Neuropathic Pain

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Neuropathic pain is pain caused by damage or disease affecting the somatosensory nervous system. Neuropathic pain may be associated with abnormal sensations called dysesthesia or pain from normally non-painful stimuli (allodynia). It may have continuous and/or episodic (paroxysmal) components. The latter resemble stabbings or electric shocks. Common qualities include burning or coldness, "pins and needles" sensations, numbness and itching.

Up to 7% to 8% of the European population is affected, and in 5% of persons it may be severe. Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord). Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain.

Cause

Central neuropathic pain is found in spinal cord injury, multiple sclerosis, and some strokes. Aside from diabetes (see diabetic neuropathy) and other metabolic conditions, the common causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, remote manifestations of malignancies, immune mediated disorders and physical trauma to a nerve trunk. Neuropathic pain is common in cancer as a direct result of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy (chemotherapy-induced peripheral neuropathy), radiation injury or surgery.

Mechanisms

Peripheral

After a peripheral nerve lesion, aberrant regeneration may occur. Neurons become unusually sensitive and develop spontaneously pathological activity, abnormal excitability, and heightened sensitivity to chemical, thermal and mechanical stimuli. This phenomenon is called "peripheral sensitization".

Central

The (spinal cord) dorsal horn neurons give rise to the spinothalamic tract (STT), which constitutes the major ascending nociceptive pathway. As a consequence of spontaneous activity arising in the periphery, STT neurons develop increased background activity, enlarged receptive fields and increased responses to afferent impulses, including normally innocuous tactile stimuli. This phenomenon is called central sensitization. Central sensitization is an important mechanism of persistent neuropathic pain.

Other mechanisms may take place at the central level after peripheral nerve damage. The loss of afferent signals induces functional changes in dorsal horn neurons. A decrease in the large fiber

input decreases the activity of interneurons inhibiting nociceptive neurons i.e. loss of afferent inhibition. Hypoactivity of the descending antinociceptive systems or loss of descending inhibition may be another factor. With the loss of neuronal input (deafferentation) the STT neurons begin to fire spontaneously, a phenomenon designated "deafferentation hypersensitivity."

Neuroglia ("glial cells") may play a role in central sensitization. Peripheral nerve injury induces glia to release proinflammatory cytokines and glutamate--which, in turn influence neurons.

Cellular

The phenomena described above are dependent on changes at the cellular and molecular levels. Altered expression of ion channels, changes in neurotransmitters and their receptors as well as altered gene expression in response to neural input are at play.

Treatments

Neuropathic pain can be very difficult to treat with only some 40-60% of people achieving partial relief.

Favored treatments are certain antidepressants (tricyclic antidepressant and serotonin-norepinephrine reuptake inhibitors), anticonvulsants (pregabalin and gabapentin), and topical lidocaine. Opioid analgesics are recognized as useful agents but are not recommended as first line treatments.

Anticonvulsants

Pregabalin and gabapentin may reduce pain associated with diabetic neuropathy. The anticonvulsants carbamazepine and oxcarbazepine are especially effective in trigeminal neuralgia. Gabapentin may reduce symptoms associated with neuropathic pain or fibromyalgia in some people. There is no predictor test to determine if it will be effective for a particular person. A short trial period of gabapentin therapy is recommended, to determine the effectiveness for that person. 62% of people taking gabapentin may have at least one adverse event, however the incidence of serious adverse events was found to be low.

Lamotrigine does not appear to be effective for neuropathic pain.

Antidepressants

Dual serotonin-norepinephrine reuptake inhibitors such as duloxetine, venlafaxine, and milnacipran, as well as tricyclic antidepressants such as amitriptyline, nortriptyline, and desipramine are considered first-line medications for this condition. While amitriptyline and

desipramine have been used as first-line treatments, the quality of evidence to support their use is poor.

Bupropion has been found to have efficacy in the treatment of neuropathic pain.

Botulinum toxin type A

Botulinum toxin type A (BTX-A) is best known by its trade name, Botox. Local intradermal injection of BTX-A is helpful in chronic focal painful neuropathies. The analgesic effects are not dependent on changes in muscle tone. Benefits persist for at least 14 weeks from the time of administration.

The utility of BTX-A in other painful conditions remains unproven.

Cannabinoids

Cannabis and a number of cannabinoid receptor agonists appear to be effective for neuropathic pain.

The predominant adverse effects are CNS depression and cardiovascular effects--which are mild and well tolerated, but psychoactive side effects limit their use.

Long-term studies are needed to assess the probability of weight gain and possible harmful psychological effects.

Dietary supplements

A 2007 review of studies found that injected (parenteral) administration of alpha lipoic acid (ALA) was found to reduce the various symptoms of peripheral diabetic neuropathy. While some studies on orally administered ALA had suggested a reduction in both the positive symptoms of diabetic neuropathy (dysesthesia including stabbing and burning pain) as well as neuropathic deficits (paresthesia), the meta-analysis showed "more conflicting data whether it improves sensory symptoms or just neuropathic deficits alone". There is some limited evidence that ALA is also helpful in some other non-diabetic neuropathies.

