Chronic Pain: *A Neuroimmune Phenomenon*

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Chronic adult pain is a common problem affecting about 19% of the European population with 61% of these people being unable to work normally resulting in absenteeism, decrease productivity and early retirement with associated negative social and economic impacts and increased demands on healthcare provision. Whilst acute pain is adaptive and protective and usually attributable to a precipitating event chronic pain is not and there is as yet no physiological benefits attributable to chronic pain. Acute pain is generally responsive to anti-inflammatory medication supplemented if necessary with a short course of opioid medication.

This is not however the case with chronic pain. Chronic neuropathic pain (CNP) in particular is notoriously difficult to treat and is the main reason for attendance at pain clinics.

The factors which affect the transition from acute adaptive pain to chronic maladaptive pain are poorly understood and are an area of investigation because of the high prevalence of chronic pain in society.

It has been noted that patient suffering from chronic pain express symptoms and demonstrate signs of sickness behavior. Sickness or pain related behavior relates to the interaction between the patient and environment, similar to what is seen in patients who have an acute infection on board.

This observation has led to the realization that pain chronicity is probably a central immune-mediated phenomenon. Ongoing research has further identified the relationship between pain and the immune system and pain is one of the four cardinal signs of inflammation.

Depression, anxiety, sleep disturbance and hyperalgesia are commonly problematic in patients with chronic pain.

It is now believed that the neuronal interface which results in these responses includes T cells, macrophages, glial cells and secreted neuropeptides. The nervous system and immune system share a common language mediated at least in part by neuropeptides, (cytokines, chemokines and neurotrophins). Bidirectional communication becomes maladaptive leading to enhanced pain signaling and chronicity.

Whilst there has always been a debate about whether pain chronicity is driven by peripheral stimulation or is solely a central effect it is now quite clear that activation of the dorsal root ganglion and dorsal horn of the spinal cord are central to the development of pain chronicity. Chronic pain occurs when automatic spontaneous non-stimulated sensory unpleasant phenomenon are experience by the patient.[1]

Neuropathic pain may be caused by lesion of the somatosensory system and is estimated to be a chronic problem in 7-8% of the general population in Europe. Access to the central nervous system in humans for the purposes of research is ethically challenging and traditionally difficult to perform. There has been much development in the field of neuroimaging however this has its limitations in terms of regular clinical application.

Chronic neuropathic pain (CNP) remains the greatest clinical challenge. Diagnosis is still heavily dependent on clinical assessment. A multitude of questionnaires are available to help clinicians diagnose CNP but many of these are quite labour-intensive to apply.

The DN4 and LANNS Questionnaires are probably the simplest and easiest to use. Laboratory testing such as nerve conduction studies and sensory evoked potentials, laser evoked potentials, punch biopsy, which can quantify Aδ and C fibres, measuring density

of intraepidermal nerve fibres and quantitative sensory testing are time-consuming and expensive.

The search for an easy to measure inexpensive biomarker continues. The management of CNP relates to both interventional / surgical therapies such as pulsing the dorsal root ganglion and spinal cord stimulation which require hospital attendance including a visit to the operating theatre with anaesthesia and are expensive to carry out.

With the high number of patients suffering from CNP it is simply not practical or within the healthcare budget to provide these expensive therapies to all patients.

Doctors are left with medication as the easiest to obtain therapeutic option however effectiveness is limited by relatively poor efficacy and deleterious side-effects. Number needed to treat (NNT) versus number needed to harm (NNH) ratios are humbling. Two of the most commonly used drug classes are the tricyclic antidepressants and opioids.[2]

As these drugs do seem to have benefit in patients with CNP their mode of action centrally must explain at least in part the pathophysiology of CNP.

Chronic post-surgical pain (CPSP) is disabling and can result in significant physical and economic morbidity for the patient. CNP is the commonest cause of CPSP and may affect up to 40% of patients having surgery depending upon the site and type of surgery.

Thoracic surgery in particular is associated with CPSP. Poor acute pain control in the immediate postoperative setting has been associated with the development of chronic pain but the aetiology is more complex than this.

We investigated the effect of thoracic surgery on human cerebrospinal fluid (CSF) neuropeptides and found that despite adequate acute pain control significant central CSF pro-inflammatory neuropeptide biosynthesis occurred in vivo in patients having a thoracotomy.[3] This was associated with the development of CPSP.

Amitriptyline is probably seen as the most effective drug in the management of neuropathic pain. We examined the effect of amitriptyline on T-cell phenotype and function on human peripheral blood mononuclear cells. This was achieved by Annexin V / propidium staining, flow cytometry and Elisa examination. Levels of secreted cytokines, chemokines and neurotrophins were measured. The results showed that there was no increase in T-cell death however the type of T-cell present was altered by amitriptyline.

The frequency of naïve T cells was significantly lowered after amitriptyline and nortriptyline therapy. The effect of interferon-gamma on CD AT cells was also reduced. Interestingly natural killer T cells are significantly higher following treatment with nortriptyline. Amitriptyline lowered the levels of interleukin 16 and tumour necrosis factor.[4] Amitriptyline is a modulator of both phenotype and function of T cells. Further examination of cerebrospinal fluid (CSF) in patients who responded well to amitriptyline demonstrated a reduction in pro inflammatory pathways of neuronal glial communication and evidence of a neurotrophic effects.[5]

Opioid medication has been used extensively to treat acute, chronic and cancer pain. It is effective in the management of acute and cancer pain however opioid medication in the management of chronic pain is a very contentious issue. This is well delineated in the CDC report 2016. Opioid related phenomena include sedation, tolerance, euphoria, reward, addiction, analgesia, depression, hyperalgesia and death.

There is growing evidence that central signaling maybe responsible at least in part for these phenomenon. Crosstalk between glia, immune cells and neurons, which we refer to as the neurommune interface, occurs by messengers which include cytokines, chemokines, neurotrophins and neuropeptides. Changes in the dynamic of these messengers may be caused by opioid therapy.

There remains debate about whether opioids are truly immunosuppressive. In vivo human opioid mural uniform ecology has remained largely unexplored. The effect of opioid therapy on expression of proteomic and neuropeptide constituents of (CSF) will provide greater insight into the pure mechanisms of action in vivo.

We examined human CSF in patients with CNP medication with opioid (predominantly oxycodone) versus patients with CNP not medicated with opioids using mass spectrometry. 432 proteins were found to be increased in baseline CSF in the patients receiving opioids versus those not receiving opioids. The 10 most differentially increased proteins included somatostatin. In addition 47 neuropeptides demonstrated decreased expression in the group receiving opioids versus the group which were not medicated with opioids.[6]

The quoted studies are referenced at the end of this article for those who wish to explore this topic further. Amitriptyline and opioids are commonly employed therapies which have significant neuroimmune effects.

The amitriptyline work demonstrates the effect is not just related to neuropeptide metabolism but also has a direct effect on T-cell expression and the receptors on the surface of T cells and the neuropeptide secreted from these cells. The opioid study demonstrates that opioid prescription has a major effect on central neuropeptide and protein biosynthesis in humans. The fact that both these drugs have an effect on immune function supports the concept that CNP is a neuroimmune phenomenon.

Again constant surveillance must be provided by both the prescribing doctor and dispensing pharmacist when these therapies are employed because affects on human central peptide and protein biosynthesis in vivo are quite extensive.

References available upon request