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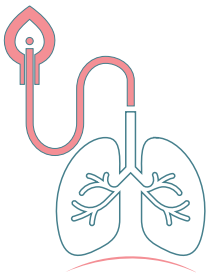

RESPIRATORY INVOLVEMENT IN CHARCOT-MARIE-TOOTH DISEASE A BRIEF OVERVIEW

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Respiratory Involvement in Charcot-Marie-Tooth Disease a Brief Overview

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What's Inside

This booklet provides a general overview of CMT-related respiratory muscle weakness and compares it to other types of respiratory impairment. The information presented is for informational purposes only and is not intended to serve as a diagnostic tool and nor is the presented information intended to replace the advice of a qualified healthcare provider. Always seek and follow the advice of your healthcare provider.

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The Basics of Respiratory Involvement in Charcot-Marie-Tooth Disease

A Brief Overview

Introduction

Charcot-Marie-Tooth disease, or CMT for short, is a group of inherited peripheral neuropathies with many causes and many different presentations. CMT is rare, affecting approximately only 3 million people worldwide, but it's the most commonly inherited peripheral neuropathy. Although CMT symptoms can be treated and well-managed, the disease itself has no known effective treatment or cure—there are no disease modifying therapies.

CMT gets its name from the three doctors who first described it in 1886: Jean-Martin Charcot (1825-1893), Pierre Marie (1853-1940), both from France, and Howard Henry Tooth (1856-1925) from England. Today, CMT as a disease name has evolved into an umbrella term that refers to many different sensory and/or motor neuropathies, axonopathies, myelinopathies, and neuronopathies. In its infancy, however, CMT described a disease that causes only lower leg muscle weakness and atrophy, or what is aptly called, "peroneal muscle atrophy." Over time, however, CMT has revealed itself to be profoundly more diverse with reaches far beyond the lower legs.

CMT can cause breathing problems, and when it does, it causes a very specific kind of respiratory

impairment called, "Neuromuscular-Induced Respiratory Muscle Weakness." In CMT, this is referred to as CMT-induced neuromuscular respiratory muscle weakness, which can be shortened to "CMT-related respiratory muscle weakness." Rather than affecting lung and airway tissues, this type of respiratory impairment is caused by a weakening of the muscles used for breathing. In CMT, the breathing muscles can become weakened as a consequence of the effects of the disease on the nerves that control these muscles. Just as the muscles of the lower legs, feet, and hands can become weakened in CMT, so to can the muscles used for breathing.

For reasons not well understood, not every CMTer will develop CMT-related respiratory muscle weakness. True to CMT, those who do develop this respiratory impairment can experience varying degrees of severity and progression over time. CMT does not preclude anybody from developing every other condition the general public can have. Just because a CMTer has symptoms of respiratory impairment does not necessarily mean the muscles used for breathing are becoming weakened. There could be other causes for the respiratory impairment. Properly diagnosing the underlying cause is essential for achieving desired treatment outcomes as the various types of respiratory impairment are treated differently from one another.

What is Respiratory Impairment?

Respiratory impairment is a very broad term used to describe any level of a reduction in the ability to adequately oxygenate the body and/or to adequately remove carbon dioxide from the body. Anything that causes respiratory impairment is considered respiratory disease. Respiratory disease can be acute—short-term, or chronic—long-term/lifelong. All respiratory

disease, whether acute or chronic, causes shortness-of-breath (SoB). Respiratory viruses and respiratory bacterial infections, such as the flu (influenza virus) and bacterial pneumonia (pneumococcus bacteria), are examples of acute respiratory disease. Emphysema and idiopathic pulmonary fibrosis are examples of chronic respiratory disease.

Respiratory disease is grouped into two basic categories: diseases of lung/airway tissue, and thoracic cavity respiratory disease. Diseases of lung/airway tissue are diseases that affect the tissues of the lungs and airways, and these are divided into two subgroups: obstructive lung disease and restrictive lung disease. Combined, these represent the three basic classifications of respiratory impairment/disease: obstructive lung disease, restrictive lung disease, and respiratory disease of the thoracic cavity (chest cavity).

What is Obstructive Lung Disease?

Obstructive lung disease is a group of lung and airway tissue diseases that impair breathing by obstructing airflow out of the lungs and airways when breathing out. People who have an obstructive lung disease cannot fully empty the lungs when breathing out, which is sometimes referred to as "air trapping." This causes a condition known as hyperinflation. Hyperinflation is a condition in which the lungs don't fully empty when breathing out, remaining somewhat inflated when the next breath begins. Examples of obstructive lung disease include Emphysema, Chronic Bronchitis, and Bronchiectasis.

What is Restrictive Lung Disease?

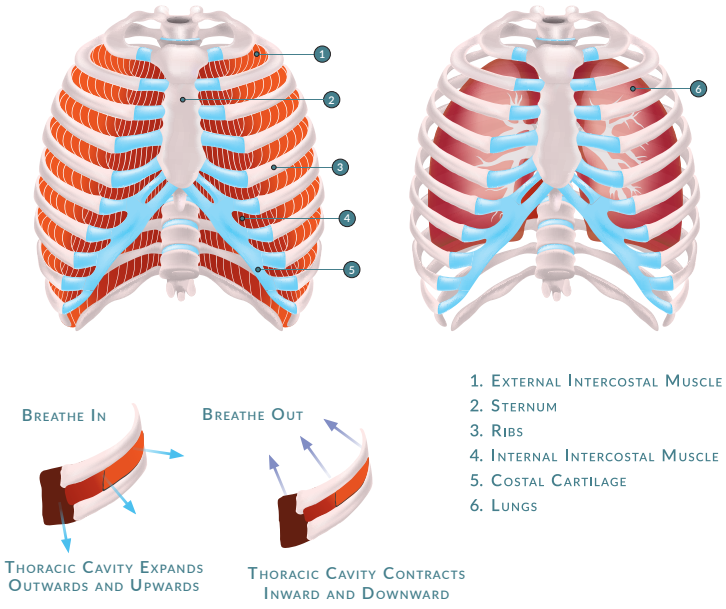
Restrictive lung disease is a group of lung and airway tissue diseases that impair breathing by restricting airflow into the lungs when breathing in. People who have a restrictive lung disease cannot fully fill the lungs with each breath. This causes a condition known as hypoinflation. Hypoinflation occurs when the lungs can't fully inflate with each breath. Restrictive lung disease often results in a reduction of lung distensibility, or what is a reduction in the ability of lung tissue to expand—a loss of lung elasticity. As a consequence, total overall lung capacity can become reduced. Examples of restrictive lung disease include Sarcoidosis, Idiopathic Pulmonary Fibrosis, and Pleurisy.

