Burning Questions: What's New in Small Fiber Neuropathy?

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Disclosures

- Principal Site Investigator for Edgewise Grand Canyon and Mesa Studies evaluating Sevasemten in Adults with Becker Muscular Dystrophy.

- Advisory Panel member for Amicus Therapeutics Pompe.

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Objectives

- Define what small-fiber neuropathy is and isn't.
- Develop an evidence-based strategy for evaluating and treating small-fiber neuropathy.
- Expose some misconceptions.
- Identify what we don't know about small-fiber neuropathy.

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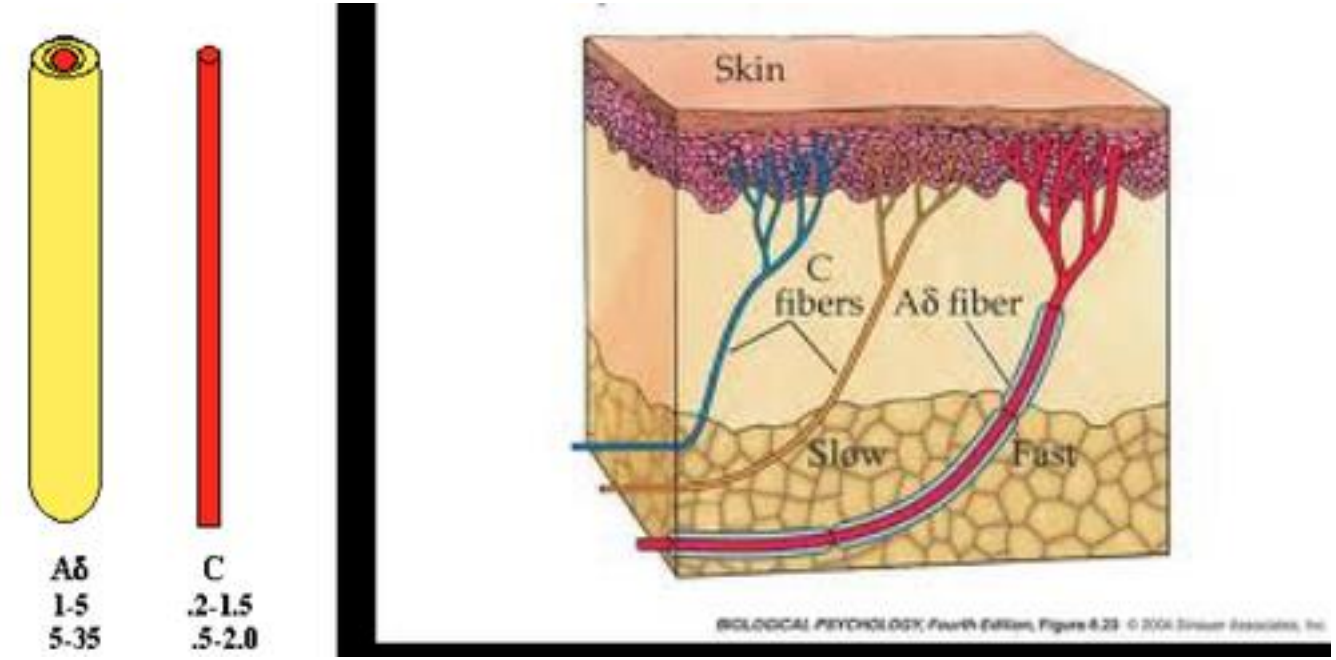
Does Small-Fiber Neuropathy Exist?

- 30% of patients eventually develop large-fiber involvement.
- Pain is not specific to peripheral neuropathy.
- Many patients have systemic illness.
- Smallest nerve fibers (C-fibers and A-delta) are difficult to assess.
- Most patients are undiagnosed.



