Review Article

DIFFERENTIAL DIAGNOSIS OF MYASTHENIA GRAVIS: A REVIEW

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Abstract

Background: Myasthenia gravis (MG) is an autoimmune neuromuscular disorder that is characterised by fatigable weakness of voluntary muscles. It is an auto immune disorder hitherto thought to be rare in our environment.

Aim: This paper aims to discuss the differential diagnosis of MG and increase the index of suspicion for these cases aiding early diagnosis.

Materials and Methods: Literature search was done using PubMed, ScienceDirect and Google scholar searches.

Conclusion: Myasthenia Gravis as an autoimmune and acquired condition manifests with various patterns of fatigable skeletal muscle weakness ranging from ocular to generalised distribution. A variety of clinical conditions that affect skeletal muscles could present as diagnostic challenges in Myasthenia Gravis. It is therefore necessary that the distinguishing clinical features and differentiating investigations in these other conditions should be borne in mind when assessing patients with muscular weakness

Keywords: Differential diagnosis, Myasthenia gravis.

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder that is characterised by fatigable weakness of voluntary muscles. The acetylcholine (ACh) receptors of skeletal muscles are the target of the autoimmune attack in most of the cases while in some, the non–ACH receptor aspects of the muscle endplate like the muscle specific receptor tyrosine kinase are also targeted.[1]

MG is the commonest disorder affecting the neuromuscular junction (NMJ).[2] It has a prevalence of 100 per million and an incidence of 2-4 cases per million.[3] Below the age of 40 years MG is 3 times more common in females than males and after the age of 50 years the incidence is higher in males.[4]

Although there is yet to be a definitive cure for MG, it is now considered a treatable condition leading to a restoration in function. Therefore, other clinical conditions that could mimic MG should be distinguished by way of their clinical features and investigations where necessary.

In this discussion a handful of the clinical conditions that serve as differential diagnoses to MG would be considered. These include congenital myasthenia syndromes, drug induced MG, Lambert-Eaton myasthenic syndrome (LEMS), hyperthyroidism, progressive external ophthalmoplegia, botulism and psychogenic MG.

The Neuromuscular Junction

The neuromuscular junction is made up of three components namely: the presynaptic nerve ending, the synaptic cleft and the folded post synaptic muscle fibre membrane. ACh is released from presynaptic vesicles in response to an action potential. ACh then interacts with the nicotinic acetylcholine receptors (AChR) in the post-synaptic receptors resulting in the production of end-plate potential that cause muscle fibre excitation. The amount of ACh released is

usually more than the amount required in triggering an action potential in the muscle. This is known as the safety margin.[2]

Pathophysiology of MG

Anti-acetylcholine receptor antibodies are found in about 85% of patients with generalised MG and in about 50% of ocular MG.[5, 6] These IgG antibodies lead to loss of function by activating the compliment system leading to the lysis of the post-synaptic muscle endplate and subsequent simplification and distortion of the folded pattern.[7] Secondly, cross linkage of AChR by divalent antibodies leads to increased turnover and loss of AchR by increased internalization and degradation.[8] Also the antibodies can directly block the ACh binding sites.[9]

In 15% of patients with generalized MG anti-Ach receptor antibodies are not found with the common assay methods.[1] About 40% of these anti-Ach receptor negative patients have antibodies against muscle specific tyrosine kinase (anti-MuSK).[10] Additionally, low affinity IgG antibodies have been demonstrated in 66% of MG patients that were classified as anti-AchR and anti-MuSK negative by conventional assays.[11] Although the exact mechanism is not well understood, the thymus has been implicated in the initiation of the autoimmune process occurring in MG with evidence of abnormal thymus in most patients (thymic hyperplasia in 60% and thymoma in 10%).[5] It has been suggested that the autoimmunity in thymomatous MG may be due to impairment in the negative selection and regulation of autoreactive T cells because of a deficiency in the expression of autoimmune regulator gene (AIRE).[12]

Clinical features of MG

Acquired MG is clinically characterised by weakness and fatigability of skeletal muscles. The weakness is worse with exercise and relieved by rest.[2] The weakness is variable and seems to worsen in the evening.[3] In about 15% of patients who are referred to as having **ocular MG** the weakness is limited to the eyes although it may later become generalised as in majority of patients where proximal weakness is more prominent than distal limb weakness.[5] The probability of the weakness remaining ocular is high if there is no extension in the first 3-4 years.[2]

Ptosis, diplopia or blurred vision are the commonest presenting features. The ptosis is initially unilateral but later becomes bilateral.[2] It could also shift from one eye to the other. Affectation of the bulbar muscles leads to dysarthria, dysphagia and chewing difficulties. Rarely severe MG with respiratory muscle and bulbar weakness can result in myasthenia crisis that is life threatening requiring intubation.[1]

Less than 15% of infants born to MG mothers could present with muscle weakness due to the passive transfer of maternal autoantibodies giving rise to **transient neonatal myasthenia**.[1] Rarely the weakness could occur in-utero giving rise to arthrogryposis multiplex congenital.[13]

