The Therapy of Congenital Myasthenic Syndromes

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Summary: Congenital myasthenic syndromes (CMSs) are heterogeneous disorders in which the safety margin of neuromuscular transmission is compromised by one or more mechanisms. Specific diagnosis of a CMS is important as some medications that benefit one type of CMS can be detrimental in another type. In some CMSs, strong clinical clues point to a specific diagnosis. In other CMSs, morphologic and *in vitro* electrophysiologic studies of the neuromuscular junction, determination of the number of acetylcholine receptors (AchRs) per junction, and molecular genetic studies may be required for a specific diagnosis. Strategies for therapy are based on whether a given CMS decreases or increases the synaptic response to acetylcholine (ACh). Cholinesterase inhibitors that increase the synaptic response to ACh and 3,4-diaminopyridine, which increases ACh release, are useful when the synaptic response to ACh is attenuated. Long-lived open-channel blockers of the AChR, quinidine, and fluoxetine, are useful when the synaptic response is increased by abnormally prolonged opening episodes of the AChR channel. Ephedrine has beneficial effects in some CMSs but its mechanism of action is not understood. **Key Words:** Congenital myasthenic syndromes, acetylcholine receptor, acetylcholinesterase, choline acetyltransferase, rapsyn, Dok-7, MuSK, cholinesterase inhibitors, 3,4-diaminopyridine, quinidine, fluoxetine.

INTRODUCTION

Congenital myasthenic syndromes (CMSs) represent a heterogeneous group of disorders in which the safety margin of neuromuscular transmission is compromised by one or more specific mechanisms. At the normal neuromuscular junction, activation of the postsynaptic acetylcholine receptors (AChRs) by acetylcholine (ACh) evokes an endplate potential (EPP) that activates the $Na_v1.4$ type voltage-dependent sodium channels giving rise to a propagated action potential. A high concentration of AChRs on crests of the synaptic folds[1] and of $Na_v1.4$ in the depth of the secondary synaptic clefts[2,3] ensures that excitation is propagated beyond the endplate (EP).[4,5] The safety margin of neuromuscular transmission is a function of the difference between the depolarization caused by the EPP and the depolarization required to activate $Na_v1.4$. All CMSs identified so far have been traced to one or more factors that render the EPP subthreshold for activating $Na_v1.4$ or to a defect in $Na_v1.4$ itself.

The factors governing the safety margin can be grouped into the following major categories: factors that affect the number of ACh molecules per synaptic vesicle, factors that affect quantal release mechanisms, and factors that affect the efficacy of individual quanta.[5] Thus, a clear understanding of the mechanisms that operate in the CMSs requires an analysis of the different ways in which these synaptic properties have been altered. They include variations in the number of AChRs per endplate, the synaptic localization of AChR and acetylcholinesterase (AChE), the fine structure of the endplate, the amplitude of miniature endplate potentials (MEPPs) and EP potentials (EPPs), the number of quanta released by nerve impulse, the number of readily releasable quanta, the probability of quantal release, and the kinetic properties of single AChRs. Combined electrophysiologic and morphologic tests can probe the involvement of these different mechanisms in CMSs. If these tests point to a candidate gene, then molecular genetic analysis becomes feasible. If a mutation is discovered in the candidate gene, then expression studies with the recombinant mutant molecule can be used to confirm its pathogenicity, analyze the electrophysiologic[6] or biochemical[7] properties of the mutant protein, and test drugs that may mitigate the disease.[8-10] The candidate gene approach, based on clinical, morphologic, and electrophysiologic findings, has pointed to defects in choline acetyltransferase (ChAT),[7] AChE,[11] AChR,[12] rapsyn,[13] muscle spe-

Table 1. *Classification of Congenital Myasthenic Syndromes Based on Site of Defect**

	Index cases
Presynaptic (8%)	
Choline acetyltransferase deficiency[†]	13
Paucity of synaptic vesicles and reduced quantal release	1
Congenital Lambert-Eaton-like	2
Other presynaptic defects	3
Synaptic space (14%)	
Endplate AChE deficiency[†]	35
Postsynaptic (73%)	
Primary kinetic defect ± AChR deficiency[†]	52
Primary AChR deficiency ± minor kinetic defect[†]	92
Rapsyn deficiency[†]	36
Na channel myasthenia[†]	1
Plectin deficiency	1
Synaptopathy (5%)	
Dok-7 myasthenia[†]	12
Total	248

AChE, acetylcholinesterase; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase. *Classification based on cohort of CMS patients investigated at the Mayo Clinic between 1988 and 2006. A single case of a CMS related to defect in MuSK has been reported by Chevessier et al.[14] [†]Genetic defect detected.

cific tyrosine kinase (MuSK),[14] and Dok-7[15] as causes of CMS.

