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NLM Citation: Abicht A, Müller JS, Lochmüller H. Congenital Myasthenic Syndromes Overview. 2003 May 9 [Updated 2021 Dec 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Congenital Myasthenic Syndromes Overview

Synonym: Congenital Myasthenia

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Created: May 9, 2003; Updated: December 23, 2021.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding congenital myasthenic syndromes (CMS) and their genetic causes and management.

The following are the goals of this overview:

Goal 1

Briefly describe the clinical characteristics of CMS.

Goal 2

Review the subtypes and genetic causes of CMS.

Goal 3

Review the differential diagnosis of CMS.

Goal 4

Provide an evaluation strategy to identify the genetic cause of CMS in a proband.

Goal 5

Inform genetic counseling of family members of a proband with CMS

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Goal 6

Review management of CMS following diagnosis: evaluations, treatment (based on genetic cause when possible) and surveillance.

1. Clinical Characteristics of Congenital Myasthenic Syndromes

Clinical Features

An individual with a congenital myasthenic syndrome (CMS) typically presents with a history of fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood, usually in the first two years. Rarely, onset is in the second to third decade of life [McMacken et al 2017, Engel et al 2018, Kao et al 2018, Rodríguez Cruz et al 2018, Finsterer 2019, Vanhaesebrouck & Beeson 2019].

In its classical presentation, CMS is limited to weakness of the skeletal muscles. Cardiac and smooth muscle are not involved. Cognitive skills, coordination, sensation, and tendon reflexes are normal. However, in some newly identified CMS subtypes, myasthenia is only one element of a more severe and complex clinical spectrum.

Severity and course of disease are highly variable, ranging from minor symptoms to progressive disabling weakness. In some subtypes of CMS, myasthenic symptoms may be mild, but sudden severe exacerbations of weakness or even sudden episodes of respiratory insufficiency may be precipitated by fever, infections, or excitement.

An absence of major pathology is noted on skeletal muscle biopsy despite considerable muscle weakness - except for *GMPPB*-related CMS, where a dystrophic pattern is found on biopsy (see Table 1).

Neonatal presentation. Some myasthenic symptoms are present at birth.

- Respiratory insufficiency with sudden, episodic apnea and cyanosis are common findings in neonates.
- Neonates with CMS can have multiple joint contractures (often described as arthrogryposis multiplex congenita) resulting from a lack of fetal movement in utero.
- Other major findings in the neonatal period may include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and facial, bulbar, and generalized weakness. Stridor in infancy may be an important clue to CMS.
- In some individuals, long face, narrow jaw, and a high-arched palate have been reported.

Childhood presentation. Individuals with onset later in childhood show abnormal muscle fatigability, with difficulty in running or climbing stairs.

- Motor milestones may be delayed.
- Affected individuals present with fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness. Ptosis may involve one or both eyelids.
- Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing may be present.
- Spinal deformity or muscle atrophy may occur.

Limb-girdle presentation. Some individuals display a characteristic "limb-girdle" pattern of weakness with ptosis and a waddling gait, usually without ophthalmoparesis ("limb-girdle myasthenia") [O'Connor et al 2018].

Prognosis. Severity and course of disease are highly variable and depend on the underlying genetic defect [Della Marina et al 2020]. Findings range from minor symptoms (e.g., mild exercise intolerance) to progressive disabling weakness. Minor myasthenic symptoms may be exacerbated by sudden onset of severe weakness or respiratory insufficiency precipitated by fever, infections, or excitement, especially in individuals with CMS with episodic apnea or endplate rapsyn deficiency.

Laboratory and Test Findings

Laboratory findings

- Serum creatine kinase (CK) concentration may be normal or slightly elevated (usually ≤10-fold normal value). CK levels may be higher only in *GMPPB*-related CMS.
- Anti-AChR and anti-MuSK antibody testing (serum) is negative.

