

# Pain in Charcot-Marie-Tooth disease: an update

## Dor na doença de Charcot-Marie-Tooth: atualização

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### ABSTRACT

Charcot-Marie-Tooth (CMT) disease, the most common inherited peripheral neuropathy, has pain as one of its clinical features, yet it remains underdiagnosed and undertreated. This literature review assessed data related to pain from CMT to determine its prevalence, type and importance as a symptom, which, unlike other symptoms, is likely to be treated. The research encompassed 2007 to 2017 and included five articles that addressed pain from CMT. All of the papers concurred that pain is frequently present in CMT patients, yet its classification remains undefined as there has been no consensus in the literature about the mechanisms that cause it.

**Keywords:** Charcot-Marie-Tooth disease; pain.

### RESUMO

A doença de Charcot-Marie-Tooth (CMT), a neuropatia periférica hereditária mais comum, tem a dor como uma de suas características clínicas, a qual permanece subdiagnosticada e subtratada. Essa revisão de literatura avaliou os dados relacionados à dor em CMT com objetivo de observar sua prevalência, tipo e importância como sintoma que, em detrimento de outros, é possível ser tratado. O intervalo da pesquisa foi entre 2007 e 2017, através de cinco artigos abordando a dor em CMT. Todos os artigos concordam que a dor é frequente nos pacientes com a doença de CMT e a sua classificação permanece indefinida por não haver consenso na literatura sobre os mecanismos da dor.

**Palavras-chave:** doença de Charcot-Marie-Tooth; dor.

Despite being considered a rare disease, Charcot-Marie-Tooth (CMT) is the most common inherited peripheral neuropathy with an estimated prevalence between 1 in 2,500<sup>1</sup> and 1 in 1,214<sup>2</sup>, depending on ethnic background and the method used to diagnose it. It is a slowly-progressive motor and sensory disorder characterized by distal weakness of the lower limbs and atrophy, but it can also affect the upper limbs distally. Disability, sensory impairment, deformities and pain are clinical features of CMT, the severity of which varies among individuals. Classification of CMT can be based on clinical, neurophysiological and genetic assessments<sup>1,2,3</sup>.

In more than 90% of the cases of CMT in which a molecular diagnosis was performed, mutations were found in four genes: *PMP22*, *GJB1*, *MPZ*, and *MFN2*. Molecular changes in these genes can produce different phenotypes. For example, duplication of the *PMP22* gene is responsible for CMT1A, the predominant type of CMT, while its deletion is responsible for hereditary neuropathy with liability to pressure palsy (HNPP), which has been considered by some authors as a type of CMT based on neurophysiology<sup>1,4,5</sup>.

Thus far, more than 70 gene mutations have been recognized as responsible for this inherited neuropathy in all of its forms. This disorder can cause demyelination, axonal loss,

or both, depending on the type of mutation. It may also be autosomal dominant or autosomal recessive and exhibit an X-linked inheritance pattern<sup>1,5</sup>.

There have been few studies that have analyzed pain in CMT patients since it has not been recognized as a relevant symptom. The lack of an assessment of this specific manifestation directly affects the treatment of pain because it is not known if it is nociceptive or neuropathic<sup>5,6</sup>.

Medication and therapies for treating CMT to reverse or slow its progression are not yet available. However, properly treating the symptom of pain is possible, as it is a concern for patients<sup>1,4</sup>.

The objective of this study was to compile the results of the primary literature on CMT pain to assess the prevalence of this clinical expression and its classification according to the type of CMT and the type of pain.

### METHODS

The Pubmed database was searched using the key words “pain” and “Charcot-Marie-Tooth disease”. Studies that focused on the prevalence and type of CMT pain published between 2007 and 2017 were included (Figure).

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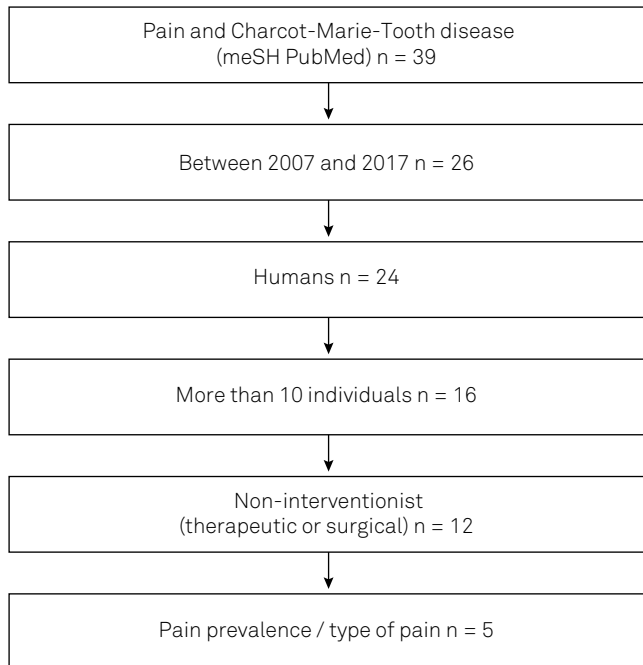


