Childhood myasthenia: clinical subtypes and practical management

Review

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In recent years, understanding of the pathogenesis and clinical presentation of distinct myasthenia subtypes has increased significantly. This article reviews the clinical manifestations of autoimmune myasthenia gravis (including myasthenia associated with anti-muscle-specific kinase antibodies), ocular myasthenia, and antibody negative myasthenia. The following treatments are examined: cholinesterase inhibitors, immunosuppressants, and thymectomy. Inherited congenital myasthenic syndromes (CMS) are now increasingly recognized, and most commonly present during childhood. This article outlines the presynaptic, synaptic basal lamina-associated, and postsynaptic classification of CMS and the clinical presentation and aetiology of individual syndromes. Relevant investigations and treatment options (including the role of pyridostigmine, 3,4-diaminopyridine, fluoxetine, and ephedrine) are discussed.

See end of paper for list of abbreviations.

The understanding of myasthenia in childhood has increased significantly during the last decade. Previously, autoimmune myasthenia gravis (AMG) and transient neonatal myasthenia (TNM) were considered to be the predominant childhood variants of a disease more commonly found in adults. In recent years, congenital myasthenic syndromes (CMS) have been increasingly recognized, and advances in molecular genetic techniques have led to the identification of gene defects responsible for this heterogeneous group of disorders. This review is a discussion of the pathogenesis, presentation, treatment, and outcome of all myasthenic syndromes of childhood. Particular emphasis is given to recent advances in the diagnosis and treatment of CMS presenting in infancy.

Childhood autoimmune myasthenia gravis (AMG)

AMG is caused by autoantibodies that bind to and reduce the number of acetylcholine receptors (AChR) at the postsynaptic membrane. AMG is considered to be the prototypical synaptic disorder.[1,2] Childhood AMG is more common in Oriental than Caucasian populations.[3] Diagnosis may be difficult in Caucasian children due to the high incidence of seronegative disease.[4] AMG is an acquired disease with a genetic basis, which is related to human leukocyte antigen (HLA)-B8 and DR3 in approximately 60% of Caucasians.[4,5] Other autoimmune disorders (type 1 diabetes and thyroid disease) may be associated in individuals with HLA seropositive disease.[5]

The initial symptoms of childhood AMG are seen after 12 months of age and are more common in females.[6] Most frequently, the initial presentation is with diplopia caused by asymmetrical ophthalmoplegia; ptosis is frequently present.[7] In the generalized form, painless fatiguability of the bulbar and limb musculature follows at a variable rate, with resultant dysphonia, dysphagia, and proximal limb weakness. Occasionally, impairment of the respiratory muscles requires ventilatory support. In some individuals, symptoms and signs of weakness remain confined to the extraocular muscles (ocular myasthenia).[7,8] However, 80% of individuals with an ocular presentation develop generalized muscle weakness within 2 years.[9]

In ocular myasthenia, AChR antibodies are not detectable in 40 to 60% of individuals. Following generalization of weakness to other muscles, AChR antibodies may be subsequently identified.[10] Variable ocular weakness is noted which may be asymmetrical. Involvement of the obicularis oculi muscle is predominant, but some generalized weakness of the facial or limb musculature may occur. As thymoma is an uncommon association, treatment options are usually restricted to medical therapy, such as cholinesterase inhibitors, and immunosuppressants, such as corticosteroids. Response to medication is variable and may be transitory.[11]

In recent years, individuals who are anti-AChR antibody negative (10–20% of all individuals with myasthenia gravis [MG])[12] have been considered most likely to have an immune mediated disorder.[10] Anti-muscle-specific tyrosine kinase (MuSK) antibodies have been found in up to 70% of anti-AChR antibody negative individuals.[13] The predominant clinical features of MG associated with anti-MuSK antibodies are facial weakness and tongue wasting due to significant and persistent bulbar muscle involvement.[14]

Recently, a comparative study of the clinical features of individuals with MG due to anti-MuSK antibodies, anti-AChR antibodies, and individuals with MG who were antibody negative, revealed that anti-MuSK positive individuals suffered more severe bulbar involvement and more myasthenic crises than individuals from the other groups; however, long-term impairment was similar in the two antibody positive groups. By contrast, the seronegative myasthenia group had a comparatively favourable long-term outcome (measured by standardized functional assessment) and required less medication.[15]

Following the presentation of AMG, symptoms occur with variable frequency and severity, and might only be demonstrable following sustained testing of affected muscle groups (e.g. eye movements or shoulder abduction). Although symptoms fluctuate, childhood AMG is a progressive disease, and myasthenic crises may occur at times of febrile illnesses, resulting in significantly increased respiratory muscle weakness and the need for intensive care.[10]

