NEUROPHYSIOLOGICAL CORRELATES BETWEEN DEPRESSION AND PAIN

Many authors contend that the symptoms of pain and depression are similar by virtue of involvement of common neurological pathways.

Pain is a complex neurochemical process involving multiple neurotransmitters and other molecules (such as cytokines) in peripheral and central pain pathways.

Depression involves depletion of certain neurotransmitters ([1]). The two neurochemicals that have been recognised as being involved in the overlapping of the phenomena of pain and depression are serotonin (5-HT) and norepinephrine (noradrenaline).

Serotonin and norepinephrine are present in virtually every organ system in the body, in the brain, the prefrontal cortex and the limbic system, areas known to be involved in mood disorders, including depression.

Research suggests that serotonergic and noradrenergic neurons may interact; serotonergic neurons have been shown to exert an inhibitory effect on noradrenergic neurons. Noradrenaline is implicated in the descending inhibitory pain pathways([2]).

Fava ([3]), exploring the role of the serotonergic and noradrenergic neurotransmitter systems in the treatment of psychological and physical symptoms of depression, pointed out that as many as 76% of patients suffering from depression are found to report somatic symptoms, including various types of pain such as headaches, stomach pain, back pain, and vague, poorly localized pain.

There is significant evidence for abnormalities of the norepinephrine (NE) and serotonin (5-HT) neurotransmitter systems in depressive disorders, and these neurotransmitters in modulating pain via descending pain pathways.

Fava suggested that "antidepressants that are particularly effective in the treatment of pain and painful physical symptoms may yield higher remission rates in major depressive disorder."

Indeed, clinical experience confirms that the older antidepressants such as tricyclics, which exert effects on both NA and 5HT, are far more effective as analgesics than the newer, more specific, SSRIs.

Blackburn-Munro recently published a paper ([4]) on the hypothalamo-pituitary-adrenal axis dysfunction as a contributory factor to chronic pain and depression, noting,

"Pain as a reflex sensory response is accompanied by a fast autonomic and delayed neuroendocrine response mediated by the sympathoadrenal and hypothalamo-pituitary-adrenal (HPA) axis, respectively.

The emotional aspect of the pain response is encoded by corticolimbic systems (including the HPA axis) to encapsulate the relationship between pain, memory, and mood.

These same systems contribute to the symptomatology of depression, a common symptom of which is pain.

Conversely, many chronic pain patients may suffer from depressive illness, which appears to develop as a consequence of chronic pain."

The PAG, DLPT, and RVM are the key regions of the brain involved in this descending pain modulation. Research shows that lesions made to these areas of the brain block pain relief

associated with the tricyclic antidepressant clomipramine, which has strong serotonergic effects as well as noradrenergic.([5])

Animal models of persistent pain provide further evidence for the involvement of serotonin and norepinephrine in the modulation and analgesia of chronic pain states.([6])

Clinical trials have shown that antidepressants acting through both noradrenergic and serotonergic receptors provide effective pain relief in the clinical setting.([7]) Studies suggest that antidepressants with combined noradrenergic and serotonergic activity provide superior pain relief compared with selective analgesics that act on either neurotransmitter alone.([8])

Wernike et al. presented the findings of their pooled-analysis study of patients with major depression treated with duloxetine, at the 19th Annual Meeting of the American Academy of Pain Medicine in February 2003.

They showed an increase in depression remission rates, the rate of improvement in depressive symptoms for duloxetine responders being double that for non-responders.

"Physical pain is often a side effect of major depressive disorder, due to chemical imbalances caused by the condition," said Dr. Wernike.

"Secondary physical symptoms such as overall aches and pains, gastrointestinal pain and back aches often complicate treatment."

It was found that higher pain scores were associated with

"lower estimated probabilities of remission both before and after accounting for the core emotional symptoms of depression."

The authors concluded:

"Pain is depressing, and less physical pain means a better chance of improvements for patients with major depression." ([9])

Further, it has been established that a number of the symptoms of depression are commonly experienced as part of a pain syndrome.

This includes synaesthetic sensations which were previously considered indications of psychotic disorder, but have now been recognised as part of centralisation of pain.

This crossover not only leads to confusion in the medical arena, but concern and even fear amongst lay personnel. The stigma of mental illness may be receding, but its spectre still haunts most patients and their families.

