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Review Article

Charcot Marie Tooth (CMT) Syndrome A Very Rare Neuro-Genetical Diseases

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As a preface:

Despite working experience of more than thirty years in the field of neurology and psychology, I have never encountered the case that I would like to introduce to you. Charcot Marie Tooth. A syndrome that is basically found in textbooks and sometimes neurologists face it from time to time. I chose this report because, for me, the process of diagnosing and confirming this disease, despite the fact that he was my patient for years, we had not paid attention to this issue.

What is Charcot Marie Tooth (CMT) Syndrome?

Charcot-Marie-Tooth (CMT) syndrome is a group of inherited disorders that affect the peripheral nerves, which are the nerves that carry signals from the brain and spinal cord to the rest of the body. CMT syndrome is named after the three physicians who first described it in 1886: Jean-Martin Charcot, Pierre Marie, and Howard Henry Tooth.

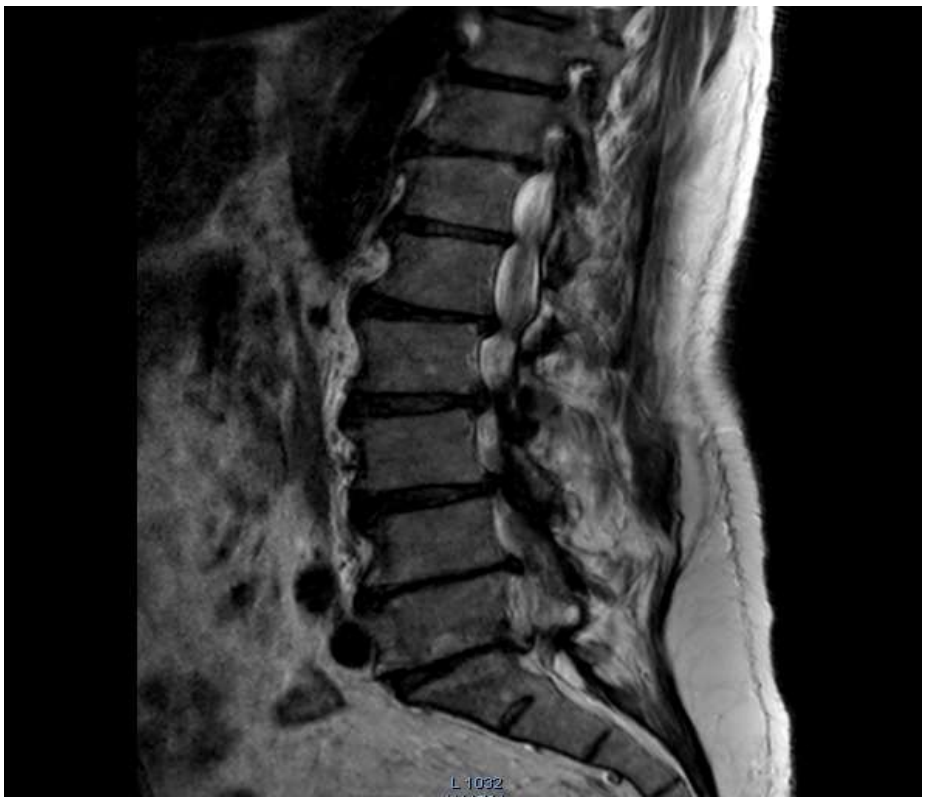
Charcot-Marie-Tooth (CMT) syndrome primarily affects the peripheral nervous system, which controls the movement and sensation of the limbs. However, some subtypes of CMT can also involve the autonomic nervous system, which controls various involuntary functions of the body such as blood pressure, heart rate, and digestion. Symptoms related to autonomic dysfunction in CMT can vary depending on the subtype and severity of the disease. Some individuals with CMT may experience symptoms such as dizziness or lightheadedness upon standing (orthostatic hypotension), sweating abnormalities, and gastrointestinal problems.

