Therapeutic Strategies in Congenital Myasthenic Syndromes

Ulrike Schara* and Hanns Lochmüller†

*Department of Pediatric Neurology, University of Essen, Germany 45122, and †Institute of Human Genetics, University of Newcastle, Newcastle, United Kingdom

Summary: Congenital myasthenic syndromes (CMS) are classified in terms of the located defect: presynaptic, postsynaptic, and synaptic. They are inherited disorders caused by various genetic defects, all but the slow-channel CMS by recessive inheritance. To date, 10 different CMS are known and further CMS subtypes and their genetic cause may be disclosed by future investigations. Prognosis in CMS is variable and largely depends on the pathophysiological and genetic defect. Subtypes showing progression and life-threatening crises with apneas are generally less favorable than others. Therapeutic agents used in CMS depend on the underlying defect and include acetylcholinesterase inhibitor, 3,4-diaminopyridine, quinidine sulfate, fluoxetine, acetazolamide, and ephedrine. Although there are no double-blind, placebo-controlled clinical trials for CMS, several drugs have shown convincingly positive clinical effects. It is therefore necessary to start a rational therapy regime as early as possible. In most CMS, however, mild and severe clinical courses are reported, which makes assessment on an individual basis necessary. This review emphasizes therapeutic strategies in CMS. **Key Words:** Congenital myasthenic syndrome, therapy, acetylcholinesterase inhibitor, 3;4-diaminopyridine (3;4-DAP), quinidine sulfate, fluoxetine, acetazolamide, ephedrine.

INTRODUCTION

The structure of the human neuromuscular junction consists of a presynaptic and a postsynaptic domain separated by the synaptic cleft. On the presynaptic side, nerve impulses trigger the release of acetylcholine (ACh) quanta into the synaptic space leading to an activation of acetylcholine receptors (AChRs) on the postsynaptic side resulting in an endplate potential. Voltage-gated sodium channels ($Na_v1.4$) play a central role in converting the local depolarization of the endplate potential into a propagated action potential that can activate muscle contraction. The safety margin of the neuromuscular transmission is a function of the difference between the depolarization caused by the endplate potential and the depolarization necessary to activate $Na_v1.4$.

This complex cascade, which is induced by a single nerve impulse, depends on normal and orchestrated activity of all pre- and postsynaptic steps.[1–4] The most important disorders affecting the neuromuscular junction are autoimmune-induced myasthenia gravis (in most cases caused by antibodies against the AChR, or the muscle-specific tyrosine kinase receptor [MuSK]) and the growing number of congenital myasthenic syndromes (CMS). This review addresses therapeutic strategies in CMS.

CONGENITAL MYASTHENIC SYNDROMES

The CMS are a genetically and clinically heterogeneous group of disorders in which the safety margin of neuromuscular transmission is compromised by several mechanisms. Today, different defects are defined according to their pathophysiological, morphological, and genetic characteristics. Presynaptic defects affect the number of molecules per synaptic vesicle, the size of a single vesicle, or the reorganization of acetylcholine. In the synaptic space, acetylcholine esterase (AChE) hydrolyzes acetylcholine into choline and acetyl-coenzyme A. Postsynaptic defects include structural and kinetic abnormalities of the AChRs. Affected are several proteins or enzymes involved in the cascade leading to a normal formation of synapses, and also clustering of AChRs, and the $Na_v1.4$ channel.[1–4]

The CMS are classified in terms of the located defect: presynaptic, postsynaptic, and synaptic. These are inherited disorders, caused by various genetic defects, and all but the slow-channel CMS by recessive inheritance.[1–5] To date, mutations in 10 different genes have been found

Address correspondence and reprint requests to: Ulrike Schara, M.D., Department of Pediatric Neurology, University Children's Hospital, University of Essen, Hufelandstr. 55, 45122 Essen, Germany. E-mail: Ulrike.Schara@uk-essen.de.

to cause a CMS: *CHAT*, coding for the presynaptic choline acetyltransferase[6]; *COLQ*, coding for the endplate acetylcholine esterase[7,8]; *CHRNA1*, *CHRNB1*, *CHRND*, and *CHRNE* coding for four different AChR subunits[9,10]; *RAPSN*, coding for the postsynaptic protein rapsyn[11]; *MUSK*, coding for the muscle-specific kinase[12]; *DOK7*, coding for the downstream of kinase 7 protein[13]; and *SCN4A*, coding for the postsynaptic voltage-gated sodium channel $Na_v1.4$.[14]

