Is arthritis pain simply nociceptive pain, or in some patients are more complex mechanisms involved? This question is addressed in the feature article in this issue of Challenges in Neuropathic Pain. Also in this issue is the first in a series of regular columns on key issues in neuropathic pain and its management from Professor Rainer Freynhagen, and we welcome his contribution to the newsletter. Lastly, the case presentation highlights the topic of complex regional pain syndrome. Visit www.neuropainhk.org for more resources from the MPNP on neuropathic pain.

Identifying a neuropathic component in arthritis pain

Osteoarthritis (OA) and rheumatoid arthritis (RA) are traditionally considered examples of nociceptive pain conditions, characterized by peripheral pain due to joint damage and inflammation. The International Association for the Study of Pain (IASP) defines nociceptive pain as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.” However, more recently, experts are recognizing that chronic pain in rheumatic conditions may arise from a number of different underlying mechanisms, not just nociceptive pain. In particular, emerging evidence suggests that a proportion of OA and RA patients experience symptoms indicative of neuropathic pain. In contrast to nociceptive pain, neuropathic pain is defined by the IASP as “pain caused by a lesion or disease of the peripheral or central somatosensory nervous system.”

For example, some patients with OA or RA describe aspects of their pain as burning, shooting or prickling, which are classic descriptors of neuropathic-type pain. Furthermore, pain intensity in OA appears to correlate poorly with radiographically assessed peripheral joint damage, suggesting the involvement of non-nociceptive pain. Although inflammation is central to the overall perception of pain in RA patients, pain persists in many patients despite sufficient suppression of inflammation using...
Anti-inflammatory drugs. This points to the possible contribution of a non-inflammatory or neuropathic element to overall pain perception in RA.

**Screening for neuropathic pain in arthritis patients**

Given that at least a subset of OA and RA patients may have multiple pain mechanisms, medications that target neuropathic pain and/or central sensitization could provide improved pain management. Several validated screening tools are available to help clinicians distinguish neuropathic from nociceptive pain. Some of these instruments, including the Neuropathic Pain Questionnaire, Identification Pain Questionnaire (ID Pain) and painDETECT, consist of only interview type questions and can be completed by the patient in the clinic setting.

The six questions of the ID Pain questionnaire are self-completed by the patient. A Chinese language version of ID Pain has been validated in Hong Kong, with the authors concluding that it is a simple and valid tool that can help clinicians identify neuropathic pain among Hong Kong Chinese patients.

The painDETECT questionnaire is another screening tool for neuropathic pain, which was originally shown to detect neuropathic pain symptoms in chronic low back pain. It comprises seven patient-completed items evaluating pain qualities (e.g., tingling or prickling, numbness, allodynia), one evaluating the course pattern of pain and one evaluating pain radiation. A recent paper examined the performance of painDETECT for identifying neuropathic pain in a variety of confirmed neuropathic pain diagnoses (e.g., painful diabetic peripheral neuropathy, posttrauma/post-surgical neuropathic pain, chronic low back pain). The analysis confirmed that painDETECT is a clinically relevant measure for discerning and characterizing neuropathic pain regardless of its aetiology. Hochman and colleagues concluded that the painDETECT appeared to be a clinically feasible self-report tool for identifying neuropathic pain symptoms in adults with knee OA.

**Prevalence of neuropathic pain in OA and RA patients**

Various studies have examined the prevalence of neuropathic pain amongst groups of arthritis patients. One such study found that about a third (34%) of adults with chronic, symmetric knee OA who participated in focus groups used pain quality descriptors suggestive of neuropathic pain, such as burning, tingling, numbness and pins and needles.

Recently, a number of groups have used the painDETECT to estimate the prevalence of neuropathic pain in arthritis patients. A study of 171 patients with knee OA found that 28% of patients were likely to have a neuropathic component to their OA pain. Moren and colleagues identified 27% of patients with OA of the knee who had “likely” neuropathic pain, corresponding closely with the earlier findings.

A study of RA patients with well-controlled clinical disease (n=100) found that 28% of the study patients had “possible” neuropathic pain and 5% had features of “likely” neuropathic pain. A second study included 159 outpatients with RA; 17% of the patients had likely neuropathic pain and 21% had possible neuropathic pain features. The most commonly reported pain qualities were electric shock-like pain attacks, followed by pain with slight pressure, and burning and prickling pain.

