Pain in Parkinson’s Disease

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Objectives

• Understand the prevalence of pain in parkinson’s
• Describe how it might present, precede onset of PD symptoms
• Describe proposed pathophysiology for pain in PD
• Understand the approach and treatment of PD pt’s w/parkinsons
Pain Prevalence

• Pain of any type is the most common reason for physician consultation in the United States, prompting half of all Americans to seek medical care annually.

(International Association for Pain Relief, 2005; Philip, 2007).
Pain Definition - IASP

• An unpleasant sensory and emotional experience associated with actual or potential physical damage
  – Multidimensional
Pain In Parkinson’s

- Do patient’s w/Parkinson’s disease experience pain?
- What type of pain?
- If so why?
  - Is it musculoskeletal?
  - Is it central?
Pain in Parkinson’s?

- Charcot > 100 years ago
  - Described Pain as a phenomena of Parkinson’s disease for greater than a century.
Pain Experienced by Patients with Parkinson’s

- Pain associated with Parkinson’s disease was not well described until Goetz and Tanner surveyed patients with Parkinson’s disease.
Goetz and Tanner

- Pt’s asked if they had pain that they felt was related directly to their Parkinson’s disease.
- Asked to describe the frequency, duration, character, severity, location and temporal qualities of the pain.
- The pain was classified by two neurologists into:
  - musculoskeletal (poorly localized, dull and aching)
  - dystonic (associated with dystonic movement)
  - Joint
  - radicular and neuritic (tingling localized to dermatomal or neuronal distribution)
  - thalamic (constant, boring and poorly localized)
• 46% directly related to Parkinson’s.
• The only identifying characteristic separating those with pain from those without was age.
  – Patients with pain were younger (62.3 vs. 68.2 years, p < 0.005).
• 74% reported muscle cramps or tightness, typically in the neck, paraspinal or calf muscles.
• 28% painful dystonias.
• 14% radicular or neuritic pain.
• 14% joint pain.
• 2% Diffuse generalized pain.
Goetz and Tanner

• Mean pain severity was 56 on a 100 point scale.
• Pain was associated with worsening of Parkinsonian symptoms in 89%.
• Musculoskeletal pains never occurred when disability was minimal.
• Radicular pain occurred equally at maximal and minimal disability.
• Because most pain was associated with worsening Parkinsonian disability
  – Authors suggested that pain is potentially controllable with antiparkinsonian medication adjustments

• 40% of patients with Parkinson’s disease reported either pain or burning.
• Most often poorly localized aching sensation in the limb most affected by Parkinson’s.
• Concluded: pain was directly related to the central nervous system dysfunction and not secondary to the peripheral motor manifestations of the disease.
Snider

• Goetz differed from Snider’s conclusion.
  – Felt it was a premature conclusion due to the high incidence of pain in the paraspinal muscles of the neck and back, which improved with ergonomic changes.

• They believed pains could be related to:
  – stooped posture
  – increased resting tone
• 450 PD pts → exam and questionnaire
  – 2/3 had chronic pain
    • 39.9% had chronic pain related to PD
    • 26% had pain unrelated to PD – mainly OA
  – Demographics
    • PD pain group – younger at PD onset, more motor complications, more severe depression
  – PD Pain – more severe (p = 0.03), but less frequently reported to MDs (p = 0.02), less freq analgesic consumption than non-PD pain
- 50 pts w/PD
  - 28 w/pain
    - No differences b/w group w/pain and one w/o
    - 57% had daily pain
    - Pain types:
      - Musculoskeletal - 50%
      - Dystonia - 21%
      - Radicular - 11%
      - Articular - 7%
      - Headache - 7%
29% showed improvement (p < 0.05)
  – Pre-medication NRS = 6.1 ± 1.8
  – Post-medication NRS = 3.3 ± 2.3
- UPDRS – no difference b/w groups except for pt’s w/pain had more difficulty walking (p = 0.00435)
Gender Differences

• Scott et al. - Questionnaire with 948 respondents asking about various aspects of their Parkinson’s disease
  – 38% Female, 62% male
  – No other significant demographic differences
Gender Differences

