Article:
Boland, EG, Mulvey, MR and Bennett, MI (2015) Classification of neuropathic pain in cancer patients. Current Opinion in Supportive and Palliative Care, 9 (2). pp. 112-115. ISSN 1751-4258

https://doi.org/10.1097/SPC.0000000000000136

Classification of neuropathic pain in cancer patients

E.G. Boland[1], M. Mulvey[2], M.I. Bennett[2]

[1]Queen's Centre for Oncology and Haematology, Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, University of Hull, UK.
[2]Academic Unit of Palliative Care, Leeds Institute of Health Sciences, University of Leeds, UK.

Corresponding Author:
Dr Elaine Boland
Consultant in Palliative Medicine and Honorary Senior Lecturer
Queen's Centre for Oncology and Haematology,
Hull and East Yorkshire Hospitals NHS Trust
Cottingham, UK
T= +44 (0) 1482461303
E = elaine.boland@hey.nhs.uk

Abstract

Purpose of review: Neuropathic pain can affect up to 40% in patients with cancer, which could be related to the tumour, treatment or from co-morbid diseases. Effective assessment to diagnose neuropathic pain is crucial in order to choose the right treatment. Recent findings: There is to date no systematic classification system; the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain developed a neuropathic pain grading system intended to be used for both clinical and research purposes and a recent review describe a step-by-step process for applying the grading system in a clinical setting for cancer pain. Summary: We have combined these recommendations to outline a clinically relevant process to classify NP in patients with cancer.

Keywords

Cancer, pain, neuropathic, assessment

Introduction

Neuropathic pain (NP) arises due to a disease or a lesion affecting the somatosensory system and can thus arise from pathology affecting either the peripheral or the central nervous system [1]. Neuropathic pain is a heterogeneous entity with various clinical key findings including spontaneous pain, which can either be continuous or dominated by paroxysms of pain. Patients may also complain of loss of sensation (numbness) or experience pain evoked by non-noxious triggers such as light brushing or cold leading to allodynia [2]. Patients with such pain may express different combinations of these symptoms. The sensations from NP can be unusual and difficult to describe; therefore many patients will neglect to report these symptoms unless prompted by their clinicians [3].

Cancer patients experience NP which can be tumour-related, treatment-related (particularly post-surgical or post-chemotherapy) or from co-morbid diseases such as diabetic neuropathy. Tumour-related neuropathic pain is often multifactorial and involves a combination of inflammatory and neuropathic mechanisms; the magnitude and relative contribution of these change as the tumour advances [4]. This classification of NP in cancer patients will be reflected in a forthcoming 11th revision of the International Classification of Diseases by the World Health Organization [5].

About 20% of pains in cancer patients are neuropathic but about 40% of patients are affected by NP because each patient experiences two pains on

average. [6]. Cancer patients with NP have been shown to have poorer cognitive, physical and social functioning than patients without NP features, which has a greater impact on their daily living [7]. For this reason, it is seen as a core component with a cancer pain classification system [8].

Some cases of neuropathic conditions are straightforward, such as patients with malignant spinal cord compression where motor and sensory changes can be detected on clinical assessment and directly visualized on magnetic resonance imaging. However, such scenarios are the exception rather than the rule. Other clinical conditions, such as metastatic bone disease, result in more of a mixed picture. The challenge is to discriminate NP from other types of pain in cancer patients and to identify the lesion or disease causing the pain [9]. The demonstration of abnormal function in the somatosensory system, including negative (hypoesthesia and hypoalgesia) and positive (allodynia and hyperalgesia) sensory phenomena can contribute towards a diagnosis of NP [9].

A recent systematic literature review on NP in cancer patients based on 22 studies demonstrated that clinical assessment methods varied and thus a standardised approach for assessing NP in cancer is needed to improve treatment outcomes [6]. Effective assessment to diagnose NP in cancer patients is crucial in order to choose the right analgesic interventions, as these will vary depending on the nature and aetiology of the pain.

