CMT Respiratory Involvement: What It Is and What It Is Not

Clarifying the Misconceptions of CMT-Related Respiratory Impairment

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When the respiratory muscles are affected by CMT, the result is a very specific kind of respiratory impairment. This respiratory impairment, however, is shrouded in misconceptions and misunderstandings that often lead to poor treatment choices and therapeutic outcomes. Charcot-Marie-Tooth Association (CMTA) Advisory Board member and CMT pulmonology expert Ashraf Elsayegh, MD, FCCP, FAASM, Division of Pulmonary/Critical Care, Cedars Sinai Medical Center, Associate Clinical Professor of Medicine UCLA School of Medicine, explains that respiratory impairment is grouped into two basic categories: diseases of lung tissue (lung disease), and diseases affecting the chest cavity (thoracic cavity respiratory disease). CMT-related respiratory impairment is a respiratory disease of the thoracic cavity, whereas diseases such as COPD are diseases of lung tissue, the two are not related nor connected, and one does not cause the other. Understanding the fundamental differences between lung disease and thoracic cavity disease is key to achieving successful therapeutic outcomes.

Charcot Marie Tooth disease, or CMT for short, is an expansive and complex inheritable neuromuscular disease that can affect motor nerves, sensory nerves, and/or autonomic nerves, or any combination of these. The motor nerves are the peripheral nerves that control skeletal muscle function. The sensory nerves are the peripheral nerves that carry sensory signals (touch, temperature, etc.) from all parts of the body to the spinal cord. The autonomic nerves are the peripheral nerves that control automatic processes, such as heart rate, organ function, etc. Because CMT affects the nerves that control skeletal muscle function, CMT has the potential to affect every skeletal muscle group, including the respiratory muscles. And when CMT does, it causes muscle weakness.

The Basics

When CMT causes respiratory impairment, it is called CMT-Induced Neuromuscular Respiratory Muscle Weakness. This is a very specific type of respiratory impairment caused by

weakened respiratory muscles. Respiratory muscles are used to expand and contract the chest cavity (thoracic cavity), which, in turn, facilitates breathing. When a CMTer's respiratory muscles become weakened due to the neuromuscular disease effects of CMT, the ability to fully expand the chest cavity so that the lungs can completely inflate and fully fill with air becomes impaired. The result is an impairment of the ability to draw a full breath, and this leads to shortness-of-breath, or SOB for short. The medical term for this scenario is hypoinflation.

Hypoinflation is a condition in which the lungs don't fully inflate when drawing a breath. CMTer's who have CMT-induced neuromuscular respiratory muscle weakness have an impaired ability to fully inflate their lungs as the result of a weakening of the muscles whose job it is to fully expand the chest cavity when taking a breath. Dr. Elsayegh explains that this type of hypoinflation is the result of weakened respiratory muscles and is not the result of lung disease. This is an important distinction. When CMT causes respiratory symptoms, the root cause is weakened respiratory muscles. The cause is not with the lungs or with the airways. CMT is not a disease of the lungs and nor is CMT a disease of the airways.

Restrictive vs. Obstructive vs. Neuromuscular

A widely held misconception is that CMT can cause both restrictive lung disease and obstructive lung disease, and CMT-related respiratory impairment is itself a restrictive lung disease. CMTers have even been diagnosed by their doctor with "CMT-Related Restrictive Lung Disease." Full disclosure: I have until authoring this article understood and described CMT-related respiratory impairment to be a restrictive lung disease. Full stop. CMT does not cause restrictive lung disease, per se (restrictive lung disease can occur as a consequence of the effects of neuromuscular respiratory muscle weakness), and CMT-induced neuromuscular respiratory muscle weakness is not a restrictive lung disease. As Dr. Elsayegh explains, CMT-induced neuromuscular respiratory muscle weakness is not a restrictive lung disease or an obstructive lung disease, and it is not any kind of lung disease. To fully understand this, we have to dive into the fundamental differences between each of these.

Restrictive lung disease is a disease of lung tissue in which the lungs cannot fully expand due to a stiffening or hardening of lung tissue. Examples of restrictive lung disease include sarcoidosis, pulmonary fibrosis, and lung disease that can occur as a consequence of scoliosis. Each of these restrict the lungs from fully inflating—a hardening of the lungs.

