Introduction

Charcot-Marie Tooth (CMT) disease is the most common inherited neurological disorder of lower motor neurons [1,2]. It is also known as hereditary motor sensory neuropathy since both motor and sensory nerves are involved. It affects 1 in every 2500 people in the United States population [3]. Patients have a family history in 80% of cases [4]. CMT is divided into several subtypes based on pattern of inheritance and results of neurophysiological studies [5].

Type 1 Variant of CMT represents 60%-70% of cases [1]. CMT 1 is inherited in an autosomal dominant pattern [5]. The genetic defect results in abnormal, unstable myelin. The myelin spontaneously breaks down, leading to uniform slowing of conduction velocity and inability of peripheral nerve cells to activate target muscles or relay sensory information from the limbs back to the brain [6,7]. Schwann cells proliferate and form concentric arrays of remyelination. The repeated cycles of demyelination and remyelination form a thick layer of abnormal myelin.
around the peripheral axons. Pathologists refer this to as the onion bulb appearance [8]. CMT1 is further subtyped into CMT1A, CMT1B, and CMTX1. CMT1A is most common and is caused by either overexpression or point mutations of peripheral myelin protein 22 (PMP22). CMT1B is least common and due to point mutations in myelin protein zero (MPZ). CMTX1 is associated with mutations in the gap-junction B1 gene responsible for encoding connexin-32.

CMT 2 is also inherited by an autosomal dominant mechanism. CMT 2 results in axonal degeneration [6]. On EMG, nerve conduction velocity is normal, but signal strength is decreased [6]. CMT 3 is a combination of demyelination and axonal loss. Type 4 is rare, and also results in a demyelination or axonal pattern.

Diagnosis is often established based on family history, blood genetic testing, and patient symptoms. If genetic testing does not confirm diagnosis, nerve biopsy may be required. Patient symptoms typically begin in the feet with limb-muscle wasting, weakness, and sensory loss. Symptoms progress in a disto-proximal distribution slowly over approximately a decade. Sensory changes with decreased sensation of vibration, touch, and pain as well as ataxia may be present but to a lesser degree [5]. Deep-tendon reflexes are reduced or absent in a distal to proximal gradient. The intrinsic weakness of foot musculature results in a pes cavus foot deformity and hammertoe deformities. Additional symptoms include hand tremors, muscle cramps, cold feet and hands, and foot callosities.

Most of the imaging literature in patients with CMT describes enlargement of lumbosacral spine nerve roots and cranial nerves with preserved T1 and T2 signal [9,10]. There are variable reports of post contrast enhancement of the nerve roots. There is limited literature describing the features of peripheral nerves in CMT. Two studies showed lower extremity fatty atrophy of different muscle compartments and intrinsic foot musculature in CMT patients [11,12]. However, the specific nerve features were not described.

A recent ultrasound study showed increased size of the peripheral foot nerves in CMT without increased Power Doppler flow [13]. There are to our knowledge no magnetic resonance (MR) or computed tomography (CT) studies that specifically address the peripheral nerves in CMT. Thus, the purpose of the study was to determine the MR and CT imaging features of lower extremity peripheral nerves in patients with CMT compared to a control population and to identify patterns of associated foot muscle denervation in patients with CMT compared to controls.