Pathophysiology of NP

The pathophysiology of NP is incompletely understood. Following a peripheral nerve injury, A-δ fibre and C-fibre primary afferent neurons become abnormally sensitive and develop pathological spontaneous activity, which leads to peripheral sensitisation. This triggers expression of sodium and calcium channels, release of various receptor proteins, and growth factors from degenerating nerve fibres. This activity provokes secondary changes in central sensory processing, leading to spinal cord hyper-excitability and central sensitisation [10]. The descending pathways also exacerbate dorsal horn excitation after peripheral nerve injury, as there is an increase in descending excitatory activity from the brainstem, as well as a reduction of descending inhibitory controls [11].

Grading system for neuropathic pain

Despite the clinical significance of NP, there is, to date, no systematic classification system, and in particular there is uncertainty surrounding the diagnosis of NP in cancer patients. This situation is likely to inhibit improvements in treatments and outcomes [12]. Standardised classification of neuropathic pain would enable more accurate diagnosis for epidemiology, health management and clinical purposes and attempt to guide the translation of results from clinical trials into clinical practice [13].

The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain developed a NP grading system intended to be used for both clinical and research purposes [1].

Four specific criteria used are summarised in Table 1. To consider possible neuropathic pain, criteria 1 and 2 must be met whilst criterion 3 or 4 must be met for diagnosing probable NP. If all 4 criteria are satisfied, the diagnosis of definite NP is reached.

Despite this grading system, there is still no standardised guidance on the implementation of this, particularly on the confirmatory tests (criterion 3), which may explain why there has been poor use of this system both in clinical practice and in the research setting. Recently, two papers have examined how to adapt the NeuPSIG grading system for patients with cancer pain [12, 14].

Mulvey et al. (2014) describe a step-by-step process for applying the grading system in a clinical setting for cancer pain, including the procedure for demonstrating sensory abnormalities. Applying the grading system in clinical practice is relatively straightforward and simple as some tests may serve a dual purpose. For example, determining the distribution of pain (criterion 1) by the use of toothpick or soft brush to delineate an area of hyperalgesia or allodynia, one can also confirm the presence sensory abnormalities (criterion 3). Likewise, criteria 2 and 4 may be met simultaneously by the use of a CT scan showing tumour growth compressing a nervous structure innervating the

relevant painful region. This demonstrates a history of a relevant disease/lesion (criterion 2) and provides an additional objective confirmatory test (criterion 4).

A recent Delphi survey about the use and adaptation of the NeuPSIG criteria for NP diagnosis to be applied in cancer patients was conducted where an international group of 29 experts participated; the results showed experts agreed on criteria 1-3 of the NeuPSIG, whereas for the fourth criteria (confirmation of lesion affecting the somatosensory system from diagnostic test or imaging) experts suggested that a distinction had to be made whether history and existing exams could explain the cause of the pain [14]. We have combined these recommendations to outline a clinically relevant process to classify NP.

Recognising neuropathic pain (Criteria 1 and 2)

This process involves identifying cancer patients with painful symptoms that match a neuroanatomical pattern. The cause of the pain needs to be established by distinguishing between cancer-related and/or treatment-related or comorbid causes in order to demonstrate a history suggestive of a lesion or disease affecting the somatosensory system.

A detailed history taking should include asking specific questions about pain characteristics, location and radiation and also reviewing oncological and general medical records. Drawing the location of pain on a body-map can be

a useful tool to indicate the distribution of pain and consider whether it is neuro-anatomically plausible. Specific screening tools help to identify patients with possible NP and may be included as part of the clinical assessment, however such tools are not intended to be diagnostic methods [15]. Examples of screening tools that aid identification are the Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale [16], the painDETECT questionnaire [17], and Douleur neuropathique (DN4) [18]. The main advantage of such screening tools is that they can easily identify individuals with possible neuropathic pain in a variety of settings.

