“NEUROPATHIC PAIN”

An Essay
Submitted for Partial Fulfillment
of Master Degree (M.Sc)
in

Anaesthesia

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2009

ACKNOWLEDGMENT

First and Foremost, I would like to express my gratitude to my family for their care and support in completing this essay.

I am deeply indebted to ***Prof. Dr. Magdv Ramzy Iskander****, Professor and Head of the Anaestheisology, ICU and Algology department, National Cancer Institute, Cairo University. I would like to thank him for always teaching, guiding, supporting and helping me through many aspects of my medical career.*

I would also like to express my deepest gratitude to ***Prof. Dr. Ashraf Monir Amin Salama,*** *Professor of Anaesthesiology, Faculty of Medicine, Cairo University for his endless patience, support and guidance all through the work.*

A very special word of thanks must be made to ***Ass. Prof.Dr. Gomaa Zohry,*** *Assistant Professor of Anaesthesiology, Faculty of Medicine, Cairo University.*

I would like to dedicate this work to my father, ***Dr. Hussein Sayed Mohamed Said****, and to my friend and brother* ***Dr. El-Moataz Billah Maged Bahgat, MAY GOD BLESS THEIR SOULS.***

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List of Abbreviations

- **AIDP:** Acute inflammatory demyelinating neuropathy
- **AMPA**: α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
- **BBB:** Blood brain barrier
- **CGRP:** Calcitonin gene-related peptide
- **CIDP:** Chronic inflammatory demyelinating neuropathy
- **CIPN:** Chemotherapy induced peripheral neuropathy
- **CNS:** Central nervous system
- **CRPS:** Complex Regional Pain Syndrome
- **DMPP:** Descending modulatory pain pathways
- **DRG:** Dorsal root ganglion
- **EFNS:** European Federation of Neurological Societies
- **EMG:** Electromyography
- **EMS**: Electrical muscle stimulation
- **GABA**: gamma amino butyric acid
- **GIRK:** G protein–coupled inwardly rectifying potassium channel
- **HRDB:** Heart Rate Response to Deep Breathing

- **IASP:** International assosciation of Study of Pain
- **IENF:** Intra-epidermal nerve fibres
- **LANSS:** Leeds Assessment of Neuropathic Symptoms and Signs
- **LEPs:** Laser-evoked potentials
- **LTP:** Long term potentiation
- **MPQ:** McGill Pain Questionaire
- **NCS:** Nerve conduction study
- **NDHN:** Nociceptive dorsal horn neurones
- **NE**: Norepinepherine
- **NK**: Neurokinin
- **NMDA**: N-methyl-D-aspartic acid
- **NP:** Neuropathic Pain
- **NPS**: Neuropathic pain scale
- **NRM**: Nucleus raphe magnus
- **PAG***:* Periaqueductal grey matter
- **PDN:** Peripheral Diabetic neuropathy
- **PHN:** Post-herpetic neuralgia
- **PNS:** Peripheral nervous system
- **QSART:** Quantitative Sudomotor Axon Reflex Test
- **QST:** Quantitative sensory testing

- **RCTs:** randomized controlled trials
- **RF:** Radiofrequency
- **RSD**: Reflex Sympathetic Dystrophy
- **SCS:** Spinal cord Stimulation
- **SEPs:** Somatosensory-evoked potentials
- **SIP:** Sympathetically independent pain
- **SMP:** Sympathetically maintained pain
- **sP:** Substance P.
- **SSNRIs**: Selective serotonin and norepinephrine reuptake inhibitors
- **SSRIs:** Selective serotonin reuptake inhibitors
- **TCA:** Tri-cyclic anti-depressants
- **TENS**: Transcutaneous electrical nerve stimulation
- **VAS**: Visual Analog Scale
- **VDS:** Verbal Descriptor Scales
- **VMM**: Ventromedian medulla
- **VSCC:** Voltage-sensitive calcium channel;
- **WDR :** Wide Dynamic Range (cell)

INTRODUCTION

DEFINITIONS:

The following pain terminology will help in making this review more comprehensible. (**International Association for Study of Pain guidelines, Pain terminology 2008, www.iasp-pain.org**)

PAIN TERMS

Nociceptor

A receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.

Noxious Stimulus

A noxious stimulus is one which is damaging to normal tissues.

Allodynia

Pain due to a stimulus which does not normally provoke pain. (pain induced by non-noxious stimuli, *e.g.* the gentle touch of clothes or the bending of a cutaneous hair by a puff of wind.) **Note:** The term allodynia was originally introduced to separate from hyperalgesia and hyperesthesia, the conditions seen in patients with lesions of the nervous system where touch, light pressure, or moderate cold or warmth evoke pain when applied to apparently normal skin. Allo means "other" in Greek and is a common prefix for medical conditions that diverge from the expected. Odynia is derived from the Greek word "odune" or "odyne," which means “pain from a specified organ or part of the body. Examples where it is also used include:

"pleurodynia" and "coccydynia" **(Backonja MM. 2003)**

Hyperalgesia

An increased response to a stimulus which is normally painful. **Note:** Hyperalgesia reflects increased pain on suprathreshold stimulation. For pain evoked by stimuli that usually are not painful, the term allodynia is preferred, while hyperalgesia is more appropriately used for cases with an increased response at a normal threshold, or at an increased threshold, e.g., in patients with neuropathy.

Hyperpathia

A painful syndrome characterized by an abnormally exaggerated reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. (Exaggerated responses to painful stimuli, with continuing sensation of pain after the stimulation has ceased)

Neuropathic Pain

Pain initiated or caused by a primary lesion or dysfunction in the nervous system. **Note:** Peripheral neuropathic pain occurs when the lesion or dysfunction affects the peripheral nervous system. Central pain may be retained as the term when the lesion or dysfunction affects the central nervous system.

