Polyneuropathy and Autonomic Neuropathy in Familial Amyloidosis

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A Peculiar Form of Peripheral Neuropathy (Andrade, 1952)

"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

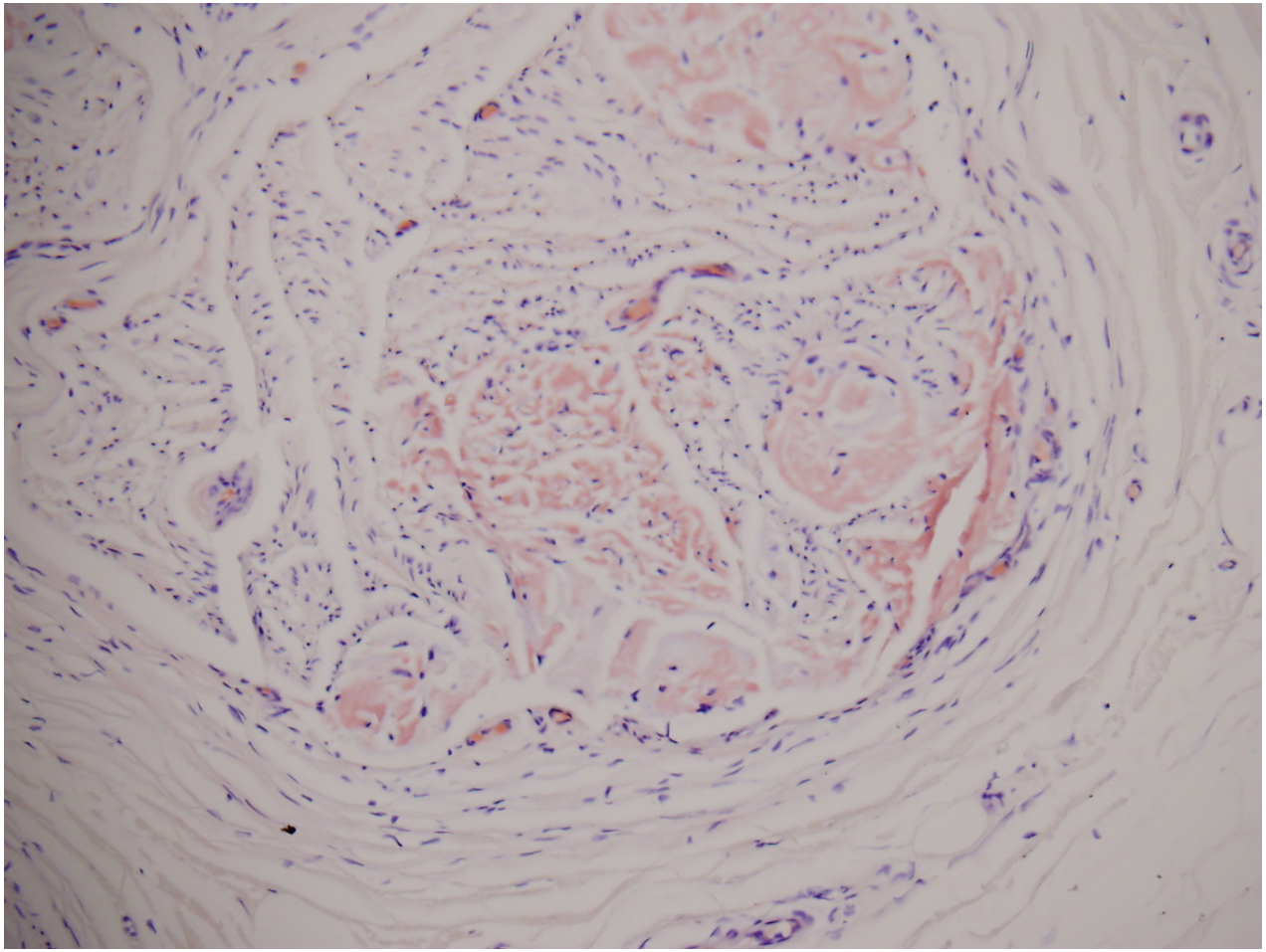
Nerve Biopsy

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

- Electron Microscopy
  - Unbranched fibrils

- Absent in 10% (multifocal)