Obstructive lung disease, commonly referred to as Chronic Obstructive Pulmonary Disease, or COPD for short, is a disease of lung tissue and airways in which the lungs can't fully empty on exhale. COPD is a blanket term for several lung diseases that are each an obstructive lung disease. Examples of obstructive lung disease are emphysema, chronic bronchitis, and asthma. Each of these either obstruct the airways inside the lungs and slow down the movement of air within the lungs or destroy the alveoli resulting in an inability to fully empty. This results in air becoming trapped in the lungs before taking the next breath—a condition called air trapping. COPD also results in hyperinflation, a condition in which the lungs become much larger in size.

Neuromuscular respiratory muscle weakness causes a type of respiratory impairment that is the result of weakened respiratory muscles due to the effects of a neuromuscular disease. The muscle weakness can progress enough to cause an impairment of the ability to fully expand the thoracic cavity causing the lungs to not fully inflate with each breath. This type of respiratory impairment is not caused by diseased or damaged lung tissue but is caused by weakened muscles. Examples of neuromuscular diseases that can cause neuromuscular respiratory muscle weakness are CMT, ALS (Lou Gehrig's disease), and Myasthenia Gravis.

Is It CMT, or…?

Restrictive lung disease, obstructive lung disease, and CMT-induced neuromuscular respiratory muscle weakness each cause SOB. How each cause SOB is different from one another. Restrictive lung disease causes SOB by impairing the ability to fully inflate the lungs due to lung tissue losing its elasticity and expandability. Obstructive lung disease causes SOB by impairing the ability to fully empty the lungs on exhale due to the airways inside the lungs becoming obstructed (usually by mucus), due to inflammation and constriction of the airways, or due to loss of lung alveoli. CMT-induced neuromuscular respiratory muscle weakness causes SOB by

impairing the ability of the chest cavity to fully expand, which then limits how much the lungs inflate with each breath. When a CMTer has respiratory symptoms, such as SOB, how can a pulmonologist know if it's due to CMT or something else?

A Pulmonary Function Test, or PFT for short, is a test that pulmonologists use for measuring pulmonary function, just as the name suggests. Specifically, a PFT is used to measure how well the respiratory system is working. A PFT measures several different parameters. The data garnered from these parameters tell the pulmonologist the overall condition of the respiratory system. The data can show if there is respiratory impairment, the data can show the severity of any present respiratory impairment, and the data can show if any present respiratory impairment is restrictive or obstructive, The data can also indicate the presence of respiratory muscle weakness. In an oversimplification, on PFT's, restrictive lung disease will show hypoinflation (the lungs not fully inflating) and obstructive lung disease will show air trapping (the lungs not fully emptying). Because of its associated hypoinflation, explains Dr. Elsayegh, CMT-induced neuromuscular respiratory muscle weakness will exhibit a restrictive lung disease pattern on PFTs. This likely is from where the confusion and misconceptions arise regarding the type of respiratory impairment CMT can cause.

CMT-induced neuromuscular respiratory muscle weakness being considered a restrictive lung disease likely has its roots in the restrictive lung disease pattern exhibited on PFT's. This type of respiratory impairment exhibits a restrictive lung disease pattern, Dr. Elsayegh explains, because CMT-induced neuromuscular respiratory muscle weakness impairs the ability to fully expand the chest cavity which in turn limits how much the lungs are able to inflate with each breath. This mimics restrictive lung disease on a PFT. However, because CMT does not affect the lungs themselves, and instead affects the muscles used for breathing, the type of respiratory impairment CMT can cause is not restrictive lung disease. Instead, it is neuromuscular respiratory muscle weakness. Knowing the difference between the two is paramount to successful treatment outcomes.

Restrictive and obstructive lung disease both cause SOB. Both can cause a lower oxygen saturation (SpO2) in the blood (hypoxemia) leading to a condition called hypoxia. Both can

cause carbon dioxide retention leading to a condition called hypercapnia. Restrictive lung disease causes hypoinflation—not getting enough air in. Obstructive lung disease causes hyperinflation—air gets in, but not all of it gets back out. These things are caused by damage to the airways inside the lungs. Neuromuscular respiratory muscle weakness causes a hypoinflation condition similar to restrictive lung disease, but because the lungs themselves are not diseased, Dr. Elsayegh explains, the condition is not truly a restrictive lung disease. However, it is imperative to understand that neuromuscular respiratory muscle weakness can also cause hypercapnia.

Common treatment approaches for restrictive and obstructive lung disease are basically oxygen as needed, an inhaler or two, and nebulizer treatments. Oxygen is used to treat hypoxemia/hypoxia, and inhalers/nebulizer treatments are used to open the airways and to prevent them from closing up. These things make sense, right? If you can't breathe right, do the therapeutic things that are designed to make you breathe right. It makes perfect sense. However, when CMT has caused the respiratory impairment, conventional therapy approaches are contraindicated. The reasons are rooted in the underlying cause of the impairment.