DIAGNOSTIC AND THERAPEUTIC STRATEGIES IN CONGENITAL MYASTHENIC SYNDROMES

Patients often suffer from unspecific clinical symptoms, including motor developmental delay with normal mental development, muscle hypotonia and weakness, exercise intolerance, and facial hypomimia with ptosis and external ophthalmoplegia, as well as episodic apneic crises with worsening of myasthenic symptoms and respiratory insufficiency.[1–4,15] The combination of these symptoms is suggestive for a CMS and calls for further work-up; data of the patient's history, the critical clinical examination, and electrophysiologic studies often disclose clinical clues to diagnosis of a specific CMS (Table 1).[2,3,16]

Therapy in CMS depends on the structural defect of the neuromuscular junction and the underlying genetic defect. Drugs with positive effects for any given form of CMS (e.g., acetylcholine esterase inhibitors for rapsyn deficiency) can show negative effects and even worsening of symptoms in another CMS (e.g., acetylcholine esterase inhibitors in acetylcholine esterase deficiency). A precise diagnosis including genetic testing is highly recommended for rational therapy.[4]

Table 1. *Clues for Diagnosis in Congenital Myasthenic Syndromes*

Ethnic origin
Mutation ε1267delG *(CHRNE)* often in SouthEast European patients and Gypsies
Mutation N88K *(RAPSN)* often in Middle European patients
Episodic apneas
Presynaptic CMS (*CHAT* mutations)
Postsynaptic CMS (*RAPSN* mutations)
Delayed pupillary light reflexes
AChE-deficiency (*COLQ* mutations)
Selective involvement of cervical, wrist and finger extensors
Slow-channel syndromes (subunits of the AChR: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*) and elder patients with AChE-deficiency (*COLQ*)
Arthrogryposis multiplex congenita
CMS caused by mutations in *RAPSN* and *CHRND*
Weekly fluctuations of the clinical symptoms
CMS with mutations in *DOK7*
Repetitive muscle action potential
AChE-deficiency (*COLQ* mutations) and slow-channel syndromes (subunits of the AChR: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*)
AChE-inhibitors with no or negative effects
No effect (sometimes short positive effect with very low dosage) or most often worsening of symptoms in AChE-deficiency (*COLQ* mutations) or in slow-channel syndromes (subunits of the AChR: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*)
No effect, only slight effects for a short time (days to some weeks) or even deterioration in patients with *DOK7* mutations

DRUGS USED IN THE THERAPY OF CMS

Therapeutic agents used in CMS include acetylcholinesterase inhibitors, 3,4-diaminopyridine (3,4-DAP), quinidine sulfate, fluoxetine, acetazolamide, and ephedrine.[3,4,13,15,17–21] Although there are no double-blind, placebo-controlled clinical trials for CMS, several drugs have shown convincingly positive clinical effects.