The patient, a 71-year-old man, for more than twenty years was my patient. At 1991, this patient suffered a war injury in his left leg, and because of this, he had foot drop along with atrophy of the muscles in his left leg. The doctors who visited him considered his problems to be foot drop caused by war injury, that is, No other occupational therapy was possible. When the orthopedic surgeons wanted to decide on the replacement of his knee joint, they rejected the operation. Why? Their reasons were that the knee joint, despite progressive osteoarthritis and a candidate for joint replacement, but because the leg muscles have atrophied and are no longer capable of serious activity, they rejected the surgery.

Before his war injury, this patient was a professional athlete and football player in his region.

Therefore, in the years after the injury, he followed his problem as neuropathy caused by war injury. Before the Covid-19 was declared a pandemic, I had a good orthopedist surgeon Dr. Deritan Thozeh at the Accident Hospital. We checked his condition together. Dr. Daritan knew that despite the chronic neuropathy caused by the injury, he was willing to undergo surgery to improve him by freeing the peroneal nerve. But after doing ENG, my friend Dr. Daritan Tozeh and I were convinced that surgery would not solve his problem because the intensity of the atrophic lesions was very high.

After two years of these events, when he complained of back pain with sciatica spreading to the right lower limb, we performed an MRI of the back and consulted with our neurosurgeon colleagues at Nene Teresa hospital No 5, my dear friend. Dr. Artid Lameh underwent laminectomy. Dr. Artid's opinion was that it is better for screw patients to undergo surgery with screws so that the body has more strength and consistency, especially in movements but the patient refused to accept such a limitation and only agreed to undergo a



laminectomy. The patient's argument was that if he accepted the surgery with screws, his limitations would increase, which he did not want. It was interesting that despite the fact that the operation Lamicectomy surgery was performed on the 4th and 5th vertebra, the patient seemed very satisfied. Two years after the surgery, the patient complained of back pain again, and after doing a Lumbo-sacral column MRI for a new evaluation, I asked my friend Dr. Artid Lameh to re-examine him. After examining the patient's MRI and

clinical examinations, Dr. Artid Lame wrote to me that unfortunately, nothing more can be done for the patient anywhere. Considering his old age, the patient should accept the existing conditions and adapt himself... Earlier, my colleague, Dr. Daritan Tozeh, an orthopedic surgeon hospital, told me that nothing could be done for the patient. It is right for him to accept this situation. In February 2023, according to my old acquaintance with the patient, I called him to tell him the opinions of the doctors. When I was doing his clinical examination on the examination bed, my mind was occupied with two serious issues. Due to very severe atrophy of the thenar and hypothenar muscles of the hands, along with the atrophy of the bilateral muscles of the legs, which had progressed a lot compared to two years ago and the situation had worsened. For me, these muscle atrophies were very unexpected. At the same time, I could not recognize it. Until this month, I asked my very good friend, Mrs. Dr. Mimoza Spahio, a neurologist, who was helpful in diagnosing and treating many of my patients, to see her as well. Interesting and rare is Charcot- Marie- Tooth. The arguments she gave, I was also convinced that what she said was completely correct. Especially the fact that she said that I had faced similar cases in the past, but what is the cause of this disease.

The Causes

Charcot-Marie-Tooth syndrome (CMT) is caused by mutations in genes that affect the peripheral nerves, which are the nerves that control movement and sensation in the limbs. There are many different types of CMT, and the specific gene mutations involved can vary depending on the type. In general, these mutations affect the structure or function of proteins that are important for nerve function, leading to damage or loss of peripheral nerve fibers. As for the prevalence of CMT in the world population CMT is a rare disorder, with an estimated prevalence of 1 in 2,500 people worldwide. The prevalence of different types of CMT can vary depending on the population and geographic region. In terms of race, CMT can affect people of all races and ethnicities. However, some types of CMT are more common in certain populations. For example, CMT type 1A, which is the most common type of CMT, is more common in people of European descent. Other types of CMT, such as CMT type 4, are more common in people of Ashkenazi Jewish descent.

