Neuropathic pain

Neuropathic pain differs from inflammatory pain both in terms of its symptoms and its management. This article outlines these differences and highlights some neuropathic pain conditions found in older patients with reference to pharmacological and non-pharmacological treatment options.

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Neuropathic pain is defined as pain "initiated or caused by a primary lesion or dysfunction in the nervous system".[1]

This is a relatively loose definition. The term dysfunction may refer to discrete disease or simply to alterations in the neurochemistry of the somatosensory system, which may be part of the normal process of response to injury. Using this definition, neuropathic pain may be a sign of either a pathological or a physiological process.

A much tighter definition has been proposed,[2] although it remains to be seen whether this new definition will gain universal acceptance. It refers to "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". Replacement of dysfunction with disease places neuropathic pain firmly in the camp of a pathological neurological condition. The consequence is that definitive diagnosis requires identification of the disease or lesion through examination and investigation. The key clinical features of neuropathic pain are outlined in Figure 2.

The prevalence of neuropathic pain has been estimated from questionnaire surveys of large populations.[3–5] Results appear to lie consistently within a narrow range (between 6·9% and 10%). Increasing age and female sex have been demonstrated to be independent predictors of chronic neuropathic pain. The natural course of neuropathic pain is highly variable from spontaneous resolution to severe, intractable pain. Data are limited and insufficient to make general conclusions. Nevertheless, it is worth keeping in mind that, in painful diabetic neuropathy at least, reduction in pain severity can actually represent progression of disease.[6]

Distinction from other types of pain

In broad terms, all pain that is not neuropathic is conventionally known as nociceptive or inflammatory. Nociceptive pain is "usual" pain—that is, pain that arises as a consequence of tissue injury, typically resulting from arrival of impulses in the cerebral cortex along thinly myelinated Aδ or unmyelinated C fibres. This is direct onward transmission, where sensation closely reflects the stimulus.

Where the initiating stimulus causes tissue injury, the resulting release of inflammatory mediators causes sensitisation of nociceptors. As a result, further trivial stimuli produce pain out of proportion to the severity of the applied stimulus (primary hyperalgesia) or pain in response to a usually non-painful stimulus (allodynia). For example, a minor burn or abrasion will result in increased sensitivity of the injured and adjacent areas to both painful and non-painful stimuli. Usually this resolves as the injury heals and is thought to serve as a reminder that the injured area requires protection. This state of persistent but ultimately resolving nociceptive pain has been termed "inflammatory pain".

In inflammatory pain, the pain system functions again as it should, with a stimulus applied peripherally being transmitted centrally to the cortex, with or without amplification. As injury heals, pain perception returns to normal in tandem.