Thus, in both OA and RA, a subset of patients display pain symptoms characteristic of neuropathic pain.

**The role of central pain-processing mechanisms in chronic OA and RA**

Various studies have suggested the neuropathic pain-like symptoms detected in rheumatic conditions, including OA and RA, may be expressions of dysregulation of central pain-processing mechanisms. A systematic literature review concluded that the central nervous system becomes hypersensitized in subjects with chronic OA pain, and that central sensitization plays a pivotal role in the pain experience of these patients. Central sensitization reflects increased activity of pain facilitation pathways and malfunctioning of descending pain inhibitory pathways, which together result in dysfunctional endogenous analgesic control. There has been less research on central pain-processing mechanisms in RA. A summary of findings from central quantitative sensory testing in OA and RA patients (Table) points to the role of a range of central pain mechanisms in these conditions.

**Optimizing pain management strategies**

Like other chronic pain states, OA and RA are likely “mixed pain” states, with inter-individual variability in the relative contributions of nociceptive, neuropathic and central elements of pain. This clearly has implications for treatment strategies. Classical treatment focuses on nociceptive targets, but these fail to adequately alleviate pain in all patients. The subset of patients with refractory pain may have greater involvement of neuropathic and/or central pain mechanisms and, as such, a mechanism-based approach to pain management could improve outcome.

For example, drugs that influence neurotransmitters and receptors involved in central pain pathways (e.g., tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, α-δ ligands) may be more effective in patients with central pain overlay than drugs like nonsteroidal anti-inflammatory drugs that target nociceptive pain.

The Figure outlines some potential therapeutic options for targeting OA pain at different levels of the pain-processing pathway.
approaches to managing OA pain, by specifically targeting the underlying pain mechanisms.6,17,18 The Special Interest Group on Neuropathic Pain (NeuPSIG) of the IASP recommends tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin and gabapentin as first-line drug treatments for neuropathic pain.19 Using these agents could improve pain control in OA and RA patients with a neuropathic pain component – patients who are likely to experience ongoing pain despite adequate suppression of inflammation.

Summary

Studies show that a subset of patients with OA and RA have a neuropathic component to their chronic pain.2,5,12 In OA, around 1 in 3 patients appear to experience neuropathic pain, while the proportion is likely lower in RA patients (around 5% to 15%).3,5,7,12 Given that neuropathic pain requires a different therapeutic approach to nociceptive pain, it is important to identify arthritic patients with neuropathic pain. Screening tools such as the PainDETECT and the ID Pain questionnaire can be used in clinical practice to screen for neuropathic pain in OA and RA. A validated Chinese version of ID Pain is available. Prescribing treatments for neuropathic pain in OA and RA may help to optimize pain management for those patients with a neuropathic pain component.

References


Table. Central quantitative sensory testing findings in osteoarthritis and rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Low pain thresholds in a widespread distribution</th>
<th>Loss of descending analgesia (conditioned pain modulation)</th>
<th>Temporal summation</th>
<th>Expanded areas of hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

CASE PRESENTATION

Complex regional pain syndrome

Presentation and investigations

A 14-year-old girl presented with sudden onset of right upper limb cramping and neuropathic pain, which occurred while at school. Symptoms included constant numbness, shooting pain and increased pain with touch. The pain was so severe that she was admitted to a hospital emergency unit and then transferred to the paediatric ward. She underwent extensive investigations for neuropathy, including MRI of the cervical spine and brain, and investigations for infective diseases, toxicology and immunological conditions, which were all within normal ranges. She suffered from severe neuropathic pain with contracture of the upper limb and disused right upper limb atrophy. The patient was trialed on high-dose steroids for 10 weeks, but she was not given a diagnosis for her condition. The patient later underwent a nerve conduction test and electromyogram, the results of which were normal.

Diagnosis

The patient’s pain was considered to be psychological, with the added gain of obtaining sick leave certificates for school. Mostly acetaminophen was given for the pain. After 3 months, a second opinion was sought at another paediatric orthopaedic hospital, and the patient was diagnosed with complex regional pain syndrome (CRPS) Type 1.