Diagnosis of MG

Cogan's lid twitch response

This was described by David Cogan. In this response the lid shows a momentary upward twitch when the patient is asked to look downwards for about 15 -20s, then to look right up back to the initial gaze.[14]

Ice pack test

Application of ice packs over affected (for about 2 minutes) muscles in MG leads to improved neuromuscular responses. The ice pack could be used as a non-invasive alternative to the Tensilon test (see below).[2]

Sleep test

This involves asking the patient to rest in a quiet and darkened room with eyes closed as if to sleep. The palpebral apertures are measured before and after the procedure. In MG the improvement of the ptosis has been postulated to be due to an increase in the amount of Ach released upon awakening.[15] This test may be impracticable in contemporary clinical situation.

Edrophonium (Tensilon)Test

This involves the use of edrophonium hydrochloride which is a short acting anticholinesterase pharmacological agent. A maximum of 10mg is given starting with an initial dose 2mg.[2] The patient is observed is for improvement in muscle function. The common side effects that could emerge include increased salivation, mild nausea and fasciculations.[16] Osserman (1952) reappraised the Tensilon test asserting that the test was positive in 90-95 % of patients with MG [17]. Although clinicians may doubt the sensitivity and specificity of this test.[5]. Nicholson et al (1983) found sensitivities of 0.92 and 0.88 for ocular and generalised MG respectively and a specificity of 0.97 for both forms of the disease.[18]

Serological tests

Serological diagnostic test include anti-AChR antibodies which are detected in 75% to 85% of patients with generalized myasthenia and in about 50% of patients with pure ocular MG.[19] Anti-Musk antibodies are found in 40% of MG patients who are negative for anti- AChR antibodies. Anti-striated

muscle antibodies are also found in about a quarter of MG patients.[20]

Electromyography (EMG)

Repetitive nerve stimulation in MG at a rate of 3 Hertz reveals a decrement in compound motor action potential CMAP.[21] The single fibre electromyogram (SFEMG) shows an increase jitter but this is not specific to MG as this is shared with other disorders of the neuromuscular junction.

Treatment of MG

MG could be treated using anticholinesterase medications, immunosuppression with corticosteroids and azathioprine, plasma exchange and intravenous immunoglobulin for those in myasthenic crisis and thymectomy for those with demonstrable thymus gland or thymoma on CT scanning.[22]

Clinical conditions considered as differential diagnoses to MG

Lambert –Eaton Myasthenic syndrome (LEMS)

This is a rare autoimmune disorder in which IgG antibodies are directed against the presynaptic voltage-gated calcium channels resulting in muscle weakness. The architecture of these channels are disrupted leading to a decrease in the number of active zones for release of ACh thereby reducing the amount of acetylcholine required for transmission of action potential in the synaptic cleft.[23]

LEMS could also occur as a paraneoplastic syndrome with the finding that about 50-60% of patients with LEMS have a tumour.[24] The tumour most commonly associated with LEMS is the small cell lung Carcinoma (SCLC).

Clinical features of LEMS

The clinical features of LEMS consist of a triad of proximal muscle weakness, autonomic symptoms and reduced or absent tendon reflexes.[25]

In LEMS, weakness often spreads proximally to distally, affecting the feet and hands, and caudally to cranially before affecting the oculo-bulbar region.[26] In about 80% of cases proximal muscle weakness of the legs is usually the first symptoms manifesting with difficulty getting out of a chair. Arm weakness could also develop quickly.[26] Only isolated cases of purely ocular symptoms have been reported in LEMS.[27] Majority of patients that have ocular or respiratory involvement early in the course of disease would have generalised weakness.[28] Autonomic dysfunction in LEMS is found in 80-96% of patients.[29, 30] The commonest symptoms is dryness of the mouth followed by erectile dysfunction and constipation, while sudomotor dysfunction, orthostatic hypotension, micturition problems and dry eyes are less common.[26] There is decreased or absent tendon reflexes in patients with LEMS. However, in about 40% of these patients there is post exercise facilitation with a brief return of the reflexes to normal range after muscle contraction. This could obliterate the decreased tendon reflexes. Hence in a suspected diagnosis of LEMS, tendon reflexes should be tested after the muscles have been rested.

In differentiating between LEMS and MG, a comparative study of patients with LEMS and MG revealed that muscle weakness in MG progressed in the cranio-caudal direction while in LEMS the converse is true.[31] In the same study it was also shown that limb weakness confined in the arms is only found in MG and not in LEMS. Ocular weakness as an initial presentation is rare in LEMS.[30, 31]

Repetitive Nerve Stimulation

Patients with LEMS have a low first CMAP which becomes lower at low stimulation frequencies (2-5 Hz).[32] However on high frequency stimulation (50Hz) or post-exercise stimulation (preferred) an abnormal increase is seen in LEMS.[33] At a 60 % cut off for CMAP increment the sensitivity of post-exercise or high frequency stimulation is 97% while the specificity is 99%.[33] Although Single-fibre electromyography (SFEMG) may be more slightly sensitive than RNS, it cannot discriminate LEMS from MG because jitter occurs in both disorders.