What is Thoracic Cavity Respiratory Disease?

Thoracic cavity respiratory disease is any respiratory disease/impairment that reduces the ability to fully expand the chest cavity with each breath while sparing lung and airway tissue. A distinction between this kind of respiratory impairment and the others is that lung and airway tissues remain healthy. Airflow into the lungs is not restricted and airflow out of the lungs is not obstructed. In respiratory diseases of the thoracic cavity, the limitations

to the chest cavity expanding fully with each breath cause a reduction in how much the lungs can inflate with each breath, and this leads to hypoinflation—the lungs under-inflate. Neuromuscular-induced respiratory muscle weakness is an example of thoracic cavity respiratory disease.

Thoracic Cavity



How Does CMT Cause Breathing Problems?

CMT can cause breathing problems by affecting the nerves that control the muscles used for breathing. Just as CMT can cause the muscles of the lower legs, feet, and hands to become weakened, for example, so to can CMT cause the muscles used for breathing to become weakened. When these muscles become weakened, they become weakened as a consequence of the effects of CMT exerted on the nerves that control

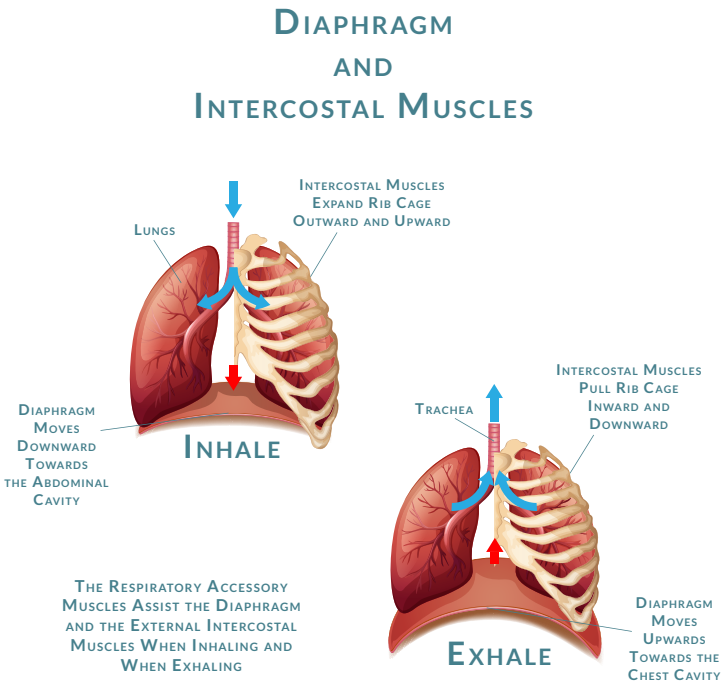
these muscles, just as is the case when the hands become weakened in CMT. The result is a reduction in the ability to fully expand the chest cavity with each breath, and this leads to a reduction in the ability to fully inflate the lungs with each breath—a condition called hypoinflation.

When talking about CMT-related respiratory muscle weakness, we frequently talk about the diaphragm and what's called the phrenic (freh-nick or free-nick) nerve. The phrenic nerve is the nerve that controls diaphragm movement. When this nerve is affected by CMT, the diaphragm can become weakened. The result is CMT-related respiratory impairment. The diaphragm and its nerve are not the only muscle (and nerve) used for breathing, and therefore, the diaphragm is not the only breathing muscle that can become weakened in CMT.

Which Muscles are Used for Breathing?

The respiratory cycle—one breath in and one breath out, is facilitated by the muscles used for breathing. The diaphragm is arguably the most important breathing muscle and starts each part of the respiratory cycle. The first part of the respiratory cycle, breathing in, starts with the diaphragm moving downward towards the abdomen. This action creates space within the chest cavity for the lungs to expand downward as they inflate with air. While this a very important muscle movement for breathing, it's not the only one.

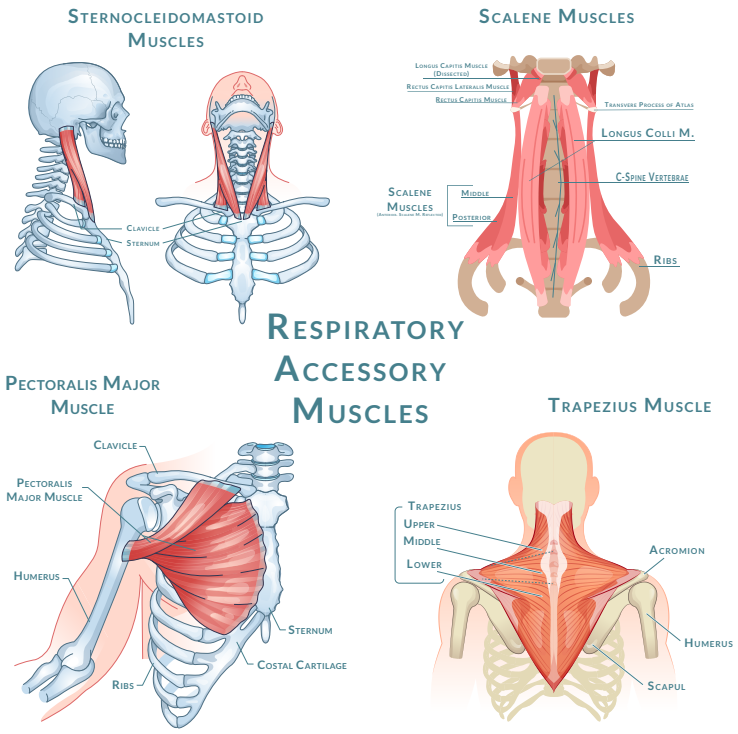
As the diaphragm moves downward into the abdomen, the external intercostal muscles of the rib cage expand the chest cavity outward. The chest cavity must expand outward if the lungs are to fully inflate with each breath. The diaphragm moving downward towards the abdomen, on its own, does not create enough space within the chest cavity for the lungs to fully inflate with each breath. The chest expanding outward is therefore a critical part of breathing. Helping the diaphragm and the external intercostal muscles are several muscles that are together collectively referred to as the respiratory accessory muscles.



What are the Respiratory Accessory Muscles? Respiratory accessory muscles are any muscle that helps the diaphragm and the external intercostal muscles to expand the chest cavity or to make the chest cavity smaller with each respiratory cycle.

