Of All The Nerve: Autonomic Nervous System Issues in Parkinson’s Disease

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Introduction to Parkinson’s Disease

- Progressive neurodegenerative disorder affecting 1% of people over 60 years of age; 0.3% of general population in industrialized countries
- Approximately one million affected Americans; 60,000 new cases yearly
- 10 million people worldwide
- Second most common neurodegenerative disease, second only to Alzheimer’s disease
- Men affected 1.5 times more than women
  - (Parkinson’s Foundation, 2018)
Motor, Non-Motor and Autonomic System Symptoms

• Well known motor symptoms
  – Tremor at rest
  – Rigidity
  – Slowness of movement (“bradykinesia”)
  – Postural instability

• Non-motor symptoms
  – Myriad of symptoms among them: cognitive, neuropsychiatric, sleep, and autonomic issues (bowel, bladder, cardiovascular, gastrointestinal, and skin issues)
Objectives for this presentation:

1. Discuss common autonomic issues in Parkinson’s disease including those affecting the cardiovascular, gastric, bowel, bladder and sexual functions.

2. Describe common autonomic issues that affect the integumentary system including seborrhea, dermatitis, and hyperhidrosis.

3. Identify additional skin issues related to Parkinson’s disease including melanoma, skin reactions to medications, and issues affecting the integumentary system due to problems with mobility.
Autonomic System and Symptoms in Parkinson’s Disease

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The Autonomic Nervous System

Autonomic nervous system (ANS)
• Controls many body systems “autonomously” - without voluntary input
• PD affects autonomic innervation to several organ systems – including cardiovascular, urinary, gastrointestinal systems (Jain 2011)
  • affects heart rate, blood pressure, sweating, sexual function, gastrointestinal and urinary function (Parkinson’s Foundation)

Impact on person with Parkinson’s and family (Tomic S, 2017)
• About 90% experience autonomic symptoms
• Often more bothersome than motor symptoms, and negatively impacts quality of life
• Side effects of PD medications may worsen ANS symptoms

(Park & Stacy, 2011)
Nursing Implications for Autonomic Symptoms

- Impact of non-motor symptoms on quality of life
- Importance of education and nursing management
  - For patients and families
  - For other clinicians
- Medications to treat non-motor symptoms complicate the medication regime and add to costs
- Work with the interdisciplinary team to best manage symptoms
Gastric and Intestinal Dysfunction in Parkinson’s: Slow Gastric Emptying

Slow gastric emptying

- Contributes to nausea, vomiting, heartburn, bloating, gas, early satiety, pain, weight loss
- Affects absorption of levodopa - PD medications are held longer in the stomach (Muller T et al 2006; Kurlan 1998; Djaldetti R et al 1996)
- Not improved by PD medications
- Treatment is limited – *Reglan is contraindicated in PD*
Management – Slow Gastric Emptying

• Small frequent low fat meals
• Regular exercise
• For nausea
  • Ginger ale, crystalized ginger
  • Ginger essential oils
• Monitor weight/educate regarding weight gain
• Over-the-counter medications for symptomatic relief
  – GERD medication
  – Gas medications
Gastric and Intestinal Dysfunction in Parkinson’s: Constipation

Constipation

• Definition: Fewer than 3 bowel movements per week or having to strain to pass stool

Divided into two types:

1. Constipation due to slow colonic transit

2. Constipation due to pelvic floor dysfunction - failure of the anal sphincter and puborectalis muscles to relax appropriately to facilitate emptying of the stool

(Rossi et al., 2015)

• PD medications contribute to constipation
Management - Slow Colonic Transit

- Increase fluid – warm water in the morning
- Increase dietary fiber / constipation “recipes”
- Pear or prune juice
- Yogurt/probiotics
- Avoid constipating foods
- Increase physical activity
- Regular toileting schedule

Medications
- Stool softeners, senna, Polyethylene glycol (miraLAX®)
- Avoid bulk laxatives if decreased fluid intake
- Use harsh laxatives only if no BM in 3-4 days
- Prescription medications
Orthostatic Hypotension

• Failure of the autonomic nervous system to regulate blood pressure due to postural changes
• Drop in BP with position change of ≥ 20mm Hg systolic and of ≥ 10 mmHg diastolic within 3 min after standing (Freeman et al 2011)
• May be present in up to 60% but not all are symptomatic —symptomatic in 30-40% (Velseboer, De Haan, Wieling, Goldstein, & De Bie, 2011).
• Prevalence increases with disease duration (Rocchi et al., 2015), severity, age and levodopa dose
Orthostatic Hypotension

- Symptoms: dizziness, lightheadedness, or syncope
- May also experience blurred vision, foggy thinking, headache, or lethargy
- Symptoms/severity may fluctuate
- Rule out other possible causes - hypovolemia, anemia, antihypertensive medications
- Levodopa and dopamine agonists contribute to low blood pressure
- Increased caregiver burden
Fluctuating Daily Blood Pressure

BP = blood pressure; nOH = neurogenic orthostatic hypotension.