Figure. Flowchart of research articles.

Only human studies were included, and those with 10 or less participants were not considered. Articles evaluating pain of only one site, such as painful feet or trigeminal neuralgia, were also excluded, as were studies that did not evaluate pain and its clinical characteristics exclusively.

As an exception, a study that evaluated the clinical features of HNPP, including pain, was included as an article of interest, as it was unusual to find pain as a clinical feature of this type of CMT<sup>1,4,5</sup>.

## DISCUSSION

Five articles<sup>5,7,8,9,10</sup> were found that assessed pain from CMT, all of which used specific pain questionnaires and scales to measure pain and its features, such as gender, type, duration, intensity and frequency. Two of the studies focused on CMT1A<sup>8,9</sup>. The number of participants with assessed pain, among other symptoms, in each study was 50, 16, 49, 176 and 39.

The most common scale used to diagnose pain was the DN4 (*Douleur Neuropathique en 4 Questions*), a pain questionnaire that uses specific questions to evaluate pain. This was used in three of the five articles<sup>7,8,9</sup>. The questionnaire includes four questions about pain quality (burning, painful cold, and electric shock); four about associated symptoms (tingling, pins and needles, numbness, and itching) and physical tests for negative (hyperesthesia to touch, hyperesthesia to pinprick) and positive (brush-evoked pain) signs in areas that the patient referred to as experiencing pain. Each positive response is given a score of 1, and each negative response is given a score of 0. The total score is calculated as the sum of the 10 items, with scores of > 4 out of

10 suggesting neuropathic pain<sup>11</sup>. The Visual Analog Scale (VAS) was used in two of the studies<sup>7,9</sup>. The VAS is a 100 mm-long line anchored by verbal descriptors, with 0 mm being no pain and 100 mm being the worst pain imaginable.

A study carried out by Ribiere et al.<sup>7</sup>, evaluating the prevalence of chronic pain from CMT, assessed 50 patients with confirmed CMT diagnoses. The 27 women and 21 men (one woman and one man were excluded due to missing data) included in the study had a mean age of 47 years and a mean duration of 20 years of pain symptoms. The group comprised 76.9% CMT1A; 13.5% CMTX; 5.8% CMT2; and 3.8% CMT4. Pain evaluation included the VAS, medication need, DN4 questionnaire, *Questionnaire Concis Sur Les Douleurs*, Neuropathic Pain Symptom Inventory, Pain Questionnaire of Saint Antoine and clinical examination. Thirty-two of the 50 patients had had pain for at least 20 years, while 18 were pain free. Of all the patients evaluated, 66% had chronic pain. The pain scale analysis determined that 62.5% of those patients with pain had neuropathic pain, with a positive DN4 in 50% of the cases. The oldest patients with the longest disease duration had mechanical pain. The most common spontaneous pain descriptor was cramps or tearing. Patients with CMT1A were found to be less affected by pain. Almost two thirds (65.4%) of the patients reported some pain with an average duration of 140 months. The mean score for the VAS was 5.5, and was > 4 in 79.4% of the cases. Analgesics were needed by 38.4% of the patients. Nearly two thirds (64.7%) of the patients presented with distal, peripheral and symmetric pain, and the feet were affected in 80% of cases. In conclusion, this study found pain to be a frequent occurrence for CMT patients with characteristics of neuropathic pain. It should be noted that the *Questionnaire Concis Sur Les Douleurs* determined that the pain had a low impact on the quality of life of the patients.

