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Scientific Review

Central pain following spinal and supraspinal lesions

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Pain is an exceedingly common sequel of spinal cord injury (SCI): Bonica[1] reported it in 69% of cases and Levi *et al*[2] in 64% of 353 patients. The majority of patients with syringomyelia suffer from central pain, and a number of other pathological conditions (infarct, tumour) affecting the spinal cord are frequently characterised by pain as a leading symptom. The proportion of patients with head (brain) injury followed by chronic pain is unknown, but is certainly significant, especially when headache is taken into account; central pain[3] is classically seen following infarcts in the cerebral part of the 'pain pathway'.[4–7] It is, however, both instructive and salutary to note that the majority of ventroposterolateral thalamic[8] and lateral medullary[9] infarcts do *not* produce central pain.

Categories of pain

There are essentially two great pathophysiological varieties of pain – nociceptive and neuropathic (neurogenic). The dysfunction between the two is more than academic, for it profoundly influences choice of treatment.

Nociceptive (tissue damage)
Pain occurs when receptors sensitive to tissue damage (nociceptors) are excited by the appropriate stimulus. They are associated with unmyelinated and small myelinated peripheral nerve fibres, and are found in all tissues except nervous tissue (but including the cranial and spinal dura mater and the nervi nervorum in the sheaths of large nerves). Messages generated in these sensory units are relayed through the central nervous system by the appropriate pathways (anterolateral funiculus of the spinal cord via reticular formation and thalamus to cortex, hypothalamus, and limbic lobe). Tissue damage can of course be accompanied by *hyperalgesia*, in which the physiological threshold of nociceptors is lowered, so that pain is experienced as a result of less intense stimulation than normally. Primary afferent C-fibre terminals and many synapses in the 'pain pathways' are sensitive to the action of opioids.

Neuoropathic (neurogenic)
Pain results from pathological changes in the nervous system itself (central or peripheral), and does not involve the activation of nociceptors. Thus interference with the 'pain pathways' into which nociceptors project (eg anterolateral cordotomy) or the administration of drugs which act mainly at synapses within that pathway (eg many opiates) have little or no effect on neuropathic pain. Indeed there is considerable evidence that damage to this projection (eg SCI, post-cordotomy dysaesthesia, 'thalamic syndrome') may cause central neuropathic pain.[6] Although neuropathic pain occurs in such conditions as causalgia, reflex sympathetic dystrophy (both now subsumed under the heading of Complex Regional Pain Syndrome) post-herpetic neuralgia, and painful diabetic neuropathy, it was first recognised and identified following damage to the CNS, and this subdivision of neuropathic pain is often referred to as 'central pain'.

Another name under which neuropathic pain sometimes masquerades is 'deafferentation pain'. While painful phantom limb is perhaps the most obvious example of this category, subtotal avulsion of the brachial plexus, usually caused by motorbike accidents, is a type of neuropathic pain all too familiar to those who deal with spinal cord disorders.

As may be deduced from the fact that there is always functional and/or structural damage to the nervous system when neuropathic pain occurs, the essential clinical corollary of this is that there is always a sensory deficit in the painful area in patients with neuropathic pain. This deficit particularly involves the small-fibre functions of sharpness discrimination (the ability to distinguish between the point and the head of a pin gently applied to the skin) and temperature discrimination (the ability to tell that eg the examiner's finger is warmer than eg a metal tuning fork, or vice versa). A recent survey of 156 cases[4] of central pain found that 91% had easily clinically demonstrable deficits of temperature and/or sharpness discrimination; such deficits are seen in 94% of 191 patients with

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post-herpetic neuralgia.[10] The present author has not seen any patient exhibiting neuropathic pain who has abnormalities of large-fibre function (touch, vibration) only, without any change in small-fibre function.

In many but not all instances, patients with neuropathic pain complain of burning (ice-burn) pain. If they have allodynia (pain produced by a non-noxious stimulus such as very light brushing with cotton wool), this is pathognomonic; but it does not occur in all cases. Allodynia, first described in syringomyelia by Spiller in 1923,[11] should be carefully distinguished from hyperalgesia, in which pain is felt at a lower threshold than normal on the application of a high-intensity stimulus (such as deep sustained pressure, which often relieves neuropathic pain), and is characteristic of tissue-damage pain.