The Incidences

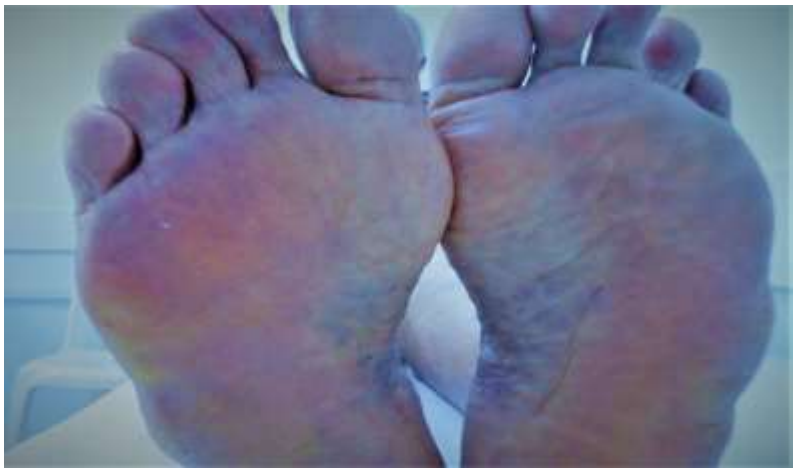
Charcot-Marie-Tooth syndrome (CMT) affects both men and women, and there is no significant difference in the prevalence or severity of the disorder between the two sexes. CMT is an inherited disorder, and the type of inheritance pattern can vary depending on the specific type of CMT. Some types of CMT are inherited in an autosomal dominant pattern, which means that a person only needs to inherit one copy of the mutated gene from one parent to develop the disorder. Other types of CMT are inherited in an autosomal recessive pattern, which means that a person needs to inherit two copies of the mutated gene, one from each parent, to develop the disorder. In some cases, CMT can also be caused by spontaneous genetic mutations that occur in individuals with no family history of the disorder. I am convinced that he is one of the rare cases of CMT caused by spontaneous genetic mutations. Now we have to see what the clinical signs and symptoms of the disease are, it is better to say with what signs or complaints the patients go to the doctors and are finally identified by the doctors. Of course, my patient's problems were mainly in the lower limbs and from the leg down. First, it started unilaterally, then it became bilateral, and then I observed the symptoms of the disease in the upper limbs, especially in the thenar and hypotenuse muscles bilaterally, but the main complaint of these patients It is basically with the symptoms of peripheral nerve disorders.

Main Complains and Symptoms

Individuals with Charcot-Marie-Tooth (CMT) syndrome may present to doctors with a variety of complaints related to their condition, depending on the subtype and severity of their disease. Some common complaints include:

- Muscle weakness and atrophy, particularly in the feet, lower legs, and hands
- Difficulty with balance and coordination
- Numbness or tingling in the extremities
- Foot deformities such as high arches or hammertoes
- Pain or cramping in the muscles
- Fatigue with physical activity
- Difficulty with fine motor tasks such as writing or buttoning clothes. When a doctor suspects CMT, they may perform a comprehensive neurological examination to assess the individual's muscle

strength, reflexes, sensation, and coordination. They may also order imaging tests such as magnetic resonance imaging (MRI) or nerve conduction studies to help confirm the diagnosis and rule out other conditions that may cause similar symptoms.



Unfortunately, we did not have access to genetic tests in our place of residence, and the patient could not remember the family pattern, genetic disease of any kind. It was interesting to note that when I saw that his movement and sensory changes had improved significantly compared to a few months ago, it was very hard for me to believe how he was able to walk even short distances in a short period of time. And for this reason, I requested that his family provide him with an electric tricycle so that he can carry out his transportation alone, otherwise he would not be able to move even a hundred miles away.