Methods and Materials

This study was Institutional Review Board (IRB) approved. The IRB approved waiver of informed consent. A retrospective review of 2 groups was performed. Group 1 consisted of 9 patients with CMT and imaging of the ankle and foot and/or knee with CT or MRI. MRI protocol included 3mm acquisitions of the ankle through the midfoot in sagittal T1 and short tau inversion recovery (STIR), coronal proton density (PD) fat suppressed, and axial T1 and T2 fat suppressed sequences. If contrast was administered, sagittal, axial, and coronal images with T1 post contrast fat suppression with 3 mm thickness were obtained. No patients were imaged for their CMT diagnosis. Reasons for examination included rule out infection, ankle sprain, and ankle/foot pain. Group 2 consisted of an age and sex matched group of controls without CMT and imaging of the ankle and foot or knee with CT or MR. Patients were imaged for ankle sprain and ankle/foot pain. The electronic medical record confirmed no clinical signs of neuropathy or history of alcoholism or diabetes in the control group. CMT patients were found by searching the Picture Archiving and Communications System (PACS) for keywords of CMT, Charcot-Marie, and Charcot-Marie-Tooth, and by retrieving cases already in known teaching files in the PACS. No upper extremity cross-sectional imaging studies of the upper extremity were found in CMT patients and thus only the lower extremity was evaluated.

Exclusion criteria included prior surgery of the nerve, known tumor of the nerve, and documented neuritis (from Leprosy, trauma, or other cause) of the peripheral nerves.

Imaging studies were independently reviewed by 2 fellowship trained musculoskeletal radiologists with 6 (JT) and 1 (SC) year of training. Mean whole nerve diameter was measured of the tibial nerve in the tarsal tunnel at the same level on the axial T1 images and soft tissue CT windows (2.5mm thickness). T1 and fat suppressed T2/STIR signal was graded as iso, hyper, or hypo relative to muscle. Post gadolinium signal was
scored as none, mild, moderate, or marked enhancement. Intrinsic foot muscle T2FS or STIR signal was graded as normal, diffuse increased T2, or patchy T2. Intrinsic foot muscle T1 signal and CT attenuation was graded as normal (Grade 0), <30% fat (Grade 1), 30-60% fat (Grade 2), >60% fat signal (Grade 3). The same imaging assessments were applied to the common peroneal nerve at the level of the proximal tibiofibular joint.

Clinical notes were reviewed to determine if type of CMT was known. Statistical analysis included calculation of the mean nerve diameter with standard deviation with t-test comparison of the nerve diameter means with p value of < 0.05. Interobserver agreement of the imaging review was also obtained with a kappa score of 0 (no agreement) to 1 (total agreement).

Results

Table 1 Compares the CMT and Control Group Results of the Tibial Nerve. 9 CMT patients had 11 examinations (2 patients bilateral) of the ankle. There were 9 MR and 2 CT studies of the ankle to assess the tibial nerve. Mean diameter of the tibial nerve in the CMT group was 6.43 mm +/- 0.94 mm (Figure 1). Mean diameter of the control group tibial nerve was 3.55 mm +/- 0.73 mm (Figure 2). Mean diameter was statistically larger in the CMT group compared to controls (p<0.001), (CI 2.0701 to 3.6899). All CMT patients and control patients had T1 and T2/STIR nerve signal graded as iso to hypointense with no post contrast enhancement (Figure 1, Table 2).

<table>
<thead>
<tr>
<th>Patients</th>
<th>CMT Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (11 exams)</td>
<td>10 (10 exams)</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>20-58 years</td>
<td>22-59 years</td>
</tr>
<tr>
<td>Sex</td>
<td>7 men; 2 women</td>
<td>7 men; 3 women</td>
</tr>
<tr>
<td>Mean fascicular diameter tibial nerve</td>
<td>6.43 +/- 0.94 mm</td>
<td>3.55 +/- 0.73 mm</td>
</tr>
<tr>
<td>T1 nerve signal</td>
<td>Iso to hypo</td>
<td>Iso to hypo</td>
</tr>
<tr>
<td>T2 nerve signal</td>
<td>Iso to hypo</td>
<td>Iso to hypo</td>
</tr>
<tr>
<td>Post gadolinium</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Patchy high T2 signal</td>
<td>88.90%</td>
<td>0%</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>82%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 2: Comparison of CMT and Control Group Imaging of the Common Peroneal Nerve.

