Leading Article

Central pain of spinal origin

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It is sad but true that even today, many physicians and surgeons (and even a number of neurologists and neurosurgeons, who should know better), speak and write of 'pain' as a single entity. Although pain as a symptom is the prime reason for one third of all consultations in primary care, it receives short shrift in hospital practice, being too frequently considered as an annoying byproduct of diseases which are otherwise important.

Nociceptive and neurogenic pain

Failure to distinguish between pain due to nociceptor activation by tissue damage (nociceptive pain) and pain due to dysfunction of the nervous system in the absence of peripheral nociceptor activation (neurogenic pain) is at the heart of the problem. The arch examples of neurogenic pain are of course causalgia (Weir Mitchell *et al.*[1]) and 'thalamic syndrome', now known as central post-stroke pain (Dejerine and Roussy[2]). The latter, of course, is *par excellence* the exemplar of central pain – for it is due not to anything affecting peripheral nerves or their terminals, but to a hole in the head. It is salutary to recall that central pain due to a hole in the spinal cord (syringomyelia) was stated by Garcin[3,4] to be indistinguishable from that due to central post-stroke pain (CPSP). The differences between nociceptive and neurogenic pains have been rehearsed elsewhere;[5,6] distinction between them is of great importance because it affects therapeutic strategies.[7] It would therefore be well to recall the essential characteristics of central pain at this juncture:

1 The pain is frequently described as 'burning', 'scalding' or 'shooting/stabbing'. This is not always the case, but should arouse suspicion. More articulate patients who describe their pain as burning and freezing at the same time are almost certainly suffering from neurogenic pain.

2 There is almost always autonomic instability, exemplified by pain exacerbation by physical or mental stress, and alleviation by relaxation (ability to *fall* asleep as easily as before, as opposed to ability to stay asleep and not to be woken by pain). More objectively, autonomic instability is frequently demonstrated by changes in cutaneous blood flow (usually but not always vasoconstriction, evidenced by lowered skin temperature) and/or sweating pattern, as shown by localised hyperhidrosis or more rarely hypohidrosis.

3 There is a partial sensory deficit. While all or any modalities may be involved in any given patient, the modalities which are critical for central neurogenic pain are sharpness and temperature discrimination. The former depends on the ability to distinguish between the head and point of a pin (and should **not** be confused with, or recorded as, 'pain'). Temperature discrimination is abnormal if the patient cannot distinguish between a cold object such as a tuning fork or spoon laid on the skin and something warm such as the examiner's finger; it does not involve the use of iced water and very hot water in dried test-tubes. If an extremity is involved, the patient will often report, on appropriate questioning, that if the affected hand or foot is placed in a basin or bath, it is impossible to gauge the temperature of the water, or tell if it is hot or cold. More than 90% of patients with central pain have a clinically evident deficit for pinprick and/or temperature as tested in the above way.

A patient with any two of the above three characteristics almost certainly has neurogenic pain; and certainly has it if there is:

4 Allodynia, defined as pain provoked by activation of peripheral fibres not connected to nociceptors. The commonest example is tactile allodynia, when pain is caused by a moving light stimulus (eg stroking, raindrops); maintained pressure does not cause allodynia and indeed frequently relieves it. This form of allodynia is subserved by rapidly-adapting low-threshold $A\beta$ mechanoreceptors.[8] Cold allodynia is also common, warm allodynia much less so. In this author's experience, all patients with central

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pain due to syringomyelia and most of those with ischaemic conditions had allodynia. Allodynia sometimes exhibits 'allachaesthesia' – pain produced at a site remote from that which is stimulated.

Allodynia must not be confused with hyperalgesia, in which the threshold of nociceptors is lowered, so that a stimulus which would normally elicit pain does so at a lower intensity than usual. Both allodynia and hyperalgesia are usually described by patients as 'tenderness'. But little practical experience is required by the clinician to distinguish between them.

Neurogenic pain of spinal origin

It is not uncommon for a lesion to cause both nociceptive and neurogenic pain at the same time; or for a particular condition to cause one or the other. In such cases, careful attention must be paid to correct diagnosis of the pain type. Syringomyelia is a case in point, for nociceptive pain frequently occurs in association with other deformities, congenital or acquired. Williams[9] states that pain is the commonest presenting symptom, occurring in 139 out of 244 cases – but without distinguishing between nociceptive and neurogenic types of pain, which he does elsewhere.[10]

Conditions affecting the spinal cord with which central pain can be associated include trauma ('concussion'),[11] total or subtotal transection (126/471 cases,[12] and hemisection;[13] ischaemia;[14–17] syringomyelia;[9,10,18–20], multiple sclerosis; and tabes dorsalis.[21] Following anterolateral cordotomy, most reports speak of 'recurrence of pain', again without distinction of type. Nociceptive pain may recur, particularly in malignant disease, because of spread of tumour or because of retraction of the area of dysfunctional spinal cord (?resolution of oedema). In such cases, the pain is the same as that for which the cordotomy was performed; and it is usually found that pinprick sensation is present in the skin of the body segments in which pain is present.[22] But when the pain is due to postcordotomy dysaesthesia (a form of anaesthesia dolorosa), the nature of the pain is frequently different from that originally complained of; and, objectively, pinprick sensation is absent in the skin of the affected body segments.[22] Foerster[23] first observed 'elevated thresholds' in cases of painful postcordotomy dysaesthesia (which White and Sweet[24] describe as 'resembling the thalamic syndrome of Dejerine and Roussy'). White and Sweet[24] also point out that painful dysaesthesia occurs in nearly 50% of patients who survive 'several years' following cordotomy.

