Cleveland Clinic

Small Fiber Neuropathy and Sarcoidosis

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Neurosarcoidosis

- Seen in 5-15% of patients with sarcoidosis
- Affects any portion of the CNS or PNS
  - Cranial neuropathies
  - Brain parenchyma
  - Meningeal disease
  - Peripheral neuropathy
- Disorder of small somatic and/or autonomic fibers which results in sensory paresthesias or autonomic dysfunction

Small Fiber Neuropathy

- Under-recognized and more common than previously thought
- Prevalence unknown
  - 44% (31/70) of severe sarcoidosis patients reported peripheral pain/paresthesias or symptoms of autonomic dysfunction
  - None with DM
  - Skin biopsy in 7 of 7 patients showed reduced IENFD

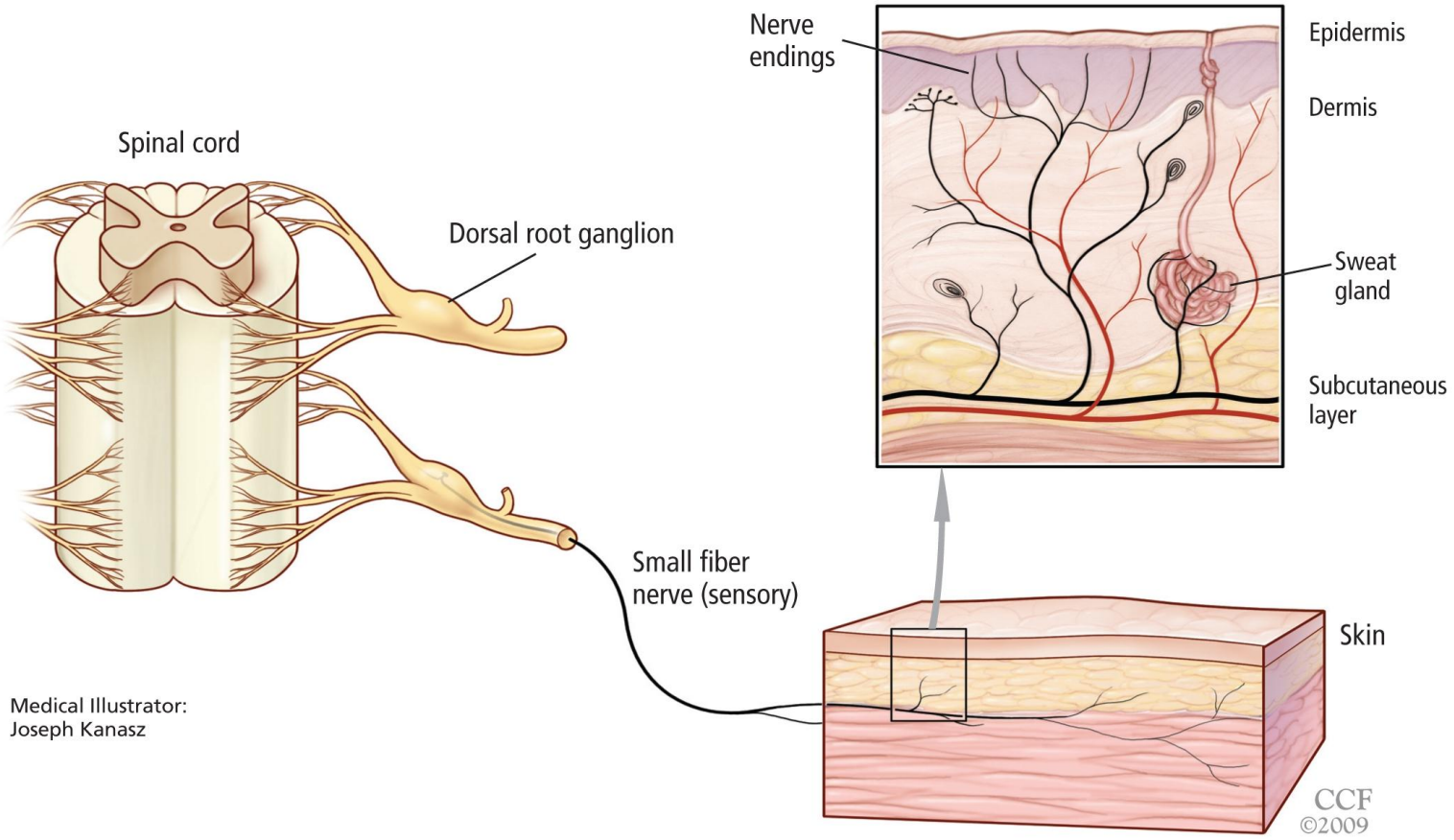
Hoitsma et al. Lancet 2002;359:2085-6

Anatomy: Small nerve fibers

- Thinly myelinated A-delta fibers and unmyelinated C-fibers
- Innervate skin and involuntary muscles (cardiac, smooth muscles)
- Clinical:
  - Somatic: burning, pins/needles, stabbing pain
  - Autonomic: dry eyes, dry mouth, orthostasis, diarrhea/constipation, sweating changes, sexual dysfunction
- Length vs non-length dependent

Tavee J, Zhou L. Cleve Clin J Med 2009; 76:297–305.

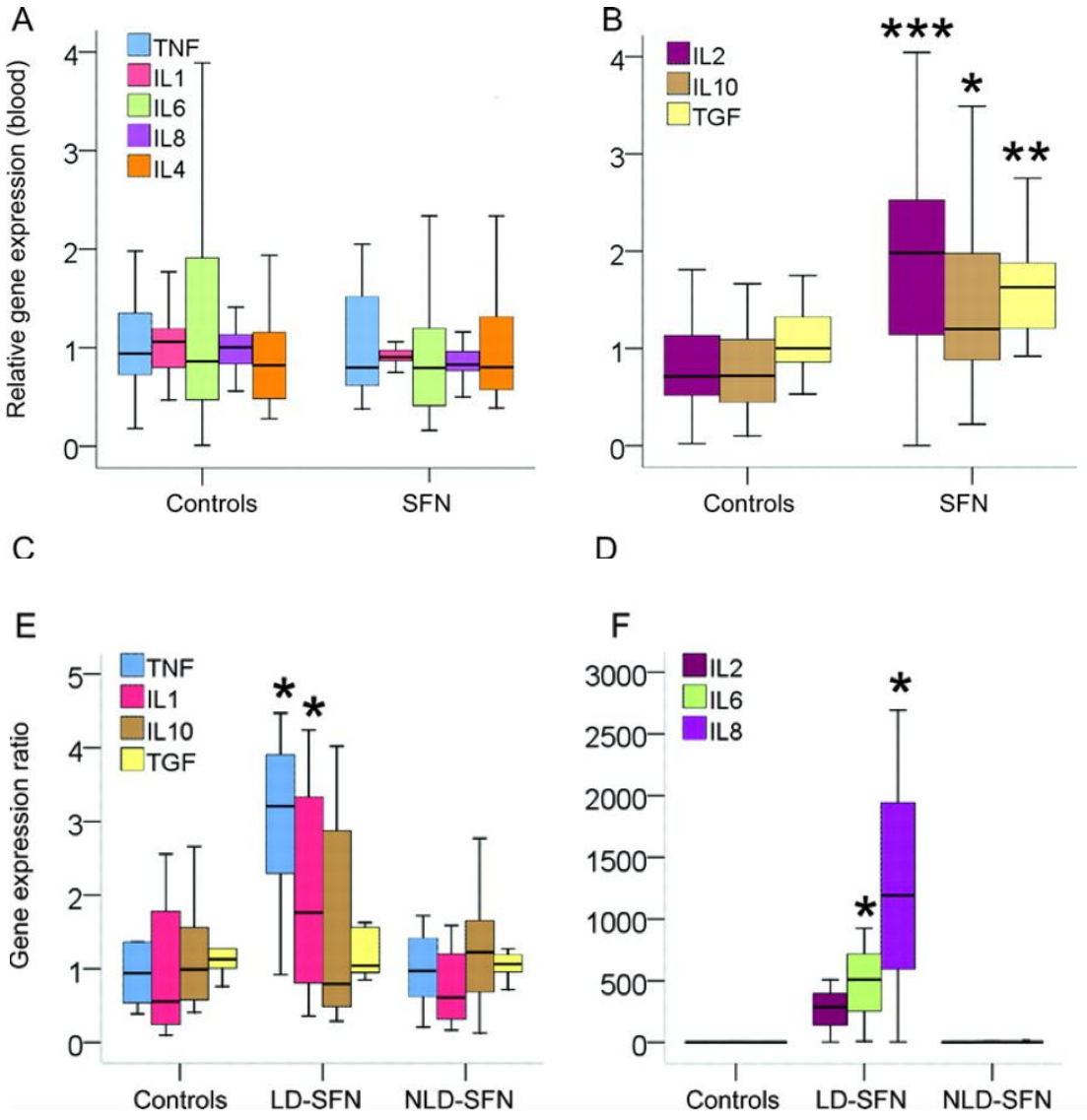
Anatomy: small fibers



Tavee J, Zhou L. Cleve Clin J Med 2009; 76:297–305.