Pathophysiology of LEMS

Antibodies to P/Q type VGCC are detected in 85-90% of LEMS patients. [26] The autoantibodies target the VGCC on the presynaptic nerve terminal of the NMJ and on the surface of the SCLCs. Transient neonatal weakness suggesting a passive transfer from an affected mother to the baby has been reported.[34] It has also been shown that immunisation of rats withy calcium channel peptides can cause an autoimmune-mediated model of LEMS.[35] Patients with LEMS should undergo screening for SCLC. This could be done by Thoracic Computerised Tomography scan and 18 fluorodeoxyglucose PET or integration of the two FDG-PET/CT.[36]

Botulism

Botulism is a rare and potentially fatal condition affecting the presynaptic neuromuscular junction. It is caused by the potent toxins of the gram-positive,

spore forming anaerobic bacteria, clostridium botulinum.

Pathophysiology

The botulinum toxin is taken up by endocytosis into the presynaptic nerve ending. The light chain is cleaved off the heavy chain of the toxin by the reduction of a single disulphide bond. The light chain then acts as zinc –dependent protease that attacks the SNARE (soluble-N-ethyl maleimide sensitive factor attachment protein receptor) protein complex. Normally the Acetylcholine containing vesicles are enabled by the SNARE proteins complex to fuse with the neural cell wall and be released into the synaptic cleft.[37] The prevention of Ach release inhibits muscle contraction leading to flaccid paralysis. It usually occurs in the context of an outbreak [38], but when it occurs as a sporadic case it could present a diagnostic challenge with other NMJ conditions like MG.

Three types of botulism has been described viz; foodborne botulism (from ingesting contaminated food), wound botulism (when wounds are infected with toxin producing bacteria) and infant botulism (occurring when c. botulinum spores germinate and produce toxin in the gastrointestinal tract of infants).[38]

Clinical features

In infants the cholinergic blockade cause symptoms ranging from mild hypotonia to severe, flaccid paralysis and absence of cranial reflexes.[39] In the food borne type, gastrointestinal symptoms like abdominal pain, constipation and diarrhoea precede the onset of neurological features.

Like MG the pattern of muscular weakness is descending in nature. However, botulism is a descending neuroparalytic process with flaccid paralysis while MG is fatigable weakness. Patients present with ocular features including, ptosis, ophthalmoplegia (with blurred or double vision), and descending (proximal) motor weakness. The disease may progress to quadriplegia and respiratory failure. There is an absence of sensory nerve damage.

The paralysis is usually symmetrical, further neurological examination may reveal strabismus and nystagmus. It is also common to notice pupillary involvement in botulism in which case the pupils are noticed to be fixed and dilated. They could also present with inability to support the neck, dysphonia, dysphagia and dizziness. There could also be associated dry mouth and sore throat. Also the deep tendon reflexes ere commonly symmetrically depressed.[38]

The pupillary involvement with decreased tendon reflexes helps to distinguish MG from Botulism. The Tensilon test is also negative in Botulism and abnormal in majority of patients with MG.

The laboratory investigations that could help in the diagnosis of botulism include detection of botulinum toxin in serum stool, or patients' food or the isolation of clostridium botulinum from stool, wound or food.[38]

Electromyography (EMG)

The demonstration of an incremental response of CMAP to high rate repetitive nerve stimulation or post exercise facilitation (preferred) of CMAP on single supramaximal stimulation is diagnostic of a presynaptic NMJ disorder. In presynaptic NMJ disorder the two consistent findings are the small amplitude of CMAP at rest and the post exercise facilitation.[40] Witoonpanich et al, 2009 also demonstrated that undertaking the pre and post exercise single supramaximal stimulations is sensitive and specific in the diagnosis of botulism. In their study at a 25% cut off single supramaximal stimulations revealed a sensitivity of 92.5% and a specificity of 100% in association with Botulism. In MG there is no post exercise facilitation of SFEMG. Pyridostigmine, 3,4 diaminopyridine, prednisolone and azathioprine are beneficial in treating LEMS but in contrast to MG there is less benefit derived. Intravenous immunoglobulins and plasma exchange.

Congenital Myasthenia Gravis

The congenital myasthenic syndromes (CMS) comprises of a rare heterogenous group of inherited disorders affecting the neuromuscular junction.[41] The defects compromise the safety margin of neuromuscular transmission by interfering with presynaptic, synaptic or post synaptic function.[42] There has been a gradual increase in the number of these syndromes over the years.[43] The defect is present before birth. Most patients with these disorders present during infancy, however some could present at childhood or adulthood.[41]

In general patients present at infancy with ophthalmoplegia, ptosis, hypotonia, fatigable weakness, feeding difficulties or respiratory failure.[41] The prenatal features of CMS include decreased foetal movements, arthrogryposis and polyhydramnios.

