PAINFUL PERIPHERAL NEUROPATHIES AND NEURALGIAS

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Neuropathy

• Damage to the peripheral nerves

• May be ‘painful’ or ‘painless’

• Paradox of impaired function with enhanced sensitivity
Neuralgias

Painful conditions caused by damage to specific nerve or nerves
Neuralgias

- Post herpetic neuralgia
- Trigeminal neuralgia
- Post traumatic/surgical
- Demyelination disease
- Entrapment
Neuritis

- Inflammation of nerve or PNS
Polyneuropathies

Motor neuron disease

Demyelinating Polyneuropathy

Distal axonopathy
eg. DM neuropathy
Painless Polyneuropathies

• Freidreich’s ataxia
• Chronic renal failure neuropathy
• Hereditary sensory and autonomic neuropathy
• Tangier disease (α-lipoprotein deficiency)
Painful Peripheral Neuropathies

PPN
Painful Peripheral Polyneuropathies

• Metabolic – Diabetes
• Inflammatory – Guillaine Barre
• Demyelination – MS
• Connective tissue – SLE
• Arteriopathy
• Vitamin deficiency
• RSI
Painful Peripheral Neuropathies

- Neuropathy - damage or loss of fibres in the peripheral nervous system
- Heterogenous group of conditions
- Stimulus independent chronic pain
- Stimulus dependent hyperalgesia
Loss of Nerve Fibres in PPN
Terminology in PPN

- Neuropathic pain
- Peripheral neuropathy
- Painful peripheral neuropathy
- Neuralgia
Terminology in PPN

- Neuropathic pain
- Neuralgia
- Peripheral neuropathy

PPN
Epidemiology of PPN

- Prevalence – 5% peripheral neuropathies in general population increasing with age. Only a minority of peripheral neuropathies experience chronic pain.

- Prevalence in diabetics – between 10% and 20%
Pathology in PPN
Pathophysiological Features of PPN

- Rapid degenerative changes
- Presence of inflammatory changes
- Coexistence of degenerative and regenerative changes
- Ischaemia – as in vasculitides
- Excitation of the ‘nervi nervorum’
Nerve Fibre Injury in PPN

- PPN often involve axonal injury in small nociceptive fibres
- Large fibres may or may not be involved
- Severe loss of small sensory fibres may be *painless*
- Selective involvement of motor or autonomic fibres are *painless*
Complete and Incomplete Lesions

- Stimulus Independent – ‘unprovoked’ pain symptoms complete disconnection between peripheral nerves and target tissue. ‘Deafferentation syndrome’
- Stimulus induced – ‘provoked’ pain symptoms where partial connection is retained
Pain in PPN
PARADOX OF PPN

Impairment or loss of nerve fibres carrying nociceptive information should result in a decrease in pain sensitivity.
Pain in PPN

- Stimulus independent on-going pain
- Stimulus dependent hyperalgesia
- Co-morbidities-sleep impairment, depression, anxiety
- Symmetrical or asymmetrical mono/oligo neuropathies
Pathological changes in PPN
DH connections

A

Spinal cord dorsal horn

Aδ/Aβ

C
Changes due to Peripheral Nerve Injury

- Nerve injury produces phenotypical changes in DRG neurones
- DRG neurone changes result in sensitisation at the primary synapse
- Also architectural changes in DH
Pathological changes in PPN
Changes due to Peripheral Nerve Injury
Changes due to Peripheral Nerve Injury

• Down regulation of Substance P production in DRG neurones – attenuation of excitation in DH

• Up regulation of trophic factors stimulates sprouting of deep DH neurones into Laminae I and II
Changes due to Peripheral Nerve Injury
DH - Laminae

Descending
(Inhibition & excitation)
PAG / Raphe / LC / reticulospinal / corticospinal

Intrinsic interneurons

Primary afferent
Aδ fibre
high t/h mechanical/thermal/chemical polymodal/cold
D-hair

C-fibre
high t/h mechanical/thermal/chemical polymodal/silent warm

Aβ fibre
low t/h mechanical

Inputs

Outputs
Spinothalamic
Post-syn. dorsal column
Spinocervical
Spinocerebellar
Spinomesencephalic
Spinoreticular

Projection
Local circuit
To ventral horn
Intersegmental
Changes due to Peripheral Nerve Injury

- Due to axotomy or neuropathy
- Upregulation of neuropeptides, VIP, CGRP, NPY, galanin
- Upregulation of enzymes, NO synthetase
- Upregulation of receptors
Intracellular Events at DH Synapse
Changes due to Peripheral Nerve Injury

- Due to Inflammatory changes
- Upregulation of VIP and substance P, but not VIP or NPY in DRG
- Activation of neuromodulators such as endorphins in DH
DH Normal Transmission

