Managing Neuropathy after Transplant

Celebrating a Second Chance at Life
Survivorship Symposium

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INTRODUCTION

What is peripheral neuropathy?
Symptoms associated with peripheral neuropathy
Other forms of neuropathy
Diagnostic tools
Risk factors
Treatment related causes of neuropathy
Treatment options

PERIPHERAL NEUROPATHY: DEFINITION

- Damage to the peripheral nerves
- Typically affects the longest nerves first “stocking-glove” neuropathy

Why is that?
SYMPTOMS

- Symptoms depend on which type of nerves are affected
  - Smallest fibers (C and A-delta): Pain, temperature
    - pain, burning, tingling, pins-needles, shocks,
    - Most common, esp. early in course
  - Autonomic nerves (A-delta):
    - Orthostatic hypotension, GI/GU and sexual dysfunction
  - Large fiber sensory nerves (A-beta): touch, pressure
    - Numbness, imbalance, difficulty with vibration sensation
  - Motor nerves (A-alpha): proprioception, motor
    - Weakness, muscle atrophy (later on)
  - Often a combination of above

AUTONOMIC NEUROPATHY

- Nerves that control involuntary bodily functions:
  - Decreased sweating
  - Difficulty adjusting to the dark
  - Lightheadedness with standing (orthostatic hypotension)
  - Digestive issues (diarrhea, constipation, poor appetite)
  - Urinary issues (retention, frequency, urgency)
  - Sexual dysfunction

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CARPAL TUNNEL SYNDROME

- Compression of the **median nerve** at the wrist
- Numbness on palmar thumb/index and middle finger
- Action induced/episodic numbness, pain and grip weakness
- Good treatment options

**DIAGNOSIS**

**Neurologic exam** (done in clinic):
- Check pinprick, fine touch, vibration and position sensation as well as reflexes, strength and balance

**Nerve conduction study/ EMG**
- Electrical study measuring nerve function
- Can be normal early on in course
### DIAGNOSIS

- **Skin biopsy:**
  - Small section of skin from three leg sites
  - Measure density of the small nerve fibers in the skin (epidermis)

- **Laboratory evaluation:** rule out factors which increase risk of neuropathy
  - Diabetes, vitamin B12 deficiency, high cholesterol, amyloidosis

### AUTONOMIC NEUROPATHY: DIAGNOSIS

- Usually based on typical clinical history: (underdiagnosed)

- **Autonomic testing:**
  - Orthostatic vital signs
  - Autonomic lab:
    - Heart rate variability
    - Quantitative sweating
    - Tilt table test
QUALITY OF LIFE

Considerable impact on physical and psychological wellbeing

- Poor balance
- Loss of recreation
- Loss of independence
- Loss of employment
- Burden of chronic pain
  - Depression/Anxiety/Insomnia/Isolation

Underestimated by clinicians

Starting to gain traction in clinical trials...

- With improved treatment and survival, researchers are more often including measures of quality of life

Sonneveld, Leukemia 2013

RISK FACTORS

- Personal Risk Factors:
  - Pre-existing neuropathy
  - Sensory changes (during chemo)
  - Smoking
  - Abnormal kidney function
  - Obesity

- Acquired Risk Factors:
  - Diabetes
  - Vitamin B12 deficiency
  - High cholesterol

Serebry, PAIN 2014
TREATMENT-RELATED CAUSES OF NEUROPATHY

WHEN CAN NEUROPATHY OCCUR?

- Initially, from the underlying cancer
  - Multiple myeloma: 15-20% have neuropathy
- Chemotherapy
- During Transplant
- Graft vs Host Disease
CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

- Bortezomib (Velcade)
  - Usually occurs within the first few courses, plateau ~ cycle 5
  - Common: 35-50% of patients
  - Painful
- Thalidomide
  - Common: 23-50% reported
  - More likely to cause weakness and constipation
- Lenalidomide
  - Less neurotoxic
- Vincristine?
  - 30-40% Sensory and motor neuropathy, 1/3 with autonomic neuropathy

TRANSPLANT-RELATED NEUROPATHY

- Immune-mediated neuropathies = complication of auto-HSCT
  - Rare (0.36%) in a study of 3,305 patients
  - Varied presentation
    - Focal severe neuropathies
      - Eg. facial nerve, ocular nerve
    - Plexopathy (disorder affecting a network of nerves as they extend through the arm or leg)