  Note: (1) Absence of anti-AChR, anti-MuSK, and anti-LRP4 antibodies in serum can help distinguish CMS from myasthenia gravis (MG), but does not exclude seronegative types of MG which lack those antibodies.
- With the exception of *GMPPB*-related CMS, major pathology in a skeletal muscle biopsy specimen is absent despite considerable muscle weakness

EMG testing. EMG testing is helpful to establish a defect in neuromuscular transmission.

- In the majority of CMS subtypes, a decremental EMG response of the compound muscle action potential (CMAP) can be evoked on low-frequency (2-3 Hz) stimulation.
  - Generally, individuals should be tested for a decremental EMG response of CMAP on low-frequency (2- to 3-Hz) stimulation.
  - In some cases, 2- to 3-Hz stimulation elicits no decremental response from rested non-weak muscle, but elicits a significant decremental response after five to ten minutes of stimulation at 10 Hz.
  - If CMAP amplitude is normal in two distal and two proximal muscles, facial muscles should be tested.
  - Alternatively, or in addition, a single-fiber EMG is a good determinant of a neuromuscular transmission defect.
  - A single nerve stimulus may elicit a repetitive CMAP (the "double response to single nerve stimulus") in individuals with endplate acetylcholinesterase (AChE) deficiency or slow-channel CMS, or in those taking high doses of AChE inhibitors.
- By contrast with the majority of CMS, some presynaptic subtypes (e.g., *PREPL*-, *SNAP25B*-, *SYT2*-, *UNC13A*-, and *VAMP1*-associated CMS) may show increment of CMAP amplitude with high-frequency repetitive nerve stimulation.

AChE inhibitors. In some subtypes of CMS, a positive response to acetylcholinesterase (AChE) inhibitors may occur. Response to AChE inhibitors is usually assessed by a controlled/supervised trial of oral AChE inhibitors and monitoring of fatigable muscle weakness and obvious clinical symptoms (e.g., ptosis, bulbar weakness).

2. Subtypes and Genetic Causes of Congenital Myasthenic Syndromes

Table 1. Congenital Myasthenic Syndromes: CMS Subtypes and Distinguishing Clinical Features

CMS Subtype [1]		% of All CMS	Gene(s) [2]	Distinguishing Clinical Features	Response to AChE Inhibitors
Post-synaptic CMS	Acetylcholine receptor (AChR) deficiency	50% [3]	*CHRNA1* *CHRNB1* *CHRND* *CHRNE*	AChR deficiency (AR) • Early onset • Mild to severe • Ptosis, EOP; bulbar, arm, leg weakness	Improvement

Table 1. continued from previous page.

CMS Subtype [1]		% of All CMS	Gene(s) [2]	Distinguishing Clinical Features	Response to AChE Inhibitors
	Slow-channel CMS (SCCMS)			SCCMS (AD) • Selective severe neck, wrist, finger extensor weakness • Childhood to adult onset • Mild to severe • Progressive ventilatory insufficiency; may require assisted ventilation	Deterioration
	Fast-channel CMS (FCCMS)			FCCMS (AR): Mild to severe	Improvement
	Defect in AChR clustering pathway	15%-20%	*RAPSN*	Early onset: • Hypotonia, respiratory failure at birth • Episodic apnea • Arthrogryposis multiplex congenita • Mild to severe Late onset: • Limb weakness in adolescence or adulthood; as in seronegative myasthenia gravis	Improvement
		10%-15%	*DOK7*	Limb-girdle pattern of predominantly proximal weakness, waddling gait, & ptosis but no EOP	Deterioration or ineffective
		<1%	*LRP4*	Respiratory failure at birth, delayed motor milestones, ptosis, ophthalmoparesis, limb weakness	See footnote 4.
		<1%	*MUSK*	Broad phenotype • Prenatal onset w/fetal akinesia deformation sequence • Early onset w/ ophthalmoplegia & respiratory failure • Isolated vocal cord paralysis [5] • Late-onset limb girdle weakness [6]	Deterioration or ineffective
	Plectin deficiency	<1%	*PLEC*	Childhood to adulthood onset: • Fatigable proximal myopathy & ptosis • W/or w/o skin blistering	Improvement

Table 1. continued from previous page.

