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OVERVIEW OF NEUROPATHIC PAIN AND ITS OUTPATIENT MANAGEMENT

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Abstract:

Patients with neuropathic pain syndrome often express a range of sensory signs and symptoms. The spectrum of these symptoms consists of "painless" to "painless but debilitating" to "painful". It is characterized by the unusual sensitivity of nociceptive receptors to stimuli (hyperalgesia) with resultant hyperstimulation of the sensory nervous system (allodynia). Stimulation of nociceptor unit receptors, with stimuli-provoked impulse generation that can be spatially and/or temporally summated through its transmission, is likely the causative mechanism of the symptoms patients usually suffer from. It is imperative to reach an exact diagnosis and to explore the pathophysiology of each patient; only when this has been achieved then is it possible to plan adequate symptom-oriented therapeutic strategies. Numerous interventions for neuropathic pain are available, but its treatment remains unsatisfactory. The available treatments mostly have modest efficacy and come with side effects that limit their use whereas some newer therapeutic approaches are preferred for outpatient management.

Aim: *In this review article, we will discuss an overview of neuropathic pain and its classification and pathophysiology, in addition to the treatment algorithm used for outpatients.*

Keywords*: Neuropathic, pain, trigeminal neuralgia, post-herpetic neuralgia, gabapentin.*

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INTRODUCTION:

Neuropathic pain is a condition that develops after a primary somatosensory nervous system lesion which is caused by a variety of pathogenic causes, and it is typically classified according to its anatomic location or etiology. Though it is generally accepted that both processes of the nervous system (central and peripheral) may have a role in the pathophysiology of these symptoms, peripheral processes, in particular, are frequently unnoticed. There aren't a rather specific set of conditions that determine the cause of neuropathic pain as the causes are heterogeneous, such as autoimmunity and metabolic disorders, and neuropathy caused by viral infections. (1)

Epidemiology:

The prevalence of neuropathic pain in females (60.5% of patients) is higher than males, reaching a peak at an age of 50–64 years. It is reported more often by manual workers especially and in rural area residents. Neuropathic pain's prevalence is calculated to range between 3% and 17% in the general population. Whereas the incidence depends on the type of pain each patient has; for example, post-herpetic neuralgia was measured as 3.9–42.0/100,000 persons/year, and 12.6–28.9/100,000 persons/year for trigeminal neuralgia. (2)

Pathogenesis:

Nociception is the neural process of deciphering noxious stimuli and converting them to a somatosensory process. Chronic pain is commonly characterized as pain that occurs on a regular basis for several months that can affect the daily life of patients. Pain is described as an unpleasant sensory or emotional experience associated with definite or impending tissue damage, on a sliding scale of severity. This stimulus activates an ion channel on a nociceptor, which will cause a cation influx that depolarizes the nociceptor generating a receptor potential. Once it reaches a sufficient magnitude to reach the activation threshold for voltage-gated Na+ channels, an action potential is generated, and it will activate the transmission of a pain signal to the spinal cord. Pain sensation arising from ongoing exposure to high-intensity stimuli leading to tissue injury can linger beyond the removal of the originating stimulus. This is the pathogenesis of post-herpetic neuralgia where the virus migrates and causes a local inflammatory response with long-lasting painful symptoms. Afferent signals at the level of the spinal dorsal horn, lead to the initiation of a sensory signal that traverses the spinal cord leading to dorsal horn output. The process underlying spinal facilitation of pain signals includes enhanced postsynaptic transmission, spinobulbospinal pathway overactivation, and loss of local inhibitory neurons. (3)

Classification:

Neuropathic pain classification represents the first methodical and all-inclusive classification up to the present moment of painful neurological disorders. Some types of neuropathic pain have specific symptoms that might allow chronic pain to be diagnosed before the 3-month mark. Trigeminal neuralgia, for example, is characterized by pain in one or more branches of the 5th cranial nerve, rapid pain paroxysms, and pain episodes triggered by harmless mechanical or orofacial stimuli. Remission periods vary among patients, but the neuralgia mostly never completely resolves. Similarly, polyneuropathy caused by type 2 diabetes or pain following a spinal cord injury mostly fluctuates in severity, thus waiting three months to diagnose persistent neuropathic pain may cause unwanted harm to the patient. However, given the lack of objective markers to distinguish acute from chronic pain, a threshold of three months was adopted since it allows for an objective criterion in accordance with accepted treatment standards and analgesic clinical trials. (4)

The suggested revision of classification distinguishes between peripheral and central neuropathic pain. It refers to a group of nine diseases that are linked to chronic or recurring pain. Extension codes for pain severity (which combines intensity, disability, and impairment), temporal features, and in addition to psychological or social variables. (5)

Diagnosis:

A potential diagnosis of neuropathic pain needs further testing to confirm that the pain is caused by the nervous system. The location of pain must correlate to the underlying somatosensory nervous system lesion or injury. Since there is no diagnostic gold standard for neuropathic pain, clinical judgment is used to make a definite diagnosis. Identification of painful symptoms and clinical history that match a neuro-anatomical or dermatomal pattern are the most important aspects of diagnosing neuropathic pain. Many of the clinical characteristics of neuropathic pain are due to nerve injury. Neuropathic pain's cardinal symptom is pain that arises in a region of altered sensation (numbness or hyper-excitability). Pain that occurs without a trigger and reactions to non-painful (allodynia) or painful stimuli are the most prominent characteristics. (6)