In neuropathic pain states, disruption of the normal

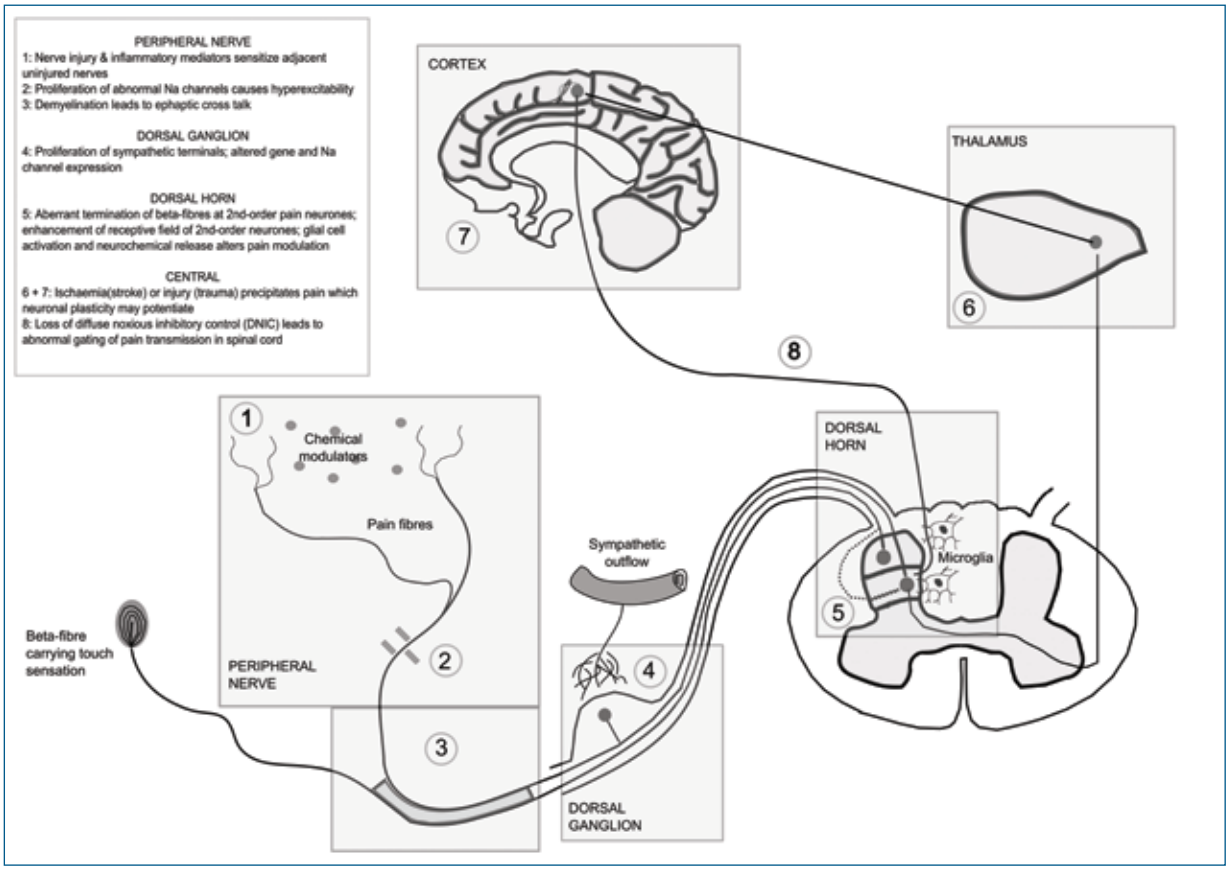

Figure 1: Highlights the potential areas of neuronal dysfunction/irritation that contribute to the "wind-up" and continuing pain sensation despite the original stimulus resolving.

anatomy and physiology of pain transmission results in continuing perception of pain, even after the initiating injury has healed. This may be a consequence of changes induced by inflammatory pain or due to injury to pain nerves themselves. Figure 1 outlines a potential areas of neuronal dyfunction that contribute to neuropathic pain.

Diagnosis

Several validated diagnostic aids exist to assist the clinician in the diagnosis of neuropathic pain: the LANSS scale,[7] Douleur Neuropathique 4 Questions (DN4),[8] painDETECT[9] and StEP.[10] Based on scores derived from these scales, pain may be described as "predominantly of neuropathic origin".

Types of neuropathic pain

Neuropathic pain occurs in diverse disease states of differing aetiologies. No single therapy is likely to be entirely effective in isolation; optimum management for most patients will occur within the context of a multi-disciplinary pain management model with access to physical and psychological therapies. The following "case-studies" highlight both common and alternative therapy options in addition to the conventional anti-neuropathic pharmacology. Topical and oral anti-neuropathic agents may be used for these conditions as illustrated by the algorithm in Figure 3, reflecting our usual practice. Specific therapies of particular benefit in individual conditions are detailed in the text.

Painful diabetic peripheral neuropathy

A 62-year-old obese hypertensive female presents to her physician with spontaneous burning sensations affecting both feet, and to a lesser extent, both hands. She describes wearing socks as "intolerable". Neurological testing reveals patchy sensory

