Polyneuropathy and Autonomic Neuropathy in Familial Amyloidosis

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“Foot Disease” in Povoa de Varzim, Portugal

- Early impairment of thermal and painful sensibilities, beginning and also predominating in the lower extremities
- Paresis in the extremities, particularly the lower ones
- Gastro-intestinal disorders
- Sexual and sphincter disorders
A Peculiar Form of Peripheral Neuropathy (Andrade, 1952)

- 74 cases from several unrelated families
- Dominant nature of transmission
- Insidious onset in second or third decade
- Progressive nature: 7-10 years
Peripheral Neuropathy

- Polyneuropathy with or without pain
- Small Fiber Neuropathy
- Autonomic Neuropathy
Symptoms of Polyneuropathy

- Tingling
- Burning pain
- Electrical or stabbing sensations
- Hypersensitivity
- Deep aching pain
- Coldness

- Imbalance
- Fatigue
- Falls
- Weakness
- Worse in feet
- Worse at night
- Symmetric
Signs of Polyneuropathy

- length-dependent weakness (feet and hands)
- loss of vibration > proprioception (large fiber)
- loss of temperature and pain (small fiber)
- reduced or absent ankle reflexes
Small Fiber Neuropathy

• prominent pain and burning in the feet, hands
• distal loss of pain and temperature sensation
• relative preservation of distal vibration sensation
• preservation of ankle reflexes on examination
Autonomic Neuropathy

- Lightheadedness or “dizziness”
- Blurred vision
- Dry eyes, dry mouth
- Cold feet
- Early satiety, constipation, diarrhea
- Urinary retention, incontinence
- Hypohidrosis
Delayed Recognition without Dysautonomia (Wang et al. 2008)

• 65 patients with amyloidosis

• Time to diagnosis
  – 12 months if dysautonomia or small fiber
  – 48 months if no dysautonomia

• Test for autonomic neuropathy if etiology unknown
• Testing abnormal even without symptoms
TTR Variants

- SMN without autonomic symptoms (Cys104- Saraiva et al 1999 and Tyr 77-Quan and Cohen 2002)
- Rapidly progressive PN (Ser 25-Yazaki et al 2002)
- Motor neuropathy (Leu 68-Salvi et al 2003)
- Multifocal demyelinating mononeuropathies (Ile 122-Breimberg and Amato 2004)
- Cardiac (Ile122-Jacobsen et al.1997)
Diagnosis

• Polyneuropathy-EMG
• Autonomic Neuropathy-Autonomic testing
• Amyloid deposition-Nerve Biopsy
• TTR-Genetic Testing
Electromyography (EMG)

Two part test:
- Nerve conduction studies
- Needle electromyography

Establish diagnosis of polyneuropathy
Distinguish demyelinating from axonal
Differentiate radiculopathy, plexopathy

Normal in small fiber and autonomic neuropathy
Autonomic Testing

Quantitative Sudomotor Axon Reflex Test
Heart rate response to deep breathing
Valsalva Maneuver
Tilt Table
Nerve Biopsy

- Amyloid deposits in endoneurium (perivascular) or subperineurial areas
- Congo Red, Thioflavine, Methyl Violet, TTR

- Electron Microscopy
  - Unbranched fibrils

- Absent in 10% (multifocal)
Amyloid Deposition
Amyloid Deposition
Amyloid Deposition
Biopsy-Alternative Sites

- Cardiac, renal
- Fat pad aspiration
- Rectal mucosa
- Accessory salivary glands (lip biopsy)
- Skin
Symptomatic Treatment

- Weakness
- Pain Management
- Autonomic neuropathy
- Weight loss
Management

Rehabilitation for weakness and balance

• Physical therapy
  • maintain strength and flexibility
  • balance
  • fall avoidance
  • cane, braces, walker, motorized vehicle

• Occupational Therapy
  • activities of daily living
<table>
<thead>
<tr>
<th><strong>Level A</strong></th>
<th>Recommended drug and dose</th>
<th>Not recommended</th>
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<tbody>
<tr>
<td></td>
<td>Pregabalin, 300–600 mg/day</td>
<td></td>
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<tr>
<td></td>
<td>Gabapentin, 900–3600 mg/day</td>
<td>Oxcarbazepine</td>
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<td></td>
<td>Sodium valproate, 500–1200 mg/d</td>
<td>Lamotrigine</td>
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<tr>
<td></td>
<td>Venlafaxine, 75–225 mg/day</td>
<td>Lacosamide</td>
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<tr>
<td></td>
<td>Duloxetine, 60–120 mg/day</td>
<td>Clonidine</td>
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<tr>
<td></td>
<td>Amitriptyline, 25–100 mg/day</td>
<td>Pentoxifylline</td>
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<tr>
<td></td>
<td>Dextromethorphan, 400 mg/day</td>
<td>Mexiletine</td>
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<tr>
<td></td>
<td>Oxycodone, mean 37 mg/day, max. 120 mg/day</td>
<td>Magnetic field treatment</td>
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<tr>
<td></td>
<td>Tramadol, 210 mg/day</td>
<td>Low-intensity laser therapy</td>
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<tr>
<td></td>
<td>Oxycodone, mean 37 mg/day, max. 120 mg/day</td>
<td>Reiki therapy</td>
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<tr>
<td></td>
<td>Capsaicin, 0.075% four times per day</td>
<td></td>
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<tr>
<td></td>
<td>Isosorbide dinitrate spray</td>
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<td>Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks</td>
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Management-OH

• Orthostatic hypotension
  – Raise head of bed 6-9 inches
  – Sit on edge of bed/dorsiflex feet
  – Fluids (8 cups/day)
  – Salt
  – 6 small meals
  – Cross legs
  – Compression stockings/Abdominal binder
  – Walker/wheelchair
Treatment-OH

- Fludrocortisone
  - Mineralocorticoid
  - 0.1-0.3 mg/day
  - Monitor potassium
  - Supine hypertension
  - Edema
Treatment-OH

• Midodrine
  – Alpha adrenoreceptor agonist
  – 10 mg three times daily
  – Up to every 4 hours
  – Avoid after 6 pm
  – Goosebumps (piloerection)