Neuropathic Pain in Charcot-Marie-Tooth Disease

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Objectives: To determine the frequency and extent to which subjects with Charcot-Marie-Tooth (CMT) disease report pain and to compare qualities of pain in CMT to other painful neuropathic conditions.

Study Design: Descriptive, nonexperimental survey, using a previously validated measurement tool, the Neuropathic Pain Scale (NPS).

Participants: Participants were recruited from the membership roster of a worldwide CMT support organization.

Main Outcome Measures: NPS pain descriptors reported in CMT were compared with those reported by subjects with postherpetic neuralgia (PHN), complex regional pain syndrome, type I (CRPS-1), also known as reflex sympathetic dystrophy, diabetic neuropathy (DN), and peripheral nerve injury (PNI).

Results: Of 617 CMT subjects (40% response rate), 440 (71%) reported pain, with the most severe pain sites noted as low back (70%), knees (53%), ankles (50%), toes (46%), and feet (44%). Of this group, 171 (39%) reported interruption of activities of daily living by pain; 168 (38%) used non-narcotic pain medication and 113 (23%) used narcotics and/or benzodiazepines for pain. The use of pain description was similar for CMT, PHN, CRPS-1, DN, and PNI in terms of intensity and the descriptors hot, dull, and deep.

Conclusions: Neuropathic pain is a significant problem for many people with CMT. The frequency and intensity of pain reported in CMT is comparable in many ways to PHN, CRPS-1, DN, and PNI. Further studies are needed to examine possible pain generators and pharmacologic and rehabilitative modalities to treat pain in CMT.

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CHARCOT-MARIE-TOOTH (CMT) disease, also referred to as hereditary motor and sensory neuropathy (HMSN), is one of the most common hereditary neuromuscular diseases, with a worldwide prevalence ranging from 14 to 282 per million, and an estimated prevalence of 26,280 in the United States.1 There are at least eight forms of HMSN. Types I, II, and X linked represent the CMT syndrome.2 The clinical features of CMT have been well described.2,6 CMT I (demyelinating form), the most common form of CMT, is characterized by markedly reduced conduction velocities in peripheral motor and sensory nerves.7,8 There are at least three forms of CMT II based on molecular genetics. CMT IA is the most common subtype, resulting from a duplication of chromosome segment 17p11.2, which is the gene locus for peripheral myelin protein (PMP-22).3-14 Patients with hereditary neuropathy with liability to pressure palsies show a large deletion including the PMP-22 gene contained in region 17p11.2. CMT IB is due to a point mutation in chromosome 1q22-q23, which codes for the production of myelin protein zero.15 CMT IC is an autosomal dominant form that does not map to chromosome 1 or 17.9

CMT II (neuronal form) is often a less severe disease than CMT I and may have more lower extremity involvement, although clinically it is not easily distinguished from type I.6,7 CMT II exhibits predominant axonal loss and resultant wallerian degeneration, with diminished motor and sensory action potential amplitudes indicative of denervation, while conduction velocities remain relatively normal.3 CMT II is genetically heterogeneous, with the locus for one form (CMT IIA) being on the short arm of chromosome 1.16 CMT X is an X-linked dominant form with a mutation in the connexin 32 gene.6 There are also several rare autosomal recessive forms of CMT.6

Previous studies have shown that CMT is a slowly progressive disorder characterized by diffuse muscle weakness and prominent distal atrophy, predominantly involving the intrinsic muscles of the feet and the peroneal muscles.3 CMT subjects produce 20% to 40% less force than healthy controls using quantitative isometric and isokinetic strength measures, even though manual muscle test scores may be normal.3,4 There is no significant side-to-side difference in strength.4,5 From a functional standpoint, the sensory deficit is usually less severe than the motor deficit.4,5

Although pain is a well-known symptom commonly associated with other neuropathies, including diabetes and Guillain-Barré Syndrome,17-20 it has only been anecdotally described in the literature as a clinical problem in CMT, primarily as cramps, paresthesias, and aching in the legs associated with peroneal muscular atrophy.21 Consistent with this, in our clinical experience, many CMT patients complain of pain. The purpose of this study was to survey people with CMT to determine the frequency and extent to which they report pain. A secondary aim was to compare the qualities of pain reported in CMT with those of postherpetic neuralgia, complex regional pain syndrome, type one, which is also known as reflex sympathetic dystrophy, diabetic neuropathy, and peripheral nerve injury.

