Neuropathic Pain

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Introduction

The incidence of neuropathic pain has been put at 20% of all patients visiting pain clinics.[1] The prevalence of neuropathic pain is not at all clear and this can be attributed to the fact that terminology defining the disease is very uncertain.

Neuropathic pain conditions are not at all a new entity. The first cases have been described in the 19th century. However, only recently has the interest in this unique pain condition arisen.

Definition of Pain

The Taxonomy Committee of the IASP (International Association for the Study of Pain) adopted the following definition for pain:[2]

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Pain is always subjective.

Classification

Pain can be classified in many different classes. However, for the purpose of this discussion, pain will be divided into two main groups:

a. Nociceptive pain
b. Neuropathic pain

Nociceptive pain:

Under normal circumstances pain is an appropriate physiologic response when a stimulus is applied to the receptor (for pain). The stimuli are mechanical, thermal or chemical. The conduction pathway of these impulses is intact and no damage has occurred to the pathway. Conduction usually occurs through the Ad nervous system.

Pain initiated in this manner is called nociceptive pain and can be effectively treated by analgesics such as NSAID's, opioids or neural blockade.

Neuropathic pain

A primary lesion in the periphery initiates pain but a dysfunction occurs either in the periphery or in the central nervous system. There is definite damage to the pathway conducting impulses. This is the cause of neuropathic pain. The sites of damage can be in the primary axon (e.g. cut nerve, the dorsal root ganglion or in the dorsal root.) The conduction of these impulses is usually by the c-fibre nervous system. This is also classified as chronic pain.

In these cases pain persists beyond the usual healing phase, or pain may result from the progressive or sustained tissue damage. Changes in the nervous system itself may present without evidence of any tissue damage.

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Complexity

Neuropathic pain is highly complex. Many factors contribute to the complexity of the condition.

1. Very often each neuropathic pain syndrome is associated with totally different clinical symptoms.
2. Often patients suffering from exactly the same neuropathic pain condition will respond differently to exactly the same treatment regime.
3. Because of unclear terminology, there is no uniformity and consistency to describe this condition.

Descriptions of Pain

The terminology by patients for neuropathic pain is widespread. Many words describing the pain have been used but the most commonly used ones are:

* Burning
* Lancinating
* Shooting
* Constricting

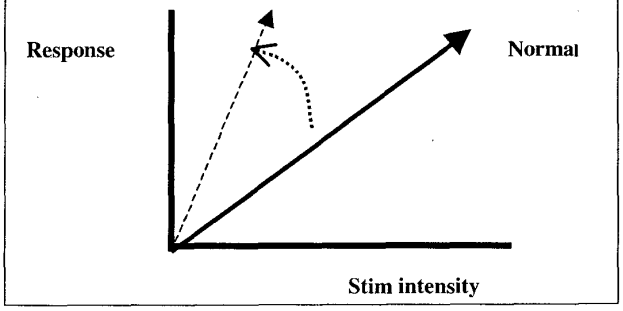
Neurological response

Neuropathic pain is associated with many neurological sequelae e.g.

* Paraesthesias
* Dysaesthesias
* Sensory loss
* Motor deficit
* Hyperalgesia
* Allodynia

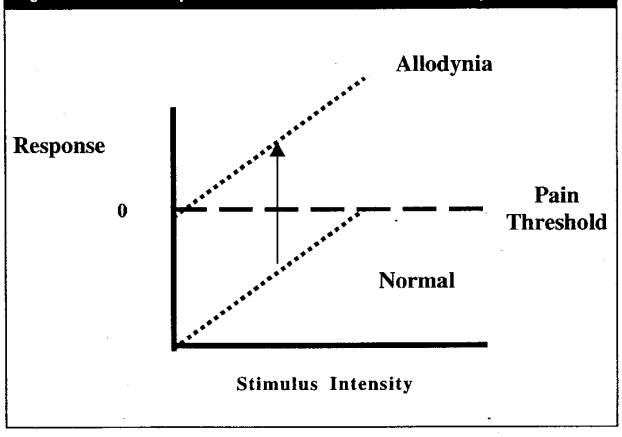
The two most important findings with the total picture of neuropathic pain are hyperalgesia and allodynia (Fig 1).[3]

Figure 1: Relationship between normal stimuli and hyperalgesia



This means that with lesser stimulus intensity the response is increased; also it means that the response on a painful stimulus is exaggerated to such an extent that it becomes unbearable for the patient.

