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Review Article

Current Perspective in Mixed Pain

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Abstract

Pain is one of the 10 leading causes of medical consultation worldwide and is the alarm symptom of the organism in situations that threaten its integrity, however, when it becomes chronic, it loses its protective capacity and becomes, in many cases, the disease itself.

According to the International Association for the Study of Pain (IASP) pain is classified as nociceptive, neuropathic and nociplastic. Mixed pain has been described years ago due to the coexistence of different types of pain.

We can conclude that we do not have a screening tool and/or treatment algorithm for mixed pain, so it is preferable that pain management begins with a rigorous assessment, using the latest available tools, followed by individualized evidence-based treatment with multimodal therapy when appropriate.

Keywords: nociceptive pain, neuropathic pain, mixed pain.

Introduction

Pain is a frequent cause of medical consultation and in acute processes it is considered the alarm symptom of the organism that alerts it of a harmful process that can be inflammatory or associated with structural damage; however, when this symptom becomes chronic, it can become the disease itself, which generates affection in different aspects of the sufferer's life, beyond the physical sphere. It is known that pain has a high prevalence and this is where its relevance lies.[1]

Nociceptive pain is considered the most frequent form of pain presentation and has been defined by the International Association for the Study of Pain (IASP) as pain that arises from actual or potential damage to neural tissue and is due to the activation of nociceptors, associated with active inflammation.[2]

Regarding to neuropathic pain, its definition was modified in 2008, excluding the concept of “dysfunction” and integrating the term “disease”, so that pain scenarios in which pathophysiological process are not identified, are no longer part of this group of pain syndromes (e.g. fibromyalgia, complex regional pain syndrome type 1, chronic low back pain, among others).[3]

Currently, neuropathic pain is considered to be "pain that originates as a direct consequence of an injury or disease affecting the somatosensory system".[4]

In addition, the concept of nociplastic pain has recently emerged, which describes the sensation or perception of pain that does not arise from a clear identifiable lesion and there is nociceptors’ activation, peripheral activation or lesion in the somatosensory system; previously it was known as dysfunctional pain or dysfunctional pain syndrome.2

On the other hand, mixed pain is a term that has been identified for several years and emerged as an explanation for pain that is not completely nociceptive or neuropathic, however, they coexist. Despite the literature and observation in clinical practice, its mechanism has not been defined, its concept is not formalized and there are no screening tools or specific therapeutic approach algorithms.[2]

This review aims to make a compilation of the information published to date on mixed pain, highlighting the missing information on the subject, for its clinical application.

Mixed pain

There has been an ongoing debate for several years on the pathophysiological classification of pain, the recent taxonomy considers two large groups of pain syndromes, those of nociceptive type and neuropathic pain models. Currently, a third group has been added: the conceptualization of nociplastic pain, which was supported by robust literature confirming changes in brain activation.[5]

The definition for nociplastic pain is: "pain arising from altered nociception despite no clear evidence of actual or potential tissue damage causing activation of peripheral nociceptors or evidence of disease or injury to the somatosensory system causing the pain". The note accompanying this definition states that patients may have a combination of nociceptive and nociplastic pain.[3]

It is clear that one of the most complex aspects of dealing with a person with pain is identifying the type(s) and mechanism(s) of pain, so it is vital to be able to clarify these points in clinical care.[6]

Thus, in medical practice a large proportion of patients express pain scenarios that cannot be categorized as solely nociceptive, neuropathic or even only of nociplastic origin, being called mixed pain syndromes, even though this term has not been accepted by the IASP.