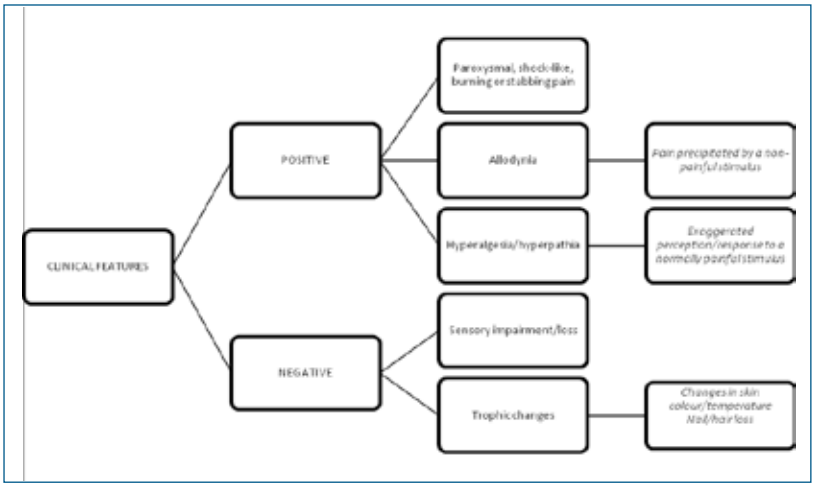

Figure 2: Key clinical features of neuropathic pain

loss to pain, temperature and vibration sense with no motor deficit. Fasting blood glucose and subsequent glucose tolerance test suggest a diagnosis of impaired glucose tolerance.

The term "painful diabetic peripheral neuropathy" refers to a distal, symmetrical sensorimotor polyneuropathy, typically a consequence of microvascular damage and deafferentation. It affects at least 50% of diabetics in the USA. Amongst type-2 diabetes patients, approximately one third of men and one fifth of women have subtle evidence of neuropathy at diagnosis.[11] Up to half of patients with neuropathy develop pain.[12] Interestingly, painful peripheral neuropathy may be the first presentation of evolving diabetes, discovered on testing as impaired glucose tolerance.[13] Tactile allodynia and mechanical and thermal hyperalgesia may be early signs, with advancing disease resulting in hypoalgesia.[14]

Early detection, optimal glycaemic control and reduction of associated vascular risk factors can delay progression.

Sciatica

A 68-year-old retired dock worker attends his physician with severe, constant, sharp burning pain in his lower back and moving down his right thigh to the right foot. Examination reveals a positive straight leg raise test at 45 degrees and altered sensation in the lower lumbar dermatomes. An MRI scan reveals herniation of lumbar intervertebral discs impinging on emerging nerve roots.

"Sciatica" is an outdated word but still in common use among patients and doctors alike. Its continued use has been disparaged, the terms "nerve root pain' or "radicular pain" are more precise.[15] Using the strictest available study criteria, that of screening by questionnaire followed by clinical examination by a neurologist,[16] prevalence of true sciatica is estimated to be 2·2%. Sciatica refers to pain that radiates down the leg from the back in a radicular distribution, implying nerve root irritation or compression from a herniated lumbar intervertebral disc, though experimental evidence suggests a role for inflammatory mediators.[17]

The pain can be differentiated clinically from somatic referred pain; for example: non-root irritants such as facet joints and sacro-iliac joint, which tend to overlap several dermatomes/myotomes. Radiating leg pain is itself a risk factor for poor outcome in patients with low-back pain[18], and the elderly are also a group with particularly poor outcomes. Radiological evidence supports the position that degenerative disc disease increases with age.[19]

The vast majority of acute attacks resolve with conservative management but there remain a small subgroup for which surgery may be more effective in providing short-term relief, specifically those with symptoms greater than two months,[20] severe nerve root compression and no/minimal back pain.[21] There is no convincing evidence to suggest long-term benefit from surgery. A recent review[22] suggests strong evidence for benefit from caudal epidural injection of steroids for lumbar spinal pain with disc herniation and radiculitis. Injury to the spinal cord is a risk of such injections, hypothesised to be due in part to particle size of the particular steroid used.

Trigeminal neuralgia

A 74-year-old male attends the Pain Clinic with an eight month history of severe paroxysmal right-sided facial pain, shock-like in character, and precipitated by shaving or brushing his teeth. Examination reveals no neurological deficit. A magnetic resonance scan and angiogram excluds space-occupying lesions, demyelinating disease or visible vascular compression of the

trigeminal ganglion. This condition produces lancinating or electrical pain, typically unilateral, occurring in the distribution of the trigeminal nerve and precipitated by stimulation of trigger zones on the face. The pain is rarely long-lasting and is punctuated by pain-free periods in between, but the paroxysms may be so frequent as to be near-constant. Several studies have demonstrated peak incidence in the sixth to seventh decades of life.[23,24]

A thorough neurological examination is essential to avoid missing rare but serious conditions such as cerebellopontine angle tumours and multiple sclerosis. Neuroimaging may be diagnostic and in some cases reveal vascular compression of the trigeminal nerve root and/or ganglion amenable to surgery. A variety of surgical options exist, with the most invasive (open microvascular decompression) providing most effective long-term symptom relief[25] but with a mortality risk, reported to be 0·2–2%.[26] Neurosurgical involvement is critical in selecting the right treatment for individual patients.

