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Review Article

Therapeutics in neuropathic pain - An overview

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ABSTRACT

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."The IASP in November 2010 further extended to define neuropathic pain as "Pain initiated or caused by primary lesion or dysfunction of the peripheral or central nervous system."Neuropathic pain is a highly unpleasant sensation, which contributes to poor quality of life which is similar to patients with serious mental illness or severe heart diseases. Correct diagnosis of neuropathic pain is always challenging. It is essential to recognize neuropathic pain, identify the underlying cause, assess the impact of pain on the quality of life of the patient, and initiate appropriate treatment. This article limits itself to discuss about the neuropathic pain pertaining to orofacial structures. It includes trigeminal neuralgia, post-herpetic neuralgia, cancer neuropathic pain, and HIV neuropathy.

Keywords: Neuropathic pain, carbamazepine, trigeminal neuralgia, gabapentin, pregabalin

Introduction

The International Association for the study of pain (IASP) defines pain as an unpleasant sen-sory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. IASP in November 2010 further extended to define neuropathic pain as "Pain initiated or caused by primary lesion or dysfunction of the peripheral or central nervous system.[1]". Neuropathic pain is a highly unpleasant sensation, which contributes to poor quality of life which is similar to patients with serious mental illness or severe heart dis-eases. [2,3] Correct diagnosis of neuropathic pain is always challenging. It is essential to recog-nize neuropathic pain, identify the underlying cause, assess the impact of pain on the quality of life of the patient and initiate appropriate treatment. This article limits itself to discuss about the Neuropathic pain pertaining to oro-facial structures. It includesTrigeminal Neural-gia, Post Herpetic Neuralgia (PHN), cancer neuropathic pain, HIV neuropathy.

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Conditions Causing Neuropathic Pain

Neuropathic pain is caused due to damage to the neural functions. Neuropathic pain is most often consequences of a disease, rather the disease itself. It could be due to traumatic nerve damage or compression, diabetes, cancer, chemotherapy, viral infection, alcohol, and surgical amputation[4] [Table 1] - conditions causing neuropathic pain]. Pain can be central or peripheral based on which it is categorized as central neuropathic pain or peripheral neuropathic pain.

Pathophysiology

The peripheral and central mechanism together may contribute to the symptoms.[5-12] This can be given as follows [Figure 1]:

1. Nociceptors evoke the pathological activity.
2. Ectopic activity of damaged neuron and dorsal root ganglion cells.
3. Increased release of neurotransmitter due to increased sodium channel activity.
4. Increased afferent pathway activity causing central sensitization of dorsal horn neurons.
5. Increased central facilitation.

Clinical Features

Neuropathic pain has a wide range of expression other than pain itself. It includes allodynia, anesthesia, hyperalgesia, hyperpathia, hypoesthesia, paraesthesia, and phantom pain. They are categorized as negative symptoms and positive symptoms. Negative symptoms include anesthesia and hypoesthesia which are due to impaired afferent or efferent conduction. Positive symptoms include all other symptoms mentioned above which are due to increased or ectopic neuronal activity.

Neuropathic pain can also be classified based on their responds to stimuli as stimulus dependent and stimulus independent. Stimulus-evoked pain occurs due to slightest stimuli such as clothing or a non-painful touch. Stimulus-independent pain is spontaneous. It is continuous or intermittent, usually burning, shooting, or shock-like. It is mainly due to decreased inhibitory input from the brain and spinal cord. Although we classify them as stimulus dependent and independent, the symptoms occur as combinations which make it difficult to categorize under one particular type.[13,14]

Table 1: Common causes of neuropathic pain

Metabolic	Multiple sclerosis
Diabetes mellitus	Monoclonal gammopathies
Vitamin B deficiency	Guillain-barre syndrome
Toxic	Genetic
Drugs - isoniazid, phenytoin, hydralazine, vincristin, vinblastine	Hereditary motor and sensory neuropathy
Metal poisoning - lead, mercury	Vascular
Trauma	Vasculitis
Phantom pain	Cerebrovascular disorder
Complex regional pain syndrome	Carcinomatous
Carpel tunnel syndrome	Paraneoplastic syndrome
Infection	Compression or infiltration of tumour
Herpes zoster	Neuralgia
HIV	Trigeminal
Epstein barr virus	Post herpetic
Immune	Hypoglossal