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using a previously validated measurement tool, the Neuropathic Pain Scale (NPS).19

METHODOLOGY

Subjects

Participants for the primary survey study were recruited from the membership roster of a large, worldwide support organization, Charcot-Marie-Tooth International, based in Ontario, Canada. All members were invited to participate through an announcement in the CMT newsletter that included a questionnaire titled “CMT and Pain Study.” Because this study was intended to use a descriptive survey, no attempt was made to subcategorize CMT based on either electrodiagnosis or DNA profiles. All forms of CMT were analyzed together as one entity. It was presumed by the investigators that the diagnostic information provided by the survey participants was accurate (ie, no medical records were reviewed to confirm their diagnosis). However, by report, all subjects included in the study had type I or type II CMT. Given the difficulty of reliably distinguishing types I and II based on clinical and electrodiagnostic data alone,3 we grouped these subjects together and will hereafter refer to both types as CMT. This study will be denoted in this report as the primary survey.

An additional 238 CMT subjects—30 of whom were in no support group and recruited directly from our neuromuscular disease clinic population, 114 of whom belonged to CMT International, and 94 of whom belonged to the CMT Association—were recruited as part of a preliminary study to determine whether persons with CMT in a support group would be more likely than CMT patients not in a support group to report pain more frequently. Approximately 40% of the CMT patients in our neuromuscular disease clinic population participate in at least one of these support organizations. The extent of participation in support groups worldwide by persons with CMT is not known, to our knowledge. This study will be denoted in this paper as the preliminary study.

Measures

The SF-36 Health Survey22 was independently administered to the 238 CMT subjects in the preliminary study. The SF-36 assesses multiple operational aspects of health, including pain, disability, and favorable or unfavorable self-evaluations of general health status.22 Data were analyzed specifically with respect to the number of CMT subjects reporting pain that interfered with their normal work (including work both outside the home and housework) during the past 4 weeks from those in no support group (90%), those in CMT International (90%), or those in the CMT Association (85%). Pearson χ² = 9.2, p > .05.

Primary Survey

For the main primary survey, 1,800 questionnaires were mailed. Approximately 15% of people on the CMT International mailing list do not have CMT and did not therefore participate. Six hundred thirty-six individuals responded to the questionnaire (40% response rate). Of these, 19 were not used because of either excessively incomplete data or inconsistent responses (ie, responses were not consistent with the question asked), leaving 617 usable questionnaires. The majority (64%) of these subjects were female; the average age of respondents was 54.6 years (SD = 16.1); and the average duration (since diagnosis) of CMT was reported as 31.7 years (SD = 18.7).

Of the 617 usable questionnaires, 440 (71%) reported having pain. These subjects were younger (mean age = 53 years, SD = 15.5) than those reporting no pain (mean age = 58.5 years, SD = 17, t (615) = 3.80, p < .001). Moreover, subjects reporting pain were more likely to be women (68%) than those reporting no pain (53%, χ²(1) = 11.49, p < .001). No significant differences in duration of CMT between the two groups emerged. Unless otherwise specifically stated, all percentages reported in the results henceforth are with respect to the 440 who reported having pain.

Pain sites and medication use. The following responses were listed as “sites of most severe pain”: low back (70%),...
level of the ANOVA tests was set at .005 (.05/10) to control for diabetic neuropathy, and peripheral nerve injury. The alpha inflation due to multiple tests. If the ANOVA was replicating the commonly found link between these two dimensions of pain experience. Discriminant validity. Table 1 presents Pearson correlation coefficients between each of the 10 NPS items. Most (41, or 91%) of these are less than .50, indicating minimal overlap (ie, less than 25% of the variance shared) between most items. The largest coefficient, .70, was between unpleasant and intense, replicating the commonly found link between these two dimensions of pain experience. The remaining coefficients greater than .50 suggest that sharp and deep pain tend to be described as intense in CMT subjects. Deep pain also tends to be described as unpleasant in this sample. Predictive validity. A series of 10 ANOVA tests was performed with the NPS responses from this sample and four other patient groups (data from a study by Galer and Jensen) to determine whether pain reported by CMT subjects was similar to, or different from, pain reported by subjects with postherpetic neuralgia, complex regional pain syndrome type 1, diabetic neuropathy, and peripheral nerve injury in that it was described as being less sensitive and unpleasant. Pain reported in CMT was also less sharp and itchy and more cold than pain reported in postherpetic neuralgia, and less cold and surface than pain reported in complex regional pain syndrome type 1.