Pathophysiology

- Axon loss
- Cytokines and immune factors
  - Increased gene expression of local and systemic cytokines
  - Responsive to anti-TNFα agents
- Oxidative stress



Üçeyler et al. Neurology 2010;74:1806-1813

Diagnostic Evaluation

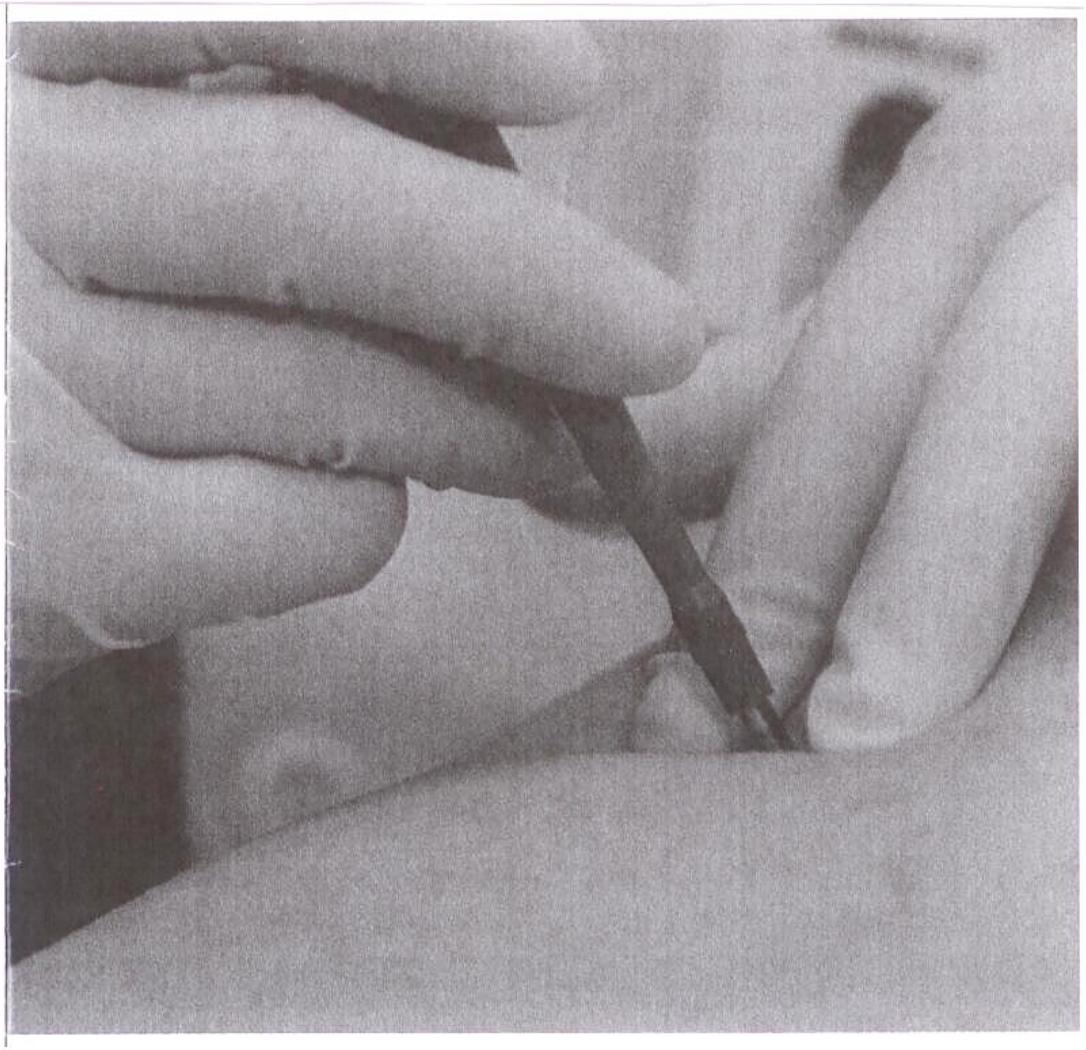
- Examination typically normal
  - May have mild sensory loss including vibration
- Nerve conduction studies and EMG normal
  - Evaluate large fibers
- Specialized testing:
  - **Skin biopsy**
  - **Quantitative sudomotor axon reflex testing (QSART)**
  - Cardiovagal/adrenergic autonomic testing: tilt table, Valsalva ratio, heart rate variability to deep breathing
  - Thermoregulatory sweat testing
- Exclusion of other etiologies: diabetes, B12, thyroid