CLASSIFICATION OF THE CMSS

Table 1 shows a site of defect-based classification of the CMSs and the frequency at which the different types of CMSs had been observed in the Mayo cohort of CMS patients. In this series, postsynaptic CMSs are the most frequent (73%) and those CMS caused by a kinetic abnormality or deficiency of AChR account for 57% of the total. Mutations in rapsyn, a protein responsible for concentrating AChR in the postsynaptic membrane, and in ColQ, the tail subunit of AChE that anchors the enzyme in the synaptic basal lamina, each account for ~14% of the cases. Each remaining syndrome accounts for 5% or fewer of the CMS cases in the Mayo cohort.

EPIDEMIOLOGY

There is no reliable information on the incidence and prevalence of CMSs. They are not uncommon, but are frequently misdiagnosed or go undiagnosed for a number of reasons: they can closely mimic other disorders (see Diagnosis and Differential Diagnosis); physicians are less familiar with CMSs than with other neurologic disorders; and the correct diagnosis of some CMSs requires specialized methods of investigation currently available only at a few medical centers. It is now known, however, that some CMSs are endemic in the Near East, where closed communities and consanguineous marriages are relatively frequent.[16,17]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Table 2 lists clinical clues to the generic and specific diagnoses of the CMSs. However, in some patients there are no clinical clues that point to a specific type of CMS. In these patients, *in vitro* analysis of parameters of neuromuscular transmission, patch-clamp recordings from single AChR channels, measurement of the number of AChRs per EP, morphologic studies that include examination of the fine structure and immunocytochemical properties of the neuromuscular junction, and in some instances molecular genetic studies, are required for making a specific diagnosis. Table 3 lists the differential diagnosis of the different forms of CMSs.

INHERITANCE

In most slow-channel patients, the opening events of the AChR channel are greatly prolonged; these syndromes are caused by dominantly inherited gain-of-function mutations in different AChR subunits. Some slow-channel syndromes with less prolonged opening events of the AChR channel are determined by recessive inheritance.[18] All other CMSs identified to date are caused by recessive loss-of-function mutations in various endplate-specific proteins.

PRINCIPLES OF THERAPY

Pharmacologic therapy is dictated by the defect underlying a given CMS. Drugs beneficial in one type of CMS can be harmful in another type. Therefore, specific diagnosis is essential for rational therapy.

It is important to monitor the effects of therapy by objective measures. Such measures include the arm elevation time, the number of times a patient can rise from squatting or from a low stool, the degree of eyelid ptosis, the number of steps they can climb or the distance they can walk before having to rest, the grade of weakness of selected muscles, maximal inspiratory and expiratory pressures, maximal expiratory flow, and the extent of the electromyogram decrement in one or more selected muscles.

In general terms, CMSs either decrease or increase the synaptic response to ACh. When a CMS reduces the synaptic response, cholinesterase inhibitors, which increase the number of AChR activated by each quantum, and 3,4-diaminopyridine (3,4-DAP), which increases the

Table 2. *Diagnostic Clues in Congenital Myasthenic Syndromes (CMSs)*

Generic diagnosis
- Fatigable weakness involving ocular, bulbar, and limb muscles since infancy or early childhood
- Similarly affected relative
- Decremental EMG response at 2- to 3-Hz stimulation
- Negative tests for anti-AChR antibodies, MuSK, and P/Q type calcium channels

Exceptions and caveats
- In some CMS the onset is delayed [37, 45]
- There may be no similarly affected relatives
- The symptoms can be episodic[7,13,44]
- EMG abnormalities may not be present in all muscles, or are present only intermittently[7,13]
- Weakness may not involve cranial muscles[40]