This group of muscles consists of the pectoralis major muscles of the chest (the pecs), sternocleidomastoid muscles of the neck, the scalene muscles of the neck, the trapezius muscle between the shoulder blades, the internal intercostal muscles of the rib cage, the innermost intercostal muscles of the rib cage, the subcostal muscles of the rib cage, the transversus thoracis muscles of the rib cage, and the abdominal muscles. Some respiratory accessory muscles are used for expanding the chest cavity outwards when breathing in, some are used for making the chest cavity smaller when breathing out, and some are used for both.

The diaphragm is used for breathing in, is used for breathing out, and is arguably the most important breathing muscle. The external intercostal muscles, however, are equally as important. The external intercostal muscles are equally as important as the diaphragm because these are the primary muscles used for expanding the rib cage with each breath. These muscles don't work alone though. They have help.



Which Muscles are Used for Breathing In?

Aiding the external intercostal muscles with expanding the chest cavity with each breath are the sternocleidomastoid muscles of the neck, the scalene muscles of the neck, the trapezius muscle between the shoulder blades, and the pectoralis major muscles of the chest (the pecs). Collectively, these muscles are the inspiratory accessory muscles (inspiratory = breathing in).

The pectoralis major muscles help with expanding the chest cavity outwards. The sternocleidomastoid muscles of the neck, the scalene muscles of the neck, and the trapezius muscle between the shoulder blades each help to expand the chest cavity by lifting the top of the rib cage to expand the chest cavity upwards. Without these muscles performing their critical inspiratory role in breathing, there wouldn't be enough room in the chest cavity for the lungs to adequately inflate with each breath.

Which Muscles are Used for Breathing Out

Breathing out means reducing the size of the chest cavity. To accomplish this, the diaphragm moves upwards from the abdominal cavity towards the chest cavity. At the same time the diaphragm is moving upwards, the rib cage is contracting inward, and the top of the rib cage is moving downward. The muscles performing this task are the innermost intercostal muscles, the subcostal muscles, and

What are the Intercostals Muscles?

The external intercostal muscles, the internal intercostal muscles, the innermost intercostal muscles, and the subcostal muscles are often simply referred to as "the intercostals." The intercostals together with the transversus thoracis muscles are collectively the muscles of the thoracic cage. The thoracic cage is the structure (ribs, intercostals, etc.) that envelops the thoracic cavity, or what is the chest cavity, or, simply, what is the rib cage.

the transversus thoracis muscles. Together with the abdominal muscles which assist the diaphragm, these are the expiratory accessory muscles (expiratory = breathing out).

The innermost intercostal muscles, the subcostal muscles, and the transversus thoracis muscles reduce the size of the chest cavity by pulling the rib cage inward and the top of the rib cage downward, returning the chest cavity to its *normal* size and the rib cage to its normal position. Combined with the diaphragm moving upward (assisted by the abdominal muscles), air leaves the lungs as we breath out.

Breathing in is an active process: muscles actively moving are required for breathing in. Breathing out is a passive process: muscles are not required to actively move for breathing out. However, muscle movement is needed to return the chest cavity back to its *normal* size and position.

Is Breathing Voluntary or Involuntary?

All of the muscles used for breathing, whether the diaphragm, the external intercostal muscles, or the respiratory accessory muscles, are skeletal muscles, and each are controlled by nerves of the peripheral nervous system. Skeletal muscle movement, whether it's a leg muscle or the diaphragm, is controlled (innervated) by a motor nerve. Motor nerves control motor function. Motor function is voluntary movement of a muscle, such as moving muscles to walk, to talk, to swing an arm, and to breathe. Breathing is voluntary, but breathing is also involuntary.

We can voluntarily control our breathing muscles. We can hold our breath by simply stopping our breathing. We can voluntarily breathe faster or slower, and we can voluntarily breathe shallow or deeply. Breathing is also an autonomic action (automatic and involuntary) in which the brain can take control of how fast and how deeply we breathe. Whether voluntary or involuntary, each nerve that controls the muscles used for breathing are motor nerves that are part of the peripheral nervous system. Each of these nerves can be affected by CMT, and therefore, as a consequence, the muscles controlled by these nerves—the muscles used for breathing, can become weakened in CMT.

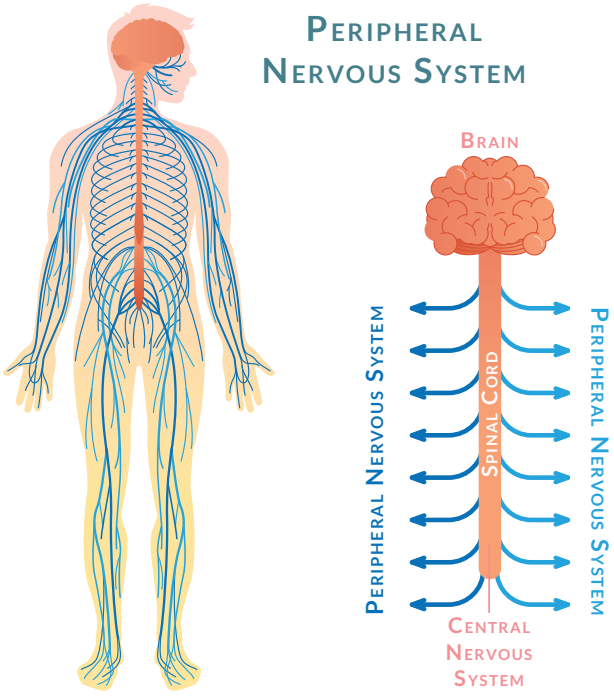
Which Nerves Control the Muscles Used for Breathing?

There are many different nerves that control the muscles used for breathing, and each nerve is quite complex. The phrenic nerve gets the most attention because it controls the diaphragm, and the diaphragm is arguably the most important muscle used for breathing. However, each of the muscles used for breathing are controlled by other various nerves.

The sternocleidomastoid and trapezius muscles are controlled by the accessory nerve, or what is cranial nerve XI (cranial nerve 11, or what is CN-XI). Although "cranial nerve" might imply brain and central nervous system, the cranial nerves are a group of twelve pairs of peripheral nerves that connect the muscles and organs of the head and torso directly to the brain rather than through the spinal cord like the other peripheral nerves.

A group of nerves, called the intercostal nerves (IC), control external intercostal muscle movement, internal intercostal muscle movement, transversus thoracis muscle movement, and abdominal muscle movement. Each of the intercostal muscle groups are controlled by intercostal nerves 3-6 (IC3-IC6). The transversus thoracis muscle is controlled by nerves IC2-IC5. The abdominal muscles are controlled by nerves IC7-IC11.

The scalene muscles are controlled by cervical spinal nerves 3-8 (C3-C8). Despite their name, these are peripheral nerves as they connect the spinal cord to something



outside of the spinal cord and brain. The lateral pectoral nerve controls the pectoralis major muscles (the pecs).