Majority of the syndromes are inherited in an autosomal recessive pattern. An exception is the slow channel syndrome with a gain-of-function mutation that is inherited in an autosomal dominant pattern. Also an x-linked inheritance pattern has been

suggested in view of the disproportionate number of males with infantile onset.[44] The clinical syndromes could either be static or slowly progressive. However, in CMS associated with episodic apnoea (CMS-EA) episodic weakness is usually induced by fever. There could also be an associated respiratory failure. Delayed pupillary light reflex is often seen in endplate ACHE deficiency while in slow channel CMS and sometimes in plectin deficiency (with skin abnormalities) myopathy could be significant.[45] Significant proportions of the children with CMS have respiratory difficulties at birth and are at risk of ventilatory failure with intercurrent respiratory illness.[46]

Neurophysiological tests are challenging in children and can give rise to false positives and negatives. The painful nature of the tests , small size of the child and the need for tests in the weak children who are prone to respiratory difficulties are practical difficulties encountered with these tests.[41] Routine Nerve conduction studies are often normal in most CMS, but CMS LEMS may show low amplitude CMAPS. Endplate AChE deficiency and slow channel CMS shows repetitive CMAPs on induction with a single supramaximal stimulus. Most forms of CMS would also show a decrement in CMAP amplitude at low rates of RNS. This trend continues at high rates of stimulation except for the CMS LEMS which shows an increment in CMAP amplitude. In most CMS electromyography is generally normal with occasional variations in motor unit action potential amplitude and waveform.[41] The SFEMG is not specific to differentiate between these syndromes and MG. Generally, at high rates of nerve stimulation, in postsynaptic transmission failure there is an increased jitter while in presynaptic transmission failure there is a decreased jitter.

The DNA screening of patients with suspected CMS is the distinguishing investigation that confirms CMS.[41] The pattern of inheritance, muscular involvement and longer term response to anticholinesterases are useful guides.[47]

Most CMS show benefit with anticholinesterases e.g pyridostigmine although endplate AChE deficiency and slow channel CMS deteriorate when anticholinesterases are given. Patients with CMS LEMS responds to 3,4-Diaminopyridine[48] while quinidine and acetazolamide are used for slow channel syndrome and endplate AChE deficiency respectively.[41, 49]

Drug induced MG

Many medications have been reported to aggravate MG while a few has been associated with the development of autoimmune MG.

Among these medications, long term use of D-penicillamine has been the most consistently implicated therapy that causes autoimmune MG.[50] D-penicillamine is used in the treatment of diseases like rheumatoid arthritis and as a chelating agent in Wilson's disease and other metallic toxic states. The pathogenesis of drug induced MG is not well elucidated however the increasing long term use of D-penicillamine seem to predispose to immune mediated disorders.[51] D-penicillamine has been shown to depress T-cell division leading to the loss of suppressor T cell control over B cells, with a resultant production of antibodies.[52] Most of the patients present with ocular symptoms (ptosis and diplopia) usually within six to seven months after commencing penicillamine.[53] Serum assay usually reveals a transient increase in antibodies to acetylcholine receptors and electromyographic findings are similar to the profile in MG with decremental response on repetitive nerve stimulation.[54] The patients often recover within weeks or months after discontinuation of the medication [53].

Other medications that has been shown to aggravate the symptoms of MG, include aminoglycoside antibiotics, statins, prednisolone, phenytoin, propranolol, oral contraceptives etc.[55-57]

Hence in order to differentiate drug induced MG from spontaneous MG an adequate clinical history of medication use and alleviation of symptoms soon after withdrawal of the offending medication should be obtained as drug induced MG usually mimics ocular MG.

Chronic progressive external ophthalmoplegia and intracranial mass lesions

Chronic progressive external ophthalmoplegia (CPEO) is a term used to describe a heterogenous group of disorders characterized by chronic, progressive, bilateral, and usually symmetric ptosis and ocular motility deficit.[58]

The manifestations of CPEO range from involvement of ocular muscles including the eyelids to systemic and encephalopathic features.[59] The aetiology of most CPEO syndromes is increasingly being linked to mitochondrial DNA mutations.[60]

The CPEO syndromes include the isolated CPEO, Kearns-sayre syndrome, Oculopharyngeal muscular dystrophy and myotonic dystrophy.

Kearns-sayre syndrome is a known mitochondrial which usually presents before the age of twenty with a progressively worsening symmetrical ophthalmoplegia.[61] The symmetric and bilateral nature of the ophthalmoplegia is usually gives rise to absent diplopia. Ptosis occurs early and is usually bilateral. Occasionally there is associated weakness of the orbicularis oculi with pupillary sparing. Other systemic findings include cardiac abnormalities, deafness and widespread muscular dystrophy.