*Clinical clues pointing to a specific diagnosis**

Endplate AChE deficiency[35]
- Repetitive CMAPs
- Refractoriness to cholinesterase inhibitors
- Delayed pupillary light reflexes

Slow-channel CMS[45]
- Repetitive CMAPs
- Selectively severe involvement of cervical and wrist and finger extensor muscles in most cases
- Dominant inheritance in most cases

Endplate choline acetyltransferase deficiency[7,46]
- Recurrent apneic episodes, spontaneous or with fever, vomiting, or excitement
- No or variable myasthenic symptoms between acute episodes
- Stimulation at 10 Hz for 5 min causes marked decrease of CMAP followed by slow recovery
- EMG decrement at 2 Hz can be absent at rest but appears after stimulation at 10 Hz for 5 min, then disappears slowly.

Rapsyn deficiency
- Multiple congenital joint contractures in one-fourth of patients
- Increased weakness and respiratory insufficiency precipitated by intercurrent infections
- EMG decrement can be mild or absent.

Dok-7 myasthenia[40,15]
- Proximal greater than distal limb and axial muscle weakness, mild facial weakness and ptosis, and normal ocular ductions in the majority
- Bulbar muscles affected in some patients
- May deteriorate on exposure to pyridostigmine

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAP, compound muscle fiber action potential; EP, endplate; MuSK, muscle specific tyrosine kinase. *There are no clinical clues to the diagnosis of the fast channel CMS, primary EP AChR deficiency, and most cases of rapsyn deficiency.

number of quanta released by nerve impulse, are used. When the synaptic response is increased, as in the slow-channel syndromes, long-lived open-channel blockers of the AChR channel, quinidine and fluoxetine, are employed.

Therapeutic agents

Anticholinesterase medications, 3,4-DAP, quinidine, fluoxetine, and ephedrine are the mainstays of therapy in CMSs.

3,4-DAP prolongs the duration of the presynaptic action potential by blocking the outward potassium current.[19,20] This increases calcium entry into the nerve terminal when it is depolarized which, in turn, increases quantal release. The recommended dose of 3,4-DAP is up to 1 mg/kg/day in divided doses. The drug is well tolerated, with generally only mild side effects. These include peripheral and perioral paresthesias, adrenergic side effects (palpitation, sleeplessness, ventricular extrasystoles), and cholinergic side

effects (increased bronchial secretions, cough, and diarrhea). Higher doses are not recommended because of possible seizures.[21,22] A previous history of seizures or potentially epileptogenic activity in the electroencephalogram are contraindications to the use of the medication. The drug is not approved for clinical use by the U.S. Food and Drug Administration, but it can be obtained as an investigational drug and used under the auspices of Institutional Review Boards. The drug is available on prescription in Canada, England, and some European countries.

The dosages and side effects of quinidine and fluoxetine are considered below, under the treatment of the slow-channel syndromes.

Ephedrine has been noted to be of some benefit in different types of CMS but its mode of action is unclear. Doses in adults range from 25 to 50 mg two to three times daily. The dosage in children is 3 mg/kg/day in divided doses. The side effects include nervousness, insomnia, palpitation, and hypertension.

Table 3. *The Differential Diagnosis of Congenital Myasthenic Syndromes*

Neonatal period, infancy, childhood
Spinal muscular atrophy
Morphologically distinct congenital myopathies (central core disease, nemaline myopathy, myotubular myopathy)
Congenital muscular dystrophies
Infantile myotonic dystrophy
Mitochondrial myopathy
Brain stem anomaly
Möbius syndrome
Congenital fibrosis of the external ocular muscles
Infantile botulism
Autoimmune myasthenia gravis*
Older patients
Motor neuron disease
Radial nerve palsy[†]
Peripheral neuropathy[†]
Limb girdle or facioscapulohumeral dystrophy
Mitochondrial myopathy
Chronic fatigue syndrome
AChR- or MuSK-seropositive and seronegative autoimmune myasthenia gravis

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AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase *Not reported in the first year of life. [†]This diagnosis was suspected in some cases of the slow-channel congenital myasthenic syndromes.