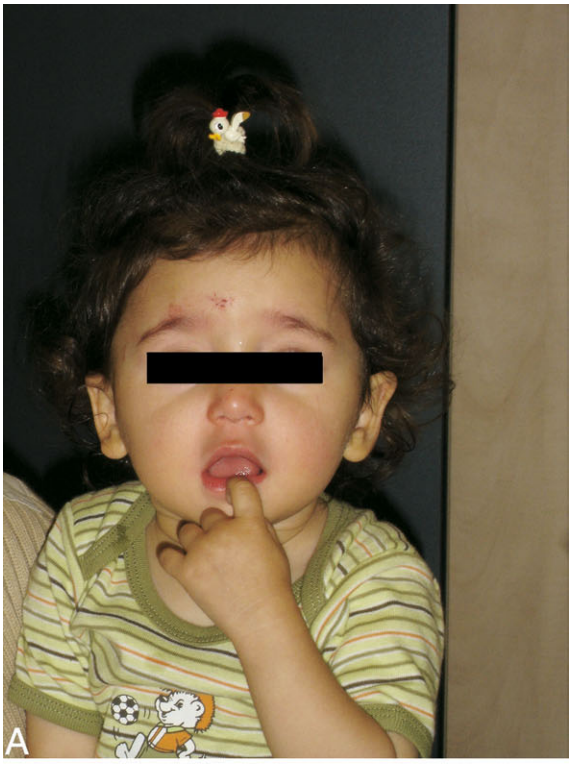
Acetylcholinesterase inhibitors

The AChE inhibitors lead to a prolonged activity of ACh in the synaptic space by blocking hydrolysis of ACh. They show positive effects in several forms of CMS: choline acetyltransferase deficiency, structural defects of the AChR subunits (FIG. 1), kinetic defects (as the fast-channel syndrome), and rapsyn deficiency. They show only temporary effects in the slow-channel syndrome and in Dok-7 deficiency, and can even worsen the clinical course in both conditions. In acetylcholinesterase deficiency, AChE inhibitors should not be given, because they may cause increased weakness and respiratory insufficiency.

It is important to find the individual dose in every patient; often 4–5 mg/kg body weight per day in four to six divided doses are helpful and well tolerated. Side effects mainly include cholinergic symptoms, such as increased bronchial secretions and production of tears, sialorrhea, cough, and diarrhea; in AChE deficiency, severe side effects are caused by a hypersensitive reaction of the muscarinic receptor.[1,3,4,15,19]

3,4-DAP

3,4-Diaminopyridine increases quantal release in presynaptic defects (FIG. 2). It prolongs the presynaptic action potential by blocking the outward potassium current, leading to an increased calcium entry into the nerve terminal. Additionally, 3,4-DAP shows positive effects in structural defects of the AChR subunits, in the fast-channel syndrome, and in rapsyn deficiency. The daily dose is up to 1 mg/kg body weight in four divided doses (in elderly patients, up to 5–20 mg four times a day). Often it is well tolerated, and side effects are only mild and cholinergic. In higher doses, however, seizures can



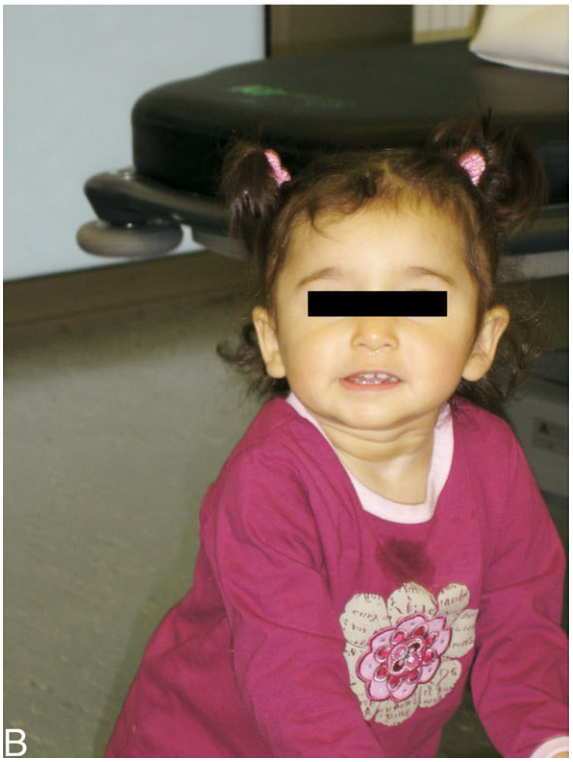


FIG. 1. A 2-year-old girl with a mutation in *CHRNE* before (A) and with (B) acetylcholinesterase-inhibitor therapy. Note the improvement of facial hypomimia with treatment.

be induced, and it is contraindicated in patients with a history of seizures. The drug is not approved for clinical use in the United States, but it can be used under special conditions; it is available in Canada, England, and in some countries in continental Europe.[1,4,22]

Quinidine sulfate and fluoxetine

Both quinidine sulfate and fluoxetine are long-lived, open-channel blockers of AChR. They shorten the duration of channel-opening events in a concentration-dependent manner; they show positive effects in slow-channel syndromes, but should not be given in other CMS.[4,21]

Quinidine sulfate should be given 15–60 mg/kg body weight per day in children, in four to six divided doses; adult patients are treated with 3 × 200 mg/day for 1 week. Then the dosage may be titrated depending on the serum level (normal value: 1–2.4 μg/mL or 3–7.5 μmol/L). Possible side effects include gastrointestinal symptoms, hypersensitivity symptoms, cardiac conduction defects, and inhibition of cytochrome P450IIDA (this last impairs several metabolic pathways).[4]