Skin Biopsy

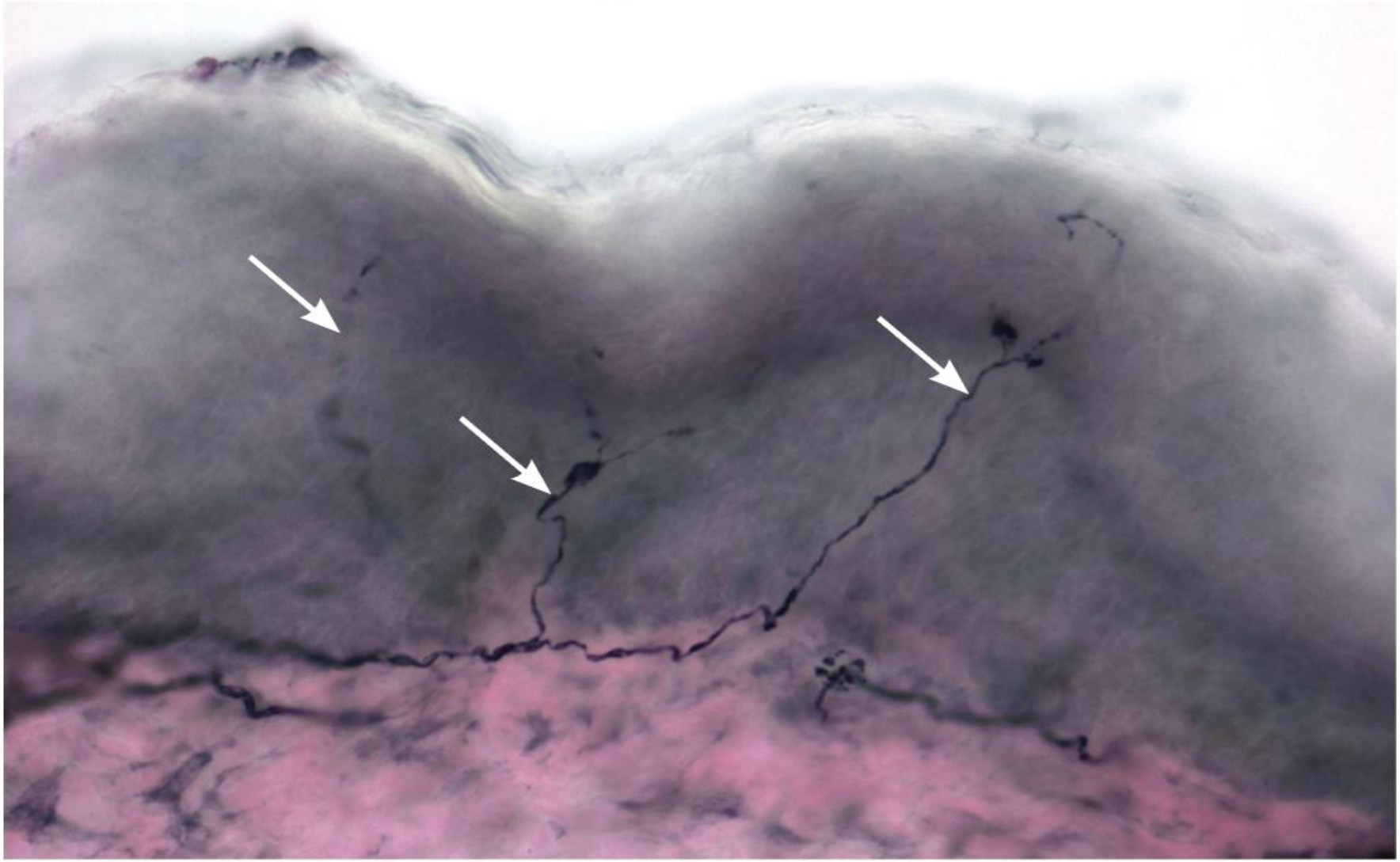
- Minimally invasive
- 3mm diameter punch biopsy ankle, distal thigh, proximal thigh
- Immunostained with PGP 9.5 panaxonal marker
- Reduced Intraepithelial nerve fiber density (IEFD)
- 88% sensitive

Low, et al. Muscle Nerve 2006;34(1):57-61
McArthur, et al. Arch Neurol 1998;55(12):1513-20.