Figure2: Relationship between normal stimuli and allodynia



This means that a usual non-painful stimulus is interpreted as pain i.e. touch of a finger on the painful area will be very painful.[4]

Etiology[5]

1. Trauma

Trauma is the main cause of this serious condition. Trauma may be serious or very mild e.g. a slight sprain of the ankle.

The neuropathic pain conditions arising from trauma may be the following:

* CRPS Type II (Complete regional pain syndrome)
* Phantom limb pain
* Spinal cord injury
* Post surgery
  - laminectomy
  - spinal fusion
  - general surgery

2. Ischaemic incident

* Central pain – post-stroke
* Thalamic pain
* Multiple sclerosis[6]

3. Metabolic Disease

* Painful diabetic neuropathy

4. Infections

* Post herpetic neuralgia
* HIV (Human Immuno Virus)

5. Cancer

* Invasion of neural tissue
* Compression of neural tissue

6. Vertebral disease (as such)

* Disc prolapse with compression

7. Other

* Atypical trigeminal neuralgia

Pathophysiology

a. Localizing the pain

When trying to identify the location of the pain, it is important to distinguish between certain patterns consistent with nerve damage. Thus, the pain may be described in terms of:

i. distribution of a single nerve or nerve root = radicular
ii. distribution of multiple nerve roots = polyradicular
iii. a large region such as that innervated by a damaged central pathway
iv. asymmetrical pain extremities[7]

b. Peripheral sensitization

After continuous stimulation of the peripheral nociceptor a situation may arise in which the dorsal horn of the spinal cord becomes hyperexitable and transforms into the situation of "wind-up".

c. Central Sensitization

Certain changes occur in the central nervous system and cause an over-activity in the dorsal horn. Neurotransmitters like substance P (sP) act on the post-synaptic neurokinin-1 (NK-1) receptors at the end of the C-fibres in the dorsal horn. This triggers intracellular calcium (Ca^{++}) release and this then upregulates the N-methyl-D-asparate (NMDA-receptors). Therefore, continuous C-fibre firing will release a larger amount of neurotransmitter and the magnesium (Mg^{++}) -ions, that normally plug the NMDA-receptors, are removed and the Ca^{++}-ions enter the receptor freely. The dorsal horn neurone will be depolarized and sensitized (i.e. wind-up). The prolonged depolarization activates the NMDA-receptor and the massive influx of Ca^{++}-ions causes the cascade of reactions within the wide dynamic range (WDR)-cell; this is called "Central sensitization".

Due to the fact that the dorsal horn neurones are altered, their response to subsequent input will be modified e.g. neurones now respond to Ab-fibre input in a distorted manner so that normally innocuous stimuli are now perceived as pain. This is allodynia.

One of the most important reactions that occur in the WDR-cells is the sprouting that takes place. [8] This means that Ab fibres grow into lamina II (which usually only receives C-fibre innervation) from laminae III, IV and V. [9] The trigger for this sprouting is believed to be damage to C-fibres but lately it has been found that nerve growth factor (NGF), neurotropins, and certain neuropeptides released by injured C-fibres may also play a role in this phenomenon. [10]

At the same time, the retrograde pain control mechanism (through the release of nor-adrenaline and serotonin), is down regulated. The normal inhibitory reaction at spinal level after a nocious stimlus is mediated by the release of gamma amino butyric acid (GABA) and glycine. After serious peripheral nerve injury it is thought that the inhibitory neurones in the spinal cord are reduced and that GABA and opioid receptors are down-regulated. It was also shown that the GABA and glycine concentrations were reduced after experimental peripheral nerve injury. [11]

Thus allodynia may arise from:

* Central sensitization
* Central reorganization of Ab-fibres
* Loss of inhibitory control

Diagnosis

History and physical examination are still the mainstay of the diagnosis. The testing of hyperalgesia, allodynia and temperature differences is of utmost importance.

Special tests like electromyography (EMG) and nerve conduction studies are standard techniques and widely available. Certain centers also use thermography to distinguish between the temperatures of two extremities.

Very often the applied treatments also serve as a diagnostic tool e.g. sympathetic blocks.