MANAGEMENT OF DIFFERENT TYPES OF CMSS

Endplate AChR deficiency with or without minor kinetic abnormality

Most patients respond favorably but incompletely to cholinesterase inhibitors. The additional use of 3,4-DAP results in further significant improvement in about one-third of the cases.[23] A favorable response to 3,4-DAP combined with pyridostigmine in unselected CMS patients was previously reported,[24] but another clinical trial of CMS patients with predominantly ocular symptoms found little response to 3,4-DAP.[25] In our experience, 3,4-DAP increases endurance and reduces lid ptosis, but external ocular muscles respond less than limb muscles and in some patients the medication becomes less effective with continued use. Patients with low-expressor or null mutations in each allele of the AChR ϵ subunit can partially substitute the fetal γ for the ϵ subunit.[26,12] They usually have a milder form of CMS and respond better to therapy than patients with low-expressor mutations in both alleles of non-ϵ subunits for which there are no substituting subunits.

Slow-channel syndromes

The slow-channel syndromes are associated with slowly decaying endplate currents, destabilization of the closed channel state, prolonged activation episodes of AChR, and an endplate myopathy caused by cationic overloading of the postsynaptic region.[27] Specific therapy for this syndrome exists in the form of quinidine and fluoxetine. Both drugs are long-lived, open-channel blockers of AChR that shorten the duration of channel opening events in a concentration dependent manner. Five μM/L of quinidine or 10 μM/L fluoxetine decreases the duration of slow-channel opening events severalfold to that of wild-type, but reduces wild-type channel opening events only by $\sim$50%.[9,10]

Adult slow-channel patients are treated with 200 mg quinidine sulfate three times daily for one week; the dose is then gradually increased to maintain a serum level of 1 to 2.5 μg/mL (3–7.5 μM/L). After a satisfactory serum level is established, equivalent doses of a slow-release form of quinidine sulfate can be employed. The doses for children are 15–60 mg/kg/day of quinidine sulfate in four to six divided doses. On this regimen, patients improve in their endurance and electromyogram tests over many months.[28]

Quinidine is contraindicated in CMSs other than the slow-channel syndrome. Untoward effects of quinidine include gastrointestinal reactions with diarrhea and cinchonism. Hypersensitivity to the drug can result in drug fever, abnormal liver function tests, hemolytic anemia, agranulocytosis, thrombocytopenic purpura, and toxic drug rash. Quinidine also worsens atrioventricular conduction defects, and can aggravate a prolonged QT interval, which predisposes to ventricular arrhythmias. Quinidine also inhibits cytochrome P450IIDA and thereby impairs the metabolism codeine, tricyclic antidepressants, other antiarrhythmic drugs, and digoxin. Administration of verapamil, cimetidine, and agents that alkalinize urine may augment the serum quinidine level, and quinidine potentiates the anticoagulant effects of coumadin.[29]

Adult patients unable to tolerate quinidine can be treated with fluoxetine in gradually increasing doses until a total daily dose of 80 to 100 mg is attained.[10] The maximal dose of fluoxetine for children has not been established. Fluoxetine is a less effective long-lived open-channel blocker of the AChR channel than quinidine but is eliminated more slowly and therefore provides more evenly sustained blood levels. Adverse effects of fluoxetine include mild nausea, nervousness, insomnia, sexual dysfunction, and hyponatremia in the elderly.[30] Fluoxetine has been reported to increase the risk of suicide-related behaviors in depressed children and adolescents.[31,32] Therefore, caution is required when the medication is used in children or adolescents and it should not be used in those with signs of depression.

Fast-channel syndromes

The fast channel syndromes are associated with fast decaying endplate currents, destabilization of the open channel state, abnormally brief activation episodes of AChR, and no anatomic footprint.[27,33] Thus, they repre-

sent a mirror image of the slow-channel syndrome. Fast-channel patients respond well to combined therapy with pyridostigmine in doses similar to those used in autoimmune MG in combination with 3,4-DAP.[23] Patients without concomitant endplate AChR deficiency respond better than patients in whom the fast-channel mutation also reduces AChR expression.