• Most common sx reported at onset of disease
  – Females rated neck pain 3rd behind tremor and writing (ahead of fumblingness, rigidity, fatigue and difficulties w/gait) vs. 7th for Men (p <0.01)
  – Low back pain was 7th for women (ahead of difficulties in gait) vs. 10th for men (p<0.01)
  – Females were significantly more annoyed by neck pain (p<0.001)
  – Females had more c/o calf pain (p<0.001)
Gender Differences

• Most common sx reported at present (at time of questionnaire)
  – Females rated neck pain 9\textsuperscript{th} (53.7\% reported) and low back pain 10\textsuperscript{th} (48.3\% reported)
  – Males rated neck pain 16\textsuperscript{th} (44.9\% reported) and low back pain (40.7\% reported)

• Presence of symptoms during the day
  – Neck pain 56.3\% rated this twice or more during the day
  – 82\% reported calf cramps at night
Gender Differences

• No difference b/w gender and duration of sx or duration of diagnosis or levodopa dose
• Females tend to be more annoyed by their symptoms, although most sx are less frequently reported by females

Why do patients with Parkinson’s Disease experience Pain?
Pain Etiology?

• Related to PD Symptoms
  – Muscle tremor
  – Rigidity
  – Postural changes imposed by rigidity
  – Dystonia
  – Dyskinesia
  – Motor fluctuation
  – Assoc to trauma from falls
  – Assoc w/gait and postural control difficulty
  – Akathesia (internal restlessness)

Broetz, et al., 2007; Bunting-Perry et al., 2010; Carr et al., 2003; Carroll et al., 2004; Ford, 1998; Loher, et al., 2002; Stacy et al., 2005; Wielinski et al., 2005
Potential Etiologies of a Central Pain Mechanism

• Postural - musculoskeletal
• Basal Ganglia
  – Substantia Nigra
• Central Dopamine
  – Brain
  – Spinal Cord
Sensory Threshold
Gerdelat-Mas. J Neurol Neurosurg Psychiatry 2007

• 13 PD pts w/o pain and 10 age matched controls
• PD pts evaluated during OFF and ON status
• Controls evaluated at baseline and after 200mg dose of levodopa to control for ON status
Sensory Threshold
Gerdelat-Mas. J Neurol Neurosurg Psychiatry 2007

• RIII reflex measured
  – Right sural nerve electrically stimulated
  – EMG measured over biceps femoris
  – Subjective rating given by patient via VAS

• PD pts
  – Lower RIII threshold in OFF
  – No difference in ON
  – Levodopa increased the RIII threshold
Conclusions:

1. Provided evidence of a dopaminergic modulation of objective pain threshold in PD patients.
2. The decrease in RIII threshold in PD patients, in the OFF condition, compared with controls, confirms the existence of a objective pain perception disturbance in PD.
Causes of PD Pain

• Fluctuations in pain severity due to dopaminergic medications such as Levodopa (Nebe & Ebersbach, 2009; Stacy et al., 2005)

• Loss of dopamine producing cells results in classic motor symptoms of PD (tremor, rigidity, and bradykinesia) and contributes to abnormal modulation of pain centrally by activation of spinal cord neurons, through dopaminergic descending pathways (Greco et al., 2008; Mylius et al., 2009)

• Individuals in the ON levadopa state reports less pain than those in the OFF levodopa state (Lim et al., 2008; Nebe & Ebersbach, 2009; Schestatsky et al., 2007)
Pathophysiologic explanation

- Musculoskeletal pain – postural or degenerative
- Neuropathic Pain - Abnormal transmission of pain in the peripheral or central nervous system
  - burning, numbness, tingling, touch sensitivity, sharp and shooting sensations or electric shocks
  - In PD, abnormalities in pain modulation related to levodopa therapy and motor fluctuation, dystonia and akathesia (Potvin et al., 2009; Tinazzi et al., 2008; Tinazzi et al, 2009)
Basal Ganglia (Substantia Nigra)

• Basal Ganglia may be involved in the:
  – Sensory-discriminative dimension of pain
  – Affective dimension of pain
  – Cognitive dimension of pain
  – Modulation of nociceptive information and sensory gating of nociceptive info to higher motor areas

Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain 1995 Jan;60(1):3-38
Evidence supporting Substantia Nigra (SN) in Pain

- SN stimulation suppressed nociceptive dc’s with an intact and transected spinal cord.