The diagnosis of childhood AMG is usually confirmed by a combination of the videotaped response to the Tensilon (edrophonium chloride) test, using single fibre electromyography (EMG) if possible (fatiguability proven by repetitive stimulation of two muscle fibres from the same motor unit) and by serological demonstration of AChR or MuSK antibodies (if present). On occasions when the diagnosis remains unclear following formal testing, the response of symptoms to treatment with pyridostigmine may be a useful 'diagnostic test'. Long-term treatment options include thymectomy for AChR positive children, oral anticholinesterase treatment (pyridostigmine), and immunosuppression with prednisolone and/or one of azathioprine, methotrexate, cyclosporine, or cyclophosphamide.[16] In the event of acute deterioration, plasma exchange and intravenous immunoglobulin are equally effective and may provide transient benefit.[16]

Transient neonatal myasthenia

TNM as a result of the transfer of the placental transfer of maternal AChR antibodies affects approximately 10% of infants born to mothers with AMG.[6,17] All infants have high antibody titres; however, there is no relationship between the likelihood of TNM and maternal disease severity. Mothers are more likely to have a second infant affected with TNM if a previous infant has been affected.[18] Clinical features of TNM include poor sucking and feeding, a weak cry, and a paucity of movements. Respiratory distress may be noted, and ventilatory support required. Treatment with neostigmine is transiently effective, and exchange transfusion may be required in severe cases. Spontaneous resolution of symptoms occurs within weeks.

Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) – classically, the association of a myasthenic syndrome with malignancy – is very rare in the paediatric population and infrequently affects individuals in their late childhood years. In adults, LEMS is caused by antibodies to voltage gated calcium channels and may be associated with malignancy (small cell lung cancer in 60% of adult cases).[19] In contrast, childhood LEMS cases rarely have concurrent malignancies, and the mechanism of weakness remains unknown.[20,21] Clinical features include proximal muscle weakness causing disordered gait, and autonomic symptoms such as constipation and a dry mouth.[22] In contrast to individuals with AMG, children with LEMS are more likely to gain symptomatic benefit from 3,4-diaminopyridine (3,4-DAP) than pyridostigmine. Immunosuppressants remain the cornerstone of long-term treatment, and both plasma exchange and intravenous immunoglobulin may be effective.[21,23]

Congenital myasthenic syndrome

Congenital myasthenic syndrome (CMS) is the collective term for a genetically heterogeneous group of hereditary congenital disorders of the neuromuscular junction itself.[24] Symptoms or signs relating to CMS are usually noted during childhood; however, in some cases CMS presents during adulthood. Children usually present within the first years of life (or occasionally in later childhood) with varied disability, ranging from mild to severe myasthenic muscle weakness. There is often a relevant family history. A diagnosis of CMS is made through a combination of clinical history, reduced EMG response of the compound muscle action potential on repetitive stimulation, and by immunocytochemical and molecular genetic investigations on muscle biopsy and DNA samples.[25] With the exception of the autosomal dominantly-inherited slow-channel syndrome, all CMS are inherited via autosomal recessive mutations which result in loss of function at the neuromuscular junction.

The prevalence of CMS remains unknown, yet with increased clinical awareness, the detected prevalence is likely to rise. Recently, Beeson et al. reviewed the number of detected cases of CMS subtypes from four international CMS referral centres and found a predominance of CMS due to postsynaptic defects.[26]

The investigation of individuals with suspected CMS is complex. Many tests for CMS are only undertaken in specialist national or international centres and performed following advice from regional or national experts.

CMS are classified according to the affected site at the neuromuscular junction: presynaptic, synaptic basal lamina-associated, or postsynaptic.[26] While this classification system reflects present knowledge about CMS, it is likely that further types of CMS will be identified in the future. Recently, fetal myasthenias have been recognized as one of the causes of arthrogryposis multiplex congenita (AMC) and are discussed separately from other CMS in this review.

Presynaptic defects

CMS due to presynatic defects are the least common group of CMS and are due to defects in the release of acetylcholine quanta (paucity of synaptic vesicles and/or reduced quantal release) or defects in acetylcholine resynthesis (caused by choline acetyltransferase [ChAT] mutation).

CONGENITAL MYASTHENIC SYNDROME CAUSED BY CHOLINE ACETYLTRANSFERASE (ChAT) DEFICIENCY

Before it was recognized that all CMS are familial and present in infancy, the term 'familial infantile myasthenia' was used to describe CMS with episodic apnoea which presents with respiratory distress and subsequent apnoea. Patients may present at birth with hypotonia and weakness, and may require ventilatory support. Following improvement, patients subsequently present with apnoea and bulbar insufficiency, most commonly precipitated by intercurrent infection. Other patients present with apnoea in early infancy (CMS with episodic apnoea should be considered in the investigation of sudden infant death syndrome, especially if it occurs in more than one child in the family) or in later childhood.[27,28] Mutations in the presynaptic ChAT gene are responsible for the disorder[29] and are inherited in an autosomal recessive manner. Prophylactic anticholinesterase medication should be commenced in patients with suspected or proven CMS caused by ChAT deficiency, and may prevent respiratory crises.[28] During crises, intravenous neostigmine or pyridostigmine may be effective.[25]