CMS Subtype [1]		% of All CMS	Gene(s) [2]	Distinguishing Clinical Features	Response to AChE Inhibitors
	Defect in skeletal muscle voltage-gated sodium channel	<1%	*SCN4A*	Phenotype overlapping w/*SCN4A*-assoc skeletal muscle sodium channelopathies: periodic paralysis, myotonia, myopathy	See footnote 4.
Synaptic CMS	Endplate AChE deficiency	10%-15%	*COLQ*	• Often severe • In some w/C-terminal missense pathogenic variants: later presentation, milder clinical course • EOP • General muscle weakness / severe involvement of axial muscles • Slow pupillary light response	Deterioration or ineffective
		1%-2%; >14 independent kinships reported	*COL13A1*	• At birth, respiratory distress & dysphagia; may resolve • Recurrent apnea triggered by infections • In adulthood, bilateral nonfatigable ptosis & marked axial weakness • Sometimes improvement of muscle weakness by adulthood	Likely ineffective
	Defects in AChR clustering pathway	<1%	*AGRN*	• Early-onset or late-onset phenotype • Persons w/late onset may present w/distal muscle weakness & wasting in addition to myasthenia	Deterioration
Pre-synaptic CMS	Defect in ACh synthesis	4%-5%	*CHAT*	• Hypotonia, respiratory failure at birth • Episodic apnea • Improvement w/age	Improvement
	Defects in ACh recycling	<1%	*SLC5A7*	• Early onset • More severe than *CHAT*-related CMS • Arthrogryposis/joint contractures, apneic crisis at birth, marked ptosis, ophthalmoplegia, & muscle fatigability • Some have limited survival, some have milder phenotypes. • Some w/learning difficulties	Some improvement
		<1%	*SLC18A3*	Similar to *SLC5A7*	Some improvement
	Defects in synaptic vesicle docking,	<1%	*SNAP25*	Myasthenia is element of a severe & complex phenotype:	See footnote 4.

Table 1. continued from previous page.

CMS Subtype [1]		% of All CMS	Gene(s) [2]	Distinguishing Clinical Features	Response to AChE Inhibitors
	priming, fusing, & exocytosis			• Developmental & epileptic encephalopathy of infancy & childhood w/diverse clinical manifestations • Severe ID, cerebellar ataxia, brain atrophy	
		<1%	*VAMP1*	• Early-onset phenotype w/ severe congenital hypotonia & muscle weakness, feeding difficulties, delayed motor development, ophthalmoparesis. • May have joint contractures or joint laxity • May have respiratory insufficiency	Likely improvement [4]
		<1%	*SYT2*	• AR: Severe congenital-onset hypotonia & weakness, w/ variable degrees of respiratory involvement; mimics severe congenital myopathy • AD: Mimics distal hereditary motor neuropathy, slowly progressive distal motor neuropathy, & myasthenic syndrome	See footnote 4.
		<1%	*PREPL*	• Congenital hypotonia, feeding difficulties, ptosis, & proximal muscle weakness • Growth hormone deficiency • See footnote 7.	Acetylcholinesterase inhibitors possibly beneficial in infancy [4]
	Defects in axonal transport of proteins	<1%	*MYO9A*	• Early onset, ptosis, ophthalmoplegia & moderate global weakness, bulbar involvement, respiratory crises • Addl CNS symptoms: ID or learning difficulties, nystagmus, oculomotor apraxia	Improvement [4]
	Defect in mitochondrial citrate carrier	<1%	*SLC25A1*	• Relatively mild CMS phenotype w/ID • Subtle mitochondrial abnormalities	Improvement [4]

Table 1. continued from previous page.