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AFTER TRANSPLANT: IMMUNE SUPPRESSANTS

- **Tacrolimus** and cyclosporine - optic neuropathy
- **Sirolimus** - mostly just in combination
- **Prednisone** - muscle weakness
- **TNF-alpha** (etanercept, infliximab & adalimumab): Guillain-Barre syndrome, cranial neuropathies, central demyelination

AFTER THE TRANSPLANT: CHRONIC GVHD

- Peripheral nervous system involvement
  - Immune neuropathies; significant weakness <1%
  - Muscle cramps 16% (but underreported) in chronic GVHD
- Central nervous system involvement
  - Rare
TWO TENETS OF TREATMENT

Target/prevent the underlying disease course

- Treat the multiple myeloma/POEMS/amyloid
- Treat comorbid risk factors: diabetes, high cholesterol & low vitamin B12
- Exercise

Target symptoms

- Topical
- Oral prescriptions
- Alternative/complementary

EXERCISE AND NEUROPATHY WHAT’S THE EVIDENCE?

Initial nerve fiber density in all patients

Standard Counseling (40)

After 12 months, nerve fiber density repeated

Exercise (60)

Singleton, ANNALS 2014
EXERCISE AND NEUROPATHY
WHAT’S THE EVIDENCE?

Standard Counseling (40)

Exercise (60)

TOPICAL TREATMENT

- Lidocaine ointment/lidocaine patch
- Capsaicin
  - Active ingredient of chili
- Compounded ointment:
  - P4 cream: (Ketamine, gabapentin, amitriptyline, baclofen, clonidine, nifedipine, tetracaine)
- CBD ointment/tincture – legality varies by state
  - Sativex (THC/CBD spray): UK study found decreased pain and increased sleep
  - Nabilone (oral): CA study also successful reduction of pain, anxiety, depression
- Successful in mice

Singleton, ANNALS

Nurmikko, Pain 2007; Toth, Pain 2012
### ORAL PRESCRIPTIONS

**Gabapentin (Neurontin):**
- The good: low cost ($12-24/mo), high efficacy
- The bad: mild sedation “head fog” esp initially, swelling

**Amitriptyline (Elavil) vs Nortriptyline**
- The good: low cost ($4-12/mo), also helps insomnia and depression
- The bad: dry mouth, constipation, sedation

**Pregabalin (Lyrica) = next generation of gabapentin**
- The good: less “head fog”
- The bad: $$$ ($44-400/mo)

**Duloxetine (Cymbalta)***
- The good: Also helps with chronic pain and depression
- The bad: $$$ ($60-200/mo)

**Oxycodone, tramadol** generally 2nd or 3rd line 2/2 SE profile & addiction potential

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### AUTONOMIC NEUROPATHY: ORTHOSTATIC HYPOTENSION

- Treatment:
  - Compression stockings (At least 15-20mmHg)
  - Abdominal binders
  - Optimizing hydration (2-3 Liters/day)
  - Optimizing salt intake (3+ grams per day)
  - Raise head of bed by 10-20 degrees
  - Meds to keep blood pressure from dropping (midodrine and florinef)

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*Callaghan, Ann Intern Med 2014, GoodRx.com*
AUTONOMIC NEUROPATHY: OTHER SYMPTOMS

- Gastroparesis: delayed emptying due to loss of normal gut motility
  - Dietary modifications
    - Small, regular meals
    - Low fat, low insoluble fiber
    - Liquid nutrition
    - Avoid carbonated beverages, smoking and alcohol
    - Hydration
  - Prokinetic meds (Reglan 15 min before a meal)
- Urinary Frequency/Urgency/Incontinence
  - Medications: terazosin, oxybutynin etc.
- Erectile dysfunction
  - Medications: Viagra, Cialis etc.

CARPAL TUNNEL SYNDROME

- Treatment
  - Neutral wrist splint (worn at night)
  - Steroid injections
  - Physical therapy
  - Carpal tunnel release surgery
COMPLEMENTARY & ALTERNATIVE MEDICINE

Supplements

Meditation

Massage

Acupuncture

Physical therapy

Electrotherapy

Brami, Critical Rev in Onc/Hem 2016; Franconi, Ev based Complementary and Alternative medicine 2013

THANK YOU
REFERENCES:

- Nurmikko T.J. et al. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double-blind, placebo-controlled clinical trial. PAIN 2007 133;210—220.

Questions?

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