<table>
<thead>
<tr>
<th>Patients</th>
<th>CMT Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (4 exams)</td>
<td>4 (4 exams)</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>41-42 years</td>
<td>40-43 years</td>
</tr>
<tr>
<td>Sex</td>
<td>3 men</td>
<td>3 men; 1 women</td>
</tr>
<tr>
<td>Mean fascicular diameter common peroneal nerve</td>
<td>6.13 +/- 0.63 mm</td>
<td>3.50 +/- 0.58 mm</td>
</tr>
<tr>
<td>T1 nerve signal</td>
<td>Iso to hypo</td>
<td>Iso to hypo</td>
</tr>
<tr>
<td>T2 nerve signal</td>
<td>Iso to hypo</td>
<td>Iso to hypo</td>
</tr>
<tr>
<td>Post gadolinium</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Patchy high T2 signal</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>25%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Figure 1: Enlarged posterior tibial nerve in 70-year-old male with Charcot-Marie Tooth (CMT) disease. (A) Axial T1-weighted (TR757, TE19), (B) T2-weighted with fat saturation (TR5000, TE78), and (C) T1-weighted with fat-saturation post-contrast (TR600, TE19) images just above the ankle reveal enlargement of the tibial nerve (arrows). Nerve signal characteristics are T1 hypointense, T2 hypointense to isointense, and no significant enhancement on post contrast images (arrows). Also observed is severe atrophy and fatty replacement of the peritendinous musculature.

Figure 2: Normal tibial nerve in a 22-year-old male control patient with chronic ankle pain after an injury eight months prior. (A) Axial PD-weighted (TR2500, TE12) and (B) T2-weighted (TR3500, TE41) with fat saturation MR images demonstrate a 2mm sized posterior tibial nerve (arrows) and normal peritendinous muscle bulk and signal characteristics.
CT attenuation of the nerve in the CMT patients was scored as equal to the control patients and of soft tissue attenuation, similar to the tendons (Figure 3). 88.9% (8/9 MRI images) in the CMT group had patchy T2 muscle signal compared to none of the control patients. 82% (9/11) of CMT studies had evidence of fatty muscle atrophy on T1 or CT images (Figure 4).

**Figure 3:** Enlarged tibial nerve in a 35 year-old female with CMT. Axial CT image at the level of the tarsal tunnel shows an enlarged tibial nerve (arrow).
Figure 4: Posterior tibial nerve enlargement and denervation changes in a 47-year-old male CMT patient. Axial ankle and short axis forefoot images are presented. (A) PD-weighted (TR2300, TE32) sequence demonstrates an enlarged posterior tibial nerve (arrows) with hypointense signal intensity. (B) T2-weighted (TR5000, TE70) image with fat saturation image at the same level reveals an enlarged hypointense posterior tibial nerve in the tarsal tunnel. (C) PD-weighted (TR1260, TE10) short axis image of the forefoot shows severe (>75%) fatty atrophy of the intrinsic foot musculature. (D) T2-weighted (TR5540, TE820) short axis sequence with fat saturation demonstrates patchy T2 hyperintense signal in the atrophied foot musculature related to denervation edema.

3 patients had 4 MR examinations of the common peroneal nerve at the level of the knee. Mean fascicular diameter of the common peroneal nerve in the CMT group was 6.13mm +/- 0.63 mm while mean diameter in the control group was 3.50 mm +/- 0.58 mm. Mean diameter was statistically larger in the CMT group compared to the controls (p < 0.05)(CI 1.58 to 3.67). All CMT patients and control patients with images of the common peroneal nerve had T1 and T2/STIR nerve signal graded as iso to hypointense with no enhancement. No patients in either group had denervation edema but 1 of 4 CMT patients had fatty atrophy on T1 graded as <30% fat. For the entire CMT group, increased T2 muscle signal was present in 8 of 16 limbs all graded as patchy hyperintense T2 signal of the intrinsic foot or calf musculature. 5 extremities were rated as >60% atrophy, 3 as 30-60% atrophy, 1 as <30% atrophy, and 1 as normal. Muscle denervation edema changes were statistically significant from control group (p<0.05).