Carbamazepine is widely considered the drug of choice for this condition[27] though its prodrug oxcarbazepine is likely to be better tolerated.

Postherpetic neuralgia

A 70-year-old male with chronic kidney disease attends his family physician with constant stabbing pain affecting the right side of his chest. Four months prior, he had developed an acute attack of herpes zoster in the distribution of the right T4 thoracic dermatome. He finds the touch of fabric on his skin precipitates pain. On examination, he has a vesicular rash consistent with reactivation of herpes. He reports marked sleep disturbance and is becoming increasingly irritable.

Postherpetic neuralgia (PHN) is a consequence of acute herpes zoster infection and can occur in the region of distribution of any affected nerve. It is defined as pain persisting for three months after resolution of the rash. Following acute herpes zoster, 20-60% of patients suffer pain for six months.

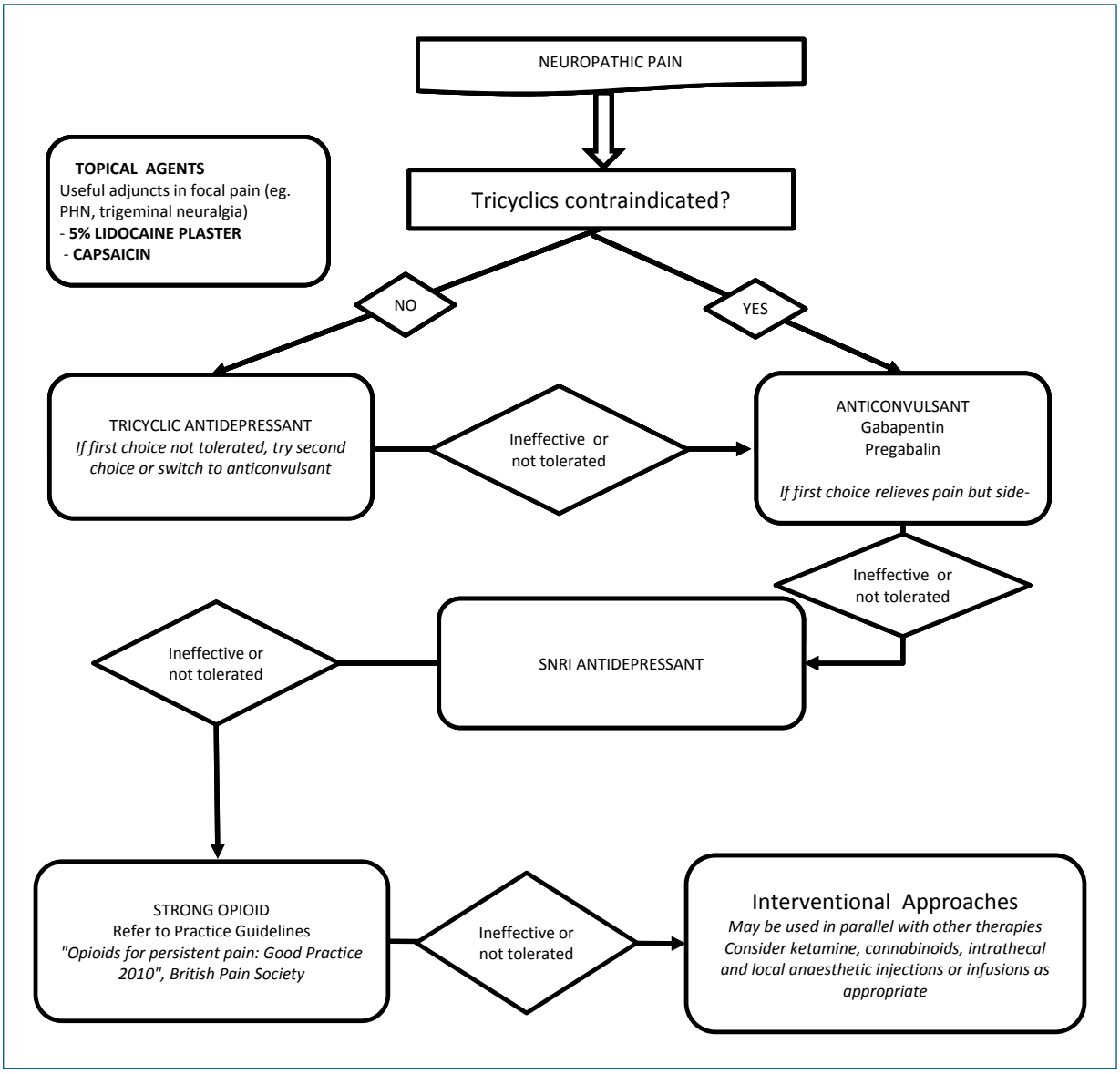

Figure 3: Algorithm for pharmacological treatment

Incidence, severity and mortality from acute herpes zoster increases steadily with age,[28] reflecting, at least in part, a decline in cell-mediated immunity.[29]

Treatment of acute zoster with antiviral drugs can reduce incidence and severity of PHN,[30] with optimum results seen when treatment is started within 72 hours of appearance of rash.[31] An attractive case exists for the vaccination of at-risk individuals; experimental use of a now-licensed (in the USA) higher potency live attenuated vaccine resulted in a greater than 50% reduction in the incidence of acute zoster and a 66% decrease in the incidence of PHN.[32]

Topical lidocaine, in the form of a 5% plaster, and topical 0·075% capsaicin ointment are both licensed in the UK for symptomatic treatment of pain from PHN.[33]

Central post-stroke pain

A 90-year-old lady was reviewed by the hospital Pain Team on the Stroke Rehabilitation ward, six weeks after developing left hemiparesis secondary to ischaemic stroke. She complained of a "dead left arm and left chest with burning". In addition to clinical signs consistent with her diagnosis, light touch and pinprick testing exacerbated the pain for several minutes after the stimulus

was applied.

Stroke patients can develop chronic pain of diverse sources, including subluxation of shoulder joint, muscle spasm and persistent headache. Many stroke patients have multiple sources of pain. In essence, the diagnosis of central post-stroke pain (CPSP) is one of exclusion in combination with hypersensitivity and sensory loss in a distribution consistent with a neurological lesion. Communication difficulties may make history taking difficult.