PAUCITY OF SYNAPTIC VESICLES AND REDUCED QUANTAL RELEASE

This extremely rare disorder was initially highlighted in a single case report of a 23-year-old female with generalized myasthenia symptoms which improved with pyridostigmine.[30] Ultrastructural studies revealed that a reduced number of quanta (discrete acetylcholine containing packages) originated from fewer than expected synaptic vesicles.[30] More recently, Maselli et al. described three children with myasthenic symptoms associated with reduced quantal release. These children were found to have normal numbers of synaptic vesicles but the endplate potential quantal content was reduced; no gene defect was subsequently identified.[31] Similarly, Milone et al. recently described a 7-year-old male with severe disability who had myasthenia symptoms since infancy and was found to have 25% of the normal degree of quantal release.[32] The molecular basis for this syndrome remains unknown.

LAMBERT-EATON SYNDROME-LIKE CMS

This extremely rare CMS (so named as there are similarities with the neurophysiological findings in LEMS) was first recognized in 1987 and has been described in two young children. Bady et al. described a hypotonic and areflexic 4-year-old female treated with guanidine,[33] and Engel et al. unsuccessfully treated a 6-month-old female with hypotonia since birth and associated severe bulbar, limb, and respiratory muscle weakness with 3,4-DAP.[25] At present, the exact mechanism and the molecular basis of LEMS-like CMS remain unknown.

Synaptic basal lamina-associated defects

Synaptic basal lamina defects are the second most common subgroup of CMS. Endplate acetylcholinesterase deficiency is the only identified defect.

ENDPLATE ACETYLCHOLINESTERASE DEFICIENCY

In this subgroup of CMS, acetylcholinesterase is absent from the synapse and the lifetime of acetylcholine in the synaptic space is prolonged, resulting in an endplate myopathy. Affected children usually present in infancy with severe disability;[34] however, a small proportion of individuals are only significantly affected during adulthood.[35] Abnormally slow pupillary response to light is noted in some patients.[34] Diagnosis is by demonstration of the lack of acetylcholinesterase from the synapse, or by finding one of a number of deleterious mutations in the collagen gene, COLQ, responsible for the defective collagen tail of acetylcholinesterase.[36] Although there are reports of individuals with endplate acetlycholinesterase deficiency responsive to ephedrine,[37] in the majority of cases, treatment has been unsuccessful; anticholinesterases are ineffective and at high doses may worsen the child's clinical state due to muscarinic side effects.

Postsynaptic defects

Postsynaptic defects are the most common subgroup of CMS and account for three-quarters of all cases. Postsynaptic defects may be caused by either disorders of the AChR (or proteins which influence the receptor function, e.g. rapsyn and plectin) or by an abnormality of endplate excitation due to a sodium channel mutation.

ACETYLCHOLINE RECEPTOR (AChR) DISORDERS

AChR disorders result from kinetic or non-kinetic abnormalities of AChR function. Further classification of the kinetic abnormalities depends on whether the opening of the channels is abnormally slow or fast.

PRIMARY KINETIC ABNORMALITY OF AChR WITH OR WITHOUT AChR DEFICIENCY

This CMS subgroup includes individuals with mutations of the AChR subunit. Depending on whether the subunit mutation has the effect of increasing or decreasing the receptor response to acetylcholine leads to the subclassification into slow and fast channel syndromes. In slow-channel syndromes, AChR channel opening is prolonged, resulting in a prolonged electrical potential and an endplate myopathy, causing rapidly progressive symptoms in early life[38] or more slowly progressive symptoms in late adulthood.[39] In slow-channel syndromes, the cervical muscles, and the wrist and finger extensors are frequently involved and the cranial muscles are spared in all but severely affected individuals. Quinidine and fluoxetine are both effective treatments.[26] In contrast, fast channel mutations result in reduced affinity for acetylcholine and subsequent premature closure of the AChR channel, leading to clinical features of variable severity similar to those seen in autoimmune myasthenia (and rarely arthrogryposis). Symptoms may be mild or severe, and usually respond to treatment with 3,4-DAP and cholinesterase inhibitors.[25]

AChR DEFICIENCY WITHOUT KINETIC ABNORMALITY

AChR deficiencies are caused by mutations in the genes encoding the AChR subunits and lead to variable myasthenia symptoms which may be mild or severe depending on the subunit affected.[25] An epsilon subunit mutation is most commonly identified[26] and results in symptoms occurring in infancy or early childhood. Clinical features associated with epsilon subunit mutation include ptosis, ophthalmoplegia,

feeding difficulties, and choking episodes but not arthrogryposis, differentiating this disorder from the characteristic phenotype of CMS due to rapsyn deficiency.[40] Treatment is with anticholinesterase drugs, and some individuals may benefit from additional treatment with 3,4-DAP.