Fluoxetine may be used in patients who are not tolerating quinidine sulfate. In contrast to quinidine sulfate, fluoxetine is eliminated more slowly, thus providing a more sustained serum level. The daily dose in adults is 80–100 mg; the maximal dose in children has not been established. Side effects include nausea, nervousness, insomnia, sexual dysfunction, and hyponatremia in

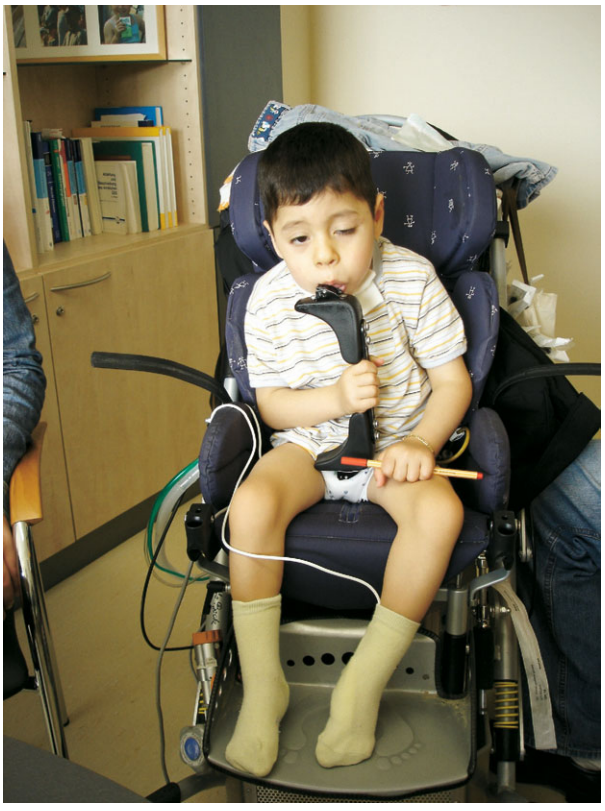


FIG. 2. A 4-year-old boy with a mutation in *CHAT*, treated with acetylcholinesterase inhibitor and 3,4-diaminopyridine. Despite positive effects of medication on myasthenic symptoms, he shows psychomotor impairment due to secondary hypoxic brain damage that could not be influenced by these drugs.

adults. In children, there can be an increased risk of suicide-related behavior, and therefore it should not be used in children and adolescents with signs of depression. Both drugs should be monitored by serum level measurements.[4,21]

Acetazolamide

Acetazolamide was reported to be beneficial in a single patient with a CMS due to *SCN4A* mutations, in addition to AChE-inhibitors. It prevented further attacks and bulbar weakness, with a daily dose of 2 × 250 mg/day.[14]

Ephedrine

Ephedrine shows positive effects in different forms of CMS, such as acetylcholinesterase deficiency and Dok-7 deficiency (FIG. 3). The mode of action is not fully understood in humans; *in vitro*, it increases the quantal release and reduces the opening time of the AChR in a dose-dependent manner.[22] Daily doses in adults vary from 25–50 mg two to three times per day. In children, it should be 3 mg/kg body weight per day in three divided doses. Often ephedrine is started with 1 mg/kg body weight per day and is increased with caution. Side effects include hypertension, nervousness, insomnia, and palpitation.[4,13,18,23]

DISCUSSION

Current therapy of CMS is symptomatic and includes different drugs and, if necessary, physiotherapy, orthoses or a wheelchair, and percutaneous gastric tube and ventilatory support, as well as genetic counseling. Various therapeutic strategies in CMS according to different underlying defects are summarized in Table 2.

The growing knowledge of the pathophysiology and molecular mechanisms at the neuromuscular junction could be used to develop more specific therapeutic agents. As in other neuromuscular disorders, further investigation of the role of apoptosis and of antiapoptotic therapy at the neuromuscular junction are necessary.[24] In the mouse model for slow-channel CMS, it was documented that activation of apoptotic pathways at the synapse is one reason for circumscribed muscle damage; however, damage was reversible by elimination of specific trigger mechanisms, protecting the neuron from the action of later components in the apoptosis, and by enhancing the caspase inhibitor pathway.[25] Another study in the slow-channel mouse model showed that a signaling system mediated by the AChR, calcium, and the inositol-1,4,5-triphosphate receptor is responsible for localized calcium overload, one factor leading to myopathy in this subtype of CMS.[26] More and more detailed information during recent years about these mechanisms and about the neural agrin–Dok-7–MuSK–Rapsyn–AChR pathway can help in developing specific agents that block aberrant pathological reactions or enhance single necessary steps in these cascades.[27–30]