CMT-induced neuromuscular respiratory muscle weakness, Dr. Elsayegh explains, typically will not cause lower oxygen levels, but can lead to higher carbon dioxide levels. This might seem counterintuitive, but the reasons for this are straightforward. Respiratory impairment caused by neuromuscular muscle weakness has no adverse effect on lung tissue or the airways inside the lungs. The lungs retain their ability to efficiently pull adequate amounts of oxygen into the bloodstream from what is able to be inhaled with each breath, even if the lungs do not fully inflate. While oxygen stays normal, carbon dioxide can rise because of an impairment of the ability to efficiently filter out and exhale adequate amounts of carbon dioxide.

In order for the lungs to empty out carbon dioxide efficiently, the lungs have to fully exhale an adequate amount of air. The lungs can only exhale the amount of air that is inhaled. If the lungs can't fill with an amount of air that is needed to adequately pull enough carbon dioxide from the bloodstream, too much carbon dioxide can remain, causing carbon dioxide levels in the body to

rise. This is hypoinflation at work. An inherent adverse effect of hypoinflation that is caused by neuromuscular respiratory muscle weakness is not lower oxygen, but higher carbon dioxide.

Remembering that hypoinflation causes shortness-of-breath, conventional wisdom states oxygen is needed. Can't breathe, need oxygen, right? Not in this case. Because hypoinflation caused by neuromuscular respiratory muscle weakness does not cause lower oxygen levels, Dr. Elsayegh explains, giving oxygen when not needed can lead to higher carbon dioxide production in the body thereby by causing carbon dioxide levels to rise even higher, and possibly to unsafe levels.

Respiratory muscle weakness does not adversely affect the inside of the lungs. Respiratory muscle weakness does not impair the lungs' ability to adequately oxygenate the blood and oxygen levels will remain normal when respiratory impairment is caused by neuromuscular respirator muscle weakness. Although CMT-induced neuromuscular respiratory muscle weakness mimics restrictive lung disease on PFT, monitoring oxygen levels during the test can reveal that the underlying root cause of any present impairment is neuromuscular respiratory muscle weakness rather than with damaged lung tissue. Another indicator that a CMTer's respiratory impairment is caused by neuromuscular respiratory muscle weakness is if there is a significant change in any indicated hypoinflation when supine (lying flat).

Typically, when lying flat in the presence of neuromuscular respiratory muscle weakness, a CMTer will have a much tougher time breathing, and especially breathing in, leading to an increase in SOB. An increased SOB when lying flat is called orthopnea. A PFT performed to include an assessment also when lying flat can highlight this difference, providing further evidence that the exhibited restrictive lung disease pattern might actually be respiratory impairment caused by neuromuscular respiratory muscle weakness. While CMT does not cause restrictive lung disease, and CMT-induced neuromuscular respiratory muscle weakness is not restrictive lung disease, there is one caveat we need to discuss.

We've established that CMT does not cause restrictive lung disease and that CMT-induced neuromuscular respiratory muscle weakness is not a restrictive lung disease. There is one situation, however, in which CMT can contribute to or even lead to restrictive lung disease. It's

well understood that CMT can cause scoliosis. Sometimes, the scoliosis can become severe enough to affect the lungs. Scoliosis can sometimes become severe enough to reduce the size of the physical space of the chest cavity. This can cause a change in the shape of the chest cavity and can significantly reduce the volume of the chest cavity. When scoliosis has become severe enough to cause this, the amount of space the lungs have to inflate becomes limited. Dr. Elsayegh explains that this can lead to restrictive lung disease. While CMT in this case might have caused the scoliosis and contributed to its progression, CMT did not directly attack the lung tissue. Rather, the restrictive lung disease is the result of a non-lung disease process acting on the lungs. This scoliosis-induced restrictive lung disease can occur with or without CMT-induced neuromuscular respiratory muscle weakness.

When scoliosis becomes severe enough to cause respiratory impairment, surgery to correct the scoliosis might be a viable treatment option. When both scoliosis-induced restrictive lung disease and CMT-induced neuromuscular respiratory muscle weakness are present, the neuromuscular respiratory muscle weakness must be treated in addition to the scoliosis-induced restrictive lung disease. One cannot be successfully treated without treating the other.