Skin Biopsy

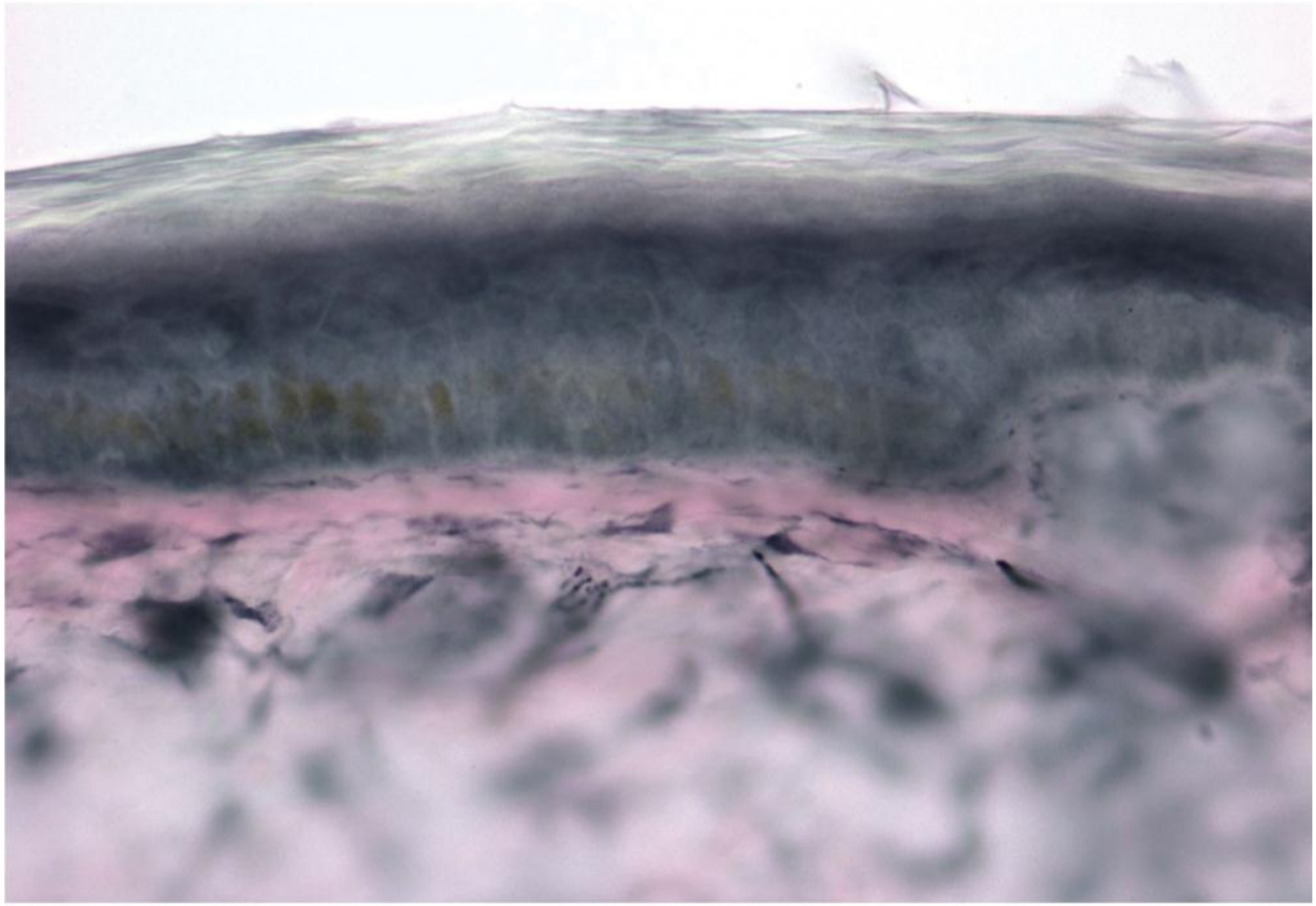


Normal skin biopsy



Tavee J, Zhou L. Cleve Clin J Med 2009; 76:297–305.