Recent publications have described the term "mixed pain" in those patients who clinically present a significant overlap of nociceptive and neuropathic symptoms in the same anatomical area.[2]

This has been highlighted in different publications using screening tools such as the Pain-DETECT questionnaire. A review of the literature in 2012 reported that between a quarter and half of patients with chronic low back pain had greater than 90% probability of having a neuropathic pain component, which was confirmed in 2016, documenting a component of pain radiating to the ankle or foot region with a dermatomal distribution with neurological signs that corresponded to a typical radiculopathy in up to 80% of patients with low back pain which was contrasted with the previous report made by Baron et al. of a neuropathic pain component in 8% of patients with low back pain.[7]

In other clinical contexts, such as osteoarthritis, a neuropathic component has been identified in up to a third of them, or, in rheumatoid arthritis, 9.3% of the subjects studied have a possible/probable neuropathic component using the Pain-DETEC questionnaire. [8]

Likewise, in another publication it was identified that in primary care and orthopedic care, pain had a mixed component in more than 59% of the sample size where a increased clinical complexity and more comorbidities were observed as well as more adverse psychosocial factors; lower health-related quality of life and lower response to the implemented treatments, requiring a higher utilization of health care resources.[9]

This report matches with Perrot's description in 2015, which highlights that the main symptom in osteoarthritis is pain with nociceptive, neuropathic and nociplastic mechanisms. A more recent study on this topic has documented that 20% to 30% of patients with osteoarthritis have mixed pain.[10, 11]

On the other hand, the term mixed pain is commonly accepted in cancer patients. The absence of a definition of mixed pain by the IASP does not reflect its non-existence, nor the lack of importance or need to define it.[12]

Cancer pain affects about 48% of early-stage patients and between 64% and 75% of patients with advanced disease. Of this percentage, half have inadequate pain control. Among the causes of treatment failure were found a lack of assertiveness in the etiopathological mechanism of pain and therefore an inadequate pharmacological therapy. In particular, in identifying the presence of neuropathic pain as a pain mechanism and with underdiagnosis, an undertreatment.[13]

In 2012, Bennet et al. determined the prevalence and etiology of neuropathic mechanisms in cancer through a systematic review of patients with oncologic pain over 12 years. Of the 22 studies that met the inclusion criteria, only 14 of these reported a confirmatory test for sensory abnormality or diagnostic lesion in the case of neuropathic pain. In their results, out of 13,683 patients, the prevalence of neuropathic pain ranged from 19% to 39% when considering the presence of mixed pain.[14]

In the oncology patient, the etiology of neuropathic pain can occur for a variety of reasons: direct neural compression by the tumor, secondary to oncologic treatments (postoperative or painful neuropathy induced by chemotherapy) or non-oncologic comorbidities. Therefore, in the evaluation of neuropathic pain in the oncologic patient, it is sized as having a neuropathic component and with a greater or lesser neuropathic component than somatic.[15]

It is important to mention that, as a screening tool for oncologic pain, the IASP Cancer Pain groups and the EAPC Network (European Association for Palliative Care Research Network) developed a NeuPSIG tool with 4 criteria for use in clinical and research settings, which is described below:

Criterion 1: Pain with a distinct neuroanatomic distribution. The distribution of pain or hyperalgesia may extend outside the primary innervation territory of a peripheral nerve root (due to referred pain or central sensitization) but must still be plausible in terms of the underlying disorder.

Criterion 2: History of an injury or disease affecting the somatosensory system. To demonstrate a history suggestive of an injury or disease affecting the somatosensory system, it is important to establish the etiology of the pain by distinguishing between disease-related, treatment-associated, or comorbid causes.

Criterion 3: Confirmatory studies of positive and negative sensory signs in the territory innervated by the injured structure. Sensory abnormalities should be consistent with the distribution of pain. Because sensitization is common in both neuropathic and nociceptive pain, it does not confirm the presence of a somatosensory system lesion or disease but may provide useful information about additional pain mechanisms and/or an alternative diagnosis. Each patient should act as his or her own control, so the sensory examination should be repeated at one site and the findings compared between the two sites. Only one sensory change is required to meet this criterion.

Criterion 4: Diagnostic studies confirming injury or disease around the site of neuropathic pain. MRI scans, CT scans and rarely nerve biopsies or laboratory studies are usually requested.