CMS Subtype [1]		% of All CMS	Gene(s) [2]	Distinguishing Clinical Features	Response to AChE Inhibitors
Pre- & post-synaptic CMS	Limb-girdle-myasthenia w/ glycosylation deficiency	<1%	*ALG2* *ALG14*	Overlap w/CDG syndromes	See footnote 4.
		1%-2%	*DPAGT1* *GFPT1* *GMPPB*	• "Limb-girdle" pattern of weakness w/predominantly proximal weakness but usually no ptosis or EOP; tubular aggregates on muscle biopsy in some • ID may occur in *DPAGT1*-assoc CMS. • *GMPPB* assoc w/high CK & muscular dystrophy.	Improvement

ACh = acetylcholine; AChE = acetylcholinesterase; AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorders of glycosylation; CNS = central nervous system; EOP = external ophthalmoplegia; ID = intellectual disability
1. CMS subtypes are grouped by site of defect and mechanism of neuromuscular junction defect.
2. Additional genes are published as CMS genes or genes with an underlying pathology of the neuromuscular junction, but to date have been reported in only one or two studies. These genes include: postsynaptic proteins *RPH3A*, *MACF1,* and *CHD8*; synaptic proteins *LAMA5, LAMB2,* and *UNC13A;* as well as T*OR1AIP1* (encoding the inner nuclear membrane protein, lamin-associated protein 1), and *DES* (the muscle-specific member of the intermediate filament protein family linking the contractile apparatus to the sarcolemmal cytoskeleton, cytoplasmic organelles, and nucleus). Note: Neuromuscular endplate pathology has been associated with autosomal recessive loss-of-function variants in *DES* rather than autosomal dominant variants (associated with *DES*-related myopathies).
3. CHRNE is by far the most common causative gene among the AChR-subunit genes *CHRNA1*, *CHRNB1*, *CHRND*, and *CHRNE*.
4. No or limited data; small number of reported individuals
5. Murali et al [2019]
6. Owen et al [2018]
7. Additional non-myasthenic features (cystinuria, learning difficulties, endocrinologic defects, hyperphagia with tendency to obesity) may be associated with homozygous deletions of the two contiguous genes *PREPL* and *SLC3A1* on chromosome 2p21 (hypotonia-cystinuria syndrome; OMIM 606407).

3. Differential Diagnosis of Congenital Myasthenic Syndromes

Myasthenia gravis (OMIM 254200). The clinical picture of congenital myasthenic syndromes (CMS) is similar to that of myasthenia gravis (MG), in which individuals have a history of fatigable weakness involving ocular, bulbar, and limb muscles; however, the myasthenic symptoms of CMS usually start at or shortly after birth rather than in adulthood, as is usual for MG. Because seronegative autoimmune MG has been reported on occasion in children younger than age two years, MG may be difficult to differentiate from CMS, especially in later childhood or adulthood. Of note, immunosuppressive therapy does not improve clinical symptoms in CMS, whereas it does in MG.

Transient neonatal myasthenia gravis. Autoimmune MG can be passed across the placenta from mother to fetus and so can affect offspring at birth.

Childhood-onset disorders. Other genetic disorders partially resembling CMS to consider include the following:

- Spinal muscular atrophy
- Spinal muscular atrophy with respiratory distress 1 (SMARD1) (OMIM 604320)
- Congenital muscular dystrophies (See Fukuyama Congenital Muscular Dystrophy for review of the major congenital muscular dystrophy phenotypes.)
- Congenital myopathies including X-linked myotubular myopathy, nemaline myopathy (OMIM PS161800), and multiminicore myopathy (OMIM 255320, 602771). Of note, several congenital

myopathies show fatigable weakness and occasionally even a decrement (a sign that the neuromuscular junction is affected).
- Congenital myotonic dystrophy type 1
- Mitochondrial myopathies (See Primary Mitochondrial Disorders Overview.)
- Congenital disorders of glycosylation
- Moebius syndrome (OMIM 157900), characterized by facial weakness or diplegia with ocular abduction deficit

Additional considerations include infantile botulism and brain stem anomalies.