Table 2: Steps in diagnosis of neuropathic pain

Step 1	History	Suggestive of neural distribution (central and peripheral)	Possible
Step 2	Clinical examination and investigation	Negative/positive sensory signs and confirmatory tests	Probable
Step 3	History+clinical finding+confirmatory tests. All positive		Definitive

Adapted from Treede RD, Jensen TS, Cambell *et al*. Neuropathic pain redefining a grading system for clinical and research purpose. Neurology 2008;70:1630-5

Assessment of Neuropathic Pain

History

A detailed history helps us to understand the nature and characteristics of pain. History will indicate if the distribution and characteristics of pain categorize it as neuropathic pain criteria or it is due to some neurological lesion or condition.[15]

Clinical Examination

In most case, neuropathic pain is a syndrome that is a constellation of signs and symptoms with numerous underlying etiologies, and hence, a complete neurological examination and sensory testing are essential to call it a neuropathic pain [Table 2]. Examining the somatosensory system reveals positive symptoms such as hyperalgesia and allodynia and negative symptoms such as paresthesia and loss of function. This enables us to understand the underlying disease or lesion.[15]

Table 3: Conditions and the drug of choice

Disorder	Clinical features	Drug of choice
Trigeminal neuralgia	Paroxysmal attacks of electric shock-like pain along the course of trigeminal nerve lasting for few second to minutes. Pain is aggravated from trigger areas by certain activities such as shaving, washing face, and brushing[3]	First line: Carbamazepaine, oxcarbazepine Second line: Lamotrigine, baclofen Third line: Gabapentin, pregabalin, amitriptyline, duloxetine or venlafaxine[34,35]
PHN	HZ is unilateral, does not cross the midline, and is localized to a single dermatome of a single sensory ganglion. In orofacial region, it affects the trigeminal nerve. Chracterized by prodromal symptoms followed by distribution of rashes along the nerve course[39]	First line: Amitriptyline or nortriptyline, pregabalin, and gabapentin along with topical lidocaine (5% paste) Second line: Topical capsaicin (0.025%) Third line: Baclofen or tramadol, memantine, lorazepam[36-38]
Central pain	Constant, spontaneous, lancinating pain, may be associated with pruritis caused due to nerve injury[40]	First line: Amitriptyline and nortriptyline, pregabalin, or gabapentin Second and third line: Lamotrigine, tramadol, or opiods (morphine/fentanyl)[35,36]
HIV neuropathy	Distal sensory neuropathy due to demylination of peripheral fibers results in severe neuropathic pain[41]	First line: Amitriptyline or nortriptyline and pregabalin or gabapentin along with serotonin reuptake drugs duloxetine or venlafaxine Second line: Tramadol or tramadol with paracetamol Third line: Lamotrigine or topical capsaicin[35-37]
Oncologic neuropathic pain	It occurs due to tumor invasion, infiltration, or abnormality in protein processing due to chemotheryapy or radiation therapy[42]	First line: Tricyclic antidepressants and anticonvulsants Second line: Tramadol and opioids Third line: Selective serotonin reuptake inhibitors[35,37,38]