CMT pain descriptors. With respect to background pain (chronic), the most frequently reported descriptors were dull (15%) and burning (8%). However, these descriptors are part of the NPS (burning is offered as an alternative to the descriptor hot in the narrative that accompanies the NPS). Non-NPS descriptors reported were tingling (3%), tight (2%), and pressure (2%). Less frequently reported (<1%) background pain descriptors included heaviness, cramping, pins and needles, and throbbing.

With respect to breakthrough (flare-up) or intermittent pain, the most frequently reported descriptors were sharp (18%), stabbing (12%), burning (3%), hot (2%), and cold (2%). Again,

Table 1: Discriminant Validity (Pearson Correlation Coefficients Between the 10 NPS Pain Descriptors)

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Intense</th>
<th>Sharp</th>
<th>Hot</th>
<th>Dull</th>
<th>Cold</th>
<th>Sensitive</th>
<th>Itchy</th>
<th>Unpleasant</th>
<th>Deep</th>
<th>Surface</th>
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<tr>
<td>Intense</td>
<td>-</td>
<td></td>
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<td>Hot</td>
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<td>.27</td>
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<td>Dull</td>
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<tr>
<td>Cold</td>
<td>.15</td>
<td>.18</td>
<td>.28</td>
<td>.21</td>
<td>-</td>
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<tr>
<td>Sensitive</td>
<td>.25</td>
<td>.24</td>
<td>.32</td>
<td>.05</td>
<td>.25</td>
<td>-</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Itchy</td>
<td>.16</td>
<td>.22</td>
<td>.28</td>
<td>.13</td>
<td>.28</td>
<td>.36</td>
<td>-</td>
<td></td>
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<td></td>
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<tr>
<td>Unpleasant</td>
<td>.70</td>
<td>.64</td>
<td>.34</td>
<td>.14</td>
<td>.18</td>
<td>.24</td>
<td>.14</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>Deep</td>
<td>.64</td>
<td>.43</td>
<td>.28</td>
<td>.26</td>
<td>.15</td>
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<td>.20</td>
<td>.65</td>
<td>-</td>
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<tr>
<td>Surface</td>
<td>.25</td>
<td>.20</td>
<td>.43</td>
<td>.02</td>
<td>.18</td>
<td>.40</td>
<td>.34</td>
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those descriptors are part of the NPS (stabbing is offered as an alternative to the descriptor sharp in the NPS). All non-NPS descriptors were reported less than 1% and included electrical, spasmodic, shooting, crushing, bruising, and pulsing.

**Discussion**

Our informal survey data indicate that neuropathic pain problems are widespread among persons with CMT, which has not been previously reported. Many other acquired, disease-related neuropathies have prominent pain features in a subpopulation of patients, including neuropathies associated with diabetes, Guillain-Barré syndrome, alcohol, human immunodeficiency virus, hypothyroidism, and chemotherapy. The fact that more women than men expressed pain has been noted in other pain studies and does not necessarily represent a gender difference in CMT per se.26

The intensity of pain reported by the CMT subjects in this survey is comparable in many ways to pain reported by subjects with other neuropathic conditions such as postherpetic neuralgia, diabetic neuropathy, and peripheral nerve injury who responded to a similar survey while attending a university-based tertiary pain clinic.25 Whereas it may not be entirely cogent to compare the painful sequelae of a neuropathy of infectious origin to that of an inherited neuropathy, we included postherpetic neuralgia because it is common and has clearly defined, consistently described, neuropathic pain. Further, although it would be quite interesting and useful to compare neuropathic pain in CMT to other forms of inherited sensorimotor and autonomic peripheral polyneuropathies, the rarity of these conditions creates significant difficulty in gathering a large enough database to create valid statistical comparisons.

Compared to pain reported in postherpetic neuralgia, pain reported by CMT subjects is less sharp, sensitive, itchy, and unpleasant but about as intense, deep, hot, dull, and surface, and more cold. Compared to pain reported in complex regional pain syndrome type 1, which is not a peripheral neuropathy but nonetheless involves neuropathic pain, CMT subjects report similar degrees of intensity, sharpness, hot, dull, itchy, and deep pain but reported their pain as less sensitive, unpleasant, surface, and cold. Compared to pain reported in diabetic neuropathy and peripheral nerve injury, pain reported by CMT subjects is similar across all NPS scales, with the exceptions of being less sensitive and unpleasant. Overall, pain reported in CMT is generally as intense, hot, dull, and deep as the pain reported in these other neuropathic conditions, although it appears to be less sensitive and unpleasant.

