Pain and Charcot-Marie-Tooth Disease

ANSWERS TO YOUR QUESTIONS

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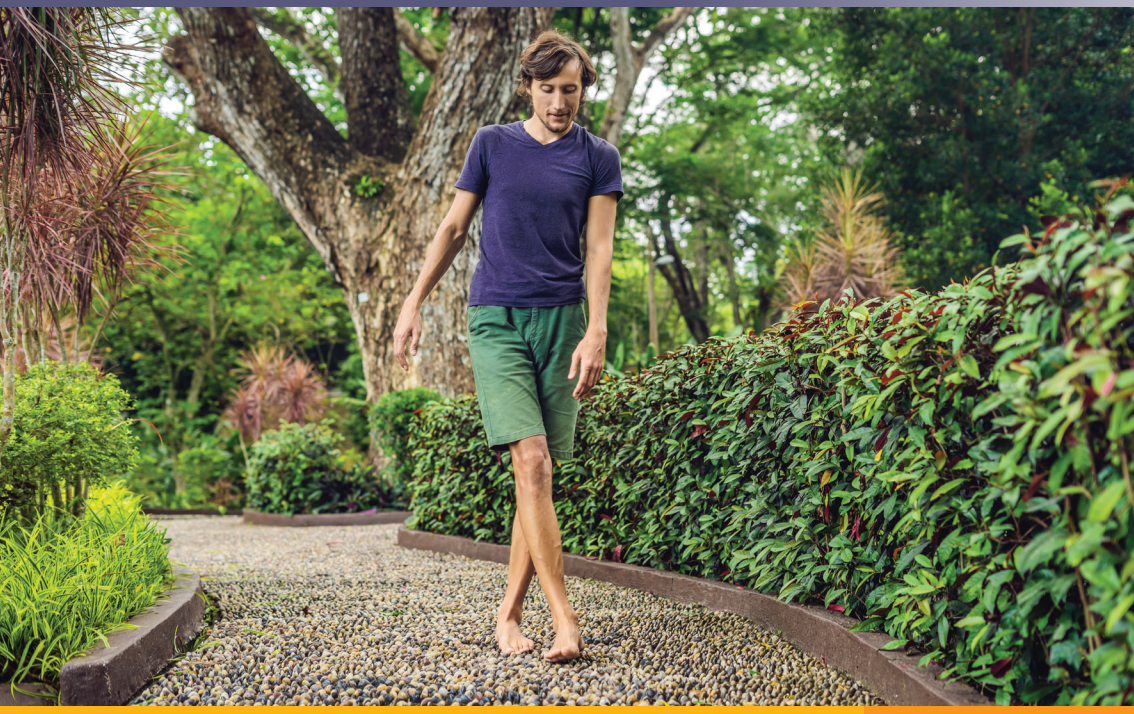

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Why this guide?

Several studies carried out in recent years have demonstrated the very common existence of pain in Charcot-Marie-Tooth (CMT) disease *[1-5]*. This pain is currently the subject of studies in order to better understand its mechanism and onset, its impact on the everyday life of patients and the measures that can be taken to relieve it *[2-4, 6-8]*. At the same time, healthcare teams are paying particularly close attention to it. In this context, this guide has been designed to answer the main questions that you or those around you have on the matter. It does not replace the explanations given by the healthcare professionals monitoring you but it may enable you to better prepare for your consultations with them and to better understand their explanations and any management proposed.

I am in pain and would like to know why

Why can CMT disease be accompanied by pain?

CMT is a group of diseases that affect the peripheral nerves that connect the central nervous system (brain and spinal cord) to the rest of the body *[8-10]*. They can therefore cause a decrease in the strength and volume of the muscles at the extremities of the limbs, particularly in the feet and legs *[8-10]*.

The onset of pain can then be explained by two mechanisms:

- Pain related to nerve damage, occurring because the nervous system no longer works normally. We refer to this case as "neuropathic" pain *[5, 7, 11, 12]*;
- Musculoskeletal pain related to muscle damage and its consequences, such as deformities of the feet, scoliosis of the spine or stiffness of the joints *[8, 13]*. We refer to this type of pain as "nociceptive" pain, because it results from excessive stimulation of the peripheral pain receptors, the "nociceptors", as a result of tissue damage or inflammation *[11]*.