Adulthood-onset disorders. Other genetic disorders partially resembling CMS to consider include the following:

- Motor neuron disease including spinal and bulbar muscular atrophy (SBMA, Kennedy disease)
- Limb-girdle muscular dystrophy (OMIM PS253600, PS603511)
- Facioscapulohumeral dystrophy
- Mitochondrial myopathy and chronic progressive external ophthalmoplegia (See Primary Mitochondrial Disorders Overview.)
- Autosomal dominant progressive external ophthalmoplegia, caused by pathogenic variants in *POLG*, *RRM2B*, *SLC25A4*, *TWNK* (*C10orf2*) (See also Mitochondrial DNA Maintenance Defects Overview.)

4. Evaluation Strategies to Identify the Genetic Cause of a Congenital Myasthenic Syndrome in a Proband

Establishing a specific genetic cause of a congenital myasthenic syndrome (CMS):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history and physical examination are directed at identifying clinical features associated with a CMS (see Table 1).

Laboratory testing is directed at identifying lab findings associated with a CMS, especially findings on EMG and response to acetylcholinesterase inhibitors.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of CMS and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **A multigene panel** that includes some or all of the genes listed in Table 2 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of some of the genes associated with CMS, some panels may not include all the genes mentioned in this overview. (3) In some laboratories, panel options

may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Congenital Myasthenic Syndromes: Genes and Frequency

Gene [1]	% of All CMS	References
AGRN	<1%	Gan et al [2020]
ALG2	<1%	Cossins et al [2013], Monies et al [2014]
ALG14	<1%	Cossins et al [2013]
CHAT	4%-5%	Arican et al [2018], McMacken et al [2018]
CHD8	Single report	Lee et al [2020]
CHRNA1	<1%	Rodríguez Cruz et al [2018], Finsterer [2019]
CHRNB1	<1%	
CHRND	<1%	
CHRNE	50%	
COL13A1	1%-2%	Rodríguez Cruz et al [2019]
COLQ	10%-15%	Mihaylova et al [2008]
DES	Single report	Durmuş et al [2016]
DOK7	10%-15%	Lorenzoni et al [2020]
DPAGT1	<1%	Selcen et al [2014], Klein et al [2015]
GFPT1	<1%	Guergueltcheva et al [2012], Bauché et al [2017]
GMPPB	<1%	Belaya et al [2015], Rodríguez Cruz et al [2016]
LAMA5	Single report	Maselli et al [2018a]
LAMB2	Single report	Maselli et al [2009]
LRP4	<1%	Selcen et al [2015]
MACF1	Single report	Oury et al [2019]
MUSK	<1%	Owen et al [2018]
MYO9A	<1%	O'Connor et al [2016]
PLEC	<1%	Mroczek et al [2020]
PREPL	<1%	Régal et al [2014]
RAPSN	15%-20%	Della Marina et al [2020]
RPH3A	Single report	Maselli et al [2018b]
SCN4A	<1%	Finsterer [2019]

Table 2. continued from previous page.

Gene [1]	% of All CMS	References
SLC5A7	<1%	Bauché et al [2016], Rodríguez Cruz et al [2021]
SLC18A3	<1%	O'Grady et al [2016], Hakonen et al [2019], Lamond et al [2021]
SLC25A1	<1%	Balaraju et al [2020]
SNAP25	<1%	Shen et al [2014], Klöckner et al [2021]
SYT2	<1%	Bauché et al [2020], Maselli et al [2021]
TOR1AIP1	<1%	Cossins et al [2020], Malfatti et al [2022]
UNC13A	Single report	Engel et al [2016]
VAMP1	<1%	Polavarapu et al [2021]

CMS = congenital myasthenic syndromes
1. Genes are listed alphabetically.

5. Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Congenital myasthenic syndromes (CMS) are typically inherited in an autosomal recessive manner. Less commonly, CMS is inherited in an autosomal dominant manner (Table 3).

