Congenital Myasthenic Syndrome (CMS)

What is Congenital Myasthenic Syndrome?

Congenital Myasthenic Syndrome (CMS) is a family of inherited neuromuscular conditions characterised by skeletal muscle weakness that worsens with physical exertion. Cardiac and smooth muscle are usually not involved. Coordination, sensation, and tendon reflexes are normal as are cognitive skills. Myasthenia (muscle weakness) is due to problems in the neuromuscular junction, which is the area between the ends of nerve cells and muscle cells where signals are relayed to trigger muscle movement. Symptoms of muscle weakness typically begin in early childhood, however they can also begin in adolescence and adulthood. The severity of the myasthenia varies greatly, with some people experiencing minor weakness and others having such severe weakness that they are unable to walk. Prevalence of CMS is unknown.

What are the different types of Congenital Myasthenic Syndrome?

The types of CMS are grouped into three main categories depending on the part of the neuromuscular junction affected. These include presynaptic (the nerve cell), postsynaptic (the muscle cell) or synaptic (the space in between the nerve and the muscle cell).

Presynaptic CMS is characterised by insufficient release of acetylcholine, a neurotransmitter that controls muscle contractions. This affects 7-8% of individuals with CMS.

The features of CMS are often present at birth; however sometimes symptoms are not noticeable until adolescence.

Postsynaptic CMS have two forms, and affect a total of approximately 75-80% of individuals with the condition. One is characterised by missing acetylcholine receptors or receptors that don't stay open long enough called "fast-channel CMS" and the second is characterised by acetylcholine receptors that are open for too long, called "slow-channel CMS".

Synaptic CMS is characterised by a deficiency of acetylcholinesterase, an enzyme which breaks down acetylcholine. This affects 14-15% of individuals with the condition. Identification of the specific subtype is important in patient care for determining the most effective treatment.

What are the features of CMS?

The features of CMS are often present at birth; however sometimes symptoms are not noticeable until adolescence. Infants with CMS may be slow to meet their crawling or walking milestones and children with CMS have visible facial weakness. Affected infants can also have periods of shallow breathing often at times of infection, fever or excitement which can cause cyanosis (blue skin or lips). An abnormal, high-pitched, musical breathing sound caused by a blockage in the throat or voice box (larynx) can also be heard in CMS infants when taking in a breath. Other symptoms of CMS are difficulties with chewing, swallowing or feeding and choking spells due to muscle weakness of the mouth and throat. The eye muscles are also commonly affected causing droopy eyelids (ptosis). Curvature of the spine (scoliosis) and in some cases joint contractures can be present.

What causes CMS?

CMS is an inherited neuromuscular condition. It is caused by alterations in genes necessary for making the acetylcholine receptor or other components or proteins of the neuromuscular junction. Mutations in the *CHRNE* gene are responsible for more than half of all cases. A large

number of cases are also caused by mutations in the *RAPSN*, *CHAT*, *COLQ*, and *DOK7* genes. Except for slow-channel CMS, the inheritance pattern for the different types of CMS is autosomal recessive. This means that it takes two copies of the defective gene, one from each parent, for the disease to be present. Slow-channel CMS is autosomal dominant; therefore, it only takes one copy of the gene from one parent to cause the disease which means that there is a 50% chance of an affected parent to pass on the disease to their child.

Diagnosis of Congenital Myasthenic Syndrome

A full comprehensive family history and physical examination is part of the diagnostic process. The physician, usually a neurologist, will be looking specifically for weakness and fatigue, particularly in response to physical exertion. The strength of eyelids and skeletal muscles may be assessed by asking the patient to look towards the ceiling without blinking and holding their arms out for as long as possible.

If physical tests are consistent with myasthenia, blood tests will be ordered to detect antibodies to the acetylcholine receptor. A negative test will rule out myasthenia gravis (MG), an autoimmune disease and may indicate possible CMS. However, it does not rule out seronegative types of MG. Electrodiagnostic tests, where an electrode is placed on the surface of a major muscle and a small shock delivered to the nerve, record the responses in the muscle to contraction.

An intravenous injection of Tensilon, a fast-acting acetylcholinesterase inhibitor may be administered as part of the diagnostic process and a temporary increase in strength after the injection would indicate CMS.

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Muscle biopsy and the absence of major pathological findings as well as genetic testing can further conclude the type of CMS and a family history of myasthenic syndrome would support this diagnosis.

Management of CMS

Non-invasive ventilation at night to help with breathing difficulties. Apnea monitors are recommended for young children.

Treatment with medications is available for many types of CMS;

- **Pyridostigmine**, a cholinesterase inhibitor, enables messages to travel from the nerve to the muscle. This is used for presynaptic CMS and postsynaptic fast-channel CMS.
- **3,4-diamino-pyridine' DAP**, increases acetylcholine release which causes electrical messages to last longer. This is used in postsynaptic fast-channel CMS.
- **Ephedrine and/or albuterol (salbutamol)** can improve muscle strength.
- **Quinidine or fluoxetine** to help faulty acetylcholine receptors to close for post synaptic slow-channel CMS.

There are no medications currently available to treat synaptic CMS.

Certain drugs should be avoided by people with CMS as they are known to affect neuromuscular transmission and exacerbate symptoms of the condition and include ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta-blockers, procainamide, quinidine.

Research into Congenital Myasthenic Syndrome

Current research studies are focusing on the development of a new mouse model of a CMS; genetic analysis of a worm model of a slow-channel myasthenic syndrome; studies of how the nerve-muscle function forms and also methods to improve diagnosis, treatment and prevention of congenital myasthenic syndrome.