Many patients with CMT can have mixed pain, i.e. neuropathic and nociceptive pain at the same time *[5, 14]*.

Like all pain, the pain patients with CMT feel is therefore not imaginary in any way, but has a precise origin, which will need to be identified in order to manage it in an adapted manner *[3, 15]*.

What do we know about the frequency of pain during the course of CMT disease?

In recent years, several studies have shown that pain in CMT disease is very common, and it is even one of the main symptoms of the disease in certain patients *[1-5, 14]*.

In a study conducted in 2018–2019 in patients with CMT1A, the most common form of CMT, 84% of patients had pain *[5]*. Of these, 6.2% had exclusively neuropathic pain, 50% had nociceptive pain and 43.8% had both neuropathic and nociceptive pain ***(Figure 1)*** *[5]*. In another study, this time concerning patients with CMT1A (76.9%) and other types of CMT (CMTX: 13.5%, CMT2: 5.8% and CMT4: 3.8%), two-thirds of patients complained of pain that had been progressing for 140 months *[1]*. On a visual scale that enables patients to rate pain intensity from 0 to 100 mm, this was on average 55/100, and was greater than or equal to 40/100 in 79.5% of cases *[1]*.

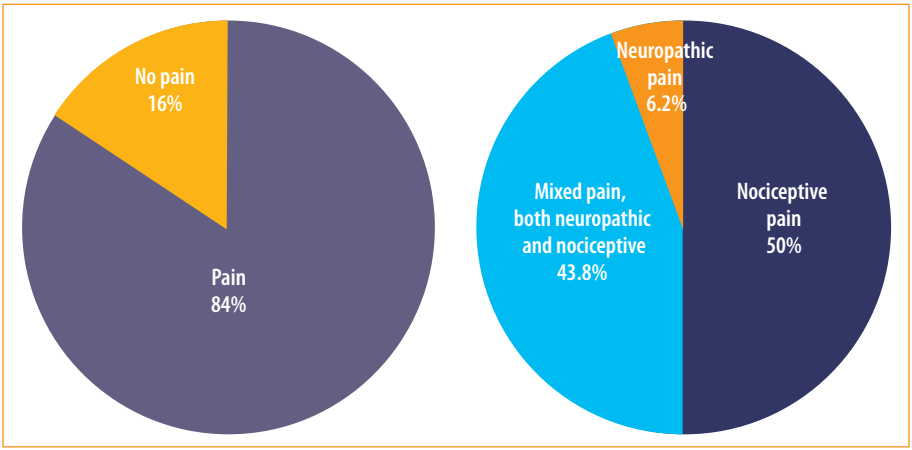

Figure 1. Frequency and type of pain in a study conducted in 2018–2019 in 19 patients with CMT1A *[5]*.

How does CMT pain manifest itself?

During the course of CMT disease, pain is most often chronic, and persistent for at least three months *[1, 8, 11]*. It can therefore have a significant impact on activities, sleep or mood, and more generally on quality of life ***(box 1, page 4)*** *[5, 8, 16-20]*.

BOX 1 Pain and quality of life in patients with CMT: a new study currently underway.

In Europe and the United States, a study developed with the help of international experts and patient associations is currently evaluating the impact of different types of CMT in everyday life, due to the data provided in real-time by the patients themselves via a smartphone app (CMT&Me) *[21]*. Expected to last for two years, this study on lifestyle focuses on the quality of life of the participants, and in particular on the intensity and impact of potential pain, by asking them through validated questionnaires *[21]*.

BOX 2 The DN4 questionnaire.

In order to identify neuropathic pain, the doctors, in a consultation, may suggest that you answer the DN4 questionnaire, DN for "neuropathic pain" (*douleur neuropathique* in French) and 4 for "4 questions", specially designed for its detection. If by completing this questionnaire, you get a total of 4 yeses (out of the 10 possible), it is highly likely that you would suffer from neuropathic pain *[11, 22]*.