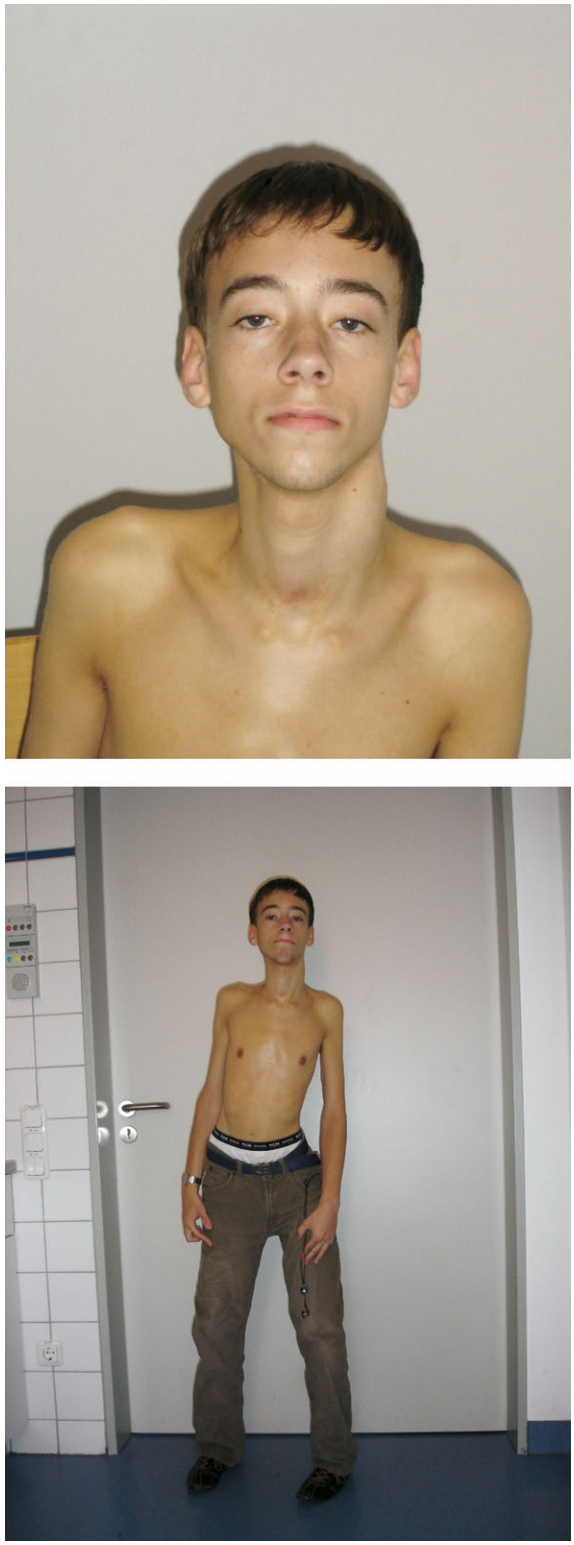


FIG. 3. An 18-year-old young man with two *DOK7* mutations and ephedrine therapy.

To date, ten different types of CMS are known, and further CMS subtypes and their genetic cause may be

Table 2. *Suggestions for a Rational Therapy in Various Types of Congenital Myasthenic Syndromes*