Management

Seven months after the severe pain attack, the patient was seen at the pain management clinic after having failed conservative rehabilitation treatment, including physiotherapy, hydroexercise and mirror therapy. She presented with a numerical pain rating scale (NRS) score of 10/10 and was unable to sleep at night. The patient was commenced on amitriptyline 10 mg nocte and pregabalin 25 mg om plus 50 mg nocte to treat the neuropathic pain, combination tramadol 37.5 mg/acetaminophen 375 mg qid as required for breakthrough pain, and baclofen 10 mg bid to facilitate rehabilitation and mobilization of her right upper limb frozen shoulder and disused fibrotic muscles. The multimodal regimen provided some pain relief (NRS 5–6/10) and improved sleep.

Over the next 3–4 months, the patient underwent a series of two ultrasound-guided right stellate ganglion sympathetic blocks, and three IV lignocaine 4–5 mg/kg infusions to desensitize the severe neuropathic pain. Thereafter, her NRS is mostly 2–3/10 and right upper limb mobilization has significantly improved. One year after the initial insult, she is able to re-enjoy school life.

Discussion

CRPS is a not uncommon, yet very debilitating, condition with different stages of presentation. The IASP (International Association for the Study of Pain) defines CRPS Type 1 as: “a syndrome usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or alodinia or hyperalgesia”. Early aggressive multidisciplinary and multimodal therapy is advised. In a recent evidence-based guideline on CRPS, the World Health Organization (WHO) analgesic ladder is advised with the exception of strong opioids, which may not help in neuropathic conditions.2 For neuropathic pain, anticonvulsants and tricyclic antidepressants may be considered. For inflammatory symptoms, free-radical scavengers (dimethylsulphoxide or acetylcysteine) are advised. Pain interventional procedures or percutaneous sympathetic blockades should be considered at an early stage. To promote peripheral blood flow in the vasocostrictive phase, vasodilator medication may be considered. Standardized early physiotherapy and occupational therapy are advised to reduce functional limitations.

References

Using neuropathic pain questionnaires for far more than only pain classification

According to the Special Interest Group on Neuropathic Pain of the IASP, neuropathic pain is “arising as a direct consequence of a lesion or disease affecting the somatosensory system”. This common type of pain is often underdiagnosed and undertreated, and it is associated with suffering, disability, impaired quality of life and increased cost. Depression, anxiety and sleep disorders are significantly more prevalent in patients with neuropathic pain compared with those without such pain.

Neuropathic pain is a challenge to healthcare providers because a reliable diagnosis of the neuropathic pain component is often difficult to accomplish in routine practice. However, the early identification of neuropathic pain components in primary and specialty care settings is crucial to avoid unnecessary delays in treatment. Given the fact that a diagnostic gold standard for neuropathic pain is still lacking, there is no doubt that screening tools based on verbal pain description, with or without limited bedside testing, can help to improve the recognition and treatment of neuropathic pain in clinical practice. Three of these tools (painDETECT, DN4, LANSS) have shown promise in identifying common neuropathic pain characteristics that derive from diverse aetiologies (eg, diabetic peripheral neuropathy, postherpetic neuralgia, low back pain or osteoarthritis). Recently, the utility of these screening tools has even been shown in novel contexts, such as cancer pain, musculoskeletal and acute pain. A promising new approach is to use these tools in clinical trials to perform subgrouping of patients to classify the profile of individual pain-related sensory abnormalities. Many patients describe distinct pain patterns during the course of the disease that might be of predictive value to distinguish neuropathic from nociceptive pain. The ultimate goal is to assess treatment efficacy for a specific symptom or symptom combination ending up in a stratified or personalized therapy. Moreover, a wider use of neuropathic pain screening tools can help to drive research and further clarify the epidemiology of neuropathic pain.

Screening tools are not designed as diagnostic tools, but they can be useful in highlighting the need for a more detailed clinical assessment. Until an international consensus on the content of a diagnostic algorithm and a standardization of the assessment process for neuropathic pain is reached, screening tools will continue to be used to aid medical practitioners in the identification of patients with ‘possible’ neuropathic pain, each of them with a fairly high sensitivity, specificity and predictive accuracy. The painDETECT questionnaire (Figure) is currently offered in 23 language versions, with a Chinese language version on its way. (https://wwwpfizerpatientreportedoutcomes.com/order-measures)

Literature