Benfotiamine is an oral prodrug of Vitamin B1 that has several placebo-controlled double-blind trials proving efficacy in treating neuropathy and various other diabetic comorbidities.

Neuromodulators

Neuromodulation is a field of science, medicine and bioengineering that encompasses both implantable and non-implantable technologies (electrical and chemical) for treatment purposes.

Implanted devices are expensive and carry the risk of complications. Available studies have focused on conditions having a different prevalence than neuropathic pain patients in general. More research is needed to define the range of conditions that they might benefit.

Deep brain stimulation

The best long-term results with deep brain stimulation have been reported with targets in the periventricular/periaqueductal grey matter (79%), or the periventricular/periaqueductal grey matter plus thalamus and/or internal capsule (87%). There is a significant complication rate, which increases over time.

Motor cortex stimulation

Stimulation of the primary motor cortex through electrodes placed within the skull but outside the thick meningeal membrane (dura) has been used to treat pain. The level of stimulation is below that for motor stimulation. As compared with spinal stimulation, which is associated with noticeable tingling (paresthesia) at treatment levels, the only palpable effect is pain relief.

Spinal cord stimulators and implanted spinal pumps

Spinal cord stimulators use electrodes placed adjacent to but outside the spinal cord. The overall complication rate is one-third, most commonly due to lead migration or breakage but advancements in the past decade have driven complication rates much lower. Lack of pain relief occasionally prompts device removal.

Intrathecal pumps deliver medication directly to the fluid filled (subarachnoid) space surrounding the spinal cord. Opioids alone or opioids with adjunctive medication (either a local anesthetic or clonidine) or more recently ziconotide are infused. Complications such as serious infection (meningitis), urinary retention, hormonal disturbance and intrathecal granuloma formation have been noted with intrathecal infusion.

There are no randomized studies of infusion pumps. For selected patients 50% or greater pain relief is achieved in 38% to 56% at six months but declines with the passage of time. These results must be viewed skeptically since placebo effects cannot be evaluated.

NMDA antagonism

The N-methyl-D-aspartate (NMDA) receptor seems to play a major role in neuropathic pain and in the development of opioid tolerance. Dextromethorphan is an NMDA antagonist at high doses. Experiments in both animals and humans have established that NMDA antagonists such as

ketamine and dextromethorphan can alleviate neuropathic pain and reverse opioid tolerance. Unfortunately, only a few NMDA antagonists are clinically available and their use is limited by a very short half life (dextromethorphan), weak activity (memantine) or unacceptable side effects (ketamine).

Opioids

Opioids are not a first-line treatments for neuropathic pain. Reviews have found little evidence supporting their effectiveness in chronic pain conditions (defined as pain lasting longer than 3 months). In some cases, opioids may contribute to a worsening of pain, leading to a cycle of taking more opioids to treat a condition that the medication itself has made worse. Due to the risk of addiction or diversion, opioids should be used only in appropriate individuals and under close medical supervision.

Several opioids, particularly methadone and ketobemidone, possess NMDA antagonism in addition to their μ-opioid agonist properties. Methadone does so because it is a racemic mixture; only the l-isomer is a potent μ-opioid agonist. The d-isomer does not have opioid agonist action and acts as an NMDA antagonist; d-methadone is analgesic in experimental models of chronic pain. Clinical studies are in progress to test the efficacy of d-methadone in neuropathic pain syndromes.

There is little evidence to indicate that one strong opioid is more effective than another. Expert opinion leans toward the use of methadone for neuropathic pain, in part because of its NMDA antagonism. It is reasonable to base the choice of opioid on other factors. It is unclear if fentanyl gives pain relief to people with neuropathic pain.

Topical agents

In some forms of neuropathy, especially post-herpetic neuralgia, the topical application of local anesthetics such as lidocaine is reported to provide relief. A transdermal patch containing lidocaine is available commercially in some countries.

Repeated topical applications of capsaicin, are followed by a prolonged period of reduced skin sensibility referred to as desensitization, or nociceptor inactivation. Capsaicin not only depletes substance P but also results in a reversible degeneration of epidermal nerve fibers. Nevertheless, benefits appear modest with standard (low) strength preparations, and topical capsaicin can itself induce pain.

Research directions

Other topical agents such as amitriptyline, gabapentin, Citrullus colocynthis extract, nifedipine, and

pentoxifylline are also under investigation.

History

The history of pain management can be traced back to ancient times. Galen also suggested nerve tissue as the transferring route of pain to the brain through the invisible psychic pneuma. The idea of origination of pain from the nerve itself, without any exciting pathology in other organs is presented by medieval medical scholars such as Rhazes, Haly Abbas and Avicenna. They named this type of pain specifically as "vaja al asab" , described its numbness, tingling and needling quality, discussed its etiology and the differentiating characteristics. The description of neuralgia was made by John Fothergill (1712-1780). In an medical article entitled Clinical Lecture on Lead Neuropathy" published in 1924 the word "Neuropathy" was used for the first time by Gordon.