In fact, if the patient has another disease along with sarcoma, especially peripheral nerve diseases caused by discopathy lesions in the neck or back, it can easily mislead the doctors. Even in this regard, ENG examinations may not be able to help differential diagnoses, in our case, it was actually the same issue. Of course, because this was a case that basically had war injuries and complications, as well as complications caused by neck and back discopathy, that's why at first glance, our minds never focused on this syndrome. Interestingly, one of the patient's complaints was dizziness and imbalance in usual walking. We had done various investigations regarding the cause of these vertigos, including ear problems or carotid artery problems, and even various blood and glandular diseases with very detailed explanations. Even examining the brain causes of vertigo the only thing we didn't pay attention to was that one of the panels might be Charcot-Marie-Tooth. Now we want to know how this syndrome can be diagnosed in time.

Diagnosis

The diagnosis of Charcot-Marie-Tooth (CMT) syndrome typically involves a combination of clinical evaluation, family history, and genetic testing. A neurologist or other specialist will begin by taking a detailed medical history and performing a physical examination, looking for signs and symptoms of CMT such as muscle weakness, foot deformities, and sensory abnormalities. The doctor may also ask about the patient's family history, as many types of CMT are inherited in a genetic pattern.

If CMT is suspected based on the clinical evaluation, the doctor may order additional tests to confirm the diagnosis. These may include:

Electromyography (EMG) and nerve conduction studies (NCS): These tests can help to evaluate the function of the peripheral nerves and muscles, and can detect abnormalities such as slowed nerve conduction velocity or muscle weakness.

These are caused by a specific neuropathy or a general neuropathy. How many times, we had performed a nerve strip test on this patient and it was always a confirmed diagnosis: radicular or peripheral neuropathy, that's all. Of course, like many of our patients, he did not have accurate information about his family genetic records and could not have, especially considering his old age, we removed this issue from our follow-up and we no longer sought to see if there is such a syndrome in their family. were facing or not

Genetic testing: This involves analyzing a blood or saliva sample to look for mutations in genes associated with CMT. Genetic testing can help to confirm the diagnosis and determine the specific type of CMT.

Muscle biopsy: In some cases, a small sample of muscle tissue may be removed for analysis to look for signs of nerve damage or other abnormalities.

Psychological problems

Living with a chronic condition like Charcot-Marie-Tooth (CMT) syndrome can have a significant impact on a person's psychological well-being. Some of the psychological problems that may be more prevalent for individuals with CMT include:

1. **Anxiety:** People with CMT may experience anxiety related to their physical symptoms, such as fear of falling or difficulty walking in public places.

2. **Depression:** Chronic pain, loss of mobility, and social isolation can contribute to depression in individuals with CMT.
3. **Body image concerns:** Physical changes associated with CMT, such as foot deformities or muscle wasting, can impact a person's self-esteem and body image.
4. **Social isolation:** Mobility limitations and fatigue can make it challenging for individuals with CMT to participate in social activities and maintain relationships, leading to feelings of loneliness and isolation.
5. **Caregiver burden:** CMT can also have a significant impact on the lives of caregivers, who may experience stress, anxiety, and depression related to their caregiving responsibilities. My patient never faced these problems due to the very close relationships he has with his friends and relatives. Whenever I wanted to understand the patient's psychological problem with questions like this, I was met with negative answers from the patient. He once said that if you mean that I will succumb to the disease, it will never be possible.

Grading

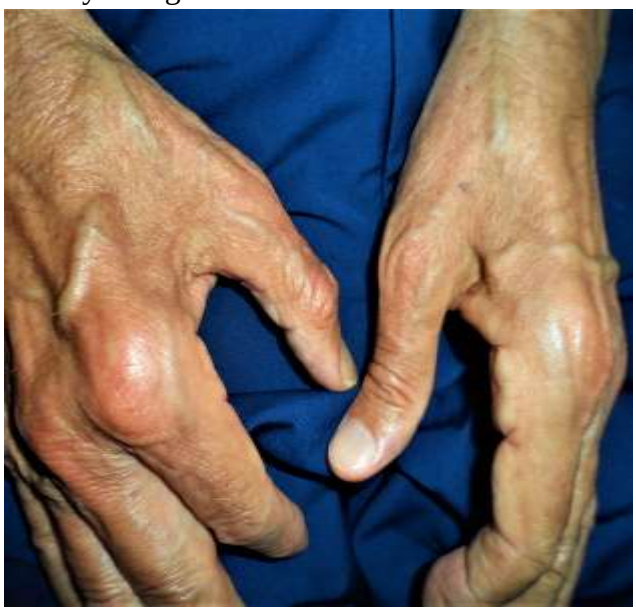
The severity of Charcot-Marie-Tooth (CMT) syndrome is often classified using a grading system based on the individual's symptoms and functional abilities. One commonly used grading system is the CMT neuropathy score (CMTNS), which assesses several aspects of the individual's condition, including motor function, sensory function, and nerve conduction studies. The score ranges from 0 to 36, with higher scores indicating greater severity of symptoms and functional impairment.