Amyloid Deposition



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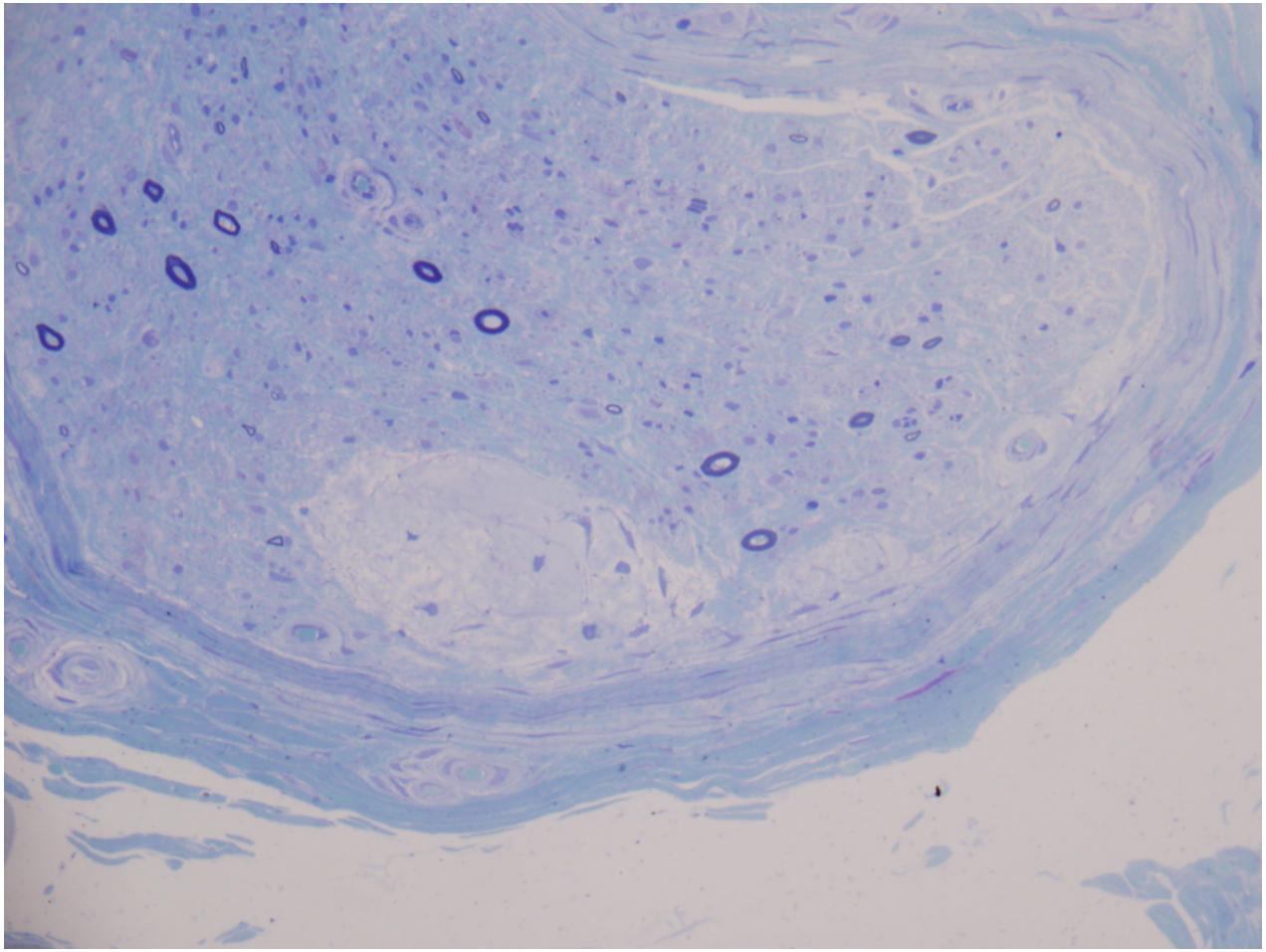