Endplate AChE deficiency

There is no satisfactory drug therapy for this disease. Cholinesterase inhibitors cannot improve neuromuscular transmission and are contraindicated because they increase respiratory secretions and inhibit butyrylcholinesterase that partially compensates for absence of AChE from the EP. Some patients are subjectively and objectively improved by ephedrine sulfate; 25 to 50 mg taken two to three times daily.[34] Alternate-day prednisone therapy had a slight beneficial effect in two patients but was ineffective in one and appeared to worsen the symptoms in another.[35] A severely ill respirator dependent infant was improved by intermittent blockade of AChR by atracurium, an agent that protects AChR from overexposure to ACh, allowing for temporary withdrawal of respiratory support.[36]

Rapsyn deficiency

Most patients respond well to pyridostigmine.[37] Some patients derive additional benefit from the use of 3,4-DAP[38] or ephedrine.

Choline acetyltransferase (ChAT) deficiency

ChAT is essential for the resynthesis of ACh from choline and acetyl-coenzyme A. Mutations in ChAT impair the catalytic efficiency of the enzyme and decrease the release of ACh during physiologic activity.[7] Because this CMS can cause abrupt episodes of respiratory arrest, prophylactic use of pyridostigmine is indicated once the diagnosis is established. Because apneic attacks occur suddenly in infants and children, the parents should be provided with an inflatable rescue bag and a fitted mask, they should be instructed in the intramuscular injection of neostigmine methylsulfate (0.5 mg/kg in infants and children), and they are advised to install an apnea monitor in the home.

Dok-7 myasthenia

Dok-7 is a recently identified protein important for activation of MuSK.[39] MuSK plays a role in maturation and maintenance of the synapse, and in directing rapsyn to concentrate AChR in the postsynaptic membrane. Mutations in Dok-7 cause progressive weakness of limb-girdle and axial muscles but only mild weakness of the facial muscles and mild eyelid ptosis. Pyridostigmine is effective in some patients, but only a few experience long-term improvement and some deteriorate even after a few days of therapy. 3,4-DAP benefited three out of

eight patients and worsened one patient. Ephedrine improved five out of five patients but in one the improvement was temporary.[40,15]

Paucity of synaptic vesicles associated with reduced quantal release

Only one patient having this disorder has been reported. This patient responded partially to pyridostigmine.[41]

Lambert-Eaton syndrome-like CMS

In the autoimmune form of the syndrome, antibodies deplete the voltage-gated calcium channel of the presynaptic membrane by antigenic modulation. This limits the ingress of calcium into the nerve terminal when it is depolarized and reduces quantal release by nerve impulse. 3,4-DAP is effective in a high proportion of patients with the autoimmune syndrome.[42] One infant with the nonautoimmune congenital form of the disease observed by the author failed to respond to 3,4-DAP.

CMS caused by defect in MuSK

In a single reported patient pyridostigmine was ineffective but 3,4-diaminopyride had a beneficial effect.[14]

CMS caused by plectin deficiency

Plectin is an intermediate filament-associated protein concentrated at sites of mechanical stress. Pathogenic mutations in plectin are associated with a simplex variety of *epidermolysis bullosa,* and, in some cases, with a progressive myopathy and a defect of neuromuscular transmission. One patient with this type of myasthenia failed to respond to pyridostigmine but was improved by 3,4-DAP.[43]

Na channel myasthenia

In a single reported patient, therapy with pyridostigmine improved the patient's endurance; additional therapy with acetazolamide, which is known to mitigate periodic paralysis due to $Na_v1.4$ mutations, prevented further attacks of respiratory and bulbar weakness.[44]

General measures

Severely affected CMS patients are born with or develop a restrictive ventilatory defect, cannot swallow, and develop progressive spinal deformities. Some CMS infants are unable to breathe at birth but can be weaned off the respirator after a few months. Ventilatory defects developing in later life initially require nocturnal and later daytime ventilatory support. Spinal deformities must be carefully monitored; if progressive and significant, corrective surgery is indicated. Surgery is best done in the early teens, after vertebral growth has ceased. Severe dysphagia requires feeding via a gastrostomy tube. With early specific diagnosis and therapy, the above life-threatening consequences of the CMSs can be mitigated or obviated.

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