The onset of pain in these patients, whether their lesion be supraspinal or spinal, is frequently later than that of other symptoms, both motor and somatosensory; we only saw immediate pain onset in one quarter of our patients with spinal infarcts. We must thus caution those who see acute spinal pathology without pain; it may follow later, and should be looked for and treated if necessary at follow-up consultations.

Supraspinal central pain used to be called 'thalamic syndrome'; but now that it is belatedly recognised that a large number of cases are due to extrathalamic lesions, it is more generally known as central post-stroke pain (CPSP).[7] Even this term is inadequate, since supraspinal stroke is far from the only cause. It has been seen following brainstem infarct,[12] subarachnoid haemorrhage, whether treated conservatively or surgically,[4,13–15] including unruptured cerebral aneurysm,[14,5] compression of the thalamus[4,14] or lateral medulla[16] by a tumour, following thalamic biopsy,[17] and in toxoplasmosis abscesses.[18] Central pain is also seen in both supraspinal and spinal multiple sclerosis (MS).

Abnormal physiology in central pain

The somatosensory deficit, particularly for sharpness and temperature discrimination, has already been referred to as a necessary criterion. Cordotomy patients in whom pathological pain returns are found to have lost their pinprick deficit; but those who develop spontaneously painful post-cordotomy dysaesthesia retain their pinprick deficit.[19] There are, however, some interesting and possibly important differences which distinguish patients with spinal from those with supraspinal central pain.

(i) Anterolateral spinal cordotomy very greatly raises mechanical pain threshold – indeed, this is the reason why the operation has been performed for unilateral malignant disease. We have found a similar rise in skinfold pinch pain threshold in syringomyelia (and in one case of syringobulbia). However, patients with lesions in the supraspinal spinothalamic pathway or ventrobasal thalamus do not have a severe deficit for mechanical (skinfold pinch) pain.[20] This means that while the (separate) modalities of sharpness discrimination and (mechanical) pain appreciation travel together in the anterolateral white funiculus of the spinal cord (together with temperature discrimination), they follow largely separate pathways in the brain.

(ii) In addition to the essential temperature/sharpness discrimination deficit, deficits for low-intensity mechanical modalities (touch, vibration) are common in patients with central pain of supraspinal origin, affecting more than 50% on clinical examination. In our experience, such a deficit of dorsal column function is rare in patients with central pain due to spinal lesions. Such observations need to be interpreted with great caution; but they could be taken to suggest that central pain may be subserved by high-threshold transsynaptic fibres[21] which have been demonstrated in the dorsal columns of the cat, if corresponding fibres exist in man.

Treatment of central pain

Many patients, particularly of course those whose pain is of traumatic origin, suffer simultaneously from nocigenic and neuropathic pain; phantom limb pain and partial avulsion of the brachial plexus ('deafferentation pain') are examples cited above. Both types of pain also frequently occur in malignant disease. It is essential, if possible, to make a diagnosis before treatment is undertaken. If this is not possible, the rule should be to treat nocigenic pain first, if only because this is usually easier and more likely to be successful than the treatment of neuropathic pain. When some measure of success has been achieved, the patient should be re-assessed – remembering that patients can have a sensory deficit without necessarily having central pain, but they can *not* have a somatosensory deficit and *have* central pain.

Quite often, relief of nociceptive pain will reveal an underlying neuropathic pain. What is important is not to assume that such pain calls for an intensification of the measures taken to relieve nociceptive pain – it has been our misfortune to see many patients afflicted with central pain continue to suffer agony from central pain on huge doses of morphine.

While the molecular biology of neuropathic pain remains largely to be unravelled, it is known empirically that noradrenergic, and perhaps to a lesser extent serotonergic, central inhibitory systems are involved, almost certainly among many others. For this reason, first-generation antidepressants such as amitriptyline and nortriptyline, which powerfully inhibit noradrenaline reuptake, are probably the most effective drugs in the treatment of neuropathic pain. Their efficacy was established by a randomised double-blind trial;[22] it has been shown that their analgesic action is independent of the antidepressant action.