CPSP may be spontaneous or evoked, affecting small or large anatomical areas and with significant impact on sleep, mood and rehabilitation. Onset can vary from immediately after the initial insult to years later. Postulated mechanisms include central sensitisation, thalamic hyperactivity and deafferentation.[34] Where available, prevalence studies suggest CPSP occurs in 1-12% of stroke patients. With an increase in longevity in the Western world, the prevalence can be expected to increase.

Drug trials are few and involve small numbers of patients; available evidence suggests a role for amitriptyline,[35] pregabalin[36] and lamotrigine.[37] Neurostimulation, including non-invasive repetitive transcranial magnetic stimulation[38] and more invasive motor cortex stimulation,[39] have been reported to be of benefit.

Future developments

Developments in molecular biology have led to identification of new targets for drug action. Ibudilast, a novel glial cell modulator, has been shown to produce reduction in reported pain scores in a Phase 2b clinical trial.[40] Experimental agents targeting Nav1·7 voltage-gated sodium channels (a source of neuronal hyperexcitability) are in development.

Other developments include new drugs, such as tapentadol, a structural analogue of tramadol with dual μ-opioid receptor agonist and norepinephrine reuptake inhibition. New formulations of established agents, such as targinact (a combination of naloxone and oxycodone) and a more concentrated capsaicin plaster are also in development.

Conclusion

Neuropathic pain exists in around 10% of pain conditions/patients and can be difficult to manage. Generic pharmacological treatment algorithms exist, based upon the clinical efficacy of anti-neuropathic drugs across a wide range of conditions, but there are also additional drugs and techniques that may be of particular use in the case studies discussed.

Future drug developments and better assessment techniques will hopefully lead to enhanced treatment for neuropathic pain states.

Conflict of Interest Statement: Dr Panickar has received an honorarium from Grunenthal for speaking at educational meetings, which was donated in its entirety to charity; Dr McGhie has received honorarium from Pfizer for educational talks

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