Non acetylcholine receptor (AChR) disorders

RAPSYN DEFICIENCY (LEADING TO AChR DEFICIENCY)

The RAPSN gene encodes rapsyn (receptor associated protein at the synapse), which is responsible for the clustering of AChR in the post-synaptic membrane. Several mutations in RAPSN have been identified of which the N88K mutation is commonly seen in patients from central or western Europe.[41] Clinical symptoms may be seen from birth to early infancy (arthrogryposis multiplex congenita, recurrent apnoea, episodic crises, and motor delay), or later in life (proximal limb weakness, ankle dorsiflexion weakness, and/or ptosis).[40,41] In individuals who present at birth or in early infancy, severe exacerbations of weakness are common during early childhood; however, in later childhood, clinical symptoms may be less pronounced.[40,42] Treatment with pyridostigmine alone may be sufficient;[40] however, some individuals benefit from the addition of 3,4-DAP.[25]

Table I: Symptoms and signs associated with myasthenic syndromes

Perinatal
Reduced fetal movements
Polyhydramnios
Arthrogryposis
Infancy
Hypotonia
Muscle weakness
Weak cry
Feeding difficulties
Recurrent choking or apnoeic episodes
Childhood
Muscle fatiguability
Respiratory failure
Ophthalmoplegia
Diplopia
Ptosis
Strabismus
Dysarthria
Dysphonia
Dysphagia

Table II: Investigation of children suspected to have myasthenia

Acetylcholine receptor antibodies
Anti-muscle-specific kinase antibodies
Tensilon (edrophonium chloride) test
Repetitive nerve stimulation
Single fibre electromyography
DNA testing for specific congenital myasthenic syndrome
(Clinicians may wish to discuss cases with colleagues at the national referral centres)

MUSCLE-SPECIFIC KINASE (MuSK) DEFICIENCY

MuSK mutations have recently been described in one patient with proven neuromuscular transmission dysfunction. Ptosis and respiratory distress were noted during the neonatal period and continued in infancy. Following a period of fluctuating mild symptoms during adolescence, weakness increased during pregnancy. Treatment with high dose pyridostigmine was ineffective but a clear improvement was noted with 3,4-DAP. The patient's brother died at 18 months of age, and analysis of post-mortem DNA revealed the same mutation as the described index case.[43]

SODIUM CHANNEL MYASTHENIA

Tsujino et al. described the only individual with sodium channel myasthenia to be identified to date.[44] A 20-year-old female experienced lifelong 3- to 30-minute episodes of respiratory and bulbar paralysis which occurred three times a month. The patient was noted to have ptosis and delayed motor development during childhood, and was easily fatigued. Respiratory support had been provided for apnoeas since infancy. Aged 20 years, the patient had bilateral ptosis in addition to widespread weakness which was exacerbated by activity. Abnormalities were found in the mechanism which usually excites endplate action potentials; subsequent genetic analysis revealed a mutation in the SCN4A gene (which encodes the skeletal muscle sodium channel).[44]

PLECTIN DEFICIENCY

Mutations in plectin are responsible for a form of epidermolysis bullosa, a progressive myopathy and a CMS.[45] Banwell et al. described an individual with a progressive myopathy and fatigability in ocular, facial, and limb muscles. A reduced EMG response was noted, however, no anti-AChR antibodies were found. Muscle biopsy samples revealed fibre necrosis and regeneration in addition to other abnormalities. Treatment with 3,4-DAP improved the patient's symptoms. Pyridostigmine was ineffective.[45]

LIMB GIRDLE CMS

Familial limb girdle myasthenia is characterized by proximal muscle weakness and muscle wasting; in contrast to other CMS, extraocular muscles are unaffected. Symptoms usually occur during the first decade of life. Recently, some cases of limb girdle myasthenia have been found to be caused by a gene mutation in exon 7 of the Dok-7 gene, leading to a deficient Dok-7 protein and reduced activation of MuSK and clustering of the AChRs; genetic screening of exon 7 is recommended to clarify diagnosis.[46] Creatinine kinase is elevated in some patients. Electrophysiological tests reveal a post-synaptic neuromuscular junction defect. Muscle biopsy shows tubular aggregates in a minority of patients. Patients may gain some benefit from treatment with anticholinesterase inhibitors, although symptoms may be worsened.[47] Recently, Slater et al. described eight individuals with limb girdle myasthenia and a characteristic waddling gait.[48] Investigation revealed that impaired neuromuscular transmission results from structural abnormalities of the neuromuscular junction, rather than from an abnormality of neuromuscular transmission.[48] Debate continues over whether a form of autoimmune limb girdle myasthenia exists, as onset is in adult life and both AChR antibodies and thymoma have been found on investigation.[49]