Oculopharyngeal muscular dystrophy occurs after 40 years of age. Most are inherited in an autosomal dominant manner.[58] Patients manifest swallowing difficulties as evidence of pharyngeal weakness. They also present with external ophthalmoplegia, ptosis and weakness of orbicularis muscle.[62]

The ocular findings in **Myotonic dystrophy** include progressive external ophthalmoplegia, orbicularis weakness, lid lag, sluggish pupils, variable myotonia, cataracts and pigmentary changes in the macula.[63] Frontal baldness, cardiac abnormalities and testicular atrophy are other typical features found in myotonic dystrophy.[63]

The family history, chronicity, absence of diplopia, symmetry and bilaterality of the ophthalmoplegia are of great aide in distinguishing CPEO from MG. The Tensilon test is negative in CPEO. Electromyography would show myotonic changes in myotonic dystrophy. Raised Lactate levels in serum and cerebrospinal fluid are suggestive of mitochondrial disease. However, muscle biopsy (presence of ragged red fibres) and serum mitochondrial DNA analysis would be more definitive in confirming mitochondrial disease. Additionally, it been demonstrated on magnetic resonance imaging that CPEO is associated with minimal extraocular muscle volume reduction despite clinically severe weakness.[59]

There is no effective treatment for CPEO although medical treatments like coenzyme Q10 with the aim of increasing mitochondrial activity.[58]

Hyperthyroidism

Neuromuscular effects of hyperthyroidism include thyrotoxic myopathies, exophthalmic ophthalmoplegia (grave's ophthalmopathy), periodic paralysis among other neurologic sequalae.[64]

Muscle weakness is common in patients with thyrotoxicosis. Patients with **thyrotoxic myopathy** have muscle weakness, proximal muscle wasting, fatigue and heat intolerance.[65] the muscles involved are those of the pelvic girdle and shoulder, occasionally there is involvement of the bulbar and oesopharyngeal muscles with resultant swallowing and respiratory.[66] The weakness is usually disproportionate to the degree of objective muscle wasting with the deep tendon reflexes being normal or hyperactive.[65] Electromyographic and nerve conduction findings are often normal. Apart from the dysfunctional thyroid function profile serum creatinine and myoglobulin levels are only raised if there is an associated rhabdomyolysis or inflammatory myopathy.[67] Most patients with thyrotoxicosis recover within weeks after euthyroid state is achieved.

Thyrotoxic periodic paralysis (TPP) is a rare syndrome that is characterised by a transient and recurrent episodes of muscle weakness, ranging from mild weakness to frank paralysis.[68] The attacks could last from a few hours to three days and is usually precipitated by alcohol, carbohydrate meals and exercise. TPP occurs when the patient is biochemically hyperthyroid and is associated with hypokalaemia.[69]

Graves' disease, as a major cause of hyperthyroidism, has been associated with MG.[70] The link between these two autoimmune diseases is poorly understood but an immunological cross reactivity between neuromuscular junction and thyroid components has been found in co-occuring Graves' disease and MG.[71] Occasionally, treatment of Graves' disease has led to the exacerbation of MG in some patients.[72] It is therefore necessary to exclude MG in hyperthyroid patients as treatment with certain agents could lead to respiratory failure secondary to MG.

In Graves' ophthalmopathy there is significant proptosis, lid retraction or lid lag. In MG and Graves' ophthalmopathy there is diplopia however in MG extraocular muscles become weaker with repetitive activity. In MG, the Tensilon test is positive. Radiological imaging in Graves' Disease reveals an increased orbital fat and swollen eye muscles.[73]

Psychogenic Myasthenia gravis

Conversion disorders could present with symptoms mimicking MG. Case reports of functional psychogenic MG and unilateral ptosis exist.[74-76] Psychogenic MG should particularly be considered in the differential diagnosis of relapsed MG. Dysregulation of the inhibitory interneuronal

mechanisms, probably involving cholinergic modulation has been put forward as a potential pathophysiological mechanism leading to conversion disorders.[77] The background psychological distress in the history with lack of significant findings on examination and investigation to support the presence of MG, could be a reason to have a high index of suspicion for this diagnosis.

Other Differential diagnosis

Acute inflammatory demyelinating polyneuropathy variant syndromes in which in addition to the acute onset there is areflexia and absence of fluctuation in weakness. Serological assay for antiganglioside antibodies is positive. Motor neuron disease presents with corticobulbar features, atrophy, muscle fasciculations and upper motor neuron signs. Cranial nerve dysfunction associated with central nervous system

Conclusion

Myasthenia Gravis (MG) as an autoimmune and acquired condition manifests with various patterns of fatigable skeletal muscle weakness ranging from ocular to generalised distribution. A variety of clinical conditions that affect skeletal muscles could present as diagnostic challenges in MG. Additionally, mimicking of the symptoms of MG could occur as a spectrum of conversion disorders (psychogenic MG). It is therefore necessary that the distinguishing clinical features and differentiating investigation in these other conditions should be borne in mind when assessing patients with muscular weakness. Advances in electrophysiological, immunological and radiological parameters have contributed significantly in helping to solve these diagnostic difficulties. This invariably, this would imply a better treatment outcome and restoration of function for those whom otherwise would have been misdiagnosed.