A number of studies also suggest that depression can enhance pain-induced impairment. In a 24-month study of 228 elderly patients with depression or pain living in retirement communities, ([10]) Mossey et al. went on to evaluate the severity of depression and pain and their dual impact on functional ability.

Initially, nearly 50% of the patients who did not suffer depression reported limitations associated with their pain. Over the course of the 2 year study, people who began experiencing depressive symptoms also reported increasing impairment associated with pain.

Furthermore, high levels of depression were consistently associated with high levels of pain-related impairment, and even low levels of depression were associated in the presence of pain, with increased healthcare utilisation.([11])

Drugs that may precipitate depression:

Some medication can actually cause clinical depression. A Canadian study in 2001 looked at 2,500 subjects and found that most medications were not associated with major depression: these included beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, lipid-lowering agents, digoxin, and diuretics.

Calcium channel blockers were significantly associated with major depression, but only in young subjects, who tended to be seriously ill and taking multiple medications.

Opiate analgesics (morphine and related drugs) were associated with major depression, but only in male subjects.

Cortico*steroids* were significantly associated with major depression. ([12]) A list of prescription drugs with known depressive side-effects include: cardiac drugs and hypertensives (blood pressure tablets), sedatives, steroids, stimulants, antibiotics, antifungal drugs and analgesics (painkillers)

Non-prescription substances, such as alcohol, are well known to have profoundly depressant properties and chronic pain patients may well resort to alcohol use either to reduce pain perception or more indirectly for anxiolysis and hypnosis.

Measurement:

Elliott et al. ([13]) discussed the usefulness of the SF-36 Health Survey as an outcome measure for chronic pain patients with and without depression.

They found that

"The SF-36 Mental Composite Score and all subscales were highly correlated with depression type in chronic pain patients. The positive predictive value of the SF-36 in classifying depression type was high. The SF-36 may be a useful clinical tool to measure health-related

quality of life in chronic pain patients. In addition, the SF-36 was able to detect major depression and demonstrate a dose-effect relationship between depression type (severity) and health-related quality of life in chronic pain patients."

Taillefer et al. ([14]) conducted a study to test a cognitive model of impairment in chronic fatigue syndrome (CFS), comparing 45 CFS and 40 Multiple Sclerosis (MS) patients on measures of functional ability, fatigue severity, depressive symptoms, somatic symptom attribution and illness worry.

Their findings supported

"the role of depression and illness cognitions in disability in CFS sufferers".

However, they noted,

"Different cognitive factors account for physical and psychosocial disability in CFS and MS. The SF-36 may be sensitive to symptom attributions, suggesting caution in its interpretation when used with patients with ill-defined medical conditions."

The Hospital Depression and Anxiety (HAD) Scale is in widespread use in many countries and is considered well validated in delineating the role of anxiety and depression in chronic pain patients.

However, some of the questions do not differentiate well the origin of symptoms, such as restlessness, being ?slowed down' and loss of enjoyment, which could be attributed to unrelieved pain as easily as depression or anxiety.

Finnish authors Estlander et al. ([15]) reported in 1995 on their analysis of the use of the modified Zung Self-Rating Depression Scale (ZSDS) in assessment of depression in chronic musculoskeletal pain patients.

They concluded that ZSDS items dealing with symptoms which could arise secondary to pain (e.g. insomnia) are more clearly related to pain severity than other indicators of depression such as feelings of hopelessness.

They remarked,

"A diagnosis of depression based on a sum score of an inventory which contains somatic-vegetative signs of depression may lead to an overestimation of depression."

Morley et al. ([16]), in the International Association for the Study of Pain, conducted a confirmatory factor analysis confirming the use of the Beck Depression Inventory in chronic pain.

They particularly remarked that depression in chronic pain

"is strikingly different from the psychiatric model of depression (e.g. DSM-IV or ICD-10), which is primarily defined by affective disturbance, and secondarily supported by cognitive and somatic symptoms."

The authors stated,

"The finding is consistent with a reconsideration of what constitutes depression in the presence of chronic pain. It also has important clinical implications: it may provide a way to distinguish depressed patients with typical cognitive biases, who require specific treatment for depression alongside pain management."

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