Graphic adapted with permission from Horacio Kaufmann. Graphic is from a single patient case and may not be representative of the nOH population.
Management of Orthostatic Hypotension

Non-pharmacological:
- Take standing reading 1-3 minutes after standing
- Assess current medication list
- Behavior modification
- Increase fluid and salt intake (if not medically contraindicated)
- Manage constipation
- Encourage small frequent meals
- Avoid hot showers and baths
- Athletic spandex shorts, spanx, or support stockings

Pharmacological:
- Fludrocortisone (florinef™), Midodrine (proamatine™), Droxidopa (northera®)
Bladder Changes

- Occurs in 25-50% (K Winge 2015)
- Present throughout all PD stages
- **Irritative** - Caused by detrusor muscle hyperreflexia - Symptoms - frequency, urgency, urge incontinence
- **Obstructive** – Caused by detrusor hyporeflexia – symptoms: urinary hesitancy, difficulty initiating a stream, overflow incontinence
- Consider non-PD causes
  - Women - prolapsed uterus
  - Men - enlarged prostate
Management of Urinary Problems

Non-pharmacological management
- Scheduled use of the bathroom, especially before leaving home
- Clothing that is easy to pull up and down
- Pads or briefs, spill-proof urinals, bedside commode, suprapubic catheters, condom catheters
- Decrease bedtime fluids
- Referral to PT - Pelvic floor exercises
- Refer to OT/PT for bed mobility/transfer strategies for nocturia

Pharmacological management
- Most are anticholinergics
- Monitor for effectiveness and side effects
The Importance of Adequate Hydration

- Dehydration may lead to hospitalization, bladder infections
- Low fluid intake will influence low blood pressure, constipation, and skin

Dehydration may occur for a variety of reasons
- Bladder changes
- Physical limitations
- May refuse thickened beverages

Management Strategies
- Encourage 8 ounces of fluid with each pill dose
- Offer smoothies, sorbets, fruit/foods with a high water content
- Refer to ST for swallowing compensations and food modification
- Refer to OT for adaptive cups and utensils, positioning strategies
Sexual Dysfunction

Sexuality

- Impaired sexual function occurs more frequently in PD than the general population – decreased sexual activity with increased severity of PD
- May be influenced by depression, physical disability, autonomic dysfunction or comorbidities
- 81% of males – erectile dysfunction, dissatisfaction with sexual life, premature ejaculation, difficulty reaching orgasm, difficulties with ejaculation
- 43% of females – difficulty with arousal, difficulty with reaching orgasm, low sexual desire, dissatisfaction with sexual life, painful sex
Diagnosis and Treatment of Sexual Dysfunction

• First step is to talk about sexual issues
  – Difficult for the patient
  – Often avoided by the provider
• Decline in intercourse does not define an unhealthy sexual relationship - Expressing love and affection in other ways
• Referral to a sex therapist
Autonomic System and Parkinson’s disease

- Common issues
- Affects quality of life
- Requires a multidisciplinary team approach for best management
References

References (continued)

Autonomic Issues in Parkinson’s Disease: Focus on Skin and Wound Issues

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Skin and Wound Issues in Parkinson’s Disease

Common autonomic skin related issues: seborrhea, dermititis, (MASD, IAD), hyperhidrosis

Other integumentary issues: Melanoma, medication-related adverse skin reactions, pressure injuries
Pathophysiology of PD

• Autonomic nervous system components: PD affects all
  – Sympathetic
  – Parasympathetic
  – Enteric

• Pathological presynaptic protein called alpha-synuclein

• Impact of PD on CV, GU, GI and motor systems

• Loss of pigmented dopaminergic neurons in brain (pigmented by melanin) (Khemani & Dewey, 2017)

• Alpha synuclein present in neurons but also in the skin (Ravn, Thyssen, Egeberg, 2017)
PD and Skin Alterations

• PD alters the integumentary system via cutaneous denervation
  – Altered thresholds for cold, warm, pain

• PD alters micro RNAs (small, endogenous, noncoding RNAs that *regulate* other protein-coding genes)
  – Micro RNAs play a role in skin morphogenesis, skin carcinogenesis, and inflammatory response
  – Micro RNAs play a role through epigenetics (changes in gene expression)
  – Theoretically could affect wound healing (Beitz, 2013)
Autonomic Issues in PD and the Skin (Ravn et al, 2017)

- Seborrhea (Seborrheic Dermatitis)
- Dermatitis
  - IAD
  - MASD
- Hyperhidrosis
- Sialorrhea
Malignant melanoma

- **Medication-related skin reactions**
  - Levodopa and MM
  - Apomorphine skin necrosis and nodules
  - Amantadine effects
  - TSD (Transdermal Skin Delivery) skin reactions

- **Pressure injuries**
Seborrheic Dermatitis

- First described in PD patients in 1927!!
- Appears as greasy facial skin associated with erythema and scaliness
- Located in sebum rich areas (scalp, face, eyebrows, nasolabial folds, upper chest)
- Greater oiliness with greater disease activity
- Exact mechanism of PD in seborrheic dermatitis is unknown
- Prevalence of seborrhea in PD as high as 52-59% (Arsic Arsenjevic et al, 2014; Ravn et al, 2017)
Seborrheic Dermatitis