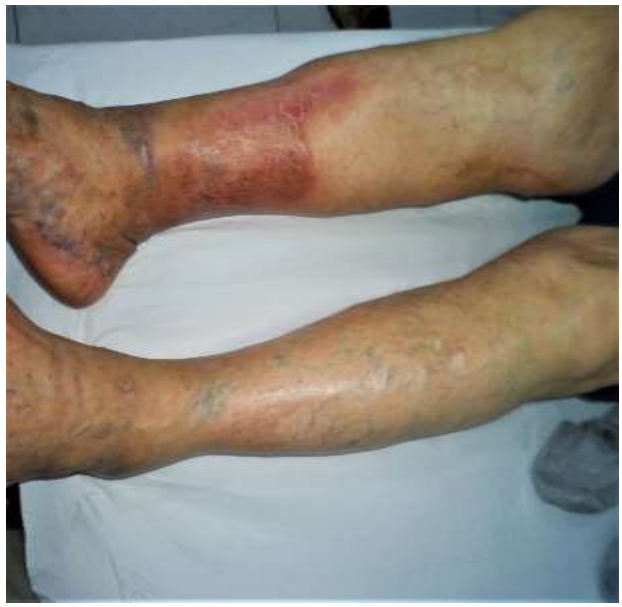
Another grading system is the CMT functional score (CMTFS), which focuses on the individual's ability to perform activities of daily living, such as walking, standing, and using their hands. The score ranges from 0 to 12, with higher scores indicating greater difficulty in performing these activities. It is important to note that grading systems such as these are primarily used for clinical and research purposes, and may not necessarily reflect the individual's subjective experience of their condition or overall quality of life.

Complications

Charcot-Marie-Tooth (CMT) syndrome can cause a range of complications that can impact quality of life and overall health. Some of the most common complications associated with CMT include:

1. Orthopedic problems and chronic pain: such as high arches, flat feet, or hammer toes, scoliosis and osteoarthritis which can make walking difficult and increase the risk of falls. in the hips, knees, and ankles.
2. **Muscle weakness and atrophy:** CMT can cause muscle weakness and atrophy, particularly in the legs and feet, which can lead to difficulty walking, climbing stairs, or performing other activities of daily living.





3. **Sensory loss:** CMT can cause sensory loss in the hands and feet, which can increase the risk of injuries or burns.
4. **Chronic pain:** CMT can cause chronic pain, particularly in the legs, feet, and lower back, which can significantly impact quality of life.
5. For patients who are diagnosed with this syndrome at an advanced age, before that, chronic pains cannot be interpreted in these patients. And if we don't focus on such diseases, we will close their case and put them aside because of their old age, especially if we have several factors in this field

6. **Respiratory complications:** In rare cases, CMT can cause respiratory complications, such as sleep apnea or respiratory failure.
7. **Psychological problems:** such as depression, anxiety, social isolation: and loneliness.
8. **Cardiovascular:** There is no clear evidence that individuals with C.M.T are at increased risk of stroke compared to the general population
9. **Hearing loss:** In some cases, CMT can cause sensorineural hearing loss, a type of hearing loss that occurs when the nerves responsible for transmitting sound signals to the brain are damaged.
10. **Alzheimer's disease or dementia:** There is currently no evidence to suggest that individuals with C.M.T are at higher risk for developing Alzheimer's disease or dementia than the general population.