FETAL CMS

Maternal autoantibodies against fetal antigens have been known to cause AMC.[50] Recently, Escobar syndrome (a form of AMC) has been found to be caused by maternal antibodies against the gamma subunit of the fetal AChR. As the affected gamma subunit changes to an unaffected epsilon subunit in late fetal development, the gamma subunit mutation results in neurological impairment and dysmorphism present from birth, but not myasthenia symptoms in later life.[51]

Clinical assessment and management of childhood myasthenia

The clinical assessment of children suspected to have a myasthenic syndrome should consist of careful antenatal and perinatal assessment. Family and developmental history-taking should focus on investigating the presence of symptoms and signs (see Table I). A critical clinical feature of myasthenia is fatiguability and this history should be specifically sought. In older children (aged 5y and older) quantitative myasthenia scoring systems can be used in evaluation.[52] These consist of a series of objective, timed, standardized tests of fatiguability, e.g. walking on a flat surface and stairs, squats, timed assessment of how long arms can be held outstretched, Gower test, and the time taken to drink a standardized volume of liquid. For older children measurement of lung function with spirometry is useful.[53]

Investigations for children suspected to have myasthenia are shown in Table II. Initial blood tests can be performed by all paediatricians (primarily to exclude immune mediated myasthenia), while some more specialized tests are only available in specialized centres. Funding for DNA testing of individuals with suspected specific CMS (undertaken in Oxford, UK) is available through the designated National Specialist Commissioning Advisory Group. Neurophysiological testing requires the skills of a trained paediatric neurophysiologist and is difficult in children due to reduced cooperation with needle placement. Repetitive nerve stimulation is more likely to be tolerated than single fibre EMG.

MANAGEMENT OF CHILDREN WITH MYASTHENIA

Signs and symptoms of myasthenia respond variably to medication. Therefore, the management of children should be undertaken by a specialized multidisciplinary team comprising of a paediatrician/paediatrician neurologist, physiotherapist, occupational therapist, psychologist, speech therapist, and dietician. The specialist services of a paediatric gastroenterologist may be required as children with bulbar symptoms may have significant dysphagia which may require nasogastric tube or gastrostomy feeding. For children with significant weakness of the respiratory musculature, nocturnal or 24-hour non-invasive ventilation requires the expertize of a respiratory paediatrician. For extremely weak children with CMS, discussion with parents when the child is clinically well is required regarding whether multiple episodes of respiratory support on paediatric intensive care are appropriate. Some children become progressively less weak with age (e.g. those with rapsyn mutation), while others experience significant neurodisability and may be considered to have a reduced quality of life. The decision of whether or not to offer supportive intensive care should be taken by experienced clinicians and parents on an individual case basis. Children suspected of having a CMS require review by a clinical geneticist. Most CMS are inherited in a Mendelian fashion, therefore the recurrence risk for siblings and future pregnancies should be discussed.

TREATMENT

For the treatment of AMG, pyridostigmine is usually the first line treatment in children; neostigmine may be preferred in neonates or infants. Subsequently, oral steroids (and other immunosuppressive agents such as azathioprine, methotrexate, cyclosporine, tacrolimus, or mycophenolate mofetil), intravenous immunoglobulin, or plasmapheresis may be of benefit. Thymectomy should generally be avoided during early childhood due to subsequent immunosuppression.

In childhood MG, indications for thymectomy include the presence of a thymoma; generalized anti-AChR positive myasthenia; ocular myasthenia with progressive generalized weakness; and non-thymoma-related autoimmune myasthenia that is unresponsive to treatment. Thymectomy is not recommended in seronegative myasthenia, anti-MuSK antibody positive myasthenia, or pure ocular myasthenia.[10,13,16] When thymectomy is performed, clinicians should be vigilant to the increased likelihood of antimuscarinic side effects of cholinesterase inhibitor medications. Pre- and postoperatively, corticosteroids rather than pyridostigmine may be used to improve weakness. In the immediate postoperative period, neostigmine may be given parenterally. A number of medications may exacerbate weakness in individuals with MG and should be avoided: gentamicin, ampicillin, erythromycin, morphine, and gadolinium-based contrast agents.

Individual treatments may be of clinical benefit, although systematic evidence is lacking.[10] Juvenile MG does not respond to 3,4-DAP and the drug is not recommended in AMG. Considering CMS, some syndromes respond to pyridostigmine (CMS due to ChAT deficiency, the fast channel syndrome, rapsyn mutation, and AChR deficiency). Slow-channel syndromes may respond to fluoxetine[54,55] and endplate anticholinesterase deficiency may respond to ephedrine.[37] 3,4-DAP has been trialled with some success in the treatment of CMS.[56]

Conclusion

Autoimmune myasthenia in children is an uncommon condition. Despite increased recognition, congenital myasthenia remains rare. Neonates, infants, and children with myasthenia may present to a variety of paediatric specialities; therefore, increased awareness of the signs and symptoms of myasthenic syndromes is required. Recent advances in molecular medicine have led to further characterization of CMS and identification of CMS subgroups which may help to direct management and aid genetic counselling. Practically, the management of myasthenia should be undertaken in conjunction with a specialist multidisciplinary team.