Mode 1 — Normal Transmission

Innocuous or noxious stimulation

Afferent input

SP glutamate

AMPA

NK1

Postsynaptic output

Normal Sensibility
DH – Facilitated transmission

Increased excitation/reduced inhibition

- Afferent input
- Presynaptic augmentation
- Increased transmitter release
- Postsynaptic facilitation

- Presynaptic facilitation
- Increased transmitter release
- Postsynaptic activity

- Retrograde signals e.g. NO
- Reduced postsynaptic inhibition
- Reduced presynaptic inhibition
Changes due to Peripheral Nerve Injury

Some neurotrophic factors (e.g. GDNF and BDNF) may reverse the above changes and block the development of neuropathic pain states.
Changes due to Peripheral Nerve Injury

- The changes that occur in DRG phenotypes produce changes in the function of the primary synapse and the DH.

- The spectrum of peptide changes may result in neuropathic pain states, and differs according to the type of nerve damage.
CLINICAL PICTURE
Patient Descriptors

• Deep aching
• Burning
• Prickling
• Electric shocks
• Tingling
Hyperalgesia in PPN

- Most commonly reported is mechanical hyperalgesia
- Brush evoked, pinprick and blunt pressure are 3 commonly observed types of mechanical hyperalgesia
- Heat hyperalgesia commonly follows tissue damage
- Cold hyperalgesia often follows traumatic nerve injury
Pain Intensity in PPN

Magnitude of on-going pain intensity correlates with nociceptive activity

(Gracely et al 1992, Koltzenburg et al 1994)
Investigations in PPN

- Nerve conduction testing, evoked potentials, electromyography
- Nerve biopsy / skin biopsy
- MRI/CT scanning
- Quantitative somatosensory testing—heat and cold thresholds to differentiate myelinated and unmyelinated fibre function
Classification of PPN
Pain Mechanisms in PPN

• Demyelination and inflammation
• Selective destruction of nerve fibres in peripheral nerves
• Changes in membrane receptors
Classification of PPN

- Traumatic
- Mononeuropathies and multiple mononeuropathies
- Polyneuropathies - metabolic, drugs, toxins, hereditary, malignant, infective
Traumatic PPN

- Amputation
- Causalgia
- Entrapment
- Painful scars
- Morton’s neuralgia
- Neuroma
Mono/Multi-mono PPN

- Diabetic
- Connective tissue
- Shingles – PHN
- Trigeminal/Glossopharyngeal
- Vascular compression
Polyneuropathies PPN

- Alcoholic
- Amyloid
- Burning Feet
- Diabetic
- Beri Beri
- Pellagra
Drug/Toxin related PPN

- Antiretrovirals
- Ethambutol
- Isoniazid
- Nitrofurantoin
- Vincristine
- Arsenic
- Thallium
- Ethylene oxide
Hereditary PPN

- Fabry’s disease
- Charcot-Marie-Tooth (V2B)
- Hereditary sensory and autonomic
Infective/Post-infective PPN

- Borreliosis
- Guillaine-Barre
- HIV
Others

- Malignancy
- Myeloma
- Trench foot
- Idiopathic
Treatments in PPN
Management of PPN

- Blocks
- Physiotherapy
- Complementary therapies
- Pharmacotherapy
- Psychotherapy/CBT
- Occupational therapy
- Patient exercise program
Sympathetic Blocks in PPN

- Intravenous regional guanethidene (IVRG)
- Lumbar sympathetic
- Stellate gangliion
- Epidural
LA blockade in PPN

- Pain often abolished by LA blockade of damaged peripheral nerves
- Stimulus independent and stimulus dependent pain can persist during LA blockade even when myelinated non-nociceptive afferents are blocked
Drugs in PPN

- Gabapentin/Pregabalin
- Anticonvulsants
- Antidepressants
- NSAIDS
- Opioids
- Anxiolytics
Diabetic PPN

• Mononeuropathy – III cranial nerve is most common but no somatosensory fibres. Pain around/behind eye?
• Diabetic amyotrophy – painful proximal neuropathy
• Symmetrical polyneuropathy – burning feet with numbness and paraesthesiae
Diabetic PPN

- Drugs
- Lignocaine infusion
- ACP
- Injections
Post Herpetic Neuralgia
Post Herpetic Neuralgia

- Drugs
- Injections
- Lignocaine patch
Trigeminal neuralgia - Nerve Compression
Trigeminal Neuralgia

- Drugs
- RF/microdecompression Gasserian ganglion
- Surgery
Painful Scar / Entrapment
Painful Scar / Entrapment

Drugs
Injection
Ultrasound guided blocks/RF lesioning