If criteria 3 and 4 are met, the diagnosis is definite neuropathic pain (DN); if criteria 1 and 2 are met, it is considered a possible DN; and if criteria 1 and 2 and 3 or 4 are met, it is considered a probable DN.[15]

Concerning the utilization of neuropathic pain assessment tools for diagnosing mixed pain, current evidence indicates that the pain DETECT instrument and the S-LANSS scale lack adequate validity in identifying the neuropathic component within patients experiencing mixed oncologic pain. This deficiency

arises from the lack of development and validation within the context of cancer pain.[16]

Regarding the pain experienced by patients undergoing chemotherapy, studies have documented that it exhibits peripheral neuropathic characteristics in 90% of the cases. Despite the advancements in cancer treatment aimed at enhancing survival rates, neuropathy remains a significant unresolved issue demanding further.[17]

A recently proposed definition for mixed pain delineates it as "a complex overlapping of different known types of pain (nociceptive, neuropathic and nociplastic) in some combination, acting simultaneously and/or concurrently conditioning pain in the same anatomical area. Any mechanism may be clinically more predominant at some point in time. Mixed pain may be acute or chronic".2

With the above mentioned, it is important to note that mixed pain is NOT the following.[2]

a) Pain due to a primary injury and its secondary effects.

b) Nociceptive pain that transitions or evolves to neuropathic pain.

c) Pain with ambiguous neuropathic pain scores obtained from screening tools such as the Pain-DETECT questionnaire.

d) Pain experienced by a non-homogeneous study group of patients.

e) Pain following a cerebral vascular event (CVE) generated by a combined peripheral and central mechanism.

f) Pain described in multiple sites

Freynhagen et al. suggested in 2020 a series of 9 questions that would lead the clinician to identify the predominant mechanisms of pain in patients with mixed pain and are listed below.[18]

1. Where exactly do you feel your pain? Please mark the painful areas on this drawing.

2. What words would you use to describe your pain?

3. How long have you been experiencing your pain?

4. On a scale of 0 to 10, how severe is your pain at rest and during movement?

5. Do you feel your pain constantly, more during movement or more at rest?

6. Is your pain related to any identifiable cause? How did it start and develop?

7. What have you done to treat your pain?

8. Has your pain caused you psychological distress?

9. Have you experienced any other symptoms or changes that have concerned you?

These questions help the clinician to elucidate the syndromic components of pain, to be able to make an assertive diagnosis and make an individualized therapeutic proposal.

However, there is currently no screening tool specifically designed for the identification of the components associated with mixed pain, nor is there a specific treatment algorithm, so it is imperative to work on it.

Conclusion

The conceptualization of mixed pain has been highlighted over time. Although it is true that this concept is not yet recognized by the IASP, in daily clinical practice a non-negligible percentage of patients can be included in this group of pain. As we continue to obtain information on the mechanisms and subtypes of pain, it can be the basis for the development of specific assessment tools, as this need is identified in order to provide individualized, evidence-based treatment to this group of patients, with multimodal therapy when appropriate. Bringing these crucial pieces together to improve chronic pain management will ultimately help improve patients' lives, which is, of course, our ultimate goal.

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Conflicts of interest

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References

1. Guillén-Núñez MR, Juárez-Lemus AM. Algología para no algólogos, Siegfried Rhein, 2020; 15-24.

2. Freynhagen R, Parada HA, Calderon-Ospina CA, Chen J, Rakhmawati Emril D, Fernández-Villacorta FJ, et al. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin. 2019;35(6):1011-1018. https://doi.org/10.1080/03007995.2018.1552042 PMid:30479161

3. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, Rief W, Sluka AK. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157(7):1382-1386. https://doi.org/10.1097/j.pain.0000000000000507 PMid:26835783

4. Benaña J. Dolor neuropático: actualización en definiciones y su tratamiento farmacológico. Rev Med Hondur; 2020; 88(1): 48-51. https://doi.org/10.5377/rmh.v88i1.11591