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References

1. Andrews PI, Massey JM, Sanders DB. (1993) Acetylcholine receptor antibodies in juvenile myasthenia gravis. *Neurology* **43:** 977–982.
2. Vincent A. (2002) Unravelling the pathogenesis of myasthenia gravis. *Nat Rev Immunol* **2:** 797–804.
3. Garlepp MI, Dawkins RL, Christiansen FT. (1983) HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *Br Med J (Clin Res Ed)* **286:** 1442–1443.

4. Compston DA, Vincent A, Newsom-Davis J, Batchelor JR. (1980) Clinical, pathological, HLA antigen and immunological evidence for disease heterogeneity in myasthenia gravis. *Brain* **103:** 579–601.
5. Toth C, McDonald D, Oger J, Brownell K. (2006) Acetylcholine receptor antibodies in myasthenia gravis are associated with greater risk of diabetes and thyroid disease. *Acta Neurol Scand* **114:** 124–132.
6. Oosterhuis HJ. (1989) The natural course of myasthenia gravis: a long term follow up study. *J Neurol Neurosurg Psychiatry* **52:** 1121–1127.
7. Afifi AK, Bell WE. (1993) Tests for juvenile myasthenia gravis: comparative diagnostic yield and prediction of outcome. *J Child Neurol* **8:** 403–411.
8. Sommer N, Sigg B, Melms A, Weller M, Schepelmann K, Herzau V, Dichgans J. (1997) Ocular myasthenia gravis: response to long-term immunosuppressive treatment. *J Neurol Neurosurg Psychiatry* **62:** 156–162.
9. Kupersmith MJ, Latkany R, Homel P. (2003) Development of generalised disease at 2 years in patients with ocular myasthenia gravis. *Arch Neurol* **60:** 243–248.
10. Vincent A, Palace J, Hilton-Jones D. (2001) Myasthenia gravis. *Lancet* **357:** 2122–2128.
11. Kusner LL, Puwanant A, Kaminski HJ. (2006). Ocular myasthenia: diagnosis, treatment and pathogenesis. *Neurologist* **12:** 231–239.
12. Sanders DB, Andrews I, Howard JF, Massey JM. (1997) Seronegative myasthenia gravis. *Neurology* **48:** S40–45.
13. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. (2001) Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* **7:** 365–368.
14. Farrugia ME, Robson MD, Clover L, Anslow P, Newsom-Davis J, Kennett R, Hilton-Jones D, Matthews PM, Vincent A. (2006) MRI and clinical studies of facial and bulbar muscle involvement in MuSK antibody-associated myasthenia gravis. *Brain* **129:** 1481–1492.
15. Deymeer F, Gungor-Tuncer O, Yilmaz V, Parman Y, Serdaroglu P, Ozdemir C, Vincent A, Saruhan-Direskeneli G. (2007) Clinical comparison of anti-MuSK- vs anti-AChR-positive and seronegative myasthenia gravis. *Neurology* **68:** 609–611.
16. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW. (2006) Guidelines for the treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* **13:** 691–699.
17. Tellez-Zenteno JF, Hernandez-Ronquillo L, Salinas V, Estanol B, da Silva O. (2004) Myasthenia gravis and pregnancy: clinical implications and neonatal outcome. *BMC Musculoskelet Disord* **5:** 42.
18. Gardnerova M, Eymard B, Morel E, Faltin M, Zajac J, Sadovsky O, Tripon P, Domergue M, Vernet-der Garabedian B, Bach JF. (1997) The fetal/adult acetylcholine receptor antibody ratio in mothers with myasthenia gravis as a marker for transfer of the disease to the newborn. *Neurology* **48:** 50–54.
19. O'Neill JH, Murray NM, Newsom-Davis J. (1988) The Lambert-Eaton myasthenic syndrome. A review of 50 cases. *Brain* **111:** 577–596.
20. Maddison P, Lang B, Mills K, Newsom-Davis J. (2001) Long term outcome in Lambert-Eaton myasthenic syndrome without lung cancer. *J Neurol Neurosurg Psychiatry* **70:** 212–217.
21. Newsom-Davis J, Murray NM. (1984) Plasma exchange and immunosuppressive drug treatment in the Lambert-Eaton myasthenic syndrome. *Neurology* **34:** 480–485.
22. Lambert EH, Eaton LM, Rooke ED. (1956) Defect of neuromuscular conduction associated with malignant neoplasms. *Am J Physiol* **187:** 612–613.
23. Maddison P, Newsom-Davis J. (2005) Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database Syst Rev* **18:** CD003279.
24. Middleton LT. (1996) Congenital myasthenic syndromes. 34th ENMC International Workshop, 10–11 June 1995. *Neuromuscul Disord* **6:** 133–136.
25. Engel AG, Ohno K, Sine SM. (2003) Congenital myasthenic syndromes: progress over the past decade. *Muscle Nerve* **27:** 4–25.
26. Beeson D, Hantai D, Lochmuller H, Engel AG. (2005) 126th International Workshop: congenital myasthenic syndromes, 24–26 September 2004, Naarden, the Netherlands. *Neuromuscul Disord* **15:** 498–512.