CMT can affect each of these many complex nerves. The question then focuses on the extent to which the muscles these nerves control become affected, and this can vary from not at all to significantly affected. When these muscles do become affected, they become weakened, just as the muscles of the feet or hands can. Not every CMTer will experience breathing muscles becoming weakened. For those who do, the breathing muscle weakness is not contained to only the diaphragm.

What are the Symptoms of CMT-Related Respiratory Muscle Weakness?

The symptoms of CMT-related respiratory muscle weakness are not unique to CMT. CMT is a neuromuscular disease that can cause respiratory muscle weakness for some. As a neuromuscular disease that can weaken the muscles used for breathing, the symptoms associated with CMT-related respiratory muscle weakness are the same as they are for neuromuscular-induced respiratory muscle weakness in general.

Symptoms of CMT-Related Respiratory Muscle Weakness Include but are Not Limited To:

- Shortness-of-Breath (SoB) (Dyspnea)
- Shallow Breathing
- Increased SoB when Lying Flat (Orthopnea)
- Increased SoB with Physical Exertion
- Weak Cough
- Obstructive Sleep Apnea
- Central Sleep Apnea
- Nocturnal Hypopnea
- Elevated Carbon Dioxide Levels

Often, the first signs of neuromuscular-induced respiratory muscle weakness is a gradual increase in difficulty getting a full breath which leads to SoB (dyspnea [disp-nee-uh]), breathing which becomes shallow, a feeling of suffocation when lying flat on your back (orthopnea [or-thop-nee-uh]), quickly becoming out of breath with any level of physical exertion, and a weak cough leading to a reduction in the ability to clear normal secretions since the muscles used for breathing are also used for coughing. Sleep disordered breathing can often develop. Sleep disordered breathing is a disruption in normal breathing when sleeping. Examples of sleep disordered breathing are Obstructive Sleep Apnea, Central Sleep Apnea, and Nocturnal Hypopnea.

What is Orthopnea?

Orthopnea is a condition in which breathing becomes difficult when lying flat, or what is called supine (soo-pine). Orthopnea is common in CMT-related respiratory muscle weakness and is often an early sign that respiratory muscle weakness is developing. In CMT-related respiratory muscle weakness, there is a reduction in the ability to fully expand the chest cavity with each breath. This becomes worsened when lying flat not only because the muscles that expand the chest cavity have to work against gravity and against the weight of the organs, but the diaphragm has to also work against the weight of the abdominal organs and lying flat removes the advantage of gravity helping to pull the diaphragm downward towards the abdominal cavity. The task of breathing can be difficult for the weakened muscles, and the result is an increase in SoB.

What is Obstructive Sleep Apnea?

Research suggests that CMT likely predisposes to obstructive sleep apnea (OSA). OSA is a condition in which the muscles of the throat (the upper airway) become weakened and collapse when sleeping. This causes the airway to become obstructed and results in breathing momentarily stopping (apnea—app-nee-uh). The muscles of the throat (the upper airway) can become weakened as a consequence of CMT, with or without respiratory muscle weakness. Hence, a likely predisposition to OSA. OSA can also be an early sign of respiratory muscle weakness in CMT. However, a CMTer can have OSA without developing CMT-related respiratory muscle weakness.

What is Central Sleep Apnea?

Central Sleep Apnea (CSA) is a condition in which there's a brief interruption in the signals from the brain to breathe. This results in breathing momentarily stopping. The difference between OSA and CSA is that CSA is not caused by an airway obstruction that causes a pause in breathing. Instead, CSA is a pause in breathing caused by a momentary interruption in the nerve signal that controls the muscles used for breathing. A CMTer can have both OSA and CSA. If the apnea events are frequent enough and/or last long enough, whether from OSA or CSA, or from both, a reduction in the body's oxygen level can occur.

What is Nocturnal Hypopnea?

Nocturnal Hypopnea is a condition in which there is a period of shallow breathing lasting at least ten seconds or longer when sleeping. Hypopnea causes hypoinflation leading to a reduction in the level of oxygen in the body and an elevation in carbon dioxide levels. Hypopnea can become especially troublesome during REM sleep for somebody who has CMT-related respiratory muscle weakness. During REM sleep, the only active muscle used for breathing is the diaphragm. When the diaphragm is weakened and not receiving any assistance from any other breathing muscle, it can't facilitate breathing as efficiently. The resulting shallow breathing (hypopnea) during REM sleep is the result of the weakened diaphragm not having the needed strength to handle respiratory demand on its own.

What is Dyspnea on Exertion?

Dyspnea on exertion describes SoB that occurs or worsens with physical activity/exertion and is often described as feeling "air starved." CMT-related respiratory muscle weakness can cause a reduction in the ability to increase Tidal Volume during periods of increased respiratory demands such as when vigorously exercising. Tidal Volume is the amount of air (volume) needed to properly oxygenate the body with each respiratory cycle (one breath in, one breath out).

Increasing Tidal Volume requires an increase in overall chest cavity expansion so that the lungs can become more fully inflated with each breath. CMT-related respiratory muscle weakness causes a reduction in the ability to fully expand the chest cavity with each breath. Therefore, as a consequence, there can be a reduction in the ability to increase Tidal Volume during periods of increased respiratory demand due to the weakened muscles. The result is an increase in shortness-of-breath, or what is dyspnea on exertion.

Does CMT-Related Respiratory Muscle Weakness Cause Elevated Carbon Dioxide Levels?

The most important concern with CMT-related respiratory muscle weakness is the potential for carbon dioxide levels to rise to unhealthy levels. In order to blow out adequate amounts of carbon dioxide from the lungs, the lungs have to first fill with enough air. CMT-related respiratory muscle weakness causes a reduction in the ability to fully inflate the lungs with each breath resulting in hypoinflation—the lungs don't inflate enough. This can lead to a reduction in the ability to blow out enough carbon dioxide to maintain healthy levels in the body.

In order to blow out enough carbon dioxide, the lungs have to inflate with an amount of air that is sufficient for blowing out enough carbon dioxide. The lungs can only blow out an amount of air equal to the amount of air that is inhaled. If the lungs are not able to inflate with the amount of air needed to then blow out enough carbon dioxide, the result can be elevated carbon dioxide levels leading to hypercapnia (high-per-cap-nee-uh). Hypercapnia is the term used to describe too much carbon dioxide in the body. Symptoms of hypercapnia include but are not limited to headaches, confusion, an inability to stay awake, and a worsening of respiratory symptoms. Ensuring carbon dioxide is maintained at a safe level is paramount in CMT-related respiratory muscle weakness.