Defect involves	Gene	Rational Therapy
Choline acetyltransferase	*CHAT*	1) AChE-inhibitors in an individual dosage, often 4–5 mg/kg BW/day in 4–6 divided doses. If necessary, additionally: 2) 3,4-DAP 1 mg/kg BW/day in 4 divided doses, up to 4 × 5–20 mg/day
Acetylcholinesterase deficiency	*COLQ*	1) Ephedrine 3 mg/kg BW/day in 3 divided doses. Begin with 1 mg/kg BW/day and increase carefully. 2) In elderly patients: 2–3 × 25–50 mg/day
Acetylcholine receptor, subunits α, β, δ, ε	*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*	Structural defects 1) AChE-inhibitors in an individual dosage, often 4–5 mg/kg BW/day in 4–6 divided doses If necessary additionally 2) 3,4-DAP 1 mg/kg BW/day in 4 divided doses, up to 4 × 5–20 mg/day Kinetic defects: slow-channel syndrome 1) quinidine sulfate 15–60 mg/kg BW/day in 4–6 divided doses 2) in case of side effects: fluoxetine, in adults 80–100 mg/day, in children a maximal dosage has not been established Kinetic defects: fast-channel syndrome 1) AChE-inhibitors in an individual dosage, often 4–5 mg/kg BW/day in 4–6 divided doses, If necessary, additionally: 2) 3,4-DAP 1 mg/kg BW/day in 4 divided doses, up to 4 × 5–20 mg/day. Quinidine sulfate and fluoxetine should be monitored by serum level measurements.
Rapsyn deficiency	*RAPSN*	1) AChE-inhibitors in an individual dosage, often 4–5 mg/kg BW/day in 4–6 divided doses If necessary, additionally: 2) 3,4-DAP 1 mg/kg BW/day in 4 divided doses up to 4 × 5–20 mg/day
Downstream of kinase-7 deficiency	*DOK7*	1) Ephedrine 3 mg/kg BW/day in 3 divided doses, begin with 1 mg/kg BW/day and increase carefully. 2) In elder patients: 2–3 × 25–50 mg/day
Muscle-specific tyrosine kinase deficiency	*MUSK*	AChE-inhibitors in an individual dosage, often 4–5 mg/kg BW/day in 4–6 divided doses *and* 3,4-DAP 1 mg/kg BW/day in 4 divided doses up to 4 × 5–20 mg/day
$Na_v1.4$	*SCN4A*	AChE-inhibitors in an individual dosage, often 4–5 mg/kg BW/day in 4–6 divided doses, *and* acetazolamide 2 × 250 mg/day

AChR = acetylcholine receptor; AChE = acetylcholinesterase; BW = body weight; 3,4-DAP = 3,4-diaminopyridine.

disclosed with future investigation. Prognosis in CMS is variable and largely depends on the pathophysiological and genetic defect. Subtypes showing progression and life-threatening crises with apneas are generally less favorable than others. Therefore, it is necessary to start a rational therapy as early as possible to avoid such situations. In most CMS, however, mild and severe clinical courses are reported, making an assessment on an individual basis necessary.[1–4,15]

Acknowledgments: We thank B. Leiendecker for her critical reading of this manuscript. U.S. and H.L. are members of the German network on muscular dystrophies (*MD-NET*) funded by the German Ministry of Education and Research (BMBF, Bonn, Germany, 01GM0601).

REFERENCES

1. Beeson D, Hantaï D, Lochmüller H, Engel AG. 126th International Workshop: Congenital Myasthenic Syndromes, 24–26 September 2004, Naarden, The Netherlands. Neuromuscul Disord 2005;15:498–512.
2. Engel AG, Ohno K, Sine SM. Congenital myasthenic syndromes. In: Engel AG, Franzini-Armstrong C, Myology. 3rd ed. New York: McGraw-Hill 2004:1801–1844.
3. Engel AG, Sine SM. Current understanding of congenital myasthenic syndromes. Curr Opin Pharmacol 2005;5:308–321.
4. Engel AG. The therapy of congenital myasthenic syndromes. Neurotherapeutics 2007;4:252–257.
5. Croxen R, Hatton C, Shelley C, et al. Recessive inheritance and variable penetrance of slow-channel congenital myasthenic syndromes. Neurology 2002;59:162–168.
6. Ohno K, Tsujino A, Brengman JM, et al. Choline acetyltransferase mutations cause myasthenic syndrome associated with episodic apnea in humans. Proc Natl Acad Sci U S A 2001;98:2017–2022.
7. Ohno K, Brengman JM, Tsujino A, Engel AG. Human endplate acetylcholinesterase deficiency caused by mutations in the collagen-like tail subunit (ColQ) of the asymmetric enzyme. Proc Natl Acad Sci U S A 1998;95:9654–9659.
8. Donger C, Krejci E, Serradell AP, et al. 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 1998;63:967–75.