Table 3. Congenital Myasthenic Syndromes: Mode of Inheritance

MOI	CMS-Related Genes						
AR	*AGRN* *ALG2* *ALG14* *CHAT*	*COL13A1* *COLQ* *DES* *DOK7*	*DPAGT1* *GFPT1* *GMPPB* *LAMA5*	*LAMB2* *LRP4* *MACF1* *MUSK*	*MYO9A* *PLEC* *PREPL* *RAPSN*	*RPH3A* *SCN4A* *SLC5A7* *SLC18A3*	*SLC25A1* *TOR1AIP1* *UNC13A* *VAMP1*
AD	*CHD8*	*SNAP25*					
AD or AR	*CHRNA1* [1]	*CHRNB1* [1]	*CHRND* [1]	*CHRNE* [1]	*SYT2* [2]		

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Heterozygous gain-of-function variants result in autosomal dominant slow-channel CMS. Biallelic loss-of-function variants result in autosomal recessive CMS.
2. Heterozygous missense variants result in autosomal dominant CMS. Biallelic loss-of-function variants result in autosomal recessive CMS.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive congenital myasthenic syndrome (ARCMS) are obligate heterozygotes (i.e., presumed to be carriers of one pathogenic variant based on family history).

- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a CMS-causing pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants, additional possibilities to consider include:
  - A large deletion (i.e., a copy number variation) in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband [Shchagina et al 2020].
- Heterozygotes (carriers) are clinically asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an ARCMS-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are clinically asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has ARCMS or is a carrier, offspring will be obligate heterozygotes (carriers) for an ARCMS-causing pathogenic variant.
- In populations with a high carrier rate and/or a high rate of consanguineous marriages, the risk to the offspring of an affected individual of being affected is increased.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an ARCMS-causing pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the ARCMS-causing pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant congenital myasthenic syndrome (ADCMS) have an affected parent.
- A proband with ADCMS may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with ADCMS caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

- The family history of some individuals diagnosed with ADCMS may appear to be negative because of failure to recognize the disorder in affected family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Reduced penetrance is unlikely to be a factor in ADCMS with severe clinical presentation at birth but may be taken into account when considering the family history of a proband with a milder late-onset form.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known ADCMS-causing pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with ADCMS has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has an ADCMS-causing pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the CMS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Myasthenia Gravis Foundation of America, Inc. (MGFA)**

Phone: 800-541-5454
Email: mgfa@myasthenia.org
www.myasthenia.org

- **MyAware: Fighting Myasthenia Together**
  Phone: 01332 290 219
  Email: info@myaware.org
  www.myaware.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Congenital Myasthenia Information Page
- **European Myasthenia Gravis Association (EuMGA)**
  www.eumga.eu/EuMGA
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **Muscular Dystrophy Canada**
  Canada
  Phone: 800-567-2873
  Email: info@muscle.ca
  www.muscle.ca
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  www.musculardystrophyuk.org
- **TREAT-NMD**
  Advancing diagnosis, care and treatment for those living with neuromuscular diseases around the world.
  www.treat-nmd.org

6. Management

While there are no recent published consensus guidelines for the management of congenital myasthenic syndromes (CMS), Thompson et al [2019] summarized the current knowledge about the treatments for the various subtypes of CMS as related to the underlying genetic cause.

This section provides information regarding recommendations for evaluations following initial diagnosis (Table 3), medical management in general and based (when possible) on the genetic cause (Table 4), and recommended surveillance for individuals with CMS.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a CMS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with a Congenital Myasthenic Syndrome