Evidence supporting Substantia Nigra (SN) in Pain

• Bilateral \textit{intranigral injections of morphine}
  – Dose-related and naloxone reversible \textit{anti-nociceptive effects}


• Bilateral \textit{intranigral injections of naloxone suppressed the anti-nociceptive effects of systemically administered morphine.}

Evidence supporting Substantia Nigra (SN) in Pain

• **Intranigral morphine** injection produces:
  – Suppresses pain-related behavior w/o altering non-noxious stimuli or producing motor impairment
  – Needle movement 1mm → reduces analgesic effect of morphine
  – **Electrolytic lesions of nigra** → reduces analgesic effect of morphine

Evidence supporting Substantia Nigra (SN) in Pain

- Lowering dopamine content in corpus striatum with electrolytic destruction of SN and 6-hydroxydopamine lesions to the SN increases pain sensitivity

Central Dopamine

• Local blockade of postsynaptic D2 receptors prevented increases in serotonin

• Increases in forebrain serotonin,
  – Largely dependent upon intact local dopaminergic neurotransmission

Brain Dopamine

• Has a role in pain – most studies suggest dysfunction can → potentiate pain
  – Decrease the effectiveness of morphine

• Intact dopaminergic systems are required for serotonin release
Central Dopamine (Spinal Cord)

• Diencephalospinal dopaminergic system
  – Fairly recent discovery – 40 years
  – **Involved in pain modulation**, autonomic and motor responses
  – Dopamine agonists mediate their actions
Spinal Cord / Dose

• Spinal Cord dopamine pathway involved in pain

• L-dopa can both increase (at low doses) and decrease (at high doses) pain
Affective Component

• Emotional factors \(\rightarrow\) increase or decrease the nerve impulses from peripheral nociceptors \(\rightarrow\) modify the patient’s perception of pain \((\text{Rugh, 1987})\)

• Depression - in approx 40% of PD pts \((\text{Marsh et al., 2006; Wertheimer et al., 2004})\)
  – Important in modulating pain and pain perception \((\text{Gagliese & Melzack, 2006})\)
Evidence from Parkinson’s Treatment
L-Dopa for Treatment of Pain

- **L-dopa for tx of painful diabetic neuropathy → decreased pain**
  

- **Herpes Zoster tx w/L-dopa → significant decrease in pain & post-herpetic neuralgia**
  

- **Levodopa, amantadine – positive results in the treatment of post-herpetic neuralgia**
  
Morphine

- Morphine for lumboradicular pain in Parkinson’s patients
  - Alleviation of pain
  - Decrease in dyskinetic movements at low doses
  - Increase in akinesia at higher doses

L-Dopa ➔ Morphine & Codeine Synthesis?

• Matsubara – Screened controls and Parkinson’s patients receiving L-dopa for urinary morphine and codeine.
  – Parkinson’s patients – significantly higher urinary codeine, some w/elevated morphine
  – Concluded: morphine & codeine are synthesized in the body from L-dopa and/or dopamine

Pain in Parkinson’s’s

• The administration of levodopa has been reported to improve the pain
  – Patients with **Parkinson’s** disease
  – **Metastatic bone pain**
    • Nixon DW. Use of L-DOPA to relieve pain from bone metastases. NEJM. 1975;292:647.
  – **Central pain** from thalamic syndrome

- 6 studies were identified.
- Stimulation sites - PVG/PAG, internal capsule (IC), and sensory thalamus (ST)
- The long-term pain alleviation rates
  - PVG/PAG plus ST/IT (87%)
  - PVG/PAG (79%)
  - ST alone (58% long-term success)

• More effective for nociceptive than deafferentation pain (63% vs 47% long-term success; p < 0.01).

• Long-term success for over 80% of pts with intractable low back pain (failed back surgery)
DBS for Pain

• Used over the past 50 years for chronic intractable pain with reported pain relief in 50 to 80 percent of patients

• Pain relief for 78 to 80 months
  – Greatest success reported in patients with failed back syndrome, trigeminal neuropathy and peripheral neuropathy
  – Kumar a and b (see above)
Conclusions

• Pain in PD is complex and multi-dimensional
  – prevalent, under-assessed, undertreated
  – has psychosocial impact on patients and their families

• Pain interferes w/life activity, regardless of the age of the individual

• Thorough, valid pain assessment and treatment during the progression of PD is indicated
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