REFERENCES

1. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: Emerging clinical and biological heterogeneity. Lancet Neurol. 2009;8(5):475-490.
2. Thomann KH, Pandya, S. Myasthenia gravis: Pathophysiology, diagnosis, differential diagnosis and management. Clin Eye Vis Care. 1995;7(1):3-13.
3. Hirsch NP. Myasthenia gravis. Lecture notes Msc Clinical Neurology, Institute of Neurology, UCL. London. 2011
4. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve. 2008;37(2):141-149.
5. Hirsch NP. Neuromuscular junction in health and disease. Br J Anaesth. 2007;99(1):132-138.
6. Meriggioli MN. Myasthenia gravis with anti-acetylcholine receptor antibodies. Front Neurol Neurosci. 2009;26:94-108.
7. Sahashi K, Engel AG, Linstrom JM, Lambert EH, Lennon VA. Ultrastructural localization of immune complexes (igG and C3) at the end-plate in experimental autoimmune myasthenia gravis. J Neuropathol Exp Neurol. 1978;37(2):212-223.
8. Heinemann S, Bevan S, Kullberg R, Lindstrom J, Rice J. Modulation of acetylcholine receptor by antibody against the receptor. Proc Natl Acad Sci U S A. 1977;74(7):3090-3094.
9. Burges J, Wray DW, Pizzighella S, Hall Z, Vincent A. A myasthenia gravis plasma immunoglobulin reduces miniature endplate potentials at human endplates in vitro. Muscle Nerve. 1990;13(5):407-413.
10. McConville J, Farrugia ME, Beeson D, Kishore U, Metcalfe R, Newsom-Davis J, et al. Detection and characterization of musk antibodies in seronegative myasthenia gravis. Ann Neurol. 2004;55(4):580-584.
11. Leite MI, Jacob S, Viegas S, Cossins J, Clover L, Morgan BP, et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. Brain. 2008;131(Pt 7):1940-1952.
12. Strobel P, Rosenwald A, Beyersdorf N, Kerkau T, Elert O, Murumagi A, et al. Selective loss of regulatory t cells in thymomas. Ann Neurol. 2004;56(6):901-904.
13. Barnes PR, Kanabar DJ, Brueton L, Newsom-Davis J, Huson SM, Mann NP, et al. Recurrent congenital arthrogryposis leading to a diagnosis of myasthenia gravis in an initially asymptomatic mother. Neuromuscul Disord. 1995;5(1):59-65.
14. Singman EL, Matta NS, Silbert DI. Use of the cogan lid twitch to identify myasthenia gravis. J Neuroophthal. 2011;31(3):239-240.
15. Odel JG, Winterkorn JM, Behrens MM. The sleep test for myasthenia gravis. A safe alternative to tensilon. J Clin Neuroophthalmol. 1991;11(4):288-292.
16. Seybold ME. The office tensilon test for ocular myasthenia gravis. Arch Neurol. 1986;43(8):842-843.
17. Osserman KE, Kaplan LI. Rapid diagnostic test for myasthenia gravis: increased muscle strength,