The nature of the painful manifestations varies, particularly depending on the mechanism involved. Neuropathic pain produces specific sensations, often described as burning, electric shocks, tingling or prickling [1,11]. They can be detected using a specific tool, the DN4 questionnaire ***(Box 2 and Figure 2)*** *[11, 22]*. Some patients also suffer from muscle cramps, which can be extremely painful and disabling ***(Box 3)*** *[23]*.

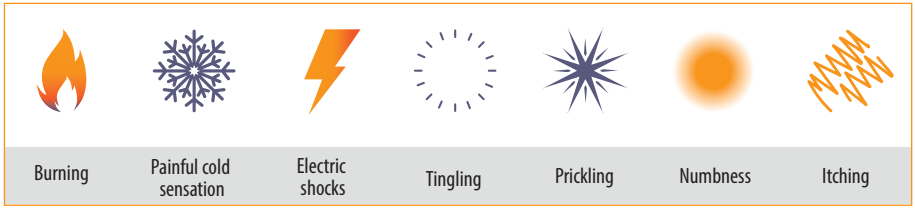

Figure 2. Typical symptoms of neuropathic pain assessed by the DN4 questionnaire *[11, 22]*.

In terms of location, the pain is most often located at the extremities of the limbs, especially in the feet, but it can also be located in the upper part of the limbs, as well as in the back or neck *[1, 3, 4]*.

BOX 3 **Muscle cramps: very common pain during the course of CMT disease.**

In an American study conducted using the database run by the Inherited Neuropathy Consortium of the Rare Diseases Clinical Research Network of the National Institute of Health, researchers questioned 110 patients with CMT who suffer with cramps in order to describe the nature of their pain *[23]*. For the purposes of the study, the patients had to complete a questionnaire about their cramps three times over a period of two months. The results showed that the median frequency of the onset of cramps was 9.3 times per week and that nearly one in four patients suffered from it on a daily basis. Furthermore, for 60% of patients, the cramps had a negative impact on their quality of life *[23]*.

During the course of CMT disease, does the intensity of the pain depend on the severity of the disease?

According to the available studies, the intensity of pain in CMT disease does not seem to correlate with the severity of the disease, or with its duration of progression *[3-5]*.

However, as with any pain, the perception of it may vary depending on the emotions, behaviours and thoughts associated with it ***(Figure 3)*** *[24]*. For example, anxiety can increase the perceived intensity of pain, while, on the other hand, positive emotions can reduce it *[25]*.

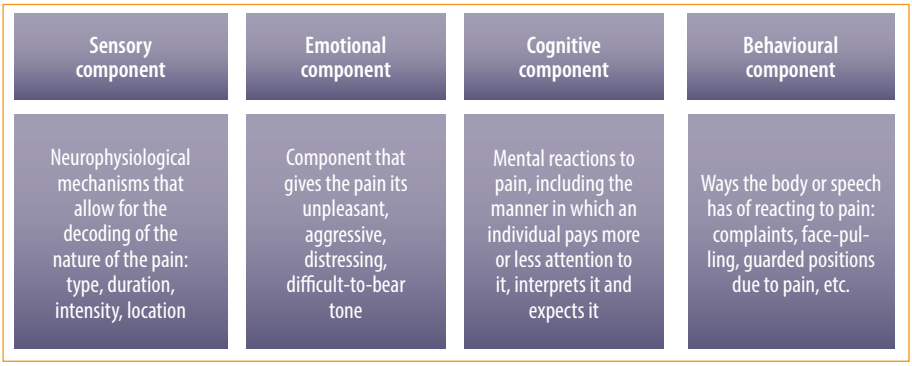

Figure 3. The perception of pain: a phenomenon specific to each individual, which depends on four components *[24]*.

I am in pain and talk about it in order for it to be relieved

Can I be sure that my pain will be taken seriously?

