MDA Muscular Dystrophy Association

Congenital Myasthenic Syndromes (CMS)

Congenital myasthenic syndromes (CMS) are a diverse group of neuromuscular disorders affecting the neuromuscular junction, the site where nerve signals are transmitted to muscles. At a normal neuromuscular junction, a nerve cell provides a signal to the muscle fiber to contract by releasing the chemical acetylcholine (ACh). ACh binds to the ACh receptor — a pore or "channel" in the surface of the muscle fiber under the nerve — allowing an inward flux of ion current that triggers muscle contraction. These contractions enable someone to move a hand, dial the telephone, walk through a door, or complete any other voluntary movement.

CMS results from flaws in genes necessary for making the ACh receptor or other components of the neuromuscular junction. The many types of CMS are grouped into three main categories named for the part of the neuromuscular junction that's primarily affected: presynaptic (the nerve cell), postsynaptic (the muscle cell), and synaptic (the space in between). However, there are additional CMS types, such as DOK7-CMS, that affect all three components.

As its name implies, CMS usually has a congenital (at or near birth) onset, but the disease can first manifest in children and even in adults. The different types vary in the kind and degree of symptoms, but generally, the earlier the symptoms appear, the more pronounced the disease is likely to be. Symptoms typically include weakness, fatigue, and droopy eyelids (ptosis).

In the past, people with CMS were often told they had myasthenia gravis (MG) and were subjected to years of ineffective immunosuppressive therapy. By identifying the genetic defects that cause CMS, MDA-funded scientists have improved the diagnosis of CMS and discovered drugs that are effective against it. While there is no cure for CMS, scientists and clinicians are pursuing better drug treatments and identifying techniques to fix or replace the underlying genetic defects through gene therapy.

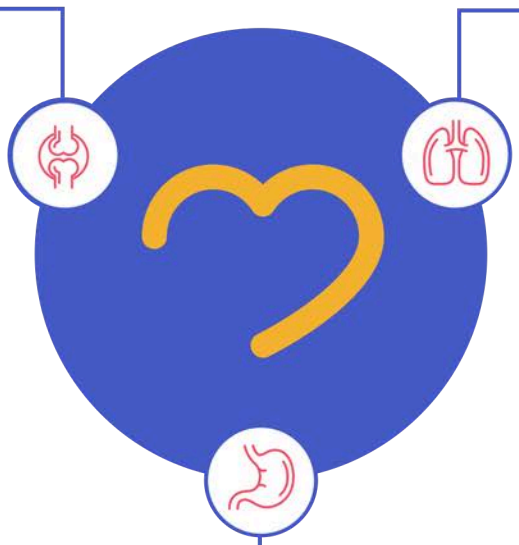
Types of CMS

- Presynaptic CMS is caused by insufficient release of ACh.
- Postsynaptic CMS, also known as ACh receptor deficiency or fast-channel CMS, is caused by ACh receptors that are missing or don't stay open long enough.
- Slow-channel CMS, another type of postsynaptic CMS, is caused by ACh receptors that stay open too long.
- Synaptic CMS is caused by a deficiency of acetylcholinesterase, an enzyme that breaks down ACh.
- Other types of CMS result from gene defects affecting the development and maintenance of the neuromuscular junction, such as mutations in DOK7.

What Are the Signs and Symptoms of CMS?

Skeleton and muscle

- Ptosis (droopy eyelids)
- Bulbar weakness impacting ability to talk, chew, swallow
- Scoliosis (curvature of the spine), in some cases
- Fatigue
- Delayed motor milestones, in some cases



Respiratory

- Episodes of apnea (temporary stop in breathing)
- Weak chest muscles leading to breathing problems

Gastrointestinal

- Feeding and swallowing challenges

To learn more about CMS, visit MDA.org or contact the MDA Resource Center at 833-ASK-MDA1 (275-6321) or ResourceCenter@mdausa.org.

What Should I Know About CMS?