Treatment

1. Goal of treatment

In treating these unfortunate patients, one must try and achieve the following:

* Cure the orginal cause of the neuropathic pain
* Permanent or temporary analgesia
* Change the way the patient copes with his/her pain or modify the patient's perception of pain

2. Psychosocial evaluation

Patients with severe, advanced neuropathic pain should

* Undergo psychosocial evaluation to establish
* A family support system
* Active coping strategies
* Undergo an MMPI (Minnesota Multiphasic Personality Inventory) test by a psychologist to establish the emotional condition of the patient
* Undergo relaxational & stress handling techniques by an occupational therapist.

3. Pharmacologic treatment

* If "Shotgun Therapy" is applied, it will be impossible to evaluate the efficacy of treatment and is thus under these circumstances wrong.
* Prescribed medication should be according to the characteristics of the circumstances whether it is;
  constant pain,
  pain causing sleep disturbances,
  pain with an inflammatory component,
  pain with spontaneous jabs,
  sympathetically maintained pain,
  pain with muscle cramps or spasms.
* It is usually under these circumstances that "off-labeling" prescribing takes place.
* There is no specific cure for "hyperalgesia". One must try and prevent peripheral sensitization by blocking the peripheral "soup" formation before the process begins e.g. COX-2 inhibitors.
* If the process has started already, use Na^+-blocking agents e.g. mexilitene.

Problems of Neuropathic Pain	
* Extreme pain	* Improper treatments
- Lifelong for some	* Multiple operations
* Family disruption	- Unsuccessful
- Sorrow for loved-one	* Loss of quality of life
* Disability	* Increased Health costs
* Unemployment	* Misdiagnosis
	- Disbelief from doctors
	- Medical aids

Treatment of choice

a. Amitriptyline [12]

* First generation TAD (tricyclic antidepressant)
* Important in the retrograde control of pain
* Increases nor-adrenaline and serotonin
* Low doses: 10 – 25 mg nocte

b. Anti-convulsants

* Carbamazepine
* Old drug [13] still used effectively but
* Fairly high rate of side-effects
* Start with low dose, gradually increase
* Maintenance of ± 900 mg / day

c. Gabapentin (Neurontin) [14, 15]

* This is the drug of choice
* It is an anticonvulsant, developed in 1994, now used exclusively for neuropathic pain
* Related to GABA
* Mechanism of action is not fully understood
* It increases the concentration and rate of synthesis of GABA in the brain
* Gabapentin binds to the $\alpha_2\delta$ subunit of the Ca^{++} channel
* It interacts with L-amino acid transporter
* It inhibits voltage activated sodium channels
* It also causes an alteration of neurotransmitter release and of serotonin blood levels
* Gabapentin has been shown to effectively alleviate allodynia in patients with neuropathic pain.[16]

d. Opioids

* Not effective against severe neuropathic pain, however, may be used early with injury to prevent possible transition of acute to chronic pain

4. Sympathetic blocks

There are three reasons for doing these blocks:-

* To provide cure or partial remission if this is a sympathetically maintained pain
* To gain further diagnostic information
* To provide prognostic information

However, if the blocks are not properly performed it is time and money wasted both for patient and physician and all the diagnostic-prognostic value will be lost.

5. Regional blocks

These are extremely important treatment methods. When applying these blocks one can actually try and reverse the process of "wind-up" that occurs in the central nervous system.

Blocks performed are

* Local nerve blocks
* Plexus blocks
* Stellate ganglion
* Lumbar plexus
* Brachial plexus
* Epidural blocks
* With or with-out catheters
* IVRA (Intravenous Regional Analgesia) with guanethidine (not very popular; but still effective)

6. *Other Methods*
* Trans electrical nerve stimulation (TENS)
* Although not very popular
* It is still used by some
* Spinal Cord Stimulation
* Very popular in the USA

Take home message

* Believe the patient's pain
* Even if you see very little clinically
* There is major emotional involvement for both patient & spouse (take this away and improve the situation)
* Extreme burden on the family
* Patient is out of work
* May be the only bread winner
* Finances are poor
* Patient & family extremely worried!

Conclusion

In the past neuropathic pain patients suffered from treatment that was less than optimal.

"In the future therapy will be more symptom-orientated than disease-orientated. Treatment options will most likely be designed to fit the specific symptom picture of a patient."
Jordi Serra; Acta Neurologica Scandinavica. 1999

Physicians should adapt to this concept of treating the specific symptoms instead of the disease.

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