I have done the MMSE test for the patient because he sometimes complained of memory disorders. But fortunately, the result of the test was about 26, which is considered normal due to the old age of the patient.

It is important for individuals with CMT to receive ongoing medical care and monitoring from a team of specialists, including neurologists and other healthcare professionals, to help manage these potential health complications and improve overall health and quality of life.

Treatment:

There is currently no cure for Charcot-Marie-Tooth (CMT) syndrome, but there are various treatment and management strategies that can help to alleviate symptoms and improve quality of life for patients. The specific treatment approach will depend on the type and severity of the disorder, as well as the individual patient's needs and preferences. Some common treatment and management strategies for CMT include:

1. **Physical therapy:** This can help to improve muscle strength, flexibility, and balance, and may also include exercises to help maintain range of motion and prevent joint contractures.
2. **Orthopetic devices:** Foot and ankle braces, ankle-foot orthoses (AFOs), and other orthopetic devices can help to support the feet and ankles, improve gait, and prevent foot drop.
3. **Pain management:** Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) or antidepressants may be prescribed to help manage pain and discomfort.

4. **Surgery:** In some cases, surgical interventions such as tendon transfer, osteotomy, or spinal fusion may be recommended to correct foot deformities, improve balance, or address other complications of CMT.
5. **Assistive devices:** Mobility aids such as canes, crutches, or wheelchairs may be recommended for patients with severe weakness or mobility impairment.

I think that considering the fact that my patient was always physically active and did professional sports, and psychologically he was in an environment where he faced less side effects, that's why even at this stage, despite being over 70 years old, there is still no reason to perform

Exercises:

Individuals with C.M.T may benefit from exercise programs designed to help maintain muscle strength, improve balance, and reduce the risk of falls. However, it is important for individuals with CMT to consult with their healthcare provider and a physical therapist before beginning any new exercise program, as some exercises may be inappropriate or even harmful for individuals with certain types of CMT.

Some examples of exercises that may be beneficial for individuals with CMT include:

1. **Stretching exercises:** Stretching exercises can help improve flexibility and reduce muscle tightness, which can be common in individuals with CMT. Stretching exercises may include calf stretches, hamstring stretches, and shoulder stretches.
2. **Strengthening exercises:** Strengthening exercises can help maintain muscle strength and reduce the risk of falls. Examples of strengthening exercises may include leg presses, squats, and hip abduction exercises.
3. **Balance exercises:** Balance exercises can help improve balance and coordination, which can be affected in individuals with CMT. Examples of balance exercises may include standing on one leg, walking heel-to-toe, and practicing tandem standing.
4. **Aerobic exercise:** Aerobic exercise, such as walking, cycling, or swimming, can help improve cardiovascular health and overall fitness.

Prognosis & Average lifespan:

The prognosis of C.M.T can vary widely depending on the specific type of the disorder and the individual patient's circumstances. In general, however, C.M.T is a chronic, progressive condition that can cause significant disability and impact quality of life over time. Some types of CMT progress slowly and may have relatively mild symptoms, while others can progress more rapidly and cause severe disability. The progression of the disorder can also be unpredictable, with some patients experiencing periods of stability or even improvement followed by sudden deterioration.

The average lifespan of individuals with Charcot-Marie-Tooth (CMT) syndrome can vary widely depending on the subtype and severity of the condition, as well as any complications that may arise.

In general, most subtypes of CMT do not significantly affect life expectancy, and many individuals with CMT are able to lead relatively normal lifespans. However, there are some subtypes of CMT that can be associated with a shortened life expectancy, particularly those that affect the heart or respiratory muscles.

It is important to note, however, that life expectancy is a complex issue and can be influenced by a wide range of factors, including the individual's overall health status, access to medical care and support, lifestyle factors, and more. As such, it is not possible to provide a definitive answer to the question of the average lifespan of individuals with CMT.