A study by Pazzaglia et al.<sup>7</sup> attempted to answer an unsolved question presented by Padua et al.<sup>11</sup> in a brief communication in 2008, and proposed to investigate the origin of pain. They investigated 16 patients affected by CMT1A in a class of moderate severity (according to the Charcot-Marie-Tooth Neuropathy Score (CMTNS)) and 14 control participants in order to characterize pain in their neurophysiological mechanisms and correlate it with their psychophysical mechanisms. The CMT patients were selected from a larger group, based on their pain complaint. Assessment of the participants with the DN4, which evaluates neuropathic pain, revealed a mean score of 4.6, with 10 patients (62.5%) having DN4 ≥ 4 and six (37.5%) with DN4 ≤ 4. This result indicated that pain was neuropathic in the study sample. This study also tested laser evoked potentials, which showed Aδ fiber impairment in this neuropathy involving the lower limbs. In comparing the DN4 scores with the laser evoked potentials outcome for CMT1A patients, the findings were consistent with higher pain scores in this questionnaire, which was indicative of higher probabilities of neuropathic pain. The study found that patients with DN4 ≥ 4 had reduced laser evoked potential amplitudes

(abnormal N2/P2 amplitude). Among the 62.5% of patients of the sample who had neuropathic pain, some also had pain in the same areas where non-neuropathic pain patients had pain (lower back, muscles, knee), suggesting the coexistence of both neuropathic and biomechanical pain<sup>6,8,11</sup>.

In a study performed by Laurà et al.<sup>9</sup> to determine the characteristic of pain, whether neuropathic or related to musculoskeletal deformities, sensory symptoms were found in 49 CMT patients. The study also determined whether pain and small fiber involvement changed over a period of two years. Pain was assessed using the specific pain scales of the DN4 and the McGill Pain Questionnaire and two pain rating scales: the 11-point Likert Scale and the VAS. Clinical impairment was evaluated using the CMTNS, while small fiber function was assessed using thermal thresholds. Pain was a complaint for 43 of the 49 patients (88%), with it being in the feet in 30 patients (61%). Other pain locations included the knees (20%), lower limbs distally (27%), lower limbs proximally (4%), hip (12%), back (20%) and hands (22%). Nineteen patients (39%) reported pain in only one location, while 11 patients (22%) had pain in two or three locations and two (4%) had pain in four different areas. The mean VAS score was 3.5. Nine patients (18%) had DN4  $\geq$  4, suggesting neuropathic characteristics, eight of whom (89%) had the pain in their feet. Women had significantly higher pain scores than men in the Likert Scale and in some domains of the McGill Pain Questionnaire. The Fatigue Severity Scale score was significantly correlated with the VAS. In a 24-month evaluation, the VAS was 4.0 and the DN4 was 1.5, which was considered an indistinguishable change. A small drop in the Likert Score was considered important for indicating mild congruent reductions in some domains of the McGill Pain Questionnaire. One or more of the thermal thresholds were abnormal in 29 patients (59%). In patients with a longer duration of the disease, the Warm Detection Threshold and Cold Detection Threshold were elevated. During the period of the study, there were no relevant differences between patients with treated or untreated arms and there was no correlation between thermal thresholds and DN4  $\geq$  4. These findings suggest that there was no association between pain and disease severity or duration, and that only a small proportion of patients with CMT1A had neuropathic characteristics. In this respect, it is more likely that pain had a multifactorial origin. Either neuropathic or musculoskeletal pain was present in 29 patients (56%) and, for 15 patients, pain was the main symptom. Biomechanical pain was found to be especially frequent in CMT1A.

A paper published by Ramchandren et al. in 2014<sup>10</sup> reported on data collected on 176 children with CMT, evaluating whether the origin of their pain was neuropathic or biomechanical. The authors hypothesized that children, who experience fewer biomechanical changes than adults, experience less pain despite the severity of the neuropathy. The Faces Pain Scale, Child Health Questionnaire, CMTNS, Six-Minute Walk Test and the Validated Foot Posture Index were used to relate ankle/foot structural deformity and child-reported pain

in pediatric CMT. The population of the study was split into two groups, one with children aged 2–7 years (parent's report) and another with children aged 8–18 years (self-report). The resulting average for the Faces Pain Scale was 2.0 "hurts a little more". The prevalence of pain was 80% according to the children's reports, and 85% according to the parent's reports. They found that children with CMT had mild to moderate pain, which compromised their quality of life. Scores reported by children and parents, respectively, were: physical quality of life -0.433 and -0.488; mental quality of life -0.293 and -0.110; CMTNS -0.102 and -0.051; and standardized Six-Minute Walk Test 0.11 and 0.019. Pain was not related to neuropathy severity as assessed by the CMTNS, which suggests that pain is not due to nerve damage alone. This paper hypothesized that the pain etiology would be due to structural changes in the feet, which was confirmed by univariate regression models. Mechanical pain in pediatric CMT cases could worsen into adulthood with the progression of joint damage; however, multivariate regression models found this not to be significant.