27. Byring RF, Pihko H, Tsujino A, Shen XM, Gustafsson B, Hackman P, Ohno K, Engel AG, Udd B. (2002) Congenital myasthenic syndrome associated with episodic apnea and sudden infant death. *Neuromuscul Disord* **12:** 548–553.
28. Barisic N, Muller JS, Paucic-Kirincic E, Gazdik M, Lah-Tomulic K, Pertl A, Sertic J, Zurak N, Lochmuller H, Abicht A. (2005) Clinical variability of CMS-EA (congenital myasthenic syndrome with episodic apnea) due to identical ChAT mutations in two infants. *Eur J Paediatr Neurol* **9:** 7–12.
29. Ohno K, Tsujino A, Brengman JM, Harper CM, Bajzer Z, Udd B, Beyring R, Robb S, Kirkham FJ, Engel AG. (2001) Choline acetyltransferase mutations cause myasthenic syndrome associated with episodic apnea in humans. *Proc Natl Acad Sci U S A* **98:** 2017–2022.
30. Walls TJ, Engel AG, Nagel AS, Harper CM, Trastek VF. (1993) Congenital myasthenic syndrome associated with paucity of synaptic vesicles and reduced quantal release. *Ann N Y Acad Sci* **681:** 461–468.
31. Maselli RA, Kong DZ, Bowe CM, McDonald CM, Ellis WG, Agius MA, Gomez CM, Richman DP, Wollmann RL. (2001) Presynaptic congenital myasthenic syndrome due to quantal release deficiency. *Neurology* **57:** 279–289.
32. Milone M, Fukuda T, Shen XM, Tsujino A, Brengman J, Engel AG. (2006) Novel congenital myasthenic syndromes associated with defects in quantal release. *Neurology* **66:** 1223–1229.
33. Bady B, Chauplannaz G, Carrier H. (1987) Congenital Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry* **50:** 476–478.
34. Hutchinson DO, Walls TJ, Nakano S, Camp S, Taylor P, Harper CM, Groover RV, Peterson HA, Jamieson DG, Engel AG. (1993) Congenital endplate acetylcholinesterase deficiency. *Brain* **116:** 633–653.
35. Shapira YA, Sadeh ME, Bergtraum MP, Tsujino A, Ohno K, Shen XM, Brengman J, Edwardson S, Matoth I, Engel AG. (2002) Three novel COLQ mutations and variation of phenotypic expressivity due to G240X. *Neurology* **58:** 603–609.
36. Donger C, Krejci E, Serradell AP, Eymard B, Bon S, Nicole S, Chateau D, Gary F, Fardeau M, Massoulie J, Guicheney P. (1998) Mutation in the human acetylcholinesterase-associated collagen gene, COLQ, is responsible for congenital myasthenic syndrome with end-plate acetylcholinesterase deficiency (Type Ic). *Am J Hum Genet* **63:** 967–975.
37. Bestue-Cardiel M, Saenz de Cabezon-Alvarez A, Capablo-Liesa JL, Lopez-Pison J, Pena-Segura JL, Martin-Martinez J, Engel AG. (2005) Congenital endplate acetylcholinesterase deficiency responsive to ephedrine. *Neurology* **65:** 144–146.
38. Milone M, Wang HL, Ohno K, Fukudome T, Pruitt JN, Bren N, Sine SM, Engel AG. (1997) Slow-channel myasthenic syndrome caused by enhanced activation, desensitization, and agonist binding affinity attributable to mutation in the M2 domain of the acetylcholine receptor alpha subunit. *J Neurosci* **17:** 5651–5665.
39. Engel AG, Lambert EH, Mulder DM, Torres CF, Sahashi K, Bertorini TE, Whitaker JN. (1982) A newly recognized congenital myasthenic syndrome attributed to a prolonged open time of the acetylcholine-induced ion channel. *Ann Neurol* **11:** 553–569.
40. Burke G, Cossins J, Maxwell S, Robb S, Nicolle M, Vincent A, Newsom-Davis J, Palace J, Beeson D. (2004) Distinct phenotypes of congenital acetylcholine receptor deficiency. *Neuromuscul Disord* **14:** 356–364.
41. Burke G, Cossins J, Maxwell S, Owens G, Vincent A, Robb S, Nicolle M, Hilton-Jones D, Newsom-Davis J, Palace J, Beeson D. (2003) Rapsyn mutations in hereditary myasthenia: distinct early- and late-onset phenotypes. *Neurology* **61:** 826–828.
42. Ohno K, Engel AG, Shen XM, Selcen D, Brengman J, Harper CM, Tsujino A, Milone M. (2002) Rapsyn mutations in humans cause endplate acetylcholine-receptor deficiency and myasthenic syndrome. *Am J Hum Genet* **70:** 875–885.
43. Chevessier F, Faraut B, Ravel-Chapuis A, Richard P, Gaudon K, Bauche S, Prioleau C, Herbst R, Goillot E, Ioos C, et al. (2004) MuSK, a new target for mutations causing congenital myasthenic syndrome. *Hum Mol Genet* **13:** 3229–3240.
44. Tsujino A, Maertens C, Ohno K, Shen XM, Fukuda T, Harper CM, Cannon SC, Engel AG. (2003) Myasthenic syndrome caused by mutation of the SCN4A sodium channel. *Proc Natl Acad Sci U S A* **100:** 7377–7382.