9. Middleton L, Ohno K, Christodoulou K, et al. Chromosome 17p-linked myasthenias stem from defects in the acetylcholine receptor ε-subunit gene. Neurology 1999;53:1076–1082.
10. Engel AG, Ohno K, Milone M, et al. New mutations in acetylcholine receptor subunit genes reveal heterogeneity in the slow-channel congenital myasthenic syndrome. Hum Mol Genet 1996;5: 1217–1227.
11. Ohno K, Engel AG, Shen XM, et al. Rapsyn mutations in humans cause endplate acetylcholine receptor deficiency and myasthenic syndrome. Am J Hum Genet 2002;70:875–885.
12. Chevessier F, Faraut B, Ravel-Chapuis A, et al. *MUSK,* a new target for mutations causing congenital myasthenic syndrome. Hum Mol Genet 2004;13:3229–3240.
13. Beeson D, Higuchi O, Palace J, et al. Dok-7 mutations underlie a neuromuscular junction synaptopathy. Science 2006;3:1975–1978.
14. Tsujino A, Maertens C, Ohno K, et al. Myasthenic syndrome caused by mutation of the *SCN4A* sodium channel. Proc Natl Acad Sci U S A 2003;100:7377–7382.
15. Hantaï D, Richard P, Koenig J, Eymard B. Congenital myasthenic syndromes. Curr Opin Neurol 2004;17:539–551.
16. Gurnett CA, Bodnar JA, Neil J, Connolly AM. Congenital myasthenic syndrome: presentation, electrodiagnosis, and muscle biopsy. J Child Neurol 2004;19:175–182.
17. Bestue-Cardiel M, Sáenz de Cabezón-Alvarez A, Capablo-Liesa JL, et al. Congenital endplate acetylcholinesterase deficiency responsive to ephedrine. Neurology 2005;65:144–146.
18. Schara U, Deschauer M, Wendt M, et al. Therapeutic effects of ephedrine in congenital myasthenic syndrome due to *DOK7* mutations. Neuromuscul Disord 2007;17:818–819 (abstract).
19. Schara U, Christen HJ, Hietala M, et al. Long-term follow-up in patients with congenital myasthenic syndrome due to *CHAT* mutations. Neuromuscul Disord 2007;17:818 (abstract).
20. Harper CM, Fukodome T, Engel AG. Treatment of slow-channel congenital myasthenic syndrome with fluoxetine. Neurology 2003; 60:1710–1713.
21. Colomer J, Müller JS, Vernet A, et al. Long-term improvement of slow-channel congenital myasthenic syndrome with fluoxetine. Neuromuscul Disord 2006;16:329–333.
22. Palace J, Wiles CM, Newsom-Davis J. 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. J Neurol Neurosurg Psychiatry 1991;54:1069–1072.
23. Sieb J, Engel AG. Ephedrine: effects on neuromuscular transmission. Brain Res 1993;623:167–171.
24. Mihaylova V, Müller JS, Vilchez JJ, et al. Clinical and molecular genetic findings in COLQ-mutant congenital myasthenic syndromes. Brain 2008;131;747–759.
25. Miller JB, Girgenrath M. The role of apoptosis in neuromuscular diseases and prospects for anti-apoptosis therapy. Trends Mol Med 2006;12:279–286.
26. Vohra BPS, Groshong JS, Zayas R, Wollmann RL, Gomez CM. Activation of apoptotic pathways at muscle fiber synapses is circumscribed and reversible in a slow-channel syndrome model. Neurobiol Dis 2006;23:462–470.
27. Zayas R, Groshong JS, Gomez CM. Inositol-1,4,5-triphosphate receptors mediate activity-induced synaptic Ca^{2+} signals in muscle fibers and Ca^{2+} overload in slow-channel syndrome. Cell Calcium 2007;41:343–352.
28. Müller JS, Baumeister SK, Rasic VM, et al. Impaired receptor clustering in congenital myasthenic syndrome with novel *RAPSN* mutations. Neurology 2006;67:1159–1164.
29. Müller JS, Baumeister SK, Schara U, et al. *CHRND* mutation causes a congenital myasthenic syndrome by impairing co-clustering of the acetylcholine receptor with rapsyn. Brain 2006;129: 2784–2793.
30. Slater CR, Fawcett PRW, Walls TJ, et al. Pre- and post-synaptic abnormalities associated with impaired neuromuscular transmission in a group of patients with 'limb-girdle myasthenia.' Brain 2006;129:2061–2076.