Only 3 patients had documentation of type of CMT diagnosis. All 3 of these patients had CMT type II. The other CMT patients had a diagnosis of their disease based on family history, typical clinical history and symptoms, and exclusion of other entities by neurological or serological testing. Interobserver agreement of nerve diameter measurements was 0.967.

Discussion

The appearance of nerves in CMT patients in the cervical spine and lumbosacral plexus have been thoroughly described [9,10]. There have been scattered case reports of enlargement of the peripheral nerves in patients with CMT on ultrasound and MRI of the knee [13,14]. This is the first study to describe the MR and CT findings of peripheral nerves in patients with CMT compared to controls. Our findings indicate that CMT patients have nerves that are of larger mean diameter than normal. However, the signal characteristics of the nerves are unchanged, likely reflecting that this is a chronic ongoing process of demyelination and not an active inflammatory process. This is important for differentiating CMT from other diseases that can cause mean nerve diameter enlargement in the extremities as the radiologist may not be privy to the diagnosis of CMT. One such differential entity is chronic inflammatory demyelinating polyradiculopathy (CIDP) [15]. CIPD is...
also a demyelinating disease of the peripheral nervous system with resultant denervation of the musculature. However, in CIDP there is infiltration with inflammatory cells (lymphocytes) [15]. On MRI, CIDP demonstrates enlarged peripheral nerves, brachial and lumbosacral plexus and nerve root enlargement [16]. The nerves are also sometimes referred to as onion bulbs, similar to CMT. A recent series of 4 patients demonstrated variability in the degree of nerve enlargement though the authors showed measurements of the tibial nerve nearly double that of our CMT group [17]. Additionally with CIDP, there is enhancement of the nerves and hyperintense T2 signal related to the inflammatory component of the process, helping in differentiation of this entity from CMT.

Additional differential diagnostic entities include Leprosy, Tuberculosis, Syphilis, Lyme disease, and Mycoplasma. These processes result in not only swelling of the peripheral nerves, but also mild to marked hyperintense T2/STIR signal [18,19]. Additionally, these entities show enhancement on post-contrast images due to alteration of the blood-nerve barrier with permeability to leakage of contrast in the nerve tissue [20]. Sonography also demonstrates enlargement with loss of fascicles, edema, and increased vascularity [20]. Although these diseases can also be bilateral, the lack of post-contrast enhancement and signal changes should suggest CIDP over the other entities. Finally, some of these entities involve the upper extremity more often than the lower extremity, such as the ulnar nerve in Leprosy, compared to the disto-proximal involvement in CMT [20].

The cause of the mean nerve diameter enlargement in patients with CMT is likely axons surrounded by layers of demyelinating and remyelinating Schwann cells. A recent study by Chhabra demonstrated mean nerve enlargement was greater in CMT type 1 than other types [21]. The presumption is that this nerve pathology accounts for the patchy T2 signal abnormality of the muscles, which is likely subacute denervation changes secondary to poor conduction of signal through the peripheral nerves. Ultimately, there is no definite treatment for CMT and denervation edema-like signal would be expected to progress over time to fatty atrophy. Due to the disto-proximal distribution, it would be expected that with disease progression, peripheral nerves of the upper extremities would also be enlarged but maintain normal signal intensity. We only found one patient in our review with CMT and an upper extremity MRI. The radial nerve was interpreted as increased in diameter with normal signal.

In conclusion, our study is the first to our knowledge providing a series of patients with CMT images of the peripheral nerves. The findings demonstrate enlarged nerves with normal MR signal and absence of enhancement. This is helpful in differentiating other causes of nerve enlargement which typically have T2 and postcontrast signal changes. However, if a CMT patient has abnormal signal in the nerve on MR, a superimposed neuritis should be suspected and imaging would be more sensitive than EMG in detecting the early changes.

References


