Neuropathic Pain

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Description

Neuropathic pain is a form of chronic pain defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system" either at peripheral or central level[1]. Neuropathic pain represents a series of heterogeneous conditions, for which examples include:

1. Painful peripheral neuropathies – traumatic nerve injury, post-traumatic or postoperative neuroma, Morton's neuralgia, entrapment neuropathy (e.g. carpal tunnel syndrome), postsurgical pain (e.g. after mastectomy, thoracotomy, phantom pain following amputation), vasculitic neuropathy, neuralgic amyotrophy, radiation-induced plexopathy, trigeminal or glossopharyngeal neuralgia, infection (e.g. postherpetic neuralgia in the area of a herpes zoster outbreak, HIV-associated sensory neuropathy), metabolic (e.g. diabetic peripheral neuropathy), cancer (e.g. tumor growth leading to pressure on, or infiltration of a nerve, multiple myeloma), drug-related (e.g. chemotherapy-induced neuropathy), autoimmune disease (e.g. Guillain-Barre syndrome), hereditary (e.g. Charcot-Marie-Tooth disease, Fabry's disease)[2].

2. Central pain syndromes - traumatic spinal cord injury or brain injury, vascular lesions in the spinal cord or brain (e.g. infarct, haemorrhage, vascular malformation), poststroke pain, autoimmune diseases (e.g. multiple sclerosis), inflammatory diseases (e.g. transverse myelitis), syringomyelia and syringobulbia, central nervous system tumours or abscesses, some cases of Parkinson's disease[2].

3. Complex painful neuropathic disorders - Complex regional pain syndrome type II[2].

Whereas various nervous system lesions or diseases may cause neuropathic pain, the clinical manifestation of the pain is similar across the different neuropathic syndromes[2]. Patients with neuropathic pain typically have symptoms of abnormal sensation or hypersensitivity in the affected area, combined or adjacent to areas of sensory deficit[2]. Negative symptoms include tactile or thermal hypoaesthesia (reduced sensation to non-painful stimuli), pin-prick hypoalgesia (reduced sensation to painful stimuli), and loss of vibratory sensation. Positive symptoms include paraesthesia (i.e. skin crawling sensation or tingling), spontaneous (not stimulus-induced) ongoing pain (e.g. burning sensation), and paroxysmal pain (e.g. shooting, electric shock-like sensations). Many neuropathic pain patients also have evoked pain (i.e. stimulus-induced pain) including mechanical dynamic and mechanical static allodynia (pain evoked by non-painful light moving touch, or light pressure, respectively), pin-prick hyperalgesia, temporal summation (increasing pain sensation from repetitive application of identical single noxious stimuli), cold and heat allodynia (pain from normally non-painful cold and warm stimuli, respectively)[2,3].

The prevalence of chronic neuropathic pain lasting more than 3 months in the general population has been estimated to be as high as 17.9%, and higher in females than males[4]. Neuropathic pain is associated with greater pain and more impact upon quality of life than other forms of pain[4]. In addition, comorbidities such as poor sleep, depression and anxiety are common in neuropathic pain patients. Thus, neuropathic pain is clearly a major health problem.

Numerous animal models of neuropathic pain involving partial nerve injury have been developed. These animal models mimic some of the clinical symptoms of neuropathic pain and have served as powerful tools to investigate the mechanisms underlying neuropathic pain. Among these mechanisms are:

1. Ectopic activity – Nerve injury results in significant changes in the expression, distribution, and phosphorylation of ion channels in sensory neurons leading to ectopic action potential discharge at the site of nerve injury and the resultant neuroma, as well as at more proximal sites including the cell body. Ectopic activity is the major driver of spontaneous pain following nerve lesions[5].

2. Peripheral sensitisation – Changes in the sensitivity of nociceptor peripheral terminals to stimuli can occur through activation of signal transducer proteins by inflammatory mediators, neurotransmitters and growth factors, or an increase in membrane excitability contributing to increased pain sensitivity[3,5].
3. Central sensitisation and spinal disinhibition – Nerve injury causes changes in the spinal cord that lead to strengthening of synaptic input from nociceptors and low-threshold mechanoreceptors onto nociceptive neurons resulting in an enhanced neuronal excitability and amplification of pain. In addition, nerve injury causes a reduction in normal inhibitory regulation through a loss of local inhibitory interneurons, a depolarised anion reversal potential, and reduced descending inhibition. Central sensitisation is associated with the generation of dynamic mechanical allodynia, pin-prick hyperalgesia, and temporal summation[5].
4. Activation of immune and glial cells – Infiltration of inflammatory immune cells and activation of resident immune and glial cells in the peripheral nervous system and spinal cord contributes to pain hypersensitivity by sensitising primary nociceptors and secondary nociceptive neurons[6].
5. Brain plasticity – Central processing of somatosensory input is altered by cortical reorganisation and neuronal plasticity in various brain regions[3].

Treatment

Treatment of neuropathic pain is challenging because many patients don't experience sufficient pain reduction. In fact, only 40-60% of patients achieve clinically meaningful pain relief with pharmacotherapy, and existing analgesics are characterised by limited efficacy and burdensome adverse effects. Recently, the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain published evidence-based guidelines for the pharmacological management of neuropathic pain[7]:

1. First-line medications – Tricyclic antidepressants (e.g. nortriptyline, desipramine), dual reuptake inhibitors of serotonin and norepinephrine (e.g. duloxetine, venlafaxine), calcium channel α2-δ ligands (e.g. gabapentin and pregabalin), and topical lidocaine[7].

2. Second-line medications that are appropriate for first-line use in certain circumstances – Opioid analgesics and tramadol should be reserved for patients who have not responded to first-line medications. However, these medications are recommended as first-line treatments for patients with acute neuropathic pain, cancer pain, and episodic exacerbations of severe neuropathic pain[7].

3. Third-line medications – Generally, these medications are reserved for patients who cannot tolerate or who don't respond adequately to first- and second-line medications. These medications include certain antidepressants (e.g. bupropion, citalopram, and paroxetine), certain antiepileptic drugs (e.g. carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid), topical low concentration capsaicin, dextromethorphan, memantine, and mexiletine[7].
4. Others - botulinum toxin, high-concentration capsaicin patch, lacosamide, selective serotonin reuptake inhibitors, and combination therapies[7].

Whereas pharmacotherapy remains the mainstay of neuropathic pain management, there are several non-pharmacological methods that can support and improve pharmacological treatment. They include psychological treatment (e.g. cognitive and behavioural techniques, hypnosis), physical treatment (e.g. massages, acupuncture), surgical techniques (e.g. nerve ablation, dorsal rhizotomy), and neuromodulation (e.g. peripheral nerve stimulation, spinal cord stimulation, deep brain stimulation, motor cortex stimulation)[8].

References

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