Screening techniques including pain questionnaires, as well as information on the disease's history and a

thorough neurological examination, are all part of the diagnostic work-up. The bedside examination is revealing and aid in diagnosis. The goal is to detect changes in sensation in the painful location, therefore responses should be compared to responses in a non-painful area. A diagnosis of neuropathic pain is generally made by a combination of typical painful sensations in an area of altered sensation on bedside examination. When in question, a more thorough evaluation employing Quantitative Sensory Testing or traditional electrophysiological may be beneficial. (2)

Management Plan:

Neuropathic pain therapy focuses on treating symptoms by mainly stopping the pain, with the causes of pain being addressed only in a few clinical conditions. From a therapeutic opinion, disrupting pain signals transmission within the primary afferent nociceptor has fewer side effects than targeting a process within the CNS. To confirm this method, local anesthetic lidocaine when injected at painful locations in patients suffering from neuropathy significantly reduced allodynia, signifying that constant nociceptor input drives neuropathic pain symptoms. (7)

Pharmacological Treatment:

The Special Interest Group on Neuropathic Pain (NeuPSIG) in their latest guidelines recommended a series of medications as first-line medications for the treatment of neuropathic pain including tricyclic antidepressants (TCAs), gabapentinoids, and selective serotonin-norepinephrine reuptake inhibitors (SNRI). Second-line medications such as Lidocaine, Capsaicin, and Tramadol have been recommended, while opioids such as morphine and oxycodone, in addition to botulinum toxin-A, were considered as third-line medications for neuropathic pain of peripheral origin. (1)

Gabapentin and pregabalin have structural similarities. Antagonism of the 2 subunits of voltage-dependent calcium channels at presynaptic receptors is thought to be their analgesic mechanism in neuropathic pain. The use of gabapentin and pregabalin is proven to be effective in post-herpetic neuralgia, diabetic neuropathy, and traumatic injury to the spinal cord. Pain can be relieved within the first or second week of use with resultant improvements in sleep and quality of daily life. However, those improvements can be substantial initially and then wane over time. Both medications have no known drug-drug interactions and are tolerated. They undergo renal excretion, so any renal injury requires dosage modification. Pregabalin is the first-line medication in patients with generalized anxiety disorders as it has concomitant anxiolytic effects.(8)

Blocking sodium channels is the major pharmacological activity of carbamazepine and oxcarbazepine. These first-line medications for trigeminal neuralgia include carbamazepine and oxcarbazepine. In studies comparing oxcarbazepine to carbamazepine, oxcarbazepine was shown to have similar analgesic benefits but fewer adverse effects with patients preferring it over carbamazepine. Neither medication is recommended as first-line therapy for cancer-related neuropathic pain due to adverse effects and drug-drug interactions. Because the outcomes of randomized controlled studies are inconsistent, lamotrigine and valproate have limited roles in the treatment of neuropathic pain. (9)

Antidepressants have been shown to help with a variety of neuropathic pain conditions. Tricyclic antidepressants (TCAs) (e.g. amitriptyline and imipramine) and selective serotonin norepinephrine reuptake inhibitors (SNRIs) are two types of antidepressants used to treat neuropathic pain (e.g. duloxetine and venlafaxine). It is apparent that antidepressants' analgesic effects are distinct from their antidepressant effects. Antidepressants, on the other hand, maybe the first medication of choice in patients with concomitant depression because of this dual function. Additionally, medications like venlafaxine are effective in the treatment of hot flashes in some patients. Moreover, neuropathic pain is reported to respond to opioids with an effect size similar to antidepressants and gabapentin/pregabalin with no proved difference between various opioids. (10)

Combination Therapy:

If a single medication is only partially successful, more drugs may be administered. In patients with severe diabetic neuropathy or post-herpetic neuralgia; recent clinical trials have shown that a combination of gabapentinoids and TCAs or opioids provides better pain relief and fewer pain symptoms than a single medication. In individuals with cancer-related neuropathic pain, gabapentin (400 mg) with imipramine (20 mg) as an add-on medication reduced pain quicker and lasted longer than those who received only one medication. Polypharmacy should be avoided whenever feasible due to the potential of additive adverse effects, drug misuse, and non-compliance. When combination therapy is needed, patients who demonstrate a partial response to the first or both drugs given alone should get sequential add-on therapy, and a reasonable strategy is to employ agents with

complementary modes of action. The severity and nature of pain, as well as side effects, should be evaluated and dosage changes made during pain therapy. (11)

The predicted side-effect profile, current comorbidities, and concomitant symptoms that may benefit from a specific medication are the most essential factors to consider. Because of a lack of analgesia or severe side effects, first-line therapies may fail. Alternatively, a partial reaction may occur, requiring the use of another medication to treat the uncontrollable aspects of pain. Maximum analgesia with the fewest adverse effects is always the objective.

CONCLUSION:

Although the technology for assessing neuropathic pain has been significantly enhanced in recent years, there is still room for improvement. This will aid in the categorization of pain disorders such as complex regional pain syndrome and fibromyalgia syndrome, which are not included by the new neuropathic pain criteria. Pain has an influence on all aspects of one's quality of life, and it is one of the most unpleasant symptoms for all patients. Neuropathic pain is a severe problem that has a significant impact on patients' quality of life. Therapy will become increasingly symptom-oriented rather than illness-oriented in the future, and treatment choices will most likely be personalized to a patient's individual constellation of symptoms.

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