Small fiber neuropathy biopsy



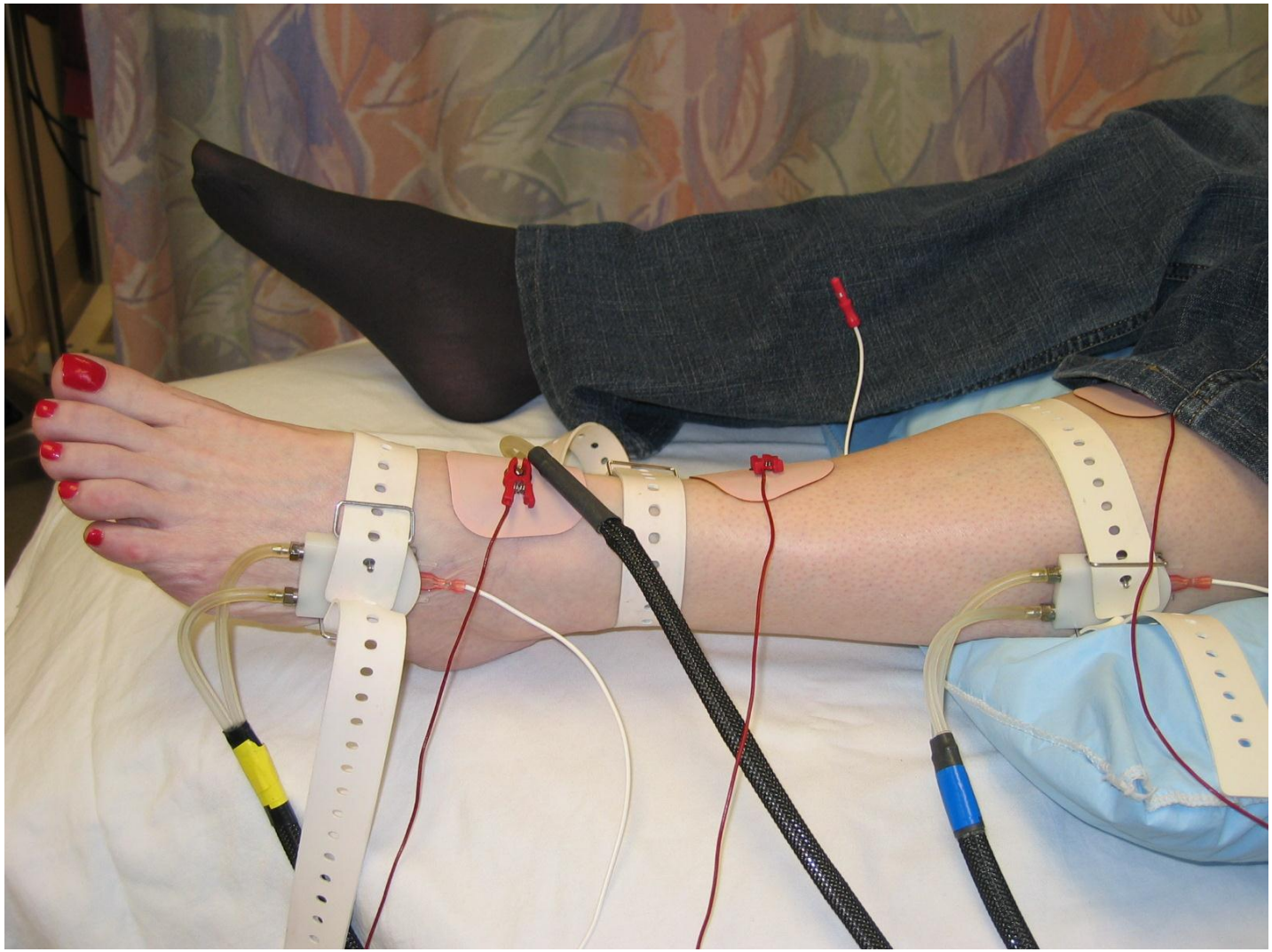
Tavee J, Zhou L. Cleve Clin J Med 2009; 76:297–305.