PHN: Post-herpetic neuralgia

Table 4: Drugs and dosage for neuropathic pain

Drugs	Dosage	Duration	Adverse effects	Evidence
Tricyclic anti-depressant[43-47]				
Amitriptyline Imipramine Nortriptyline	25–150 mg/day, titrated weekly by 10 mg/day from 25 mg/day	6-8 weeks	Sedation, confusion, anxiety, anticholinergic effects such as dry mouth, increased intraocular pressure, constipation, urinary retention, orthostatic hypotension	Rowbatham *et al*. (2005) - A parallel group study Chandra *et al*. (2006) - RCT with GPT
Serotonin-norepinephrine reuptake inhibitors[48-50]				
Duloxetine	30–120 mg/day titrated weekly by 30 mg/day from 30 mg/day	4 weeks	Asthenia, fatigue, nausea, vomiting, dry mouth, sedation, drowsiness, tremors. Its use is limited in patients with renal, hepatic and cardiovascular dysfunction	Ruskin *et al*. (2005) Wernick *et al*. (2006) Parallel-group RCTs
Venlafaxine	37.5–225 mg/day titrated weekly by 37.5 mg/day from 37.5 mg/day	4-6 weeks		Kadiroglu *et al.* (2008) - RCT
Anticonvulsant[33,38,45,51,52]				
Gabapentin	300–3600 mg/day titrated weekly by 300 mg from 300 mg/day	3-8 weeks	Fatigue, drowsiness, dizziness, hyponatremia. Special precautions with cardiac problems, hepatic and renal failure is necessary	Wiffen *et al*. (2006) - RCT with placebo
Pregabalin	150-600 mg/day titrate by 50 mg/day from150 mg/day	4 weeks		Vanseventel *et al*. (2006), Sidal *et al*. (2006), Vranken *et al*. (2009) - RCT with placebo
Carbamazepine	100-1200 mg/day titrated by 100 mg/day from 100 mg/day	4 weeks		Cruccu *et al*. (2008) Gronseth *et al*. (2006) - SR with 12 RCTs
Oxcarbazepine	300-1800 mg/day	4 weeks		Grosskopf *et al*. (2006) Parallel-group study with Placebo
Topical Anesthetic[53-55]				
Lidocaine	3 plasters /day	3 weeks		Frank *et al*. (2009)- Cross over study Silver *et al*. (2007)-parallel group study Ho *et al*. (2008) - Crossover study
Opioids[56-58]				
Morphine	30-120mg / day titrated by increasing 5 mg every 3 days from 15 mg/day 12 h	4-6 weeks	Constipation, vomiting, nausea, dizziness, drowsiness, headache, dry mouth, Abuse, addiction, withdrawal syndrome and suicidal tendency are the risks.	Raja *et al*. (2002) - Crossover study Edward *et al*. (2006)- Crossover study
Fentanyl	25-100 micro g/h	4 weeks		
Oxycodone	20–60 mg/day	4 weeks		Gimbel *et al*. (2003), Jensen *et al*. (2005), Hanna *et al*. (2008) - RCT with placebo
Others				
Capsaicin[59-61]	0.025%	4 weeks	Skin rash, erythema, burning sensation	Backonja *et al*. (2008)-RCT
Cannadidiols[62]	1-2 sprays every 4 h maximum 4 sprays on day one and titrated gradually	4-6 weeks		Nurmiko *et al*. (2010) - RCT

Screening and Assessment Tools

These tools are used to distinguish neuropathic pain and non-neuropathic pain.

The McGill pain questionnaire describes the quality and characteristic of pain. The descriptors fall into four major groups, sensory, affective, effective, and miscellaneous. It have 102 descriptive words under these 4 categories along with these pain rating index is also recorded which is the sum of the rank value of the scoring given in the above 4 categories. It also includes present pain index based on a scale of 0–5. Although it gives a detailed description on the characteristics of pain, it is not widely used as it lacks specificity, it is time-consuming, and it has a language barrier.[16,17]

Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale enables differentiating neuropathic pain from non-

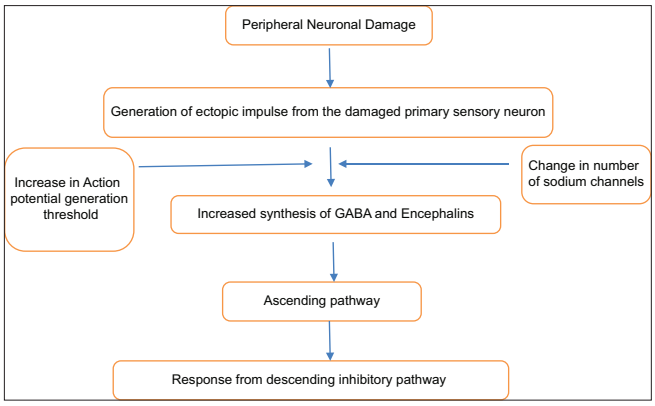

Figure 1: Pathophysiological interaction

neuropathic Pain. It has five symptom item and two clinical examination item. The score lies between 0 and 24 if its below and if its above 12 it is considered as neuropathic pain. It was modified, and later, modified with five items related to the quality of pain as self-reported scale S-LANSS. This has high sensitivity and specificity and is commonly used in epidemiology studies in general population.[18,19]