without fasciculations, after intravenous administration of edrophonium (tensilon) chloride. J Am Med Assoc. 1952;150(4):265-268.
18. Nicholson GA, McLeod JG, Griffiths LR. Comparison of diagnostic tests in myasthenia gravis. Clin Exp Neurol. 1983;19:45-49.
19. Lindstrom J. Immunological studies of acetylcholine receptors. J Supramol Struct. 1976;4(3):389-403.
20. Lunn M, Hanna M, Howard R, Parton M, Reilly M. Nerve and muscle diseases. In: Clarke C, Howard R, Rossor M, Shorvon S, eds. Neurology: A Queen Square Textbook. West Sussex, UK: John Wiley & Sons; 2009:337-410.
21. Muradyan N, Klissurski M, Alexandrov AS, Ishpekova B. Repetitive nerve stimulation of accessory nerve in diagnostic assessment of patients with myasthenia gravis. C. R. Acad. Bulg. Sci. 2012;65(3):411-418.
22. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. Lancet. 2001;357(9274):2122-2128.
23. Fukunaga H, Engel, A. G., Osame, M., and Lambert, E. H. Paucity and disorganization of presynaptic membrane active zones in the Lambert-Eaton myasthenic syndrome. Muscle Nerve. 1982;5(9):686-697.
24. Titulaer MJ, Maddison P, Sont JK, Wirtz PW, Hilton-Jones D, Klooster R, et al. Clinical Dutch-English Lambert-Eaton Myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. J Clin Oncol. 2011;29(7):902-908.
25. O'Neill JH, Murray NM, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. Brain. 1988;111(Pt 3):577-596.
26. Titulaer MJ, lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011;10(12):1098-1107.
27. Rudnicki SA. Lambert-Eaton myasthenic syndrome with pure ocular weakness. Neurology. 2007;68(21):1863-1864.
28. Titulaer MJ, Wirtz PW, Wintzen AR, Verschuuren JJ. Re: Lambert-Eaton myasthenic syndrome with pure ocular weakness. Neurology. 2008;70(1):86; author reply 86-87.
29. Lorenzoni PJ, Scola RH, Kay CS, Parolin SF, Werneck LC. Non-paraneoplastic Lambert-Eaton myasthenic syndrome: a brief review of 10 cases. Arq Neuropsiquiatr. 2010;68(6):849-854.
30. Titulaer MJ, Wirtz PW, Kuks JB, al. e. The Lambert-Eaton myasthenic syndrome 1988-2008: a clinical picture in 97 patients. J Neuroimmunol. 2008;201-202:153-158.
31. Wirtz PW, Sotodeh M, Nijnuis M, Van Doorn PA, Van Engelen BG, Hintzen RQ, et al. Difference in distribution of muscle weakness between myasthenia gravis and the Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry. 2002;73(6):766-768.
32. AAEM Quality Assurance Committee. Practice parameter for repetitive nerve stimulation and single fiber emg evaluation of adults with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome: summary statement. Muscle Nerve. 2001;24(9):1236-1238.
33. Oh SJ, Kurokawa K, Claussen GC, Ryan HF Jr. Electrophysiological diagnostic criteria of Lambert-Eaton myasthenic syndrome. Muscle Nerve. 2005;32(4):515-520.
34. Lecky BR. Transient neonatal Lambert-Eaton syndrome. J Neurol Neurosurg Psychiatry. 2006;77(9):1094.
35. Komai K, Iwasa K, Takamori M. Calcium channel peptide can cause an autoimmune-mediated model of Lambert-Eaton myasthenic syndrome in rats. J Neurol Sci. 1999;166(2):126-130.
36. Titulaer MJ, Wirtz PW, Willems LN, van Kralingen KW, Smitt PA, Verschuuren JJ. Screening for small-cell lung cancer: a follow-up study of patients with Lambert-Eaton myasthenic syndrome. J Clin Oncol. 2008;26(26):4276-4281.
37. Horowitz BZ. Botulinum toxin. Crit Care Clin. 2005;21(4):825-839.
38. Werner SB, Chin J. Botulism-diagnosis, management and public health considerations. Calif. Med. 1973;118(5):84-88.
39. Fox CK, Keet CA, Strober JB. Recent advances in infant botulism. Pediatr Neurol. 2005;32(3):149-154.
40. Witoonpanich R, Vichayanrat E, Tantisiriwit K, Rattanasiri S, Ingsathit A. Electrodiagnosis of botulism and clinico-electrophysiological correlation. Clin Neurophysiol. 2009; 120(6):1135-1138.
41. Nogajski JH, Kiernan MC, Ouvrier RA, Andrews PI. Congenital myasthenic syndromes. J Clin Neurosci. 2009;16(1):1-11.

