Pain in Parkinson's Disease

David F. Drake, M.D. Director, Interventional Pain Clinic McGuire VAMC Richmond, VA

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

Multidimentional

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 Patient's with Parkinson's

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

Goetz C, Tanner C, Levy M, et al. Pain in Parkinson's Disease. Mov Disord. 1986;1:45-9.

- 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.

- 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

Snider

Snider SR, Fahn S, Isgreen WP, Cote LJ. Primary sensory symptoms in parkinsonism. Neurology. 1976;26:423-9.

- 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

Negre-Pages, Movement Disorders (2008)

- 450 PD pts \rightarrow 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 <u>— more severe (p = 0.03), but less frequently reported to MDs</u> (p = 0.02), less freq analgesic consumption than non-PD pain

Elton Gomes Da Silva - Arq Neuro 2008

- 50 pts w/PD

- 28 w/pain
 - No differneces 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%

Elton Gomes Da Silva - Arq Neuro 2008

- 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)

- 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

- 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)

- Most common sx reported at present (at time of questionnaire)
 - Females rated neck pain 9th (53.7% reported) and low back pain 10th (48.3% reported)
 - Males rated neck pain 16th (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

- 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

Scott B, Borgman A, Engler H, Johnels B, Aquilonius SM. Gender differences in Parkinson's disease symptom profile. Acta Neurol Scand 2000:102:37-43.

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

Sensory Threshold

Gerdelat-Mas. J Neurol Neurosurg Psychiatry 2007

• Conclusions:

- 1. Provided evidence of a dopanimergic modulation of objective pain threshold in PD patients.
- The decrease in RIII threshold in PD patients, in the OFF condition, compared with controls, confirms the existence of a an 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, numbress, 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

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

Li J, Ji YP, Qiao JT, Dafny N. suppression of nociceptive responses in parafascicular neurons by stimulation of substantia nigra: an analysis of related inhibitory pathways. Brain Res 1992 Sep 18;591(1):109-15.

- Bilateral intranigral injections of morphine
 - Dose-related and naloxone reversible anti-nociceptive effects

Baumeister AA, Hawkins MF, Anticich TG, Moore LL, Higgins TD. Brain Res 1987 May 12;411(1):183-6.

 Bilateral intranigral injections of naloxone suppressed the anti-nociceptive effects of systemically administered morphine.

Baumeister AA, Anticich TG, Hawkins MF, Liter JC, Thibodeaux HF, Guillory EC. Brain Res 1988 Apr 26;447(1):116-21.

- 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

Baumeister AA, Nagy M, Hebert G, Hawkins MF, Vaughn A, Chatellier MO. Further studies of the effects of intranigral morphine on behavioral responses to noxious stimuli. Brain Res 1990 Aug 13;525(1):115-25.

 Lowering dopamine content in corpus striatum w/electrolytic destruction of SN and 6-hydroxydopamine lesions to the SN

 increases pain sensitivity

Lin MT, Wu JJ, Chandra A, Tsay BL. Activation of striatal dopamine receptors induces pain inhibition in rats. J Neural Transm 1981;51(3-4):213-22.

Central Dopamine

- Local blockade of postsynaptic D2 receptors prevented increases in serotonin
- Increases in forebrain serotonin,
 - Largely dependent upon intact local dopaminergic neurotransmission

Mendlin A, Martin FJ, Jacobs BL. Dopaminergic input is required for increases in serotonin output produced by behavioral activation: an in vivo microdialysis study in rat forebrain. Neuroscience 1999;93(3):897-905

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
 - Lindvall O, Bjorklund A, Skagerberg G. Dopamine-containing neurons in the spinal cord: anatomy and some functional aspects. Ann. Neurol. 1983;14:255-260.

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 → increase or decrease the nerve impulses from peripheral nociceptors → modify the patient's perception of pain (Rugh, 1987)
- Depression in approx 40% of PD pts (Marsh et al., 2006; Wertheimer et al., 2004)
 - Important in modulating pain and pain perception (Gagliese & Melzack, 2006)

Evidence from Parkinson's Treatment

L-Dopa for Treatment of Pain

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

Ertas M, Sagduyu A, Arac N, Uludag B, Artekin C. Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy. Pain 1998 Apr;75(2-3):257-9.

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

Kernbaum S, Hauchecorne J. Administration of levodopa for relief of herpes zoster pain. JAMA 1981 Jul 10;246(2):132-4.

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

Thompson M, Bones M. Nontraditional analgesics fro the management of postherpetic neuroalgia. Clin Pharm 1985 Mar-Apr;4(2):170-6

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
 - Berg D, Becker G, Reiner K. Reduction of dyskinesia and induction of akinesia induced by morphine in two parkinsonian patients with severe sciatica. J Neural Transm 1999;106(7-8):725-8.

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

Matsubara K, Fukushima S, Akane A, Kobayashi S, Shoino H. Increased urinary morphine, codeine and tetrahydropapaveraline in parkinsonian patients undergoing L-3,4dihydroxyphenylalanine therapy: a possible biosynthetic pathway of morphine form L-3,4dihydroxyphenylalanine in humans. J Pharmacol Exp Ther 1992 Mar;260(3):974-8.

Pain in Parkinson's

 The administration of levodopa has been reported to improve the pain

Patients with Parkinson's disease

• Nutt JG, Carter JH. Sensory symptoms in parkinsonism related to central dopaminergic function. Lancet. 1984;ii:456-457.

Metastatic bone pain

• Nixon DW. Use of L-DOPA to relieve pain from bone metastases. NEJM. 1975;292:647.

- Central pain from thalamic syndrome

• Grant R, Behan P. Resistant thalamic pain treated by levodopa. Brit Med J. 289 (1984)1272.

Deep brain stimulation for pain relief: a metaanalysis (Bittar RG, J Clin Neurosci 2005 Jun;12(5):515-9)

- 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)

Deep brain stimulation for pain relief: a metaanalysis (Bittar RG, J Clin Neurosci 2005 Jun;12(5):515-9)

- 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
 - Kumar K, Wyant GM, Nath R. Deep brain stimulation for control of intractable pain in humans, present and future: a ten-year follow-up. Neurosurgery. 1990;26:774-81. a.
 - Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery. 1997;40:736-46.
 - Levy RM, Lamb S, Adams JE. Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. 1987;21:885-93.
 - Richardson DE. Deep brain stimulation for the relief of chronic pain. Neurosurg Clin N Am. 1995;6:135-44.
- 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

Note: This presentation is being recorded

- By participating in this meeting, you agree that your communications may be recorded, including Q & A that may arise.
- The purpose of recording the meeting is to save and archive this information in the National Implementation Center SharePoint for those unable to participate in the live presentation.
- No educational credit will be issued to those accessing the archived recording.

CME/CEU Credit for this Program

- A certificate of completion will be awarded to participants and accreditation records will be on file at the Employee Education System. In order to receive a certificate of completion from EES, you must register in the TMS, attend 100% of the program and complete the evaluation as directed in SEES. After submission of your evaluation in SEES you will be sent a certification of completion via e-mail.
- A certificate of completion will be awarded to participants and accreditation records will be on file in the VA Talent Management System (TMS). For all VA TMS users, completion certificates will be available in the Completed Works section of your VA TMS account. Non-VA TMS account holders will be provided a copy of their completion certificate via Email.
- It is the program participant's responsibility to ensure that this training is documented in the appropriate location according to his/her locally prescribed process.
- Note: <u>Submit Online Evaluation by January 30, 2012</u> for continuing education credit to be awarded