The neuropathic pain questionnaire (NPQ) is another questionnaire with 12 items (10 sensory and 2 affective), and it helps describe pain but does not reveal the etiology. A modification of this NPQ short forms with 3 items with discriminative properties to differentiate between neuropathic pain and non-neuropathic pain.[19,20]

The douleur neuropathique 4 questions have 7 items related to symptoms and 3 related to clinical examination. The 7 symptoms can be used as self-reported questionnaire also. Each question is graded with 1 point if positive, and hence, the total score ranges between 0 and 10, if the score is more than 4, it is categorized as neuropathic pain.[21,22]

Pain detect questionnaire is again a self-reported questionnaire with 9 items. It pain has 5 sensory descriptors used in joint pain as it specifically has one item to whether pain is located in joints.[14,15]

Pain quality assessment scale is a self-reported tool. It has 20 descriptors each graded from 0 to 10, and the sum total tells the intensity of pain.[23]

In the neuropathic pain symptom inventory, it has 12 items, 10 symptom descriptors, and 2 items to evaluate spontaneous and paroxysmal spontaneous pain. Each parameter is graded from 0 to 10, and the sum total describes the intensity of pain.[24]

Neurophysiology

Eliciting the neurophysiology in neuropathic pain would be of great value in diagnosing and managing the disease. Though not widely accepted and practiced nerve conduction studies can help us elicit the intensity of pain. This includes microneurography, recording pain related reflex and functional neuroimaging.[15]

Microneurography

Is a minimally invasive technique in which single axon recordings from peripheral nerve is done on subjects when they are awake. It provides valuable information on physiology and pathophysiology of all nerve fiber group.[25-28]

Pain-related Reflexes

Pain related reflexes are diagnostically useful tool for facial pain. Early R1 blink reflex and early SP1 masseter inhibitory reflex effectively reveal symptomatic forms of Trigeminal Neuralgia. The early R1 blink reflex is positive in ophthalmic post-herpetic neuralgia (PHN) as well. Nociceptive blink reflex was delayed in patients with atypical odontalgia.[15]

Functional Neuroimaging

Positron emission tomography and functional magnetic resonance imaging measure cerebral blood flow (rCBF) or metabolic activity of the brain. In unilateral spontaneous neuropathic pain, there is decreased resting rCBF in contralateral thalamus. Thalamic hypoperfusion may be a marker of neuropathic and restoration of thalamic blood flow for treatment monitoring. However, there is no sufficient data to declare it.[29,30]

Skin Biopsy

A punch biopsy of skin in the painful areas allows immunostaining and visualization of the intradermal terminals of A delta and C to measure intraepidermal nerve fiber density (IENFD). In Post Herpetic Neuralgia IENFD of the affected site shows lower density than the contralateral mirror image skin. The allodynia is due to surviving irritable nociceptors. In complex regional pain syndrome, there are quantitative and qualitative changes in skin innervation.[31,32]

Management of Neuropathic Disorder

Neuropathic pain cannot be considered as a disease but is an effect of underlying clinical conditions. An injury or damage in the nervous system causes neuropathic pain, and hence, a proper understanding of the underlying cause helps us to diagnose and manage the disease better [Table 4]. Frequent reassessment is also required to provide an effective therapy to the patient. The therapeutic guidelines provided in Tables 3 and 4 are based on a review of guidelines on the management of neuropathic pain.

Conclusion

Neuropathic pain management is not only just management of the disease but also management of symptoms alone. The management of neuropathic pain starts from assessing the pain itself. To choose a suitable medicine for an individual patient, we should analyze the clinical condition, select management options wisely, determine the dosage required, check for any comorbities condition, monitor the

outcome, reassess the condition ,and do necessary modification in the drugs prescribed and the dosage if required.

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