Does CMT-Related Respiratory Muscle Weakness Affect Oxygen Levels?

Oxygen levels in CMT-related respiratory muscle weakness typically remain normal. Lung tissue is left unharmed in this type of respiratory impairment. Lung tissue retains the ability to adequately pull oxygen into the body. An exception would be a reduction in oxygen levels as a consequence of sleep disordered breathing (OSA, CSA, Nocturnal Hypopnea) that can lead to a reduction in the level of oxygen in the body. Oxygen levels, however, will typically return to normal after waking and becoming upright because the lung tissue is able to pull adequate amounts of oxygen into the body once sleep disordered breathing has resolved.

This is a brief and general overview of the symptoms associated with CMT-related respiratory muscle weakness. A CMTer who has CMT-related respiratory muscle weakness, whether diagnosed or otherwise, might have all the discussed symptoms, might have additional symptoms, or might have only a couple of the discussed symptoms. The degree of severity of each symptom as well as the overall severity of the associated respiratory impairment can be quite variable from CMTer to CMTer. For reasons not well understood, not every CMTer will develop respiratory muscle weakness. If experiencing any of the discussed symptoms, or any additional respiratory symptoms, consult your healthcare provider and follow their guidance.

How is CMT-Related Respiratory Muscle Weakness Diagnosed?

Doctors use a specialized test called a pulmonary function test (PFT) to assess the overall condition of the respiratory system. A PFT is a non-invasive battery of tests measuring many different complex metrics that collectively combine to provide a picture of how well the respiratory system is functioning. Results can exhibit a normal *pattern* on PFT, can exhibit an obstructive lung disease *pattern*, can exhibit a restrictive

lung disease *pattern*, or can exhibit a combination of obstructive and restrictive lung diseases.

Obstructive respiratory diseases such as emphysema and bronchiectasis exhibit an obstructive pattern on PFT. An obstructive pattern on PFT is the result when there is an obstruction to air flow out of the lungs. An obstruction to airflow out of the lungs leads to hyperinflation—the lungs can't completely empty and remain somewhat inflated due to diseased lung and/or airway tissue.

Restrictive lung diseases such as idiopathic pulmonary fibrosis and sarcoidosis exhibit a restrictive pattern on PFT. A restrictive pattern on PFT is the result when there is a restriction to airflow into the lungs. A restriction to airflow into the lungs leads to hypoinflation—the lungs are not able to fully inflate with each breath.

PFT data can show evidence of an obstructive lung disease by the data pattern revealed in the test results. PFT data can show evidence of a restrictive lung disease by the data pattern revealed in the test results. PFT data can show evidence of both an obstructive lung disease and a restrictive disease by the data pattern revealed in the results. CMT-related respiratory muscle weakness does not cause either an obstructive lung disease or a restrictive lung disease, so how does a PFT help a doctor with diagnosing the type of respiratory impairment CMT can cause?

What Does CMT-Related Respiratory Muscle Weakness Look Like on PFT?

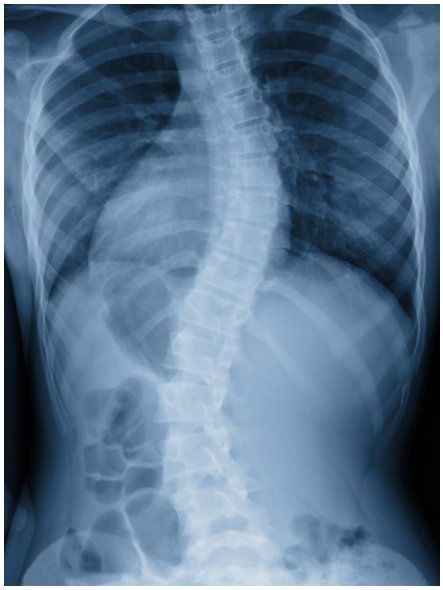
Obstructive lung disease and restrictive lung disease are types of respiratory disease that affect lung and airway tissue. Obstructive lung disease causes hyperinflation and this can be seen on PFT. Restrictive lung disease causes hypoinflation, and this, too, can be seen on PFT. The type of respiratory impairment CMT can cause is neither of these. Instead, the type of respiratory disease impairment CMT can cause is thoracic cavity respiratory disease.

Obstructive lung disease causes an obstruction to airflow out of the lungs. Restrictive lung disease causes a restriction to airflow into the lungs. Thoracic cavity respiratory disease causes a reduction in the ability to fully expand the chest cavity with each breath resulting in a reduction in the ability to fully inflate the lungs with each breath. When the lungs are not able to fully inflate with each breath, the result is hypoinflation. Therefore, on PFT, CMT-related respiratory muscle weakness will exhibit a restrictive lung disease pattern on PFT due to the resulting hypoinflation. CMT-related respiratory impairment is not a restrictive lung disease, but there is a caveat.

Restrictive Lung Disease as a Consequence of CMT-Induced Scoliosis

CMT does not cause restrictive lung disease. Restrictive lung disease is a type of respiratory impairment in which there is a restriction to airflow into the lungs, and this leads to hypoinflation. The type of respiratory impairment CMT can cause also leads to hypoinflation.

However, in restrictive lung disease, airflow into the lungs is restricted because lung and/or airway tissue is diseased. This is not the case with CMT. In CMT, airflow into the lungs is not restricted. Instead, there is a reduction in the ability to fully inflate the with each breath, and when properly treated, the lungs are able to fully inflate—airflow into the lungs is not restricted.



Scoliosis Xray

Scoliosis is somewhat common in CMT. Scoliosis is an abnormal side-to-side curvature of the spine. Scoliosis can sometimes become severe enough to cause a reduction in the overall size of the chest cavity. When this happens, there's a reduction in the expandability of the chest cavity and this then limits the total inflatability of the lungs leading to a reduction in total lung capacity. Overtime, a reduction in lung distensibility (how much the lungs can inflate) can occur and as a consequence, a restriction to airflow into the lungs. A restriction to airflow into the lungs equals restrictive lung disease.

CMT-induced scoliosis often presents challenges for the CMTer. However, rarely does CMT-induced scoliosis become severe enough to impact the lungs. When it does, corrective surgery to straighten the spine is warranted. Although CMT does not cause restrictive lung disease, restrictive lung disease can occur as a consequence of CMT-induced scoliosis should the scoliosis become severe enough to impact breathing.

Spirometry as a Quantifier of Respiratory Muscle Weakness

In addition to demonstrating a restrictive lung disease pattern on PFT, the weakened respiratory muscles that lead to the type of respiratory impairment that CMT can cause can be quantified by a series of tests performed during PFT called spirometry. Spirometry is typically a part of any PFT. But when performed while lying flat (supine), then compared to spirometry values when upright, the numerical data can quantify any present respiratory muscle weakness.