Breathe Easy, Young Padawan

CMT has no known effective treatment that directly treats the disease itself. However, many of the things that CMT causes can successfully be treated, and this includes CMT-induced neuromuscular respiratory muscle weakness. The treatment approaches are different, however, than they are for diseases of lung tissue such as COPD. Restrictive and obstructive lung disease treatments target lung tissue—the airways inside the lungs that are diseased or damaged. For CMT-induced neuromuscular respiratory muscle weakness, the treatment approaches target the weakened muscles—the muscles are the culprit, not the lungs. Inhalers, nebulizer treatments, and supplemental oxygen typically have no effect on CMT-induced neuromuscular respiratory muscle weakness because these things do not treat respiratory muscles that have been weakened by a neuromuscular disease.

CMT specialists, including Dr. Elsayegh, prefer to treat CMT-induced neuromuscular respiratory muscle weakness with what is called non-invasive ventilatory support. A non-invasive ventilator, or NiV for short, is a BiPap, only better. Most have heard of CPAP and BiPap. Both are commonly used to treat obstructive sleep apnea (OSA). CPAP, which stands for Continuous Positive Airway Pressure, is a small tabletop machine that outputs air at a specified pressure, through a hose connected to a mask that is worn by the person. BiPap, which stands for Bi-Level Positive Airway Pressure is the same, except this machine will drop the pressure down for exhaling. Both are designed to treat OSA by working to keep the upper airway open when sleeping. NiV takes things a step farther by providing what's called volume support.

A non-invasive ventilator is a small tabletop machine just like a CPAP and BiPap, complete with a hose connecting the machine to a mask that is worn by the person. It even looks like a CPAP or BiPap set up. An NiV can be used to treat OSA, and is the preferred treatment for CMTers who have OSA, but an NiV adds additional capabilities CPAP and BiPap do not have. In an oversimplification, NiV provides volume support by delivering a volume of air that is equal to the tidal volume of the lungs. Lung tidal volume is the amount of air the lungs need to move in or out of the lungs with each respiratory cycle in order to maintain adequate oxygenation. A respiratory cycle is one breath in, one breath out. The machine delivers a consistent volume of air with each respiratory cycle. The volume of air, being equal to the lungs' tidal volume, helps the lungs to inflate more fully, and with less muscle effort, thereby easing the overall workload of the respiratory muscles. With some of the respiratory muscle workload being alleviated, the muscles are given a break. Because the muscles don't have to work as hard, breathing is easier. NiV isn't just for sleeping though. NiV can also be used during the day, and many CMTer's who use NiV, including this CMTer, use it during the day when needed. Sometimes, the respiratory muscles just need a rest, and NiV can provide that assistive rest.

The respiratory muscles facilitate breathing. They also are involved in coughing. When the respiratory muscles weaken, a weak cough can develop. A weak cough can impede the natural ability to clear secretions. Not being able to clear secretions can lead to increased SOB, respiratory infections, pneumonia, and other adverse health effects. A device called a cough assist can help with clearing secretions which in turn helps to prevent further illness. Along with

NiV, a cough assist device is a common therapy for CMTers who have CMT-induced neuromuscular respiratory weakness.

The Specialized Specialist

While CMT can cause respiratory impairment, not every CMTer will develop it. CMTers, whether they have CMT-induced neuromuscular respiratory muscle weakness or not, can also develop diseases that effect lung tissue, such as COPD or sarcoidosis for example. CMT does not cause these other respiratory diseases, of course, but CMT-induced neuromuscular respiratory muscle weakness can complicate the management of lung disease, and vice-versa. Being able to know the full extent and root cause of any present respiratory impairment is paramount, and a CMTer who has respiratory impairment of any kind is usually best served by a neuromuscular pulmonologist for getting to the root cause of the impairment. What is a neuromuscular pulmonologist?

A neuromuscular pulmonologist is a pulmonologist who specializes in respiratory impairment that is caused by neuromuscular disorders that affect the respiratory system. Pulmonologists are highly trained and specialized doctors who treat people who have a wide range of respiratory conditions. A neuromuscular pulmonologist encompasses all of that training and specialized skill, then adds a neuromuscular component that other pulmonologists might not have. I don't mean to discount the skill and expertise of pulmonologists. A pulmonologist who specializes in neuromuscular respiratory diseases though, has the specialized training, experience, and specialized skillset for recognizing and treating neuromuscular respiratory muscle weakness that CMT can cause, and that other pulmonologists might not recognize because of its similarities to restrictive lung disease. Treating CMT-induced neuromuscular respiratory muscle weakness as though it is restrictive lung disease ignores the neuromuscular respiratory muscle weakness and treats lung tissue that might not be diseased or damaged, and this can lead to a worsening of symptoms. A neuromuscular pulmonologist will know forthrightly how to recognize and treat these different components, and this can lead to better treatment outcomes for CMTers.