5. Trouvin AP, Perrot S. New concepts of pain. Best Pract Res Clin Rheumatol. 2019;33(3):101415. https://doi.org/10.1016/j.berh.2019.04.007 PMid:31703792

6. Argoff C. Distinguishing Neuropathic, Non-Neurophatic, and Mixed Pain. Pract Pain Manag, 2017;17(1).

7. Baron R, Binder A, Attal N, Casale R, Dickenson AH, Treede RD. Neuropathic low back pain in clinical practice. Eur J Pain. 2016;20(6):861-873. https://doi.org/10.1002/ejp.838 PMid:26935254 PMCid:PMC5069616

8. Ito S, Kobayashi D, Murasawa A, Narita I, Nakazono K. An Analysis of the Neuropathic Pain Components in Rheumatoid Arthritis Patients. Intern Med. 2018;57(4):479-485. https://doi.org/10.2169/internalmedicine.9235-17 PMid:29225253 PMCid:PMC5849541

9. Ibor PJ, Sánchez-Magro I, Villoria J, Leal A, Esquivias A. Mixed Pain Can Be Discerned in the Primary Care and Orthopedics Settings in Spain: A Large Cross-Sectional Study. Clin J Pain. 2017;33(12):1100-1108. https://doi.org/10.1097/AJP.0000000000000491 PMid:28244943

10. Perrot S. Osteoarthritis pain. Best Pract Res Clin Rheumatol 2015; 29:90-97. https://doi.org/10.1016/j.berh.2015.04.017 PMid:26267003

11. Zolio L, Lim KY, McKenzie JE, Yan MK, Estee M, Hussain SM, Cicuttini F, Wluka A. Systematic review and meta-analysis of the prevalence of neuropathic-like pain and/or pain sensitization in people with knee and hip osteoarthritis. Osteoarthritis Cartilage. 2021;29(8):1096-1116. https://doi.org/10.1016/j.joca.2021.03.021 PMid:33971205

12. Grond S, Radbruch L, Meuser T, Sabatowski R, Loick G, Lehmann KA. Assessment and treatment of neuropathic cancer pain following who guidelines. Pain. 1999 Jan 1;79(1):15-20. https://doi.org/10.1016/S0304-3959(98)00138-9 PMid:9928771

13. Fainsinger RL, Nekolaichuk C, Lawlor P et al. An international multicentre validation study of a pain classification system for cancer patients. Eur J Cancer 2010;46:2896-904. https://doi.org/10.1016/j.ejca.2010.04.017 PMid:20483589

14. Bennett MI, Rayment C, Hjermstad M, Aass N et al. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012 Feb;153(2):359-365. https://doi.org/10.1016/j.pain.2011.10.028 PMid:22115921

15. Reis-Pina P, Acharya A, Lawlor, P. Cancer pain with a neuropathic component: a cross-sectional study of its clinical characteristics, associated psychological distress, treatments, and predictors at referral to a cancer pain clinic. Journal of pain and symptom management, 2018, 55(2), 297-306. https://doi.org/10.1016/j.jpainsymman.2017.08.028 PMid:28870800

16. Higashibata T, Tagami K, Miura T, Okizaki A, Watanabe Y et al. Usefulness of painDETECT and S-LANSS in identifying the neuropathic component of mixed pain among patients with tumor-related cancer pain. Supportive Care in Cancer, 2020: 28(1), 279-285. https://doi.org/10.1007/s00520-019-04819-9 PMid:31041583

17. Fallon MT. Neuropathic pain in cancer. Br J Anaesth. 2013;111(1):105-111. https://doi.org/10.1093/bja/aet208 PMid:23794652

18. Freynhagen R, Rey R, Argoff Ch. When to consider "mixed pain"? The right questions can make a difference! Current Medical Research and Opinion, 2020, 36:12, 2037-2046. https://doi.org/10.1080/03007995.2020.1832058 PMid:33012210