Confirmatory and diagnostic tests (Criteria 3 and 4)

A systematic search for neurological abnormalities is necessary to identify a lesion in the somatosensory system. Clinical examination, specifically looking for sensory signs, accepts or rejects the hypothesis of possible neuropathic pain that has been based on the history. Bedside tests of somatosensory functions (Criterion 3) can help identify sensory abnormalities, however this simple testing on its own has a low power of distinguishing neuropathic pain from non-neuropathic pain [19]. The sensory phenomena to examine include: light touch using a cotton bud tip or soft brush, pinprick using a monofilament or a toothpick, vibration using tuning fork, deep pressure using examiners' thumb, painfully cold & hot thermo rollers or test tubes. Responses should be compared with a non-painful adjacent or contralateral area to establish alterations in sensory function. These tests would highlight a decreased or increased sensitivity (hypo- or hyperphenomena) thus demonstrating altered

sensory processing and should be consistent with the distribution of the pain. Only one sensory abnormality needs to be present to meet the requirement.

In a clinical research context, a more robust laboratory test for Criterion 3 would include quantitative sensory testing; a psychophysical technique requiring co-operation from the patient measuring warmth (a C fibre–mediated sensation), cooling (an Aδ-mediated sensation), and vibration (a sensation mediated by large, myelinated Aβ afferents). If the result for one or more of these sensory tests are abnormal, it may imply that there is a signal dysfunction along the sensory pathways anywhere between the receptors, the sensory or associated cortices [20].

To confirm the presence of a lesion affecting the somatosensory system, imaging such as magnetic resonance imaging or computed tomography imaging should be requested, if not already present in the patient's notes (Criterion 4).

The evaluation of NP in cancer patients is summarised in Table 2.

Discussion

Cancer-related NP is often undiagnosed and is accompanied by disability, poor quality of life, distress and increased cost to the healthcare system. Assessment and classification of pain should be a fundamental part of the management to control cancer pain [21].

When a patient presents with pain in clinical practice, questioning the patient about the symptoms and performing an examination together with use of screening tools might alert the physician that the pain could probably be neuropathic. There is still no gold standard for diagnosing NP; nevertheless, the NeuPSIG grading system is beneficial for robust assessment of NP. However, the patient population needs to be specified as has been described by Mulvey el al in the adapted version of the NeuPSIG grading system for cancer pain [9, 12].

Conclusion

Despite the increased recognition of neuropathic pain in cancer and non-cancer classifications systems, there remain several important clinical and research questions. Firstly, what role do neuropathic pain symptom screening tools have in establishing possible neuropathic pain as part of the NP grading system? Secondly, is the number of positive confirmatory tests from criterion 3 and 4 of the grading system associated with a spectrum of symptom severity? Thirdly, does a rigorously applied standardised grading system, including demonstration of sensory abnormalities, lead to more robust diagnosis and ultimately improved treatment outcomes for patients?

Financial support and sponsorship: None

Conflicts of interest statement

All authors declare no conflicts of interest with this manuscript and its content.

Key points

- Neuropathic pain arises due to a disease or a lesion affecting the somatosensory system.

- Neuropathic pain in patients with cancer is common and can have an effect on their cognitive, physical and social functioning.

- Existing gold standard assessment can be adapted to cancer patients.