1. Onset usually begins in infancy but can also appear later in childhood or even adulthood.
2. Initial symptoms usually include fatigue, muscle weakness, and droopy eyelids (ptosis).
3. In general, the earlier symptoms appear, the more pronounced the disease will be.
4. CMS is caused by mutations in genes that are responsible for encoding parts of the acetylcholine (ACh) receptors or other parts of the neuromuscular junction (the site where nerve signals are transmitted to muscles).
5. Different types of CMS are categorized according to the site in the neuromuscular junction that is affected: presynaptic, postsynaptic, and synaptic.
6. Since scientists have identified the genetic defects that cause most CMS, they are now working on techniques to replace or fix the genes through gene therapy.
7. Like myasthenia gravis (MG), CMS is characterized by weakness and fatigue due to problems at the neuromuscular junction. Unlike MG, CMS is an inherited disease caused by mutations in the gene. CMS is not an autoimmune disease and does not respond to immunosuppressant drugs.
8. Cholinesterase inhibitors can help treat some but not all types of CMS.

How Is CMS Treated?

While there is no cure for CMS, there are medications and other treatments that can help manage symptoms and improve quality of life.

Cholinesterase inhibitors, also known as anticholinesterases, boost levels of ACh and may help manage presynaptic CMS, as well as ACh receptor deficiency and fast-channel CMS (types of postsynaptic CMS).

ACh receptor deficiency and fast-channel CMS may also be treated with drugs containing amifampridine, which enhances ACh release.

Slow-channel CMS (a type of postsynaptic CMS) does not respond to cholinesterase inhibitors. Treatment for slow-channel CMS may include quinidine or fluoxetine, both of which restrict the influx of ions through the ACh receptor ion channel.

Beta-adrenergic agonists such as albuterol are effective in many types of CMS, especially those caused by DOK7 and COLQ deficiency.

Physical and/or occupational therapy may help manage muscle weakness and fatigue, as well as help with activities of daily living (ADLs).

Speech therapy may be recommended to address issues with swallowing, such as disphagia.

For sleep apnea and other breathing challenges, it is important to see a pulmonologist and/or a respiratory therapist. Devices such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) may be recommended.

Symptoms by Type of CMS

- Presynaptic CMS commonly appears as CMS with episodic apnea (CMS- EA). It has its onset in infancy and causes ocular weakness (weakness in muscles controlling the eyes), which can cause droopy eyelids. It also causes bulbar weakness (named for the nerves that originate from the bulblike part of the brainstem), making it difficult to talk, chew, swallow, and hold up the head. This type is also characterized by episodes of apnea (a temporary stop in breathing).
- Postsynaptic CMS (ACh receptor deficiency, fast-channel CMS) has symptoms ranging from mild to extreme. In infants, it may cause severe weakness, feeding and respiratory problems, and delayed motor milestones (sitting, crawling, walking). Childhood- and adult-onset cases often cause droopy eyelids and fatigue but usually don't interfere with daily living.
- Postsynaptic CMS (slow-channel CMS) causes extreme weakness in infant-onset cases, often leading to loss of mobility and respiratory problems in adolescence. Adult-onset cases may not be disabling.
- Synaptic CMS can cause extreme weakness, with feeding and respiratory difficulties from birth or early childhood. Weakness also causes delayed motor milestones (sitting, crawling, and walking) and often leads to reduced mobility and scoliosis (curvature of the spine).

MDA Glossary

Acetylcholine (ACh)
A chemical that binds to a receptor in the muscle, twisting it open and allowing an inward flux of electrical current that triggers muscle contraction

Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP)
Respiratory devices that assist in moving air in and out of the lungs

Dysphagia
Difficulty swallowing

Neuromuscular junction
The place where nerve cells connect with the muscles they control

Neuromuscular junction disorder
A condition that is a result of the destruction, malfunction, or absence of one or more key proteins involved in the transmission of signals between muscles and nerves

Postsynaptic
The muscle cell component of the neuromuscular junction

Presynaptic
The nerve cell component of the neuromuscular junction

Ptosis
Drooping of the eyelids

Synaptic
The space in between the nerve and muscle cell of the neuromuscular junction