System/Concern	Evaluation	Comment
Neuromuscular	Assessment of strength & motor function; in children, assessment of motor, speech, & cognitive development	
Respiratory function	• Baseline pulmonary function tests incl forced vital capacity in sitting & supine positions & blood gas exchange • Polysomnography to identify persons w/nocturnal hypoventilation • Review of history for symptoms of hypercapnia: daytime headache, restless sleep, loss of concentration, snoring, recurrent respiratory infections, weight loss	Respiratory studies may be normal between episodes in persons who experience acute crises.
Feeding ability	• Assessment of feeding abilities (sucking, swallowing, gastroesophageal reflux) • Eval of growth parameters to determine need for feeding interventions incl gavage feeding or gastrostomy insertion	
Contractures / Joint issues	• Assessment by physiatrist &/or orthopedist • Radiologic exam if spinal curvature noted	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of CMS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CMS = congenital myasthenic syndromes; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Medications Used in CMS

The choice of medication varies with the CMS subtype [Schara et al 2012, Finsterer 2019, Thompson et al 2019, Vanhaesebrouck & Beeson 2019, Huang et al 2021]; thus, genetic testing will help guide management. However, individual clinical situations may demand an immediate therapeutic trial. While monotherapy is the usual course of treatment for congenital myasthenia, a combination of drugs may be necessary to optimize the therapeutic effect and to minimize side effects [Thompson et al 2019].

Side effects of drugs used to treat myasthenic symptoms should be carefully monitored. If necessary, individual doses should be adjusted or treatment stopped.

Acetylcholinesterase (AChE) inhibitors (pyridostigmine). Although the majority of individuals with CMS benefit from AChE inhibitors (pyridostigmine), some myasthenic symptoms may remain refractory to treatment even in individuals who are otherwise responsive. Certain CMS subtypes (see Table 1), including slow-channel CMS, *COLQ*-related endplate AChE deficiency, and *DOK7*-related CMS, are refractory to or deteriorate with AChE inhibitors. See Table 5 for recommendations for treatment of those CMS subtypes.

3,4-diaminopyridine (3,4-DAP). Alternatively or in addition to AChE inhibitors, the potassium channel blocker 3,4-DAP may be used. This drug increases the release of ACh and prolongs the presynaptic action potential. Of note, two children with fast-channel CMS (FCCMS; caused by autosomal recessive loss-of-function variants of the genes encoding the acetylcholine receptor [AChR] subunits that shorten the time that the AChR channel is open) died when started on 3,4-DAP [Beeson et al 2005]. Although a relation to 3,4-DAP has not been proven, clinicians must be cautious when using 3,4-DAP in young children and in individuals with FCCMS.

Ephedrine (adrenergic agonist) treatment shows positive effects in different subtypes of CMS [Schara et al 2012, Rodríguez Cruz et al 2015] (see Table 5). It is well tolerated by most individuals and improvement in strength can be profound.

Albuterol, a beta-2-agonist, is effective in several CMS subtypes, in particular in endplate AChE deficiency, and in patients with *DOK7* pathogenic variants. Moreover, in patients with CMS responsive to AChE inhibitors, it may mitigate the detrimental effects on the endplate fine structure caused by long-term anticholinesterase treatment [Vanhaesebrouck et al 2019].

Table 5. Congenital Myasthenic Syndromes: Medication Recommendations for Certain Genetic Causes and Subtypes

Gene(s) / Subtype(s) [1]	Treatment	Comments	References
AChR subunit genes [2] / Slow-channel CMS	Adults: fluoxetine [3] Children & teenagers: quinidine [4]	In those w/pathogenic variants in 1 of the AChR subunit genes but w/the **AChR deficiency subtype**, quinidine may be detrimental.	Chaouch et al [2012], Thompson et al [2019]
COLQ / Endplate AChE deficiency *DOK7* / Defect in AChR clustering pathway	**One of the following:**		
	Ephedrine	Well tolerated by most persons; improvement in strength can be profound.	Wargon et al [2012], Thompson et al [2019]
	Albuterol	First-line treatment or alternative to ephedrine in AChE deficiency	Wargon et al [2012], Witting & Vissing [2014], Thompson et al [2019]

1. For a detailed summary of treatment options in rare CMS subtypes see Thompson et al [2019].
2. CHRNA1, *CHRNB1*, *CHRND*, *CHRNE*
3. Fluoxetine may induce suicidal ideation; thus, caution is strongly suggested in its use in childhood.
4. Quinidine has some major side effects including *torsade de pointes* (a potentially life-threatening arrhythmia), hypotension, cinchonism (or quininism), and hypersensitivity reactions. In individuals with CMS, adverse effects including exacerbation of weakness and development of respiratory failure may occur.