Neuromuscular pulmonologists can be difficult to find. They are a rare specialist among

specialists. Dr. Elsayegh's advice for finding a neuromuscular pulmonologist is to simply start calling pulmonology offices. Ask them if the doctor sees neuromuscular patients. If they do, ask them how many neuromuscular patients they see in a week. If they see less than 25 neuromuscular patients, or so, per week, they likely will not have the neuromuscular experience that CMTers who have respiratory impairment need, and the CMTer should probably keep searching. Neuromuscular clinics who offer pulmonology care have neuromuscular pulmonology expertise and are ideal. There are even some CMT clinics, such as the CMTA's Centers of Excellence CMT clinic at Cedars Sinai that offer respiratory care for CMTers. Dr. Elsayegh happens to be the neuromuscular pulmonologist who treats CMTers with respiratory impairment at this clinic. These clinics would be the preferred treatment centers, for obvious reasons.

In Closing

CMT is an extremely complex disease that can affect many things. While CMT can cause respiratory impairment, it doesn't cause it for every CMTer. The severity of CMT-induced neuromuscular respiratory muscle weakness can be widely variable. The reasons for this are unknown. Published literature depicts CMT-induced respiratory muscle weakness as exceedingly rare. Anecdotal evidence, coupled with a growing case count of CMTers presenting with CMT-induced neuromuscular respiratory muscle weakness suggests that respiratory involvement in CMT is higher than published literature suggests. How high is unknown at publication as there doesn't seem to be publicly available prevalence data. By anecdotal evidence in the CMT community, CMT-induced neuromuscular respiratory muscle weakness is likely under-diagnosed or often misdiagnosed as something it's not (such as restrictive lung disease).

Successful treatment outcomes for CMT-induced neuromuscular respiratory muscle weakness depend on proper diagnosis. Proper diagnosis requires a thorough understanding of the fundamentals of the type of respiratory impairment neuromuscular respiratory muscle weakness causes. A specialist who understands these fundamentals and who understands the nuances of neuromuscular respiratory muscle weakness, such as a neuromuscular pulmonologist, will have the experience and specialized training that a CMTer needs when respiratory impairment has developed. Treatments that target lung disease while ignoring a CMTer's neuromuscular

respiratory muscle weakness will likely be of no benefit, especially when there isn't any present lung disease. A neuromuscular pulmonologist will know these differences and will know how to expertly treat the underlying neuromuscular respiratory muscle weakness.

A CMTer who has CMT-induced neuromuscular respiratory muscle weakness can also additionally have lung disease. CMT does not cause lung disease, but when a CMTer has lung disease in addition to CMT-induced neuromuscular respiratory muscle weakness, both conditions must be treated together as separate conditions if treatment is to be successful. CMTers don't have to suffer with breathing issues. There are many non-invasive treatment options available, and these treatments can give back a CMTer's life.

About the Authors

Ashraf Elsayegh, MD, FCCP, FAASM is a distinguished physician and researcher based in Los Angeles, California. With over 18 years of experience, Dr. Elsayegh is a foremost expert in the field of pulmonary medicine as it relates to neuromuscular disease. He currently practices at Cedars-Sinai Medical Center and is an associate clinical professor at UCLA School of Medicine. His clinical and research interests revolve around respiratory function in the neuromuscular patient with special interest in diaphragm dysfunction. Dr. Elsayegh has authored and published numerous articles and textbooks in the field of pulmonary medicine and pulmonary complications in neuromuscular patients. In addition, he has lectured worldwide on these topics. Dr. Elsayegh has been treating neuromuscular patients, including those with Amyotrophic Lateral Sclerosis (ALS) and Charcot-Marie-Tooth (CMT), for over 18 years. He is an adviser on numerous boards in the fields of pulmonary medicine, critical care medicine, sleep medicine, and neuromuscular disease.

Kenneth Raymond is a CMTer who was first diagnosed with Type 1 CMT in late 2002, at the age of 29. He was genetically confirmed to have CMT1A a year later. He was subsequently diagnosed with CMT-induced neuromuscular respiratory muscle weakness in 2019. Kenneth has

devoted his life since diagnosis to studying, researching, and learning all things CMT, with an emphasis on the genetics of CMT as they relate to everyday CMTers. As a member of the Charcot-Marie-Tooth Association's Advisory Board, Kenneth is a CMT advocate who is committed to raising CMT awareness through fact-based information rooted in the latest understandings of CMT.