Quantitative Sudomotor Axon Reflex Test (QSART)

- Measures sweat output in response to acetylcholine iontophoresis
- Reflects function of postganglionic sympathetic unmyelinated sudomotor fibers
- Output and latency compared to normative values
- Left forearm, proximal leg, distal leg and foot
- Current is 2 mA for 5 minutes
- 72% sensitivity

Novak, et al. Neurology 2001;56(7):861-868

QSART



Treatment Options

- Immune-modulating therapy
- Pain management
- Supportive care

Immune-modulating therapy

- Intravenous Immune globulin
  - 400mg/kg/D IV for 5 days
  - Repeat monthly at least for 3 months
  - Adjust dose as needed and taper when possible
  - Helpful for SFN with somatic and autonomic involvement
- TNF-α blockers
- Corticosteroids
- Erythropoetin
  - Neuroprotective in animal models of neuropathy
  - TNF-α antagonist
  - ARA 290 avoids hematopoetic/thrombotic effects

Hotisma etal. Sarcoidosis Vasc Diffuse Lung Disease 2006;23:73-77
Heaney et al. Muscle Nerve 2004;29:447-450
Parambil et al. Resp Med 2011;105:101-5
Bianchi etal. Proc Natl Acad Sci USA. 2004;101:823–828.

Pain Management

- Medications
- Spinal cord stimulation
- Intrathecal pain pump

First line: Antidepressants

Antidepressants	Dosages (per day)	Common side effects
Amitryptiline	20-150 mg	Sedation, weight gain, anticholinergic effects, sexual dysfunction (side effects most prominent in amitryptiline)
Nortryptiline	20-150 mg	
Desipramine	20-200 mg	
Duloxetine	60-120 mg	
Venlafaxine	75-225 mg	Anxiety, insomnia, weight loss anticholinergic effects, sexual dysfunction, arrhythmia

Anticonvulsants	Dosages (per day)	Common side effects
Gabapentin	300-3600 mg	Sedation, dizziness, peripheral edema, weight gain
Pregabalin	150-300 mg	Similar to gabapentin, but worse
Topiramate	25-400 mg	Weight loss, sedation, cognitive slowing, renal stones, paresthesias
Zonegran	100-600mg	Weight loss, sedation, cognitive slowing, renal stones
Levetiracetam	500-3000mg	Dizziness, sedation, irritability

Non-opioids: Topical agents

Topical anesthetics	Dosages (per day)	Common side effects
Lidocaine 5% patch	3 patches for 12 hrs	Local edema, burning, erythema
Capsaicin cream	0.025-.25% TID-QID	Burning, worse with heat exposure
Capsaicin 8% patch	Apply 60-90 minutes	Burning, worse with heat exposure

Acetyl L Carnitine

- Chemotherapy PN
  - Oral 1gm TID for 8 weeks in 25 patients with PN due to paclitaxel or cisplatin
  - Improved sensory neuropathy symptoms in 60% pts
- Antiretroviral PN:
  - Oral 2gm/D for 4 weeks in 20 HIV+ pts
  - Mean pain intensity score was significantly reduced
- Diabetes PN:
  - Oral 500 and 1000 mg TID for 6 and 12 months in 1335 patients with diabetic PN
  - 27% with pain, all significantly improved in 1000mg TID group

Bianchi et al. Eur J Cancer 2005;41:1746-50
Oslo et al. J Periph Nerv Sys 2006;11:72-6.
Sima et al. Diabetes Care 2005;28:96–101.

Natural supplements

- Alpha-lipoic acid
  - Natural cofactor of dehydrogenase complex
  - IV 600mg/D in patients with DM distal sensory and autonomic neuropathy -14 treatments
  - Oral dose and length of treatment not well established
- Vicks vaporub
- Horse liniment cream
- Juiceplus® (or Costco equivalent: Juice festiv®)

Ziegler et al. Diabetes Care 1999;22:1296–301

Supportive treatment

- Nutrition: Food as medicine
- Gluten-free diet
- Avoid/reduce EtOH intake
- Exercise, exercise, exercise
  - Aqua therapy
  - Recumbent bike
- Mind body therapies: tai chi, qigong, meditation, yoga, pilates
- Massage
- Transcutaneous electrical stimulation

Prognosis

- Ambulation and strength are preserved
- Pain can last months to years if untreated
- Markedly affects quality of life
- Remitting and relapsing
- Slow progression