If indeed the pain experienced by people with CMT is etiologically related to the actual neuropathy, then, as with other painful neuropathies, it is hypothesized that the pain may be generated from ectopic impulses propagated from the site of injury and the adjacent dorsal root ganglia.25 Moreover, as with other neuropathies, there may be more than one mechanism contributing to pain generation, including neurogenic inflammation, abnormal involvement of the sympathetic nervous system, and neuromorphic changes within the central nervous system.13,25 Although CMT subjects describe their pain similarly to other patients with neuropathic pain syndromes, the pain may not be originating from damaged nerve.

One other likely significant pain generator in CMT is the musculoskeletal system. CMT subjects have significant muscle weakness, producing 20% to 40% lower force than healthy controls using quantitative strength measurements of earlier studies.4 This weakness may place a higher stress on the musculoskeletal system and contribute to pain generation. Furthermore, other studies have documented that CMT subjects have a reduced range in functional aerobic capacity during exercise testing despite having normal or relatively normal pre-exercise pulmonary function and exercise heart rate, blood pressure, and maximum ventilation.4 This implies that people with CMT, as a whole, may be deconditioned. Deconditioned states are usually associated with a decreased pain tolerance, which may be a factor that negatively affects quality of life for persons with neuromuscular disorders, including CMT.25

Inasmuch as the low back was the most frequently reported site of most severe pain, it is quite likely that musculoskeletal pain and physical deconditioning play some role in pain production in CMT. Although that role was not specifically addressed by this study, it does warrant further investigation since there are likely multiple pain generators and mechanisms at work in CMT. Arguably, other pain inventories such as the McGill Pain Questionnaire or the Brief Pain Inventory may better assess the overall somatic qualities of pain.29-31 The NPS is a newer pain scale, containing 10 pain descriptors specific to neuropathic pain, which was the focus of this study and the reason we chose this measurement tool. Although the NPS items were specifically chosen to reflect neuropathic pain, it is also very likely that they describe chronic pain due to other etiologies. However, there were very few reported pain descriptors noted by CMT subjects that were not on the NPS (only tingling, tight, and pressure). This implies that the NPS descriptors do accurately assess many of the pain components reported by CMT subjects. Certainly the average rating of each indicates that most of the items describe the pain experience of this sample.

There are several notable limitations to this informal survey study. Because of the open nature of a questionnaire-based study, there remains a possibility of selection bias, with a chance that a greater number of CMT subjects with pain than those without responded to the invitation to participate. Our initial SF-36 survey data indicate that being in a support organization does not, in and of itself, necessarily influence the frequency of reporting pain. The higher percentages of CMT subjects reporting pain in the SF-36 survey (85% to 90% versus 71% for the primary survey) is likely due to the more expansive nature of the inquiry question in the SF-36, i.e., having any pain that interfered with their normal work (including work both outside the home and housework) during the past 4 weeks. In the primary survey, we had an overall 40% response rate with 71% of responding CMT subjects reporting at least one site of chronic pain, and 39% reporting disability due to this pain. Thus, even taking possible bias into account, this still represents a substantial number (440) of CMT subjects reporting pain.

Inasmuch as the primary survey assessed incidence and severity, many time- and site-specific variables were not specifically addressed, such as time of day for peak pain, number of hours per day with pain, or even triggering physical or psychologic events. These factors warrant further investigation to better define possible pain mechanisms and generators in CMT.

**Conclusion**

Our survey data indicate that neuropathic pain is a significant problem for many people with CMT, frequently requiring pharmacologic intervention and significantly interrupting their activities of daily living. The frequency and intensity of pain reported by subjects with CMT is comparable in many ways to pain reported by subjects with other neuropathic conditions, including postherpetic neuralgia, complex regional pain syndrome type 1, diabetic neuropathy, and peripheral nerve injury. This preliminary survey study clearly defines a need for further pain-site-specific studies to better define the mechanisms of pain in CMT. This information could then be used to identify...
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Supplier
a. SPSS Inc., 444 North Michigan Avenue, Chicago, IL 60611.