenic mechanisms of MuSK-Ab-positive MG.

COMMENT
No thymoma in MuSK positive MG.


We report a 60-year-old male with thymoma-associated myasthenia gravis with anti-MuSK antibodies. In October 2010, he had diplopia, ptosis, and dysphagia. He was diagnosed to have MG in February 2011. The neurological examination disclosed external ophthalmoplegia, bilateral ptosis, mild dysphagia, and fatigability. Repetitive nerve stimulation of the right facial nerve showed CMAP decrement greater than 10%. Patients showed an improvement in ptosis after administration of edrophonium. Anti-acetylcholine receptor antibody was negative, and anti-muscle specific receptor tyrosine kinase antibody was 66.8 nmol/l (cut-off value: 0.05 nmol/l). Prednisolone (50 mg every other day) were started. Contrast-enhanced chest MRI showed a mediastinal mass suggestive of thymoma. Extended thymectomy was performed in March 2011. Histological examination disclosed a type B1 thymoma. After resection of the tumor, the symptoms of MG improved with prednisolone (100 mg every other day). This is a rare case of MG with anti-MuSK antibodies and thymoma, which has been reported previously only in 2 cases.
COMMENT
Or is there?

SCIENCE


Abstract: Muscle-specific kinase (MuSK) is essential for each step in neuromuscular synapse formation. Before innervation, MuSK initiates postsynaptic differentiation, priming the muscle for synapse formation. Approaching motor axons recognize the primed, or prepatterned, region of muscle, causing motor axons to stop growing and differentiate into specialized nerve terminals. MuSK controls presynaptic differentiation by causing the clustering of Lrp4, which functions as a direct retrograde signal for presynaptic differentiation. Developing synapses are stabilized by neuronal Agrin, which is released by motor nerve terminals and binds to Lrp4, a member of the low-density lipoprotein receptor family, stimulating further association between Lrp4 and MuSK and increasing MuSK kinase activity. In addition, MuSK phosphorylation is stimulated by an inside-out ligand, docking protein-7 (Dok-7), which is recruited to tyrosine-phosphorylated MuSK and increases MuSK kinase activity. Mutations in MuSK and in genes that function in the MuSK signaling pathway, including Dok-7, cause congenital myasthenia, and autoantibodies to MuSK, Lrp4, and acetylcholine receptors are responsible for myasthenia gravis.

COMMENT
Tells us what MuSK is doing there in the first place.

MYCOPHENOLATE MOFETIL


Abstract : OBJECTIVE: To test the hypothesis that mycophenolate mofetil (MMF) with prednisone provides better control of myasthenic weakness than prednisone alone in the initial management of generalized myasthenia gravis (MG). METHODS: Eighty immunosuppression naive subjects with mild to moderate generalized, acetylcholine receptor positive MG at 13 centers were randomized to 2.5 g/day MMF plus 20 mg/day prednisone (n = 41) or placebo plus 20 mg/day prednisone (n = 39) and followed in a double-blind fashion for 12 weeks. Subjects over 18 years of age were included if judged to be candidates for immunosuppression; excluded were those with thymoma or severe oropharyngeal or respiratory muscle weakness. The primary measure of efficacy was change in the quantitative MG (QMG) score from baseline to week 12. Study completers could take open-label MMF for an additional 24 weeks, while prednisone was reduced to the minimally effective dosage. RESULTS: The mean change in QMG score was similar in the treated (-4.4 +/- 5.1) and placebo (-3.6 +/- 5.0) groups (p = 0.71). The dosage of prednisone was reduced by a similar amount in both groups during the open-label phase. Subjects tolerated the study drug well, without unexpected adverse events. CONCLUSIONS: This study demonstrated no benefit of mycophenolate mofetil (MMF) with 20 mg/day prednisone compared to 20 mg/day of prednisone alone after 12 weeks. This may be due to greater than predicted benefit from the prednisone dosage used, the short duration of the study, or the absence of any benefit of MMF in this population of patients with myasthenia gravis.


Abstract : BACKGROUND: This prospective, randomized, double-blind, placebo-controlled, phase III trial assessed the efficacy, safety, and tolerability of mycophenolate mofetil (MMF) as a steroid-sparing agent in patients with myasthenia gravis (MG). METHODS: Patients with acetylcholine receptor antibody-positive class II-IVA MG (MG Foundation of America [MGFA] criteria) taking corticosteroids for at least 4 weeks were randomized to MMF (2 g/day) or placebo for 36 weeks. The primary endpoint was a composite measure defined as achievement of minimal manifestations or pharmacologic remission (MGFA post-intervention status), with reduction of corticosteroid dose on a set schedule. Secondary endpoints included disease severity, quality-of-life scores, and safety. RESULTS: A total of 44% of MMF-treated (n = 88) and 39% of placebo-receiving (n = 88) patients achieved the primary endpoint (p = 0.541). Improvements in mean quantitative MG, MG activities of daily living, and 36-item Short-Form
health survey scores were similar in both groups. Numbers of adverse events were similar in both groups. The most commonly reported adverse events in the MMF-treated group were headache (12.5%) and worsening of MG (11.4%), and in the placebo group, worsening of MG (20.5%) and diarrhea (10.2%). CONCLUSIONS: Initiation of mycophenolate mofetil (MMF) treatment was not superior to placebo in maintaining myasthenia gravis (MG) control during a 36-week schedule of prednisone tapering. There were no significant differences in the primary or secondary endpoints between the study groups. MMF was well tolerated and adverse events were consistent with previous studies. Experience from this large, international, multicenter, phase III study employing full MG Foundation of America guidelines will aid the design of future MG studies.

COMMENT

Two studies showed no benefit of MM in improving MG control, or in reducing the dose of prednisone needed to control the disease.


Abstract: Two recent randomized, controlled trials failed to demonstrate a benefit of mycophenolate mofetil (MMF) over prednisone in the treatment of myasthenia gravis (MG). We reviewed our experience with MMF in MG to determine whether these trials may have been unsuccessful because of their short duration and the unpredicted benefit of prednisone. We reviewed outcomes and prednisone dosage for all our acetylcholine-receptor (AChR)-antibody positive MG patients treated with MMF alone or with prednisone for at least 3 months. The percentage of patients with a desirable outcome (MG-specific Manual Muscle Test score <4 or Myasthenia Gravis Foundation of America post-invention status of minimal manifestations or better) began to increase after 6 months; 80% of those followed for >24 months had a desirable outcome. Prednisone dose decreased after 12 months; after 25 months, 54.5% of patients took no prednisone and 75% took <7.5 mg/day. This retrospective analysis provides class IV evidence that MMF begins to improve AChR-positive MG after 6 months, both with prednisone and as monotherapy.

COMMENT

Undeterred, a retrospective study performed because of concerns the international study treatment was too short (although it was 9 months). Wouldn’t it have been good to compare the MM +/- prednisone patients with prednisone alone, or perhaps azathioprine +/- prednisone? More controlled studies in the offing perhaps?

CME ANSWERS:

1. Probably not
2. Anti-LRP4
3. Lower