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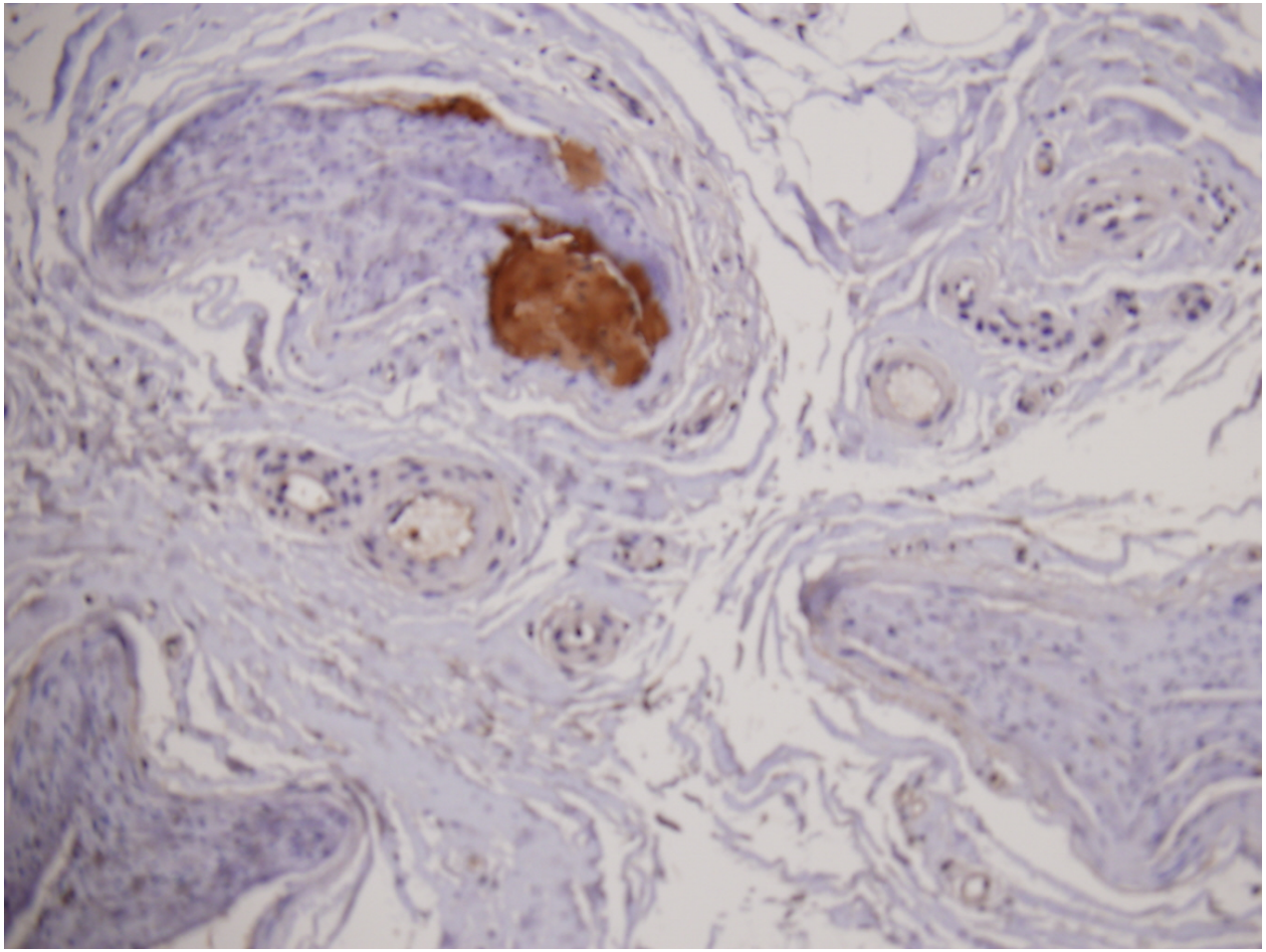

Biopsy-Alternative Sites

- 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 1. Summary of recommendations

(Evidence based Guidelines: MN 2011)

	Recommended drug and dose	Not recommended
Level A	Pregabalin, 300–600 mg/day	
Level B	Gabapentin, 900–3600 mg/day	Oxcarbazepine
	Sodium valproate, 500–1200 mg/d	Lamotrigine
	Venlafaxine, 75–225 mg/day	Lacosamide
	Duloxetine, 60–120 mg/day	Clonidine
	Amitriptyline, 25–100 mg/day	Pentoxifylline
	Dextromethorphan, 400 mg/day	Mexiletine
	Morphine sulfate, titrated to 120 mg/day	Magnetic field treatment
	Tramadol, 210 mg/day	Low-intensity laser therapy
	Oxycodone, mean 37 mg/day, max. 120 mg/day	Reiki therapy
	Capsaicin, 0.075% four times per day	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks	

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)