Mixed pain

Pain can be broadly grouped into four categories namely nociceptive, neuropathic, mixed and pain of unknown origin. Mixed pain is a combination of nociceptive and neuropathic pain. This article serves to highlight the presence of mixed pain syndromes and their diagnosis and management.

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The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It is important to assess and treat pain effectively as it increasingly interferes with daily life as age increases.[1] In general pain can be broadly grouped into four categories namely nociceptive, neuropathic, mixed and pain of unknown origin.

Nociceptive pain

Nociceptive pain is caused by a known noxious stimulus to a nociceptor (pain receptor) and can be somatic or visceral. Somatic pain is due to injury of bones, joints or soft tissues (as in fractures, cancer metastases and arthritis), while visceral pain is due to inflammation, distension and stretching of internal organs.

Neuropathic pain

Neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Mixed pain

Mixed pain is a combination of nociceptive and neuropathic pain.[2]

Prevalence

The Chronic Pain Coalition states that chronic pain affects 7.8 million people of all ages in the UK. Unfortunately the true incidence of neuropathic pain is unknown, but it is generally believed that it is under diagnosed and under treated.[3] The prevalence of neuropathic pain has been estimated to be as low as 1%to 2% by Bennet and Bowsher[4] and as high as 8% in the UK primary care survey.[5] In diabetes, neuropathic pain is estimated to affect 16% to 26%[6,7] and in post-herpetic neuralgia (PHN) it ranges from 8% to 19%. So the wide prevalence estimate range causes uncertainty when estimating the size of the problem.[8]

This lack of clear prevalence data makes it impossible to calculate the prevalence of mixed pain. Despite this, the category of mixed pain should not be ignored as its pathogenesis is a combination of that for neuropathic and nociceptive pain, which by definition alone is more complicated both from a diagnostic as well as a management perspective.

For years osteoarthritis pain has been assumed to be purely nociceptive not neuropathic but a growing body of literature suggests otherwise. Two research studies in patients with low back pain used screening tools for neuropathic pain that suggested that 37% and 54% of patients respectively had pain of predominantly neuropathic origin.[9] These studies lend evidence to the fact that there is more pain of a mixed origin than was previously thought.

Diagnosis

Pain assessment is critical to optimise pain management and or interventions. Pain in general can be acute or chronic and if chronic can have acute exacerbations. Acute pain clinically is easier to treat as it has a finite time period, that is "it will go away." Pain of mixed origin is usually chronic.

Chronic pain is a different case all together. First general assessment is needed, which should include the patient's own description of the pain. A patient's use of specific adjectives can guide the physician as to the type of pain. For example, neuropathic pain is often described as burning, shooting, tingling, radiating,

lancinating, numbness or even like a fire or an electrical jolt.[10,11]

Nociceptive pain on the other hand can be somatic or visceral and is often described as achy, throbbing, or dull, deep, and stretching. It is also usually well localised. It is generally found in arthritis, bone or spine metastases, low back pain, and orthopaedic procedures as well as after abdominal or thoracic surgery or venous obstruction. From a clinical perspective patients seem to have more difficulty describing neuropathic pain.

In the case of mixed pain syndromes, healthcare professionals are likely to hear elements of both neuropathic and nociceptive pain described by the patient.[12]

There are no clear guidelines for diagnosing mixed pain as a syndrome in its own right. So it seems reasonable to combine the diagnosis and management of the two components in this case. When it comes to diagnosing the nociceptive component most practitioners will be well practiced in examining there patients to determine this. In practice, clinicians face daily arthritic, cancer, post surgical and traumatic pain in their patients. The problem once having diagnosed their patient's pain is to decide whether there is a neuropathic component to the pain or not.

When dealing with pain patients where there may be a neuropathic component, guidelines recommend the use of diagnostic screening tools like DN4, pain detect or LANSS to differentiate between neuropathic and nociceptive pain.[13] These tools are based mainly on pain descriptors and symptoms and have been reviewed for diagnostic accuracy.[14]

A number of experts reached consensus concerning a grading system of the likelihood or certainty of neuropathic pain in a patient. This implies that not all the pain in an individual will be neuropathic.[15]

The grading system is as follows:

1. Possible neuropathic pain: where the patient history points to a relevant lesion, injury or disease and pain in a plausible neuroanatomical area
2. Probable neuropathic pain: The criteria from above and either:

i. A diagnostic test confirming a lesion or disease, or
ii. Negative or positive sensory signs confined to the neuroanatomical area.