CMTers who have CMT-related respiratory muscle weakness typically have a much more challenging time breathing when lying flat. Spirometry values, therefore, are often significantly worse when supine compared to when upright and this finding can correlate with the respiratory muscle weakness that leads to the type of respiratory impairment CMT can cause.

Spirometry is a set of tests that doctors can perform bedside. This means that this is something that can be done during a routine pulmonology visit if the doctor has the specialized equipment in their office for this. Pulmonary function testing is often performed in a lab setting due to the highly specialized equipment. Often, PFT labs are not equipped to perform supine spirometry as they often don't have the means by which to lay the patient flat. However, with a little bit of creativity, chairs and whatnot can be set up to accommodate a supine position. If not, and the CMTer has an increased

Example of Bedside Spirometry Assessment

difficulty with breathing when supine, they likely have respiratory muscle weakness, and, barring any other cause, supine spirometry is not needed to quantify the muscle weakness.

Spirometry values when lying flat compared to when upright that are consistent with what is seen with neuromuscular-induced respiratory muscle weakness is not by itself diagnostic for CMT-related respiratory muscle weakness. Rather, it's one set of data, that when combined with other important PFT data, can help the doctor to arrive at the proper diagnosis. Proper diagnosis is key for successful treatment outcomes.

How Do I Find a Neuromuscular Pulmonologist?

Finding a neuromuscular pulmonologist can sometimes be a challenging task. Neuromuscular clinics that have pulmonology services available are an ideal clinic. The Charcot-Marie-Tooth Association has several Centers of Excellence CMT clinics that provide pulmonology care: Cedars-Sinai in Los Angeles, CA, The University of Colorado in Aurora, CO; Nemours Children's Hospital in Orlando, FL; the University of Florida in Gainesville, FL; Rush University in Chicago; HSHS St. Elizabeth's Hospital in O Fallon, IL; Atrium Health Neurosciences Institute in Charlotte, NC; and the University of Utah in Salt Lake

City, UT each provide pulmonology or respiratory therapy services according to the CMTA website.

The Muscular Dystrophy Association provides patient care for CMT and includes pulmonology care services at all of their clinics. Many University health systems have a pulmonology clinic with neuromuscular expertise. Each of these are a great starting point for any CMTer who might be experiencing CMT-related respiratory muscle weakness.

When a neuromuscular pulmonologist is not available, a pulmonologist who recognizes that neuromuscular disease can present diagnostic and treatment challenges not seen in other respiratory diseases is an invaluable physician and care team member. A CMTer can develop any respiratory disease that any non-CMTer can. It is critically important to rule out all other causes for the respiratory impairment when diagnosing any breathing problem that a CMTer has.

How is CMT-Related Respiratory Muscle Weakness Treated?

Although there isn't yet an available treatment for CMT, the many symptoms and presentations of the disease are quite treatable and manageable. This is especially true for CMT-related respiratory impairment. CMT-related respiratory muscle weakness often first reveals itself as obstructive sleep apnea. Obstructive sleep apnea (OSA) is quite common in the general public and is fairly common in CMT. The go-to treatment for OSA is CPAP.

What is CPAP?

CPAP Machine
(Continuous Positive Airway Pressure)
Pressure-Only Therapy

CPAP stands for Continuous Positive Airway Pressure. CPAP is a small tabletop device that sends pressurized air through a hose that connects to a mask worn by the person. The pressure, which is less than 0.5psi if the machine settings are maxed out, remains constant and keeps the airway open so the person can breathe well while sleeping (the pressure settings are usually in cmH2O (centimeters of water), and max setting is 25cmH2O which is equal to 0.355psi). The pressure the machine sends to the mask is determined during a sleep study. The general public tends to tolerate CPAP therapy quite well. Some, however, can have difficulty with exhaling against the constant pressure of air CPAP sends to the mask, even though the pressure is quite low. When this happens, an option called BiPap is often the next step.

What is BiPap?

BiPap stands for Bi-level Positive Airway Pressure. BiPap, just like CPAP, is a small tabletop device that sends pressurized air through a hose to a mask worn by the person. Where BiPap differs from CPAP is that BiPap sends pressurized air to the mask for keeping the airway open when breathing in, but then automatically reduces the amount of pressure

for breathing out—BiPap provides a higher pressure for breathing in and a lower pressure for breathing out. Although the maximum pressure BiPap can send to the mask is still less than 0.5psi, the pressure can be uncomfortable for some to breathe out against (max, like CPAP, is 25cmH2O). For this reason, BiPap can automatically reduce the pressure for breathing out (for example, down to 5cmH2O for breathing out), and this can lead to a greater ease of use for the person. Sometimes, however, BiPap isn't successful. When this happens, another therapy option called VPAP is often the next viable step.

What is VPAP?

VPAP is the acronym for Variable Positive Airway Pressure. VPAP, too, is a small tabletop device just like CPAP and BiPap, and it also sends pressurized air through a hose that connects to a mask worn by the person. As the name suggests, VPAP can provide a variable pressure, and does so throughout the use cycle, automatically adjusting the pressure up or down as needed based on any OSA the machine detects. While BiPap provides a variable pressure with one pressure setting for breathing in and a lower pressure for breathing out, these pressures are set and don't vary. VPAP, however, takes it a step farther by having the capability to automatically adjust the pressure up or down as needed throughout the use cycle. Hence, variable.

CPAP, BiPap, and VPAP have been in use for many years, and they generally treat conditions such as OSA with relative ease.

CMT-related respiratory muscle weakness provides treatment challenges the general public doesn't typically have. Successful treatment with any of these three options rests on the person having normal respiratory muscle strength—no weakened respiratory muscles as a consequence of a neuromuscular disease.

When the muscles used for breathing become weakened, the lungs' ability to inflate with an amount of air equal to Tidal Volume especially when asleep becomes reduced. Ensuring proper Tidal Volume is essential for maintaining adequate oxygen levels in the body and adequate carbon dioxide levels (*see* ***What is Dyspnea on Exertion?***). To treat this, doctors have used BiPap or VPAP and increase the difference between the high pressure setting for breathing in and the low pressure setting for breathing out. Often called a *pressure break differential*, the greater the difference between high and low pressure provides a theoretical higher Tidal Volume for the user. Managing Tidal Volume helps to manage oxygen and carbon dioxide levels. Using pressure support to provide volume support is a difficult challenge for doctors though. There's newer technology that greatly reduces these challenges.