Central Pain

Pain initiated or caused by a primary lesion or dysfunction in the central nervous system.

Dysesthesia

An unpleasant abnormal sensation, whether spontaneous or evoked.

Hyperesthesia

Increased sensitivity to stimulation. Hyperesthesia includes both allodynia and hyperalgesia, but the more specific terms should be used wherever they are applicable.

(Backonja MM. et al. 2005)

Hypoalgesia

Diminished pain in response to a normally painful stimulus.

Hypoesthesia

Decreased sensitivity to stimulation, excluding the special senses.

Causalgia

A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes.

Complex Regional Pain Syndrome (CRPS)

It is also known as Reflex Sympathetic Dystrophy (RSD), which is a chronic neurological syndrome characterized by:

- Severe burning pain extreme sensitivity to touch
- Pathological changes in bone and skin
- Excessive sweating and tissue swelling **(Perez RSGM et al. 2001.)**

CRPS - Type I and Type II

- CRPS Type I (also referred to as RSD) - cases in which the nerve injury cannot be immediately identified
- CRPS Type II (also referred to as Causalgia) - cases in which a distinct "major" nerve injury has occurred
- CRPS is best described in terms of an injury to a nerve or soft tissue (e.g. broken bone) that does not follow the normal healing path
- CRPS development does not appear to depend on the magnitude of the injury. The sympathetic nervous system seems to assume an abnormal function after an injury. **(Janig WF et al. 1996.)**

Classification of Pain

Table 1: **(Zimmerman et al. 2001)**

Pain is classified according to:
Time
--Acute or chronic pain
Etiology
--Malignant or nonmalignant
Physiological mechanism
--Nociceptive --Neuropathic

Table 2: **(Carole T. et al 2005)**

Acute vs. Chronic Pain

Acute Pain		**Chronic Pain**	
•	Short duration	•	Long duration (>six months)
•	Identifiable pathology	•	Pathology may be unclear
•	Predictable prognosis	•	Unpredictable prognosis
•	Treatment typically with analgesics	•	Treatment needs to be multidisciplinary

Physiological Classifications

Nociceptive

--Somatic

--Visceral

Neuropathic

--Results from irritation or damage to the nervous tissue

Nociceptive pain is divided into somatic, and visceral. Nociceptive pain is detected by specialized transducers attached to A-delta and C fibers. Neuropathic pain results from irritation or damage to the nervous system. Visceral pain is diffused, poorly localized, and often referred. **(Zieglgansberger W. et al 2005)**

Patients and their physicians are familiar with acute pain or pain caused by injury. The term, nociceptive pain, is applied when pain is perceived to be in relation to tissue damage associated with an identifiable somatic or visceral lesion. The pain is presumed to be related to ongoing activation of primary afferent neurons responsive to noxious stimuli (nociceptors). Researchers have long since appreciated that, in the presence of injury, nociceptors may become hyper excitable. **(Gilron I. et al. 2006)**When comparing acute to chronic pain, less is known about the etiology of chronic pain. Chronic pain often occurs in the absence of ongoing illness or after healing is completed. A fundamental difference between inflammatory pain with tissue hypersensitivity and neuropathic pain is that in the former, the pain is relieved when inflammation has resolved; and in the latter, it may persist after healing of the primary event. In summary, nociceptive pain is greatly relieved when healing is complete, while neuropathic pain persists. **(Jain KK. et al. 2008)**

Neuropathic pain has variable characteristics. It may mimic the quality of somatic pain, but it is also frequently described as being continuous burning, shock-like or paresthetic. Neuropathic pain syndromes may be associated with referred pain, spontaneous pain (which is characteristically burning or shooting in nature), allodynia, hyperalgesia, or hyperpathia. It may or may not have a paroxysmal element. Spontaneous pain may be conceptualized as “stimulus independent” while hyperalgesia and allodynia are perceived as “stimulus dependent” pain. **(Ossipov MH et al. 2001)**

Neuropathic pain syndromes can be subclassified according to broad sets of speculated mechanisms. Some neuropathic pain syndromes are presumed

to involve a predominating peripheral generator (*e.g.*, compressive or entrapment neuropathies, plexopathies (which is a disturbance of nerve plexuses), radiculopathies and polyneuropathies). Other syndromes appear to depend on processes that predominantly reside in the spinal cord, brain or both (*e.g.*, pain due to spinal cord injury or post-stroke pain), hence making it possible to classify neuropathic pain into central and peripheral neuropathic pain syndromes. **(Baron R. 2000)**

Focusing on symptoms and etiology has not provided a suitable model for understanding or intervention. However, an extensive range of mechanisms, which operate at the peripheral, spinal cord and supraspinal levels with supporting symptoms are now being described. **(Farquhar-Smith 2007)** No particular injury or disease process is associated with a unique pain mechanism, and many different mechanisms may produce the same symptom. In any given patient suffering neuropathic pain, a number of mechanisms are usually operating at the same time, and they usually change over time. Knowledge of these mechanisms is helpful. They explain how pain can be felt when there is no activity and how activity may make pain worse. They explain how pain can be triggered by the slightest touch, how pain can spread beyond the site of trauma and, with the change of mechanisms over time, how one agent may be useful at one time but become frustratingly useless later on. These mechanisms give a better understanding of the mode of action of some of our rudimentary interventions. **(McCaffery et al. 1999)**

It has been recently found that neuropathic changes may be associated not only with direct trauma to neural tissue, but also with continuous or severe nociceptive (pain) input from inflammatory lesions. **(Taylor B. 2001)**