Anterolateral cordotomy is of course performed in order greatly to raise the threshold for nociceptive pain;[25] our own quantitative studies show that it is raised 100-fold in the feet by percutaneous cervical cordotomy,[22,26] and the quantitative observations we have made in other conditions (spinal ischaemia, syringomyelia) have also revealed a greatly raised threshold for tissue-damage pain. Yet supraspinal

lesions causing central pain with almost identical symptoms only raise the threshold for nociceptive pain by 30% on average.[22,27,28] The implications for the anatomy of central (nociceptive) 'pain pathways' are discussed in reference 11.

Reaction to noxious stimuli is the easiest thing to test clinically, and there has been a tendency to overlook other sensory deficits. In fact, patients with syringomyelia and other cord lesions[29] and spinal cord injury,[30] as well as central pain of supraspinal origin, have a partial deficit to other modalities as well, notably pinprick and thermal (particularly cold) stimuli. The painful area is smaller than the area of sensory deficit;[30] though there is a tendency for the deficit to be quantitatively less marked in less painful or painfree areas;[29,30] allodynia, triggered from large rapidly-adapting 'touch' fibres, cannot be elicited from outwith the painful area. Isolated deficit of large fibre function (touch, vibration, kinaesthesia) may or may not be present in central pain; it does not appear to be associated with the pathophysiological mechanism in the way that small (perhaps particularly A delta) fibres are.

Treatment

The most important reason for distinguishing between nociceptive and neurogenic pains is that not only do the latter *not* usually respond very well to conventional analgesics; but their response to antidepressant treatment depends on how early it is instituted – which in turn depends on not wasting precious time 'trying' analgesics.

The response of neurogenic pains to first generation adrenergically-active antidepressants (particularly amitriptyline; also nortriptyline, desipramine, or maprotiline) has been known for some time and was validated by a double-blind trial in 1982,[31] which also showed that its pain-suppressant action is independent of its antidepressant action. More recently, amitriptyline has been shown, in a double-blind trial, to be effective in central post-stroke pain.[32]

In CPSP, there is evidence that the earlier antidepressant therapy is started, the more effective it is.[7] The difficulty with many conditions causing spinal pain, as with cerebral stroke, is that the pain frequently does not come on until some time after the insult has occurred, or begun. It is thus difficult to know when to begin therapy. This problem is further vitiated by the fact that not all patients with any given condition necessarily develop central pain. If one were certain that all, or even the majority, of patients with a given diagnosis would go on to develop central pain, there would be a lot to be said for initiating low-dose treatment with amitriptyline as soon as the diagnosis has been made.

Ever since carbamazepine was found to be effective for the treatment of trigeminal neuralgia (an extremely atypical neurogenic pain), anticonvulsants have been used for the treatment of other neurogenic pains,

motivated more by hope than experience on the part of the therapist. Leijon and Boivie[32] found the drug to be of no statistically significant value in the treatment of CPSP; and a recent meta-analysis[33] has suggested that anticonvulsants are of value only in trigeminal (and glossopharyngeal) neuralgia, diabetic neuropathy, and migraine prophylaxis. However, we achieved rapid and permanent relief to tabetic lightning pains of 20 years standing with sodium valproate;[34] and would advocate their use in any patient with shooting pain who has not responded to antidepressant monotherapy. Once again we reiterate the importance of prescribing antidepressant in the first instance for any neurogenic pain. Our usual practice is to begin with a starting dose of 10 or 25 mg at bedtime, increased after one week to 20 or 50 mg nocte, and augmented by weekly increments until 50 or 75 mg are being taken orally. Unlike treatment for depression, in which much higher doses are used, a patient whose neurogenic pain does not respond to maintained therapy with 75 mg nocte is unlikely to respond to an even higher dose. In our experience, higher doses are only justified if there is an suboptimal response to 75 mg. All antidepressants cause dry mouth, the commonest cause of non-compliance. This can be overcome by co-prescribing artificial saliva spray, or chewing gum for those prepared to use it. Patients should be warned not to expect an immediate effect from antidepressants. In our experience, it is worth waiting 6–8 weeks on full dose before abandoning/changing a drug or adding mexiletine[7] and/or an anticonvulsant. However, McQuay et al.[35] have found a shorter, dose-related, response time.

For those patients failing to respond to medical treatment, considerable success has been obtained from the implantation of stimulating electrodes over the spinal cord.[36] This is an expensive, but rewarding, form of treatment, which has been succesful in many types of central pain, including tabes dorsalis.[37] An extensive review, with a very large number of references, has recently been published by Simpson,[38] to which the reader is referred. He lists 'partial spinal cord lesion' as a condition in which the success of spinal cord stimulation is reasonably likely. It is also pointed out by several authors quoted that success is more likely in patients who use descriptors more typical of neurogenic pain (burning, sharp, etc).

For optimal and cost-effective results, great care must be taken in patient selection. In addition to the diagnostic criteria described above, alleviation or exacerbation of pain by rubbing over a nerve trunk, transcutaneous nerve stimulation and injection of hypertonic saline into an interspinous ligament in an affected segment may be used to evaluate suitability. Nowadays the electrodes are usually placed epidurally, and for a trial period of up to a week the leads are externalised. Response must be carefully monitored, changing the parameters of stimulation, the electrode pairs activated, and if necessary the position of the electrode. If satisfactory results are obtained, the electrode leads are internalised and connected to a subcutaneous receiver in which a current can be induced by an external coil. Our own preliminary results with quantitative sensory perception threshold testing suggest that in patients in whom pain is successfully relieved, changes in temperature thresholds are apparent 10 min after the end of stimulation, whereas in unsuccessful cases this is not so. If these findings can be confirmed in more extensive studies, they may offer useful guidance on whether or not to internalise temporary stimulating electrodes.

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