With the technologies and treatment options that are available today, CMT specialists do not recommend these pressure-only therapies for their CMT-related respiratory impairment patients. Instead, a type of treatment called, "volume support," is the go-to therapy.

What is Volume Support?

Example of AVAPS Machine
(Average Volume Assured Pressure Support)
Therapy Targets Tidal Volume

CPAP, BiPap, and VPAP each have one thing in common: they're design limited to only pressure support. These three therapies provide air pressure for keeping the airway open when sleeping. They each accomplish this in their respective way, but they are designed only for keeping the airway open. CMT-related respiratory muscle weakness presents with treatment needs that exceed the design limitations of pressure-only devices such as CPAP, BiPap, and VPAP. In addition to needing pressure support to keep the airway open, CMT-related respiratory muscle weakness also needs volume support. There are two types of non-invasive volume support commonly used: AVAPS and iVAPS.

What is AVAPS?

AVAPS stands for Average Volume Assured Pressure Support. AVAPS is a type of non-invasive ventilator, or NIV. Non-invasive ventilator is a scary word. However, this type of NIV, like CPAP, BiPap, and VPAP (which are also types of NIV), is a small tabletop device that sends air through a hose that connects to a mask worn by the person—it's non-invasive. The full set up looks just like a BiPap, and its purpose is to help the person breathe more easily so that proper oxygen and carbon dioxide levels can be maintained.

CPAP, BiPap, and VPAP have one design purpose and only one: to keep the airway open by delivering pressurized air to the airway. For this reason, these are each called, "pressure-only," therapy. AVAPS provides an additional advantage pressure therapy alone cannot. In addition to pressure therapy, or what is pressure support, AVAPS provides what is called, "volume therapy," or what is volume support. What's this?

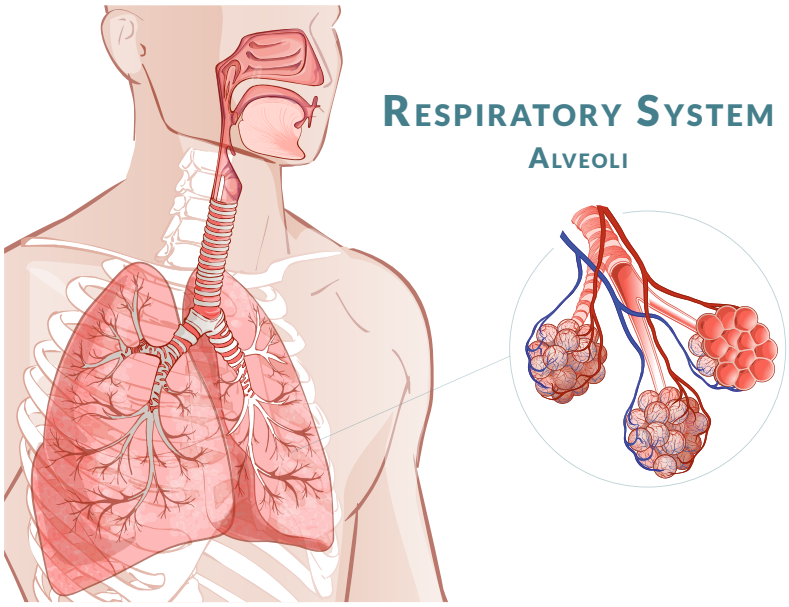
If the design purpose of CPAP, BiPap, and VPAP is to keep the airway open, the AVAPS design purpose is to not only keep the airway open with pressure support, but to also help the lungs more fully inflate with each breath via volume support.

In addition to sending pressurized air to a mask and into the person's airway, AVAPS sends a measured amount (volume) of air to the mask with each breath, and this volume of air is consistent with each breath. The amount of air delivered with each breath is equal to the person's Tidal Volume. Tidal Volume is the amount of air needed with each respiratory cycle (one breath in, one breath out) to keep the body properly oxygenated and to keep carbon dioxide levels low. The Tidal Volume general rule-of-thumb for adult women is 450ml of air, and for adult men 500ml of air. iVAPS is very similar to AVAPS.

What is iVAPS?

iVAPS is the acronym for Intelligent Volume Assured Pressure Support. iVAPS functions just like AVAPS, but with a difference. The volume support provided by AVAPS is based on Tidal Volume. The difference with iVAPS is that, in addition to providing Tidal Volume, iVAPS attempts to calculate negative space within the lungs and to then provide extra volume for filling the calculated negative space. This is also referred to as "targeting alveolar volume." Alveoli are the millions of tiny air sacs within the lungs that transfer oxygen into the blood and carbon dioxide out of the blood. Because iVAPS is designed to target alveolar volume, this is a preferred treatment for obstructive lung diseases that cause the tiny air sacs in the lungs to collapse, such as COPD.

Although CMT-related respiratory muscle weakness is not COPD and does not cause COPD, some doctors prefer iVAPS over AVAPS for their CMT-related respiratory muscle weakness patients. An advantage iVAPS has over AVAPS is that volume doesn't vary with AVAPS but iVAPS can be set up to vary delivered volume as needed throughout the use cycle. Variable volume capability can accommodate changes in Tidal Volume needs where AVAPS remains locked into one consistent volume with each breath.



iVAPS
(Intelligent Volume Assured Pressure Support)
Therapy Targets Alveolar Volume

Why is Volume Support Important?

When somebody has CMT-related respiratory muscle weakness, they have a reduction in the ability to fully inflate the lungs with each breath. The volume of air delivered by volume support is the volume of air equal to the person's Tidal Volume (whether AVAPS or iVAPS).

This helps the lungs to inflate more fully with each breath and with less required muscle effort. In addition to more fully inflating the lungs with each breath, this provides a needed rest for the breathing muscles because they don't have to work as hard to maintain breathing, to maintain adequate ventilation.

Because volume support provides a measured amount of air with each breath, it provides an advantage over the use of the *pressure break differential* technique with BiPap or VPAP. Volume support can provide a controlled consistent amount of air delivered with each breath. Pressure cannot achieve this. The pressure support of AVAPS and iVAPS, however, is an important part of treatment.

The pressure support of AVAPS and iVAPS, which functions just as VPAP does with varying pressures as needed throughout the use cycle, helps to keep the airway open so the volume of air the machine is delivering can get to where it's needed—the lungs. The pressure support part of the therapy then reduces the pressure of the air for breathing out, just as VPAP does. This allows for the user to fully exhale before taking the next breath without having to "fight" against the higher pressure that's used for keeping the airway open when breathing in. Essentially, AVAPS and iVAPS are both a VPAP but with added volume support.