- Treat skin with topical steroids (hydrocortisone 1% cream) and/or topical antifungals (for yeast) (e.g., ketoconazole 2% cream)
- Treat hair with dandruff shampoos (e.g., Head & Shoulders or Selsun Blue) (Goldenberg, 2013)
- Seborrhea and seborheic dermatitis improves with dopamine therapy in PD
- Can also use topical calcineurin inhibitors (tacrolimus cream 0.1% or pimecrolimus 1% cream) (Arsic Arsenijevic et al, 2014; Goldenberg, 2013)
Moisture-Related Dermatitis

- **IAD (Incontinence-associated Dermatitis)**
  - Risk worsens with bowel/bladder dysfunction
  - Combination of feces/urine most damaging to skin: creates a basic pH (think lye)

- **MASD (Moisture-Associated Dermatitis)**
  - Can be associated with excessive sweating or excessive salivation
  - Can be associated with leaking percutaneous tubes (e.g., PEJ tube) (When LCIG (Levodopa-Carbidopa Intestinal Gel) (Duodopa) used via PEG) (Skovranek et al, 2016)
Hyperhidrosis (Dyshidrosis)

- Affects 30-60% of PD patients (too much sweat)
- Can also have hypohidrosis but much less common
- Often precedes motor symptoms by 2 to 10 years
- Predominantly affected areas are head and trunk
- Becomes more prevalent with disease progression
- Some studies suggest that excessive sweating worsens with poor disease control, off periods, and dyskinesias (Skovranek et al, 2016)
- Botulinum A toxin (Botox) for axillary sweating (A level recommendation)
Sialorrhea

- Exact patho-mechanism of PD in sialorrhea is not well understood
- PD patients may have difficulty swallowing but sialorrhea occurs in addition to this change
- May respond to botulinum toxin injection in lingual, parotid, and salivary glands
- Skin protectants around mouth can be used but must not be oil or petrolatum-based due to risk for aspiration (lipoid pneumonia) (Harris et al, 2011)
- May require drug therapy (e.g., anticholinergics)
- Notably sialorrhea can improve with good response to Levodopa (Critchlow, 2017)
Malignant Melanoma

• **Exact risk of MM in PD is unclear**
  – Not sure if PD related or Levodopa therapy related
  – OR of 1.83 of MM in PD patients (Huang et al, 2015)
  – Recent studies suggest Levodopa is *not* risk factor but PD itself is the factor
  – Possible link between alpha-synuclein and melanin. Alpha synuclein involved in both melanin synthesis and dopaminergic neuronal cells
  – Neuromelanin is produced by catecholaminergic neurons in brain: Different from peripheral melanins
  – Need yearly thorough skin assessment for MM detection
Medication Side Effects (AEs)

Levodopa and MM – Likely not related; potentially MM and disease itself are related

Apomorphine skin necrosis or skin nodules have been reported (Skovrnak et al, 2016)

- Recommendations for skin nodules (up to 92% of treated patients affected (Katzenschlager et al, 2005)

Amantadine (Symmetrel)

- Associated with livedo reticularis (mottled skin reaction looks like fish net stockings); usually lower extremities

- Likely related to interruption of blood distribution in dermal arteries (RAVN et al, 2017; Skovrnak et al, 2016)

- May need to discontinue drug if patient is intolerant of skin appearance
Management of Apomorphine Therapy – Related Skin Nodules

- Rotation of choice of infusion sites
- Use of Teflon needles
- Adjusting delivery through the skin to an optimal angle (i.e., 45-90 degrees)
- Maintaining skin hygiene and using emollients at the infusion site
- Choosing a lower concentration (e.g., 5mg/ml)
- Massaging Infusion Site (using a spikey rubber ball or vibratory device)
- Applying ultrasound treatment
- Use of silicone gel dressings (Bhidayashiri et al, 2016; Katzenschlager et al, 2005)
Medication Delivery Systems

• TSD Patches
  – Skin reactions can occur with use of TSD patches
  – Transdermal selegiline and rotigotine have been used with adverse skin reactions reported
  – Rotigotine patch used in PD
  – Selegiline patch use in major depressive disorder (MDD)
Mobility Issues with Disease Progression

- **Pressure Injury Risk**
  - Increased pressure on bony prominences
  - Inability to reposition self as mobility declines
  - Issues with cognitive decline
  - Increased risk with fecal/urinary incontinence
Skin as PD Diagnostic

• Alpha synuclein, presynaptic neuronal protein, found in CNS and peripheral autonomic nervous system
• Some studies showing higher levels of alpha synuclein in skin punch biopsies of PD patients
• Potential for skin biopsies to be used for early PD diagnosis in the future (Ravn et al, 2017)
• Potential for pre-motor marker of PD in the future
Summary

- PD non-motor issues associated with skin
- PD skin issues associated with PD therapy (drugs or drug delivery systems)


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