- Better classification of cancer NP will improve clinical practice and research

References

1. Treede, R.D., T.S. Jensen, J.N. Campbell, G. Cruccu, et al., Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology, 2008. 70(18): p. 1630-5.
2. Moisset, X. and D. Bouhassira, Brain imaging of neuropathic pain. NeuroImage, 2007. 37 Suppl 1: p. S80-8.
3. Smith, E.M., C.M. Bridges, G. Kanzawa, R. Knoerl, et al., Cancer treatment-related neuropathic pain syndromes-epidemiology and treatment: an update. Current pain and headache reports, 2014. 18(11): p. 459.
4. Urch, C. and R. Suzuki, Pathophysiology of somatic, visceral and neuropathic cancer pain., in Cancer pain, B.M. Sykes N, Yuan C., Editor 2008: New York: CRC Press. p. 3-12.
5. Treede, R.D., W. Rief, A. Barke, Q. Aziz, et al., A classification of chronic pain for ICD-11. Pain, 2014(In Press).
6. Bennett, M.I., C. Rayment, M. Hjermstad, N. Aass, et al., Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain, 2012. 153(2): p. 359-65.
7. Rayment, C., M.J. Hjermstad, N. Aass, S. Kaasa, et al., Neuropathic cancer pain: prevalence, severity, analgesics and impact from the European Palliative Care Research Collaborative-Computerised Symptom Assessment study. Palliative medicine, 2013. 27(8): p. 714-21.
8. **Knudsen, A.K., N. Aass, R. Fainsinger, A. Caraceni, et al., Classification of pain in cancer patients-a systematic literature review. Palliative medicine, 2009. 23(4): p. 295-308.[Comprehensive review of important domains in cancer pain assessment]

9. *Haanpaa, M., N. Attal, M. Backonja, R. Baron, et al., NeuPSIG guidelines on neuropathic pain assessment. Pain, 2011. 152(1): p. 14-27. [Definitive guidance in assessment of neuropathic pain]
10. Baron, R., Mechanisms of disease: neuropathic pain-a clinical perspective. Nature Clinical Practice Neurology, 2006. 2(2): p. 95-106.
11. D'Mello, R. and A.H. Dickenson, Spinal cord mechanisms of pain. Br J Anaesth, 2008. 101(1): p. 8-16.
12. ** Mulvey, M.R., R. Rolke, P. Klepstad, A. Caraceni, et al., Confirming neuropathic pain in cancer patients: applying the NeuPSIG grading system in clinical practice and clinical research. Pain, 2014. 155(5): p. 859-63.[Guidance on adapting NeuPSIG assessment of NP for cancer patients]
13. Finnerup, N.B., J. Scholz, N. Attal, R. Baron, et al., Neuropathic pain needs systematic classification. European journal of pain, 2013. 17(7): p. 953-6.
14. ** Brunelli, C., M.I. Bennett, S. Kaasa, R. Fainsinger, et al., Classification of Neuropathic Pain in Cancer Patients: A Delphi Expert Survey Report and EAPC/IASP Proposal of an Algorithm for Diagnostic Criteria. Pain, 2014.[Consensus study reporting important assessment items in cancer NP]
15. Mulvey, M.R., M.I. Bennett, I. Liwowsky, and R. Freynhagen, The role of screening tools in diagnosing neuropathic pain. Pain management, 2014. 4(3): p. 233-43.
16. Bennett, M., The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain, 2001. 92(1-2): p. 147-57.
17. Freynhagen, R., R. Baron, U. Gockel, and T.R. Tolle, painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Current medical research and opinion, 2006. 22(10): p. 1911-20.
18. Bouhassira, D., N. Attal, H. Alchaar, F. Boureau, 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): p. 29-36.
19. *Rasmussen, P.V., S.H. Sindrup, T.S. Jensen, and F.W. Bach, Symptoms and signs in patients with suspected neuropathic pain. Pain, 2004. 110(1-2): p. 461-9.[Important study of relationship between symptoms and signs in NP]
20. Shy, M.E., E.M. Frohman, Y.T. So, J.C. Arezzo, et al., Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology, 2003. 60(6): p. 898-904.
21. Kaasa, S., G. Apolone, P. Klepstad, J.H. Loge, et al., Expert conference on cancer pain assessment and classification-the need for international consensus: working proposals on international standards. BMJ supportive & palliative care, 2011. 1(3): p. 281-7.