Today, pain management is a fundamental right of any person and a priority for healthcare professionals *[26]*. If you are suffering, it is therefore important to let your doctor know, so that he/she can take it into account and offer you suitable treatment *[27]*. Don't worry about being a bother or appearing "oversensitive to pain". Do not wait too long to discuss it either as pain is more difficult to relieve when it becomes chronic *[11]*. Once treatment has been implemented, it is also important to mention if you have not been completely relieved: it can then be modified to be better adapted to you *[26]*.

Do not hesitate to talk to your doctor about your pain because it is only you who can describe it *[27]*.

What are the means available to relieve it?

The means available to relieve pain include medical treatments and non-medical approaches ***(Table)***, which are complementary *[8, 26]*. They are chosen on an individual basis, after having assessed the mechanisms and all other characteristics of the pain (location, age, intensity, factors modifying its perception, repercussions, etc.) and considering the patient as a whole *[24, 26, 27]*.

Medical treatments	For neuropathic pain: medicinal products from the antidepressant or antiepileptic family, used for their action on the nervous system, or local treatment in the form of a skin patch when the pain is located on a limited surface area For musculoskeletal pain: analgesic medicines (varying in strength depending on the intensity of the pain) or anti-inflammatory medicine products.
Non-medical approaches	Transcutaneous electrical nerve stimulation in the case of neuropathic pain located on a limited surface area Physical techniques: physical therapy, muscle massages, balneotherapy, adaptation of an orthopaedic device Mind-body techniques: relaxation, sophrology, hypnosis Acupuncture

Table. Main means of pain relief *[8, 10, 12, 15, 26]*.

Sometimes several consultations are necessary, particularly if the pain is chronic *[24, 27]*. In addition, referral to a facility specialising in the management of chronic pain may be suggested to you ***(Box 4)*** *[27]*.

BOX 4 **Chronic Pain Facilities in Practice.**

In these facilities, consultations are provided by healthcare professionals from different disciplines (doctors, nurses, psychologists, etc.), who are experts in pain assessment and treatment *[27]*. Do not hesitate to talk to your neurologist, who will review the relevance of a consultation with you *[27]*.

In all cases, healthcare professionals will assess the efficacy of the care with you, not only in terms of reducing the pain and reducing the use of analgesic medicines but also in terms of the impact on daily life, sleep, as well as physical and psychological well-being *[24, 26]*.

Can physical activity help relieve pain?

In CMT disease, regular physical activity (adapted to the muscle abilities of each individual) develops muscle strength and decreases sensations of fatigue and pain *[28, 29]*. Exercise also helps fight against potential excess weight, which, by increasing motor difficulties, may become an aggravating factor for pain *[30, 31]*. Physical activity is therefore recommended for pain, alongside the exercises performed during physiotherapy *[10]*. When choosing a sport, feel free ask any questions you may have to the rehabilitation doctor monitoring you.

Nadine Attal declares that she has conflicts of interest with Pfizer, Grunenthal, Novartis, Upsa, Air Liquide, Merz Pharma, Novaremed over the past 3 years for scientific advice or symposium (not related to the content of this guide).

Shahram Attarian declares that he has no conflict of interest.