On examination in the case of neuropathic pain the patient may exhibit:

- Spontaneous pain (no stimulus) eg. burning sensation, intermittent shooting, electric or shocklike pain) and or
- Evoked pains (evoked by mechanical, thermal or chemical stimulus).[13,16]

The above tools, grading system, characteristics and examination should give a clear picture of the presence of a neuropathic component. This combined with clinical and examinatory evidence of nociceptive pain will mean a mixed picture exists and both components will need to be considered in the treatment options.

Irrespective of whether pain is of one type or mixed, Dalton and McNaull advocate a universal adoption of a 0 to 10 scale for clinical assessment of pain in order to determine pain intensity.[17]

From a clinical perspective a single measurement out of ten where zero is no pain and ten is the worst possible pain is of little use on its own. However serial measurements can be a useful tool to guide, stop or change therapy. It is also important to establish if the pain is constant and if extra or breakthrough pain occurs. This will guide medication use as a long acting and short acting agent may well need to be used together (ie. one agent for the continuous pain and a short acting agent for breakthrough pain).

Buzz words in chronic pain management and for that matter in chronic disease management as a whole are yellow flags. Yellow flags (Box 2) are psychosocial factors that can suggest increased risks of progression to chronic pain and distress.[18] Time is often a limiting factor in evaluating yellow flags in primary care but awareness of psycho-social factors is important because if there are large psycho-social components referral to a pain service and the use of pain management programs or CBT may well be needed sooner than later.[19]

There was also red flags—these do not specifically exclude pain management but are important to highlight the need for urgent scanning, treatment or hospital admissions to insure that diagnosis is clear and so are paramount in any assessment.

Investigation

Clinically, investigations are there to clarify diagnosis and exclude sinister pathologies (ie red flags). In general radiology should only

Box 1: Examples of red flags

- Features of Cauda Equina Syndrome
- Severe worsening of pain, especially at night or when lying down
- Significant trauma
- Weight loss
- History of cancer
- Fever
- Use of intravenous drugs or steroids
- Patients over the age of 50 years

be used where clarification of diagnosis is needed or surgery is being considered. Blood tests will be dictated by the overall medical assessment and history. It is however important to consider unusual causes of neuropathic pain like nutritional neuropathies, these include alcohol induced, vitamin b 1, 3, 6, 12 deficiencies, vitamin E deficiencies and folic acid.

Treatment

For chronic pain management a bio-psycho-social approach is always needed where possible.

From a pharmacological side, both neuropathic and non neuropathic agents will probably be needed in combination to treat mixed pain. The patients concomitant pathologies and drug interactions need to be considered when using any pharmacological agents for pain.[20]

In neuropathic pain, opioids alone will not always be sufficient so antidepressants and anticonvulsants are often needed as adjuvant treatment.

Box 2: Examples of yellow flags

- Attitudes and belief that all pain and activity are harmful
- The presence of "sickness behaviours"—avoidance, extended bed rest
- Low or negative moods
- Social withdrawal
- Compensation pending
- Heavy work, unsociable hours
- An overprotective family OR obvious lack of familial or social support.

In somatic pain, nonsteroidal anti-inflammatory drugs are the treatment of choice in patients who can tolerate them (care in renal failure and GI bleed risk need to be considered). Muscle relaxants, bisphosphonates and opiates may also be needed.

In visceral pain, opioids are the treatment of choice but adverse events including constipation need to be considered.[21] Nonsteroidal anti-inflammatory drugs are useful where tolerated but it is very important to consider each patient as an individual. If patients are on aspirin most non specific COX medications will prevent the platelet protective effect of aspirin. So either a COX2 specific NSAID needs to be used or a NSAID with a long half life like naproxen. It is good practice if NSAIDS are used long term to combine their use with a proton pump inhibitor.