Non-Pharmaceutical Treatment

In addition to medication therapy, a multidisciplinary approach to the clinical management of the affected individual greatly improves quality of life and can influence survival. Management should be tailored to the individual, the specific CMS subtype, and the rate of progression.

Depending on the individual clinical situation, clinical management may include the following:

- Physical and occupational therapy
- Speech therapy
- Orthotics or a wheelchair
- A percutaneous gastric tube
- Ventilatory support

Prevention of Primary Manifestations

Sudden respiratory insufficiency or apneic attacks provoked by fever or infections are common in individuals with pathogenic variants in *CHAT* or *RAPSN*, even if the myasthenic symptoms are mild between crises. These individuals should receive prophylactic anticholinesterase therapy.

Note: Less frequently, acute respiratory events may also occur in other CMS subtypes. Parents of infants are advised to use apnea monitors and be trained in CPR.

Surveillance

Regular surveillance of muscle strength and respiratory function is recommended, usually at least every six months in children and every 12 months in adults. In some individuals, especially those with *COLQ* and *DOK7* pathogenic variants, slowly progressive respiratory impairment is seen with increasing age. Symptoms of nighttime hypoventilation should be considered.

Agents/Circumstances to Avoid

A number of drugs are known to affect neuromuscular transmission and therefore exacerbate symptoms of myasthenia gravis (e.g., ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta-blockers, procainamide, and quinidine). These drugs are not absolutely contraindicated and may be used with caution in CMS. See Myasthenia Gravis: Cautionary Drugs for a more complete list.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures – especially newborns or young children, who could benefit from early treatment to prevent sudden respiratory failure. Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Neurologic/neuropediatric examination and electrophysiologic testing (repetitive nerve stimulation) if the pathogenic variant(s) in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Data on pregnancies in CMS are limited. Seventeen pregnancies were reported in eight French individuals with CMS [Servais et al 2013]. According to these data pregnancy was a frequent cause of clinical exacerbation but the vast majority of individuals recovered their pre-pregnancy clinical status six months after delivery. The children's outcome was excellent, except for one newborn who developed a severe neonatal (autosomal dominant) slow-channel CMS. Pregnant individuals should be closely followed by neurologists during the course of pregnancy. Careful respiratory and cardiac surveillance should be initiated in consultation with obstetric specialists.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Chapter Notes

Author Notes

Dr Hanns Lochmüller's lab website: lochmullerlab.org

Revision History

- 23 December 2021 (ha) Comprehensive update posted live; scope changed to overview
- 14 July 2016 (ha) Comprehensive update posted live
- 28 June 2012 (cd) Revision: targeted mutation analysis of *CHRNA1* no longer listed in the GeneTests™ Laboratory Directory as being available clinically
- 22 March 2012 (me) Comprehensive update posted live
- 26 September 2006 (aa) Revision: clinical testing available for: mutation scanning of *RAPSN*, *CHAT*, *COLQ*, *CHRNB1*, and *CHRND*; sequence analysis of *CHRNE* and *CHRNA1*; targeted mutation analysis of *RAPSN* mutation p.N88K, *CHAT* mutation p.I305T, and *CHRNA1* mutation p.G153S; prenatal diagnosis for *CHAT*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *COLQ*, and *RAPSN*
- 20 September 2005 (aa) Revision: sequence analysis for *RAPSN* clinically available
- 8 August 2005 (me) Comprehensive update posted live
- 9 May 2003 (me) Review posted live
- 30 January 2003 (aa) Original submission

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