With pressure support ensuring the air gets to where it needs to go, the volume support can then assist the weakened respiratory muscles with adequate ventilation. Adequate ventilation, which is a full enough breath to adequately oxygenate the body, and a full enough breathe to also then remove adequate carbon dioxide from the body when breathing out, leads to better sleep quality and leads to an improvement in overall health. Volume support, such as AVAPS and iVAPS, isn't just for sleeping though. AVAPS and iVAPS can also be used during the day as needed.

How do You Know Which Therapy is Right for You?

Not every person who has CMT has or will develop CMT-related respiratory muscle weakness. Treating OSA in CMT is just like treating OSA in the general public when there isn't any present CMT-related respiratory muscle weakness. In this situation, CPAP is generally the preferred choice of doctors and will usually lead to a successful outcome. If CPAP is uncomfortable, BiPap or VPAP can be great options.

NIV with volume support equipment can become expensive. For this reason, health insurance carriers might require starting with a lower-cost option first, with CPAP often being the lowest cost therapy. When CPAP doesn't work, the next step would usually be BiPap, then VPAP

before transitioning to volume support with AVAPS or iVAPS. Insurance carriers will sometimes require certain benchmarks be met at each step before advancing to the next level of therapy. Because health insurance is highly individualized, it's best to speak with your insurance carrier about NIV coverage.

If a person who has CMT has any degree of CMT-related respiratory muscle weakness, regardless of the presence of something like OSA, volume support is the therapy CMT specialists prefer. When a person has CMT-related respiratory muscle weakness, pressure-only support is not able to successfully treat the underlying cause of the respiratory impairment: breathing muscles that have become weakened as a consequence of the of the neuromuscular affects exerted by CMT on the nerves that control these muscles. Therapy must include volume support in addition to pressure support if treatment is to be successful.

What Kind of Doctor Treats CMT-Related Respiratory Muscle Weakness?

A pulmonologist diagnoses and treats respiratory impairment.

A pulmonologist is a doctor who specializes in respiratory impairment and diseases of the lungs and airway. CMT-related respiratory muscle weakness is a type of respiratory impairment that carries certain diagnostic and treatment challenges. A CMTer who has CMT-related respiratory muscle weakness is best served by a neuromuscular pulmonologist.

A neuromuscular pulmonologist is a pulmonologist who specializes in respiratory impairment caused by a consequence of neuromuscular disease. Neuromuscular pulmonology isn't necessarily a certified subspecialty of medicine, but a neuromuscular pulmonologist is a pulmonologist who has specialized training, experience, and skill with recognizing and treating the nuances associated with CMT-related respiratory muscle weakness that aren't often present in other types of respiratory impairment such as COPD.

Your Breathing Can be Treated

CMT-related respiratory muscle weakness will exhibit a restrictive lung disease pattern on PFT due to its associated hypoinflation. Although the type of respiratory impairment CMT can cause is not a restrictive lung disease, it's imperative to rule out the presence of any restrictive lung disease as the treatments for this are different than they are for CMT-related respiratory muscle weakness. Treating CMT-related respiratory muscle weakness while not treating any other present respiratory disease will lead to unsuccessful treatment outcomes and will likely lead to an overall worsening of respiratory symptoms and overall health.

Although there are no available disease modifying treatments (DMT) for CMT at this time, the many symptoms and presentations of CMT can be treated and well managed, and this includes CMT-related respiratory muscle weakness. Treatment and symptom management approaches are highly individualized and what works well for one might not be quite so great for another. A CMTer, however, does not have to suffer with respiratory impairment.

Resources

The Charcot-Marie-Tooth Association Centers of Excellence CMT clinics that provide pulmonology care or respiratory therapy services according to the CMTA website:

Cedars-Sinai Los Angeles, CA.

Cedars-Sinai Charcot-Marie-Tooth/Hereditary Neuropathy Center
127 S San Vicente Blvd
Ste A6600
Los Angeles, CA 90048
Clinical Director: Richard A. Lewis, MD
Appointments: Tami Kendra, 310-423-4268
Email: nmprogram@cshs.org

The University of Colorado Aurora, CO.

1635 Aurora Ct Ste 4200
Aurora, CO 80045
Visit Clinic Website
Clinical Director: Vera Fridman, MD
Appointments: 720-848-2080

Nemours Children's Hospital, Orlando, FL.

6535 Nemours Pkwy

Orlando, FL 32827

Clinical Director: Migvis Monduy, MD

Clinic Coordinator: Kelly Wydronkowski

Appointments: 407-650-7715

The University of Florida Gainesville, FL.

Norman Fixel Institute for Neurological Diseases

3009 SW Williston Rd

Gainesville, FL 32608

Clinical Director: James Wymer, MD, PhD

Appointments: 352-294-5400

Rush University, Chicago, IL.

1725 W Harrison St Ste 1118

Chicago, IL 60612

Clinical Director: Ryan D. Jacobson, MD

Appointments: 312-942-4500

HSHS St. Elizabeth's Hospital, O Fallon, IL.

3 St. Elizabeth, Suite 5000

O Fallon, IL 62269

Clinical Director: Raghav Govindarajan, MD

Appointments: 618-641-5803

Atrium Health Neurosciences Institute, Charlotte, NC.

1010 Edgehill Road N

Charlotte, NC 28207

Clinical Director: Urvi Desai, MD

Appointments: 704-446-1900

The University of Utah, Salt Lake City, UT.

175 N Medical Dr East

Salt Lake City, Utah

Clinical Director: Russell Butterfield, MD, PhD

Appointments: 801-585-7575

The Charcot-Marie-Tooth Association Centers of Excellence CMT Clinic Listing:

https://www.cmtausa.org/living-with-cmt/find-help/cmta-centers-of-excellence/

The Muscular Dystrophy Association (MDA) has long been a provider of patient care services for many non-muscular dystrophies, and this includes CMT. According to the MDA website, they have over 150 care centers in the US. Most, if not all, include neuromuscular respiratory expertise and can provide pulmonolgy care for CMTers.

To locate an MDA care center near you:
https://www.mda.org/care/mda-care-centers

Neuromuscular Pulmonary Care in Los Angeles, CA.:

Cedars-Sinai Division of Pulmonary/Critical Care

Ashraf M. Elsayegh, MD
Cedars-Sinai Medical Center
2080 Century Park E
Ste 507
Los Angeles, CA. 90048
310-556-0335 - Fax: 310-556-0330

Neuromuscular Pulmonary Care in southeast Michigan:

The University of Michigan Assisted Ventilation Clinic

1500 Medical Campus Dr.
SPC 5361
Ann Arbor, MI. 48109
888-287-1084 - Fax: 734-936-3494

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