42. Engel AG. Current status of the congenital myasthenic syndromes. Neuromuscul Disord. 2012;22(2):99-111.
43. Ohno K, Engel AG. Congenital myasthenic syndromes: gene mutations. Neuromuscul Disord. 2004; 14(1):117-122.
44. Bundey S. A genetic study of infantile and juvenile myasthenia gravis. J Neurol Neurosurg Psychiatry. 1972;35(1):41-51.
45. Banwell BL, Russel J, Fukudome T, Shen XM, Stilling G, Engel AG. Myopathy, myasthenic syndrome, and epidermolysis bullosa simplex due to plectin deficiency. J Neuropathol Exp Neurol. 1999;58(8):832-846.
46. Robb SA, Muntoni F, Simonds AK. Respiratory management of congenital myasthenic syndromes in childhood: Workshop 8th December 2009, UCL Institute of Neurology, London, UK. Neuromuscul Disord. 2010;20(12):833-838.
47. Palace J, Beeson D. The congenital myasthenic syndromes. J Neuroimmunol 2008;201–202:2–5.
48. Palace J, Wiles CM, Newsom-Davis J. 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. J Neurol Neurosurg Psychiatry. 1991;54(12):1069-1072.
49. Harper CM, Engel AG. Quinidine sulfate therapy for the slow-channel congenital myasthenic syndrome. Ann Neurol. 1998;43(4):480-484.
50. Barrons RW. Drug-induced neuromuscular blockade and myasthenia gravis. Pharmacotherapy. 1997;17(6):1220-1232.
51. Dawkins RL, Christiansen FT, Garlepp MJ. Autoantibodies and HLA antigens in ocular, generalized and penicillamine-induced myasthenia gravis. Ann N Y Acad Sci. 1981;377:372-843.
52. Merryman P, Jaffe IA. Effect of penicillamine on the proliferative response of human lymphocytes. Proc. Soc. Exp. Biol. Med. 1978;157(1):155-158.
53. Katz LJ, Lesser RL, Merikangas JR, Silverman JP. Ocular myasthenia gravis after D-penicillamine administration. Br J Ophthalmol. 1989;73(12):1015-1018.
54. Argov Z, Nicholson L, Fawcett PR, Mastaglia FL, Hall M. Neuromuscular transmission and acetylcholine receptor antibodies in rheumatoid arthritis patients on D-penicillamine. Lancet. 1980;1(8161):203-212.
55. Adams SL, Mathews J, Grammer LC. Drugs that may exacerbate myasthenia gravis. Ann Emerg Med. 1984;13(7):532-538.
56. Argov Z, Mastaglia FL. Drug therapy: Disorders of neuromuscular transmission caused by drugs. N Engl J Med. 1979;301(8):409-413.
57. Keogh MJ, Findlay JM, Leach S, Bowen J. Statin-associated weakness in myasthenia gravis: a case report. J Med Case Rep. 2010;4:61.
58. Lee AG, Brazis PW. Chronic progressive external ophthalmoplegia. Curr Neurol Neurosci Rep. 2002;2(5):413–417.
59. Ortube MC, Bhola R, Demer JL. Orbital magnetic resonance imaging of extraocular muscles in chronic progressive external ophthalmoplegia: specific diagnostic findings. J AAPOS. 2006;10(5):414-418.
60. Vilarinho L, Santorelli FM, Coelho I, Rodrigues L, Maia M, Barata I, et al. The mitochondrial DNA A3243G mutation in Portugal: clinical and molecular studies in 5 families. J Neurol Sci. 1999;163(2):168–174.
61. Zanssen S, Molnar M, Buse G, Schröder JM. Mitochondrial cytochrome b gene deletion in Kearns-Sayre syndrome associated with a subclinical type of peripheral neuropathy. Clin Neuropathol. 1998;17(6):291-296.
62. Leigh JR, Zee DS. The neurology of eye movements. 5th ed. Oxford, UK: Oxford University Press; 2015.
63. Anastasopoulos D, Kimmig H, Mergner T, Psilas K. Abnormalities of ocular motility in myotonic dystrophy. Brain. 1996;119 (Pt 6):1923-1932.
64. Feibel JH, Campa JF. Thyrotoxic neuropathy (Basedow's paraplegia). J Neurol Neurosurg Psychiatry. 1976;39(5):491-497.
65. Kung AW. Neuromuscular complications of thyrotoxicosis. Clin Endocrinol (Oxf). 2007;67(5):645-650.
66. Sweatman MC, Chambers L. Disordered oesophageal motility in thyrotoxic myopathy. Postgrad Med J. 1985;61(717):619-620.
67. Hardiman O, Molloy F, Brett F, Farrell M. Inflammatory myopathy in thyrotoxicosis. Neurology. 1997;48(2):339-341.
68. kung AW. Thyrotoxic periodic paralysis: a diagnostic challenge. J Clin Endocrinol Metab. 2006;91(7):2490–2495.

69. Nora NA, Berns AS. Hypokalaemic, hypophosphatemic thyrotoxic periodic paralysis. Am J Kidney Dis. 1989;13(3):247-249.

70. Sahay BM, Blendis LM, Greene R. Relation between myasthenia gravis and thyroid disease. Br Med J. 1965;1(5437):762-765.

71. Mappouras DG, Philippou G, Haralambous S, Tzartos SJ, Balafas A, Souvatzoglou A, Lymberi P. Antibodies to acetylcholinesterase cross-reacting with thyroglobulin in myasthenia gravis and Graves's disease. Clin Exp Immunol. 1995;100(2):336-343.

72. Lakhal K, Blel Y, Fysekidis M, Mohammedi K, Bouadma L. Concurrent Graves disease thyrotoxicosis and myasthenia gravis: the treatment of the former may dangerously reveal the latter. Anaesthesia. 2008;63(8):876-879.

73. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. Am J Ophthalmol. 2006;142(1):147-153.

74. Frame F, Thompson SA, Man TM, Edwards MJ, Rosenzweig I. Psychogenic myasthenia gravis. J Neuropsychiatry Clin Neurosci. 2011 Fall;23(4):E1.

75. Matsumoto H, Shimizu T, Igeta Y, Hashida H. Psychogenic unilateral ptosis with ipsilateral muscle spasm of orbicular oculi. Acta Med Indones. 2012;44(3):243-245.

76. Peer Mohamed BA, Patil SG. Psychogenic unilateral pseudoptosis. Pediatr Neurol. 2009;41(5):364-366.

77. Munts AG, Koehler PJ. How psychogenic is dystonia? Views from past to present. Brain. 2010;133(Pt5):1552-1564.