Although pain is considered an uncommon symptom of HNPP, a study<sup>5</sup> performed in 2015 reviewed clinical and neurophysiological features of 39 patients with HNPP, and found pain to be a complaint at disease onset for six patients (15%), with three others reporting pain at some point of the disease (approximately 8%). Out of the six patients with pain as an initial symptom, three presented with chronic painful sensorimotor polyneuropathy affecting the lower limbs, which was phenotypically indistinguishable from CMT1<sup>1,5</sup>.

The data are detailed in the Table.

Pain prevalence could not be obtained from the reviewed studies because the methods used to select the study samples varied. Two out of the five studies included only CMT1A patients. One study included only patients with referred pain, while another study only evaluated children.

The specific questionnaires adopted for pain assessment also varied among the studies. Furthermore, Ribiere et al.<sup>7</sup> demonstrated that DN4 has a specificity of only 81.2%, which could explain the discordance in the results of these studies.

Only two studies correlated small fiber involvement and pain to explain pathophysiology. Pazzaglia et al.<sup>8</sup> correlated clinical scales of pain with small fiber neurophysiological data, while Laurà et al.<sup>8</sup> correlated pain scales with thermal thresholds. Whereas laser evoked potentials were found to be significantly related to DN4 scores, with lower amplitudes for DN4 scores  $\geq$  4, thermal thresholds showed no correlations between small fiber function and pain scales. These two studies also had contrasting conclusions about the pain origin.

Laurà et al.<sup>9</sup> and Ramchandren et al.<sup>10</sup> agreed that pain was not correlated with the severity of CMT.

An important bias of the Ramchandren et al.<sup>10</sup> study, however, was the differences in the cognitive development of the reporting children and parents. Since CMT is a hereditary disease, parents affected by CMT could report higher scores for their children.

Table. Detailed Data

Study	Ribiere et al., 2012 <sup>7</sup>	Pazzaglia et al., 2010 <sup>8</sup>	Laurà et al., 2014 <sup>9</sup>	Ramchandrem et al., 2014 <sup>10</sup>	Oliveira et al., 2016 <sup>5</sup>
Participants	50	16	49	176	39
Female gender	56%	81.25%	59.18%	51%	46.1%
Duration of the disease (mean years)	20	-	34	-	8.2
Mean age	49.5 (14–85)	41 (19–63)	41.5 (19–64)	12 (2–18)	32 (6–77)
CMT 1A / 2 / X / 4	76% / 6% / 14% / 4%	100%	100%	-	-
VAS (mean)	5.5	-	3.7	-	-
DN4 ≥ 4	40.6%	62.5%	18%	-	-
Faces Pain Scale (mean)	-	-	-	2.0 “hurts little more”	-
CMTNS	-	-	-	6.1 (8–18y n=128). 4.3 (2–7y n=14)	-
Mean severity	-	moderate	moderate	mild to moderate	-
Pain most common location	Distal locations (73.5%)	Distal extremities (hand and feet)	feet (61%)	-	Lower limbs (12.8%)
Pain prevalence	60%	100%	28%	80% / 85% *	23%
Type of pain	Neuropathic	Neuropathic	Neuropathic and biomechanical	-	-

VAS: visual analog scale; DN4: *Douleur Neuropathique en 4 Questions*; CNTNS: Charcot-Marie-Tooth neuropathy score; \*parent report

In conclusion, there are few studies in the literature about pain from CMT disease. In the last 10 years, only five studies assessed pain using specific pain questionnaires. All five studies were in agreement that pain has a high frequency of occurrence and a strong impact on CMT patients. Among the studies there were more assessments of CMT1A because it is the most common type of CMT. Only three papers mentioned pain classification, and there was no consensus among them whether it was caused by biomechanical or

neuropathic mechanisms. Two papers concluded that pain was more likely to be due to a neuropathic origin, while one of them found multifactorial pathways. There was no consensus on whether the frequency of pain varied among the specific types of CMT.

More research is needed to elucidate how to deal with CMT pain, to improve patient pain management and quality of life, and to direct the treatment of pain from CMT, which is currently general, and common to other neuropathies.

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