Pregnancy:

In general, there is no prohibition for individuals with C.M.T to become pregnant. However, like any pregnancy, there may be additional considerations or precautions that need to be taken to ensure the health and safety of both the mother and baby. Some factors that may need to be considered in individuals with CMT include:

1. **Mobility**: Pregnancy may impact mobility, balance, and coordination, which may be challenging for individuals with CMT. It may be important to monitor and support mobility throughout the pregnancy, and to consider adaptations such as mobility aids or physical therapy.
2. **Delivery:** The method of delivery may need to be carefully considered in individuals with CMT, as some delivery methods may be more challenging or risky. For example, vaginal delivery may be more difficult if there is weakness or atrophy in the pelvic floor muscles. A caesarean section may

be recommended in some cases.

3. **Pain management:** Pain management during labor and delivery may be more complicated for individuals with CMT, as they may be more sensitive to pain medications or at increased risk for side effects such as dizziness or confusion.
4. **Genetics**: Some types of CMT are hereditary, which means there may be a risk of passing the condition on to the baby. Individuals with CMT who are considering pregnancy may want to consult with a genetic counselor to discuss the risk of inheritance and any potential genetic testing that may be available.

Do's and don'ts of C.M.T

Individuals with Charcot-Marie-Tooth (CMT) syndrome should be aware of certain do's and don'ts to help manage their symptoms and maintain their overall health. Here are some examples:

Do's:

- **Stay active:** Regular exercise can help maintain muscle strength, improve balance, and reduce the risk of falls. However, it is important to consult with a healthcare provider and a physical therapist before beginning any new exercise program.
- **Wear appropriate footwear:** Wearing supportive, comfortable shoes can help improve walking ability and reduce the risk of falls.
- **Practice good posture:** Good posture can help reduce strain on the muscles and joints, which can be important for individuals with CMT. A physical therapist can provide guidance on proper posture techniques.
- **Use assistive devices as needed:** Braces, orthotics, or other assistive devices can help support the feet or ankles, correct foot deformities, and improve walking ability.
- **Manage stress:** Stress can exacerbate CMT symptoms, so it is important to practice stress-reducing techniques, such as deep breathing, meditation, or yoga

Don'ts:

- Overexert yourself: Overexertion can exacerbate CMT symptoms and lead to muscle fatigue or injury. It is important to avoid activities that are too strenuous or that cause pain or discomfort.
- Wear high heels or unsupportive footwear: High heels or unsupportive footwear can worsen walking ability and increase the risk of falls. It is important to wear supportive, comfortable shoes that fit well.
- Don’t Smoke or use tobacco products: Smoking can worsen CMT symptoms and increase the risk of developing complications such as cardiovascular disease.
- Ignore symptoms: It is important to monitor symptoms and seek medical attention if they worsen or if new symptoms develop.
- Neglect your overall health: Maintaining overall health is important for individuals with CMT, as other conditions such as obesity or diabetes can exacerbate CMT symptoms. It is important to maintain a healthy diet, manage stress, and get regular check-ups with a healthcare provide

I shared this case with the patient when the diagnosis was confirmed. I argued with a simple and eloquent statement that the problems he had and has and in these years he had referred to specialist doctors and medical centers to overcome them. And according to himself, he did not see any prospects for them because when he operated on the back, the muscle weakness of his hands became the subject of his work and mind, and in the same way, sleeplessness, muscle weakness, imbalance, and dizziness became the subject of his problems, unfortunately, day by day. He would have gone, but it was of no use to him except for raising psychological problems. When I told him all the issues of Charcot- Mari e-Tooth in simple language, he breathed a sign of relief and said that I put my denial on the ground for years and from then on he returned to a normal life, whereas before It wasn't a week that he didn't visit different doctors, useless and fruitless visits. But today I testify that it has become very far from those days. Why? Because he understood that he has a genetic disease and he was not involved in it, and he has to adapt himself to the complications of this patient, and this means better health.

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