Opiates are commonly used long term and good practice includes the use of anti-constipatory medications especially in an ageing population. The patients should always be advised regarding side effects and warned regarding their responsibility if they are drivers.

The British Pain Society has written guidance on opiate prescribing in persistent non malignant pain, some of the salient points are summarised here.

- While there is no right or wrong patient for opioid therapy, they should only be used as first line therapy where other evidence-based interventions are not available for the condition being treated.
- It is unlikely in ongoing persistent pain that complete pain relief will be achieved with opiates alone. So the goal is to reduce pain sufficiently so as to improve physical function and quality of life.
- A team approach including associated health team members, the patient and family is useful so that goals and potential adverse events can be addressed.
- For good practice regular monitoring of opiate use in persistent pain is advised and before starting them the patient assessment needs to include screening questions for depression and substance misuse.
- Modified release opioids instead of injectables are advised in persistent pain.
- If useful relief of pain is not achieved at doses of between 120–180mg morphine or equivalent per 24 hours

then referral to a specialist in pain medicine is strongly recommended.
- If there is any worry regarding misuse of opiates in pain management a referral to a pain specialist and addiction service is needed.[22]

Box 3: NICE recommendations

Medication name	Starting dose	Maximum
Amitriptyline	10mg/day at night	75mg/day at night
Duloxetine	60mg/day	120mg/day
Pregabalin	75mg bd=150mg/day	300mg/bd= 600mg/day
Tramadol	50–100mg/dose max qds	400mg/day

NICE guidance

For neuropathic pain there is new NICE guidance for pharmaceutical management. These have divided neuropathic pain into diabetic neuropathic pain and general neuropathic pain. For general neuropathic pain the guidelines suggest amitriptyline or pregabalin as first line treatment and imipramine or nortriptyline as an alternative to amitriptyline if it is effective but side effects prevent its use. Regular clinical review is advised.

Second line combination therapy is suggested or a change in therapy if no benefit is achieved. Here it is suggested that amitriptyline is added to pregabalin or vice versa. Third line onward referral is suggested with the proviso that tramadol (Ultram) can be added in or substituted for first and second line drugs while awaiting the referral.

In the case of diabetic neuropathic pain, duloxetine (Cymbalta) is suggested as first line with amitriptyline as an alternate if duloxetine is contraindicated or not tolerated. Second line therapy would be swapping to amitriptyline or pregabalin or adding in pregabalin. It is not advisable to add amitriptyline to duloxetine or vice versa due to their similar mechanisms of action. Third line is as for general neuropathic pain. The full guidance can be viewed on line at www.nice.org.uk/nicemedia/live/12948/47936/47936.pdf

NICE also recommend that higher doses should be considered in consultation with a pain service or consultant. Clinically lower doses may be needed in older patients. Amitriptyline can be obtained in liquid form for lower doses.

Gabapentin does not appear in the guideline, which is aimed at primary care only. This is currently under review.

It is also suggested in the guidance that if focal or localised neuropathic pain is present, lidocaine 5% medicated plaster (Versatis) should be considered.

From a clinical perspective referral to a pain service should be considered at any stage when the treating physician feels out of their depth or where it is likely that interventions are needed.

In the patient with mixed pain a combination of neuropathic treatments as listed above and NSAIDS and opiates may be needed to cover all aspects of the patient's pain. The key is always ongoing regular review. When opiates are used it is very important for regular review to prevent adverse events, tolerance and potential for addiction. When in doubt it is always preferable to ask the local pain service or consultant.

While pharmacology of pain is a mainstay of treatment in primary care, the patient as a whole needs to be considered and concomitant associated problems like yellow flags and depression must not be ignored. This may mean earlier referral to a pain service.

Conclusion

The assessment and management of pain in patients with mixed pain is complicated. Once such pain is diagnosed it is then the responsibility of healthcare professionals to act on findings. Mixed pain is likely to need a poly-pharmaceutical approach to manage the different types of pain. No clear guidelines specific to mixed pain are currently available.

Ongoing review will be needed especially if opiates are being used.

Conflict of interest: none declared

References

Available on request from editorial office