45. Banwell BL, Russel J, Fukudome T, Shen XM, Stilling G, Engel AG. (1999) Myopathy, myasthenic syndrome, and epidermolysis bullosa simplex due to plectin deficiency. *J Neuropathol Exp Neurol* **58:** 832–846.
46. Beeson D, Higuchi O, Palace J, Cossins J, Spearman H, Maxwell S, Newsom-Davis J, Burke G, Fawcett P, Motomura M, et al. (2006) Dok-7 mutations underlie a neuromuscular junction synaptopathy. *Science* **313:** 1975–1978.
47. Rodolico C, Toscano A, Autunno M, Messina S, Nicolosi C, Aguennouz M, Laura M, Girlanda P, Messina C, Vita G. (2002) Limb-girdle myasthenia: clinical, electrophysiological and morphological features in familial and autoimmune cases. *Neuromuscul Disord* **12:** 964–969.
48. Slater CR, Fawcett PR, Walls TJ, Lyons PR, Bailey SJ, Beeson D, Young C, Gardner-Medwin D. (2006) Pre- and post-synaptic abnormalities associated with impaired neuromuscular transmission in a group of patients with 'limb-girdle myasthenia'. *Brain* **129:** 2061–2076.
49. Oh SJ, Kuruoglu R. (1992) Chronic limb-girdle myasthenia gravis. *Neurology* **42:** 1153–1156.
50. Vincent A, Newland C, Brueton L, Beeson D, Riemersma S, Huson SM, Newsom-Davis J. (1995) Arthrogryposis multiplex congenita with maternal autoantibodies specific for a fetal antigen. *Lancet* **346:** 24–25.
51. Hoffman K, Muller JS, Stricker S, Megarbane A, Rajab A, Linder TH, Cohen M, Chouery E, Adaimy L, Ghanem I, et al. (2006) Escobar syndrome is a prenatal myasthenia caused by disruption of the acetycholine receptor fetal gamma subunit. *Am J Hum Genet* **79:** 303–312.
52. Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. (2005) Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. *Neurology* **64:** 1968–1970.
53. Zielonka T, Kostera-Pruszczyk A, Ryniewicz B, Korczynski P, Szyluk B. (2006) How accurate is spirometry at predicting restrictive pulmonary impairment in children with myasthenia gravis. *J Physiol Pharmacol* **57**(Suppl 4)**:** 409–416.
54. Harper CM, Fukodome T, Engel AG. (2003) Treatment of slow-channel congenital myasthenic syndrome with fluoxetine. *Neurology* **60:** 1710–1713.
55. Colomer J, Muller JS, Vernet A, Nascimento A, Pons M, Gonzalez V, Abicht A, Lochmuller H. (2006) Long-term improvement of slow-channel congenital myasthenic syndrome with fluoxetine. *Neuromuscul Disord* **16:** 329–333.
56. Anlar B, Varli K, Ozdirim E, Ertan M. (1996) 3,4-diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol* **11:** 458–461.

List of abbreviations

3,4-DAP	3,4-diaminopyridine
AChR	Acetylcholine receptors
AMG	Autoimmune myasthenia gravis
ChAT	Choline acetyltransferase
CMS	Congenital myasthenic syndrome
HLA	Human leukocyte antigen
LEMS	Lambert-Eaton myasthenic syndrome
MG	Myasthenia gravis
MuSK	Muscle-specific tyrosine kinase
RAPSN	Receptor associated protein at the synapse
TNM	Transient neonatal myasthenia