Leijon and Boivie[23] established the effectiveness of amitriptyline in central pain in a double-blind cross-over trial, and Bowsher[24] recorded significant improvement in 60% of patients with supraspinal central pain. The usual dosage of ami- or nor- triptyline is to start with 10 or 25 mg at night for a few days, then increase to 25 or 50 mg, and after a week to 50 or 75 mg (whichever can be tolerated). There may be no positive response for several weeks, so treatment should not be abandoned early. On the other hand, increasing the dose when there is no response is rarely if ever of benefit, although a cautious increase to 100 mg may be attempted if 75 mg yields only partial relief after 2 months. More recent (and acceptable) SSRI antidepressants are unfortunately far less effective. Dry mouth is the commonest side-effect of ami- and nor- triptyline, and the most frequent cause of non-compliance. It may be overcome, at least in part, by the co-prescription of artificial saliva spray; or, in those parts of the world where the habit is established, chewing gum.

As with postherpetic neuralgia,[25] however, there is a marked difference in the response of patients beginning treatment soon after or long after the onset of pain, the effect being much more favourable in cases treated early. This response to antidepressant treatment is one of several factors pointing to a dynamic physiopathology of neuropathic pain, with the condition becoming more intractable the longer it is allowed to last. Such considerations led the pre-emptive treatment of elderly at-risk (of post-herpetic neuralgia) shingles patients with low-dose amitriptyline;[26] only half as many treated patients developed post-herpetic neuralgia as untreated patients. In conditions in which the development of central pain is a high risk, such as SCI and syringomyelia, it may therefore prove useful to initiate low-dose (10–25 mg nocte) pre-emptive treatment with amitriptyline or nortriptyline at the earliest possible opportunity.

We have found that the addition of mexiletine to stabilised amitriptyline dosage may bring about dramatic relief in 70% of CPSP cases unresponsive to antidepressant alone.[24] We have started with a high dose (400 mg orally, followed by 200 mg 6 h) in hospitalised and BP-monitored patients; and have seen effects (or not) within 3 days. Relieved patients may then be discharged on the highest oral dose which does not cause dizziness or unsteadiness, usually 200 mg two or three times a day.

Anticonvulsants have been extensively used in the attempt to relieve central pain. Carbamazepine has been shown to be ineffective in CPSP,[23,27] but this has not greatly discouraged their use. Lamotrigine has been advocated for central pain,[28] and great hopes are held out for gabapentin, a release facilitator of endogenous GABA, which has been shown to be effective in some painful neuropathies, and anecdotally in central pain.

N-methyl D-aspartic (NMDA) transmitter receptors play a role in neuropathic pain, and NMDA receptor antagonists, such as ketamine,[29–31] are being used to treat neuropathic (including central) pain. More effective NMDA transmitter receptors are being sought.

Although morphine and substances with similar properties are usually of little value in neuropathic pain, the opioid methadone follows a different metabolic pathway to morphine, and unlike opiates has some NMDA receptor antagonist properties;[32,33] it also has noradrenaline reuptake inhibitory activity.[34]

Conclusion

Central pain is a form of neuropathic (neurogenic) pain and is a consequence of lesions in the spinal cord or brain. Its pathophysiology is completely different from that of nociceptive (non-neural tissue damage) pain, and it responds poorly, if at all, to therapeutic measures which are frequently effective in the latter. There does not seem, on present evidence, to be any pathophysiological difference between spinal and supraspinal central pain – but it appears to follow a higher proportion of spinal than of supraspinal lesions. The most effective treatment to date (though far from perfect) appears to be adrenergically-active antidepressants. They are more effective the earlier they are used; and in instances such as spinal cord injury where the likelihood of central pain is very high, there is a case for their pre-emptive use. New drugs, with different actions, are in the pipeline, and stimulation techniques may also be effective in some intractable cases.

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