Bibliography

1. Ribiere C et al. Pain assessment in Charcot-Marie-Tooth (CMT) disease. Ann Phys Rehabil Med 2012;55(3):160-73.
2. Ramchandren S et al. Effect of pain in pediatric inherited neuropathies. Neurology 2014;82(9):793-7.
3. Laurà M et al. Pain and small fiber function in Charcot-Marie-Tooth disease type 1A. Muscle Nerve 2014;50(3):366-71.
4. Azevedo H et al. Pain in Charcot-Marie-Tooth disease : an update. Arq Neuropsiquiatr 2018;76(4):273-6.
5. Azevedo H et al. Prevalence and characterization of pain in patients with Charcot-Marie-Tooth disease type 1A. Arq Neuropsiquiatr 2021;79(5):415-9.
6. Padua L et al. Charcot-Marie-Tooth and pain : correlations with neurophysiological, clinical, and disability findings. Neurol Sci 2008;29(3):193-4.
7. Pazzaglia C et al. Mechanisms of neuropathic pain in patients with Charcot-Marie-Tooth 1A : a laser-evoked potential study. Pain 2010;149(2):379-85.
8. Tucker-Bartley A et al. Pain phenotypes in rare musculoskeletal and neuromuscular diseases. Neurosci Biobehav Rev 2021;124:267-90.
9. Bouche P. Neuropathie périphérique. Rev Prat 2003;53:67-73.
10. Protocole national de diagnostic et de soins. Neuropathies héréditaires sensitivomotrices de Charcot-Marie-Tooth. Texte du PNDS. Mars 2020.
11. Jedryka F et al. Bases neurophysiologiques, mécanismes physiopathologiques d'une douleur aiguë et d'une douleur chronique. Rev Prat 2018;68(4):e157-64.
12. Moisset X et al. Traitements pharmacologiques et non pharmacologiques de la douleur neuropathique : une synthèse des recommandations françaises. Douleur analg 2020;33:101-12.
13. Colomban C et al. Clinical spectrum and gender differences in a large cohort of Charcot-Marie-Tooth type 1A patients. J Neurol Sci 2014;336(1-2):155-60.
14. Gemignani F et al. Sensory manifestations in Charcot-Marie-Tooth disease. J Peripher Nerv Syst 2004;9(1):7-14.
15. Bird TD. Charcot-Marie-Tooth (CMT) hereditary neuropathy overview. 1998 Sep 28 (Updated 2019 Janv 24). In : Adam MP et al. editors. GeneReview® (Internet). Seattle (WA): University of Washington, Seattle;1993-2021.
16. Johnson NE et al. Quality-of-life in Charcot-Marie-Tooth disease: the patient's perspective. Neuromuscul Disord 2014;24(11):1018-23.
17. Bjelica B et al. Neuropathic pain in patients with Charcot-Marie-Tooth type 1A. Neurol Sci 2020;41(3):625-30.
18. Bjelica B et al. Quality of life in hereditary neuropathy with liability to pressure palsies is as impaired as in Charcot-Marie-Tooth disease type 1A. Acta Neurol Belg 2021;121(6):1481-6.
19. Schorling E et al. Health-related quality of life and satisfaction with german health care services in patients with Charcot-Marie-Tooth neuropathy. J Neuromuscul Dis. Prépublication en ligne, 2021. doi: 10.3233/JND-210667.
20. Souza CC et al. The impact of pain and nocturnal cramps on sleep quality in Charcot-Marie-Tooth disease: a case-control study. Sleep Sci 2021. doi: 10.5935/1984-0063.20210025.
21. Thomas FP et al. Patient-reported impact of Charcot-Marie-Tooth disease: protocol for a real-world digital lifestyle study. Neurodegener Dis Manag 2021;11(1):21-33.
22. Bouhassira D et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114(1-2):29-36.
23. Johnson NE et al. Prospective study of muscle cramps in Charcot-Marie-Tooth disease. Muscle Nerve 2015;51(4):485-8.
24. ANAES. Évaluation et suivi de la douleur chronique chez l'adulte en médecine ambulatoire. Mise à jour : 06/06/2007.
25. Lumley MA et al. Pain and emotion: a biopsychosocial review of recent research. J Clin Psychol 2011;67(9):942-68.
26. Passard A. Thérapeutiques antalgiques, médicamenteuses et non médicamenteuses. Rev Prat 2020:e13-31.
27. HAS. Douleur chronique : reconnaître le syndrome douloureux chronique, l'évaluer et orienter le patient. Consensus formalisé. Décembre 2008.
28. Djordjevic D et al. Effects of self-selected exercise on strength in Charcot-Marie-Tooth disease subtypes. Can J Neurol Sci 2017;44(5):572-6.
29. El Mhandi L et al. Benefits of interval-training on fatigue and functional capacities in Charcot-Marie-Tooth disease. Muscle Nerve 2008;37(5):601-10.
30. Mannil M et al. Rehabilitation in Charcot-Marie-Tooth disease type 1. ACNR 2014;14:25-7.
31. Donlevy GA et al. Association between body mass index and disability in children wirh Charcot-Marie-Tooth disease. Neurology 2021;97(17):e1727-36.

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