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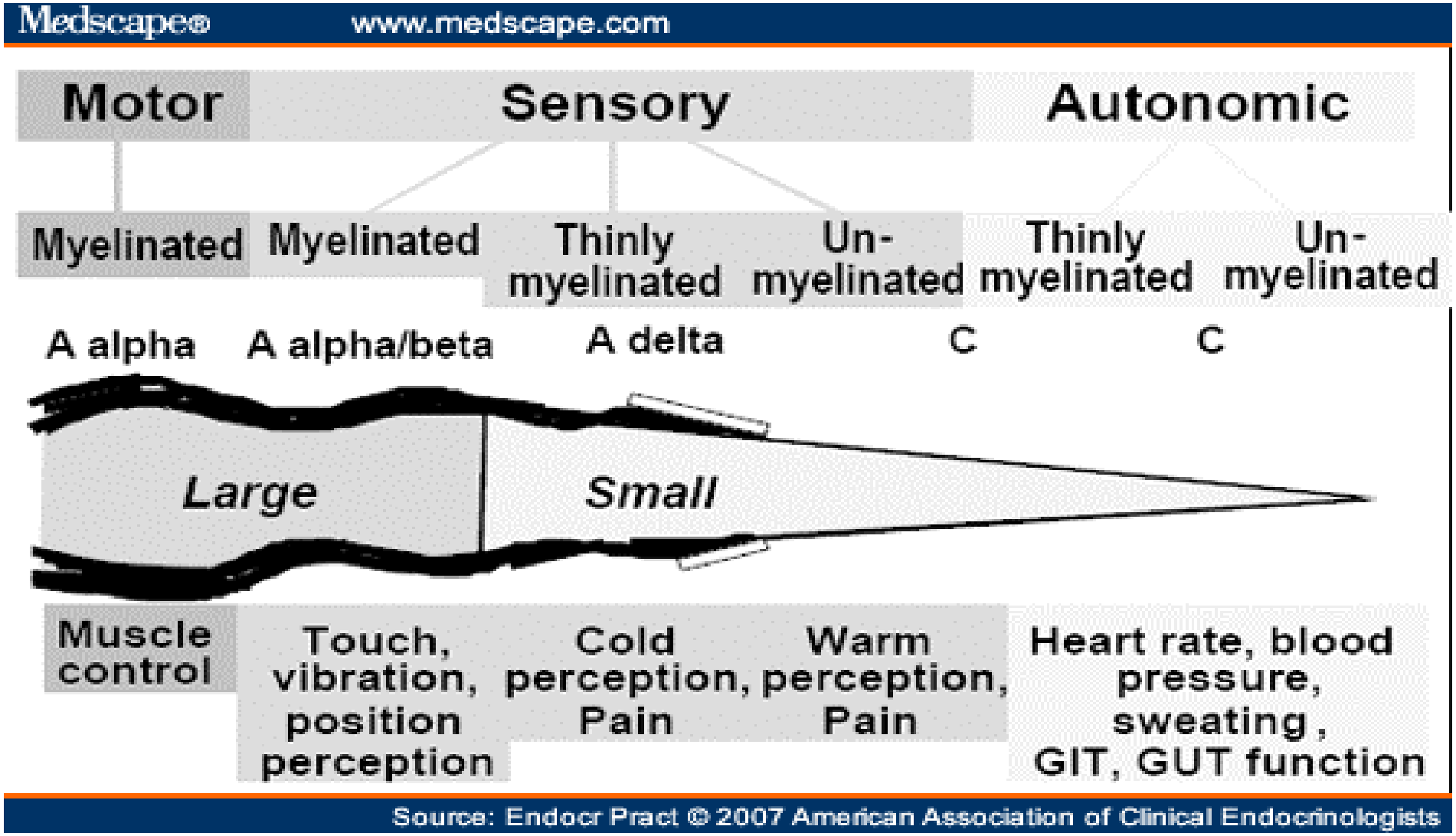
What is Small-Fiber Neuropathy?



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How is SFN Defined?

- Combination of positive and negative sensory symptoms/examination findings.
  - Preserved reflexes, preserved vibratory sensation.
  - If no clinical findings, 50% will have complete resolution of symptoms at 18 months.
- 50% of patients will have autonomic symptoms.
- Confirmatory testing is recommended but problematic.

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What Conditions are associated with SFN?

Table 2 Breakdown of Patients With Causal SFN at Onset (n = 28)

Primary cause	n (%)
Diabetes[a]	14 (50.0)
HIV	1 (3.5)
Sjögren syndrome[b]	2 (7.1)
Systemic lupus	1 (3.5)
AL-amyloid	1 (3.5)
Hereditary transthyretin-amyloid	1 (3.5)
Fabry disease	1 (3.5)
Lewy body disease	1 (3.5)
Postviral	1 (3.5)
Multifactorial including diabetes[c]	5 (17.9)

Abbreviation: SFN = small fiber neuropathy.
[a] Two patients with diabetes had treatment-induced small fiber neuropathy: 1 after gastric bypass surgery, another from insulin, both with rapid hemoglobin A1c correction.
[b] Met seropathologic diagnostic criteria for Sjögren syndrome.[26]
[c] Diabetes plus a rheumatologic or endocrine syndrome (n = 1 psoriatic arthritis, n = 1 ankylosing spondylitis [HLAb27 positive], n = 1 seronegative rheumatoid arthritis, n = 1 multiple autoimmune markers, n = 1 gigantism).

Johnson SA, Shouman K, Shelly S, Sandroni P, Berini SE, Dyck PJB, Hoffman EM, Mandrekar J, Niu Z, Lamb CJ, Low PA, Singer W, Mauermann ML, Mills J, Dubey D, Staff NP, Klein CJ. Small Fiber Neuropathy Incidence, Prevalence, Longitudinal Impairments, and Disability. Neurology. 2021 Nov 30;97(22):e2236-e2247. doi: 10.1212/WNL.0000000000012894. Epub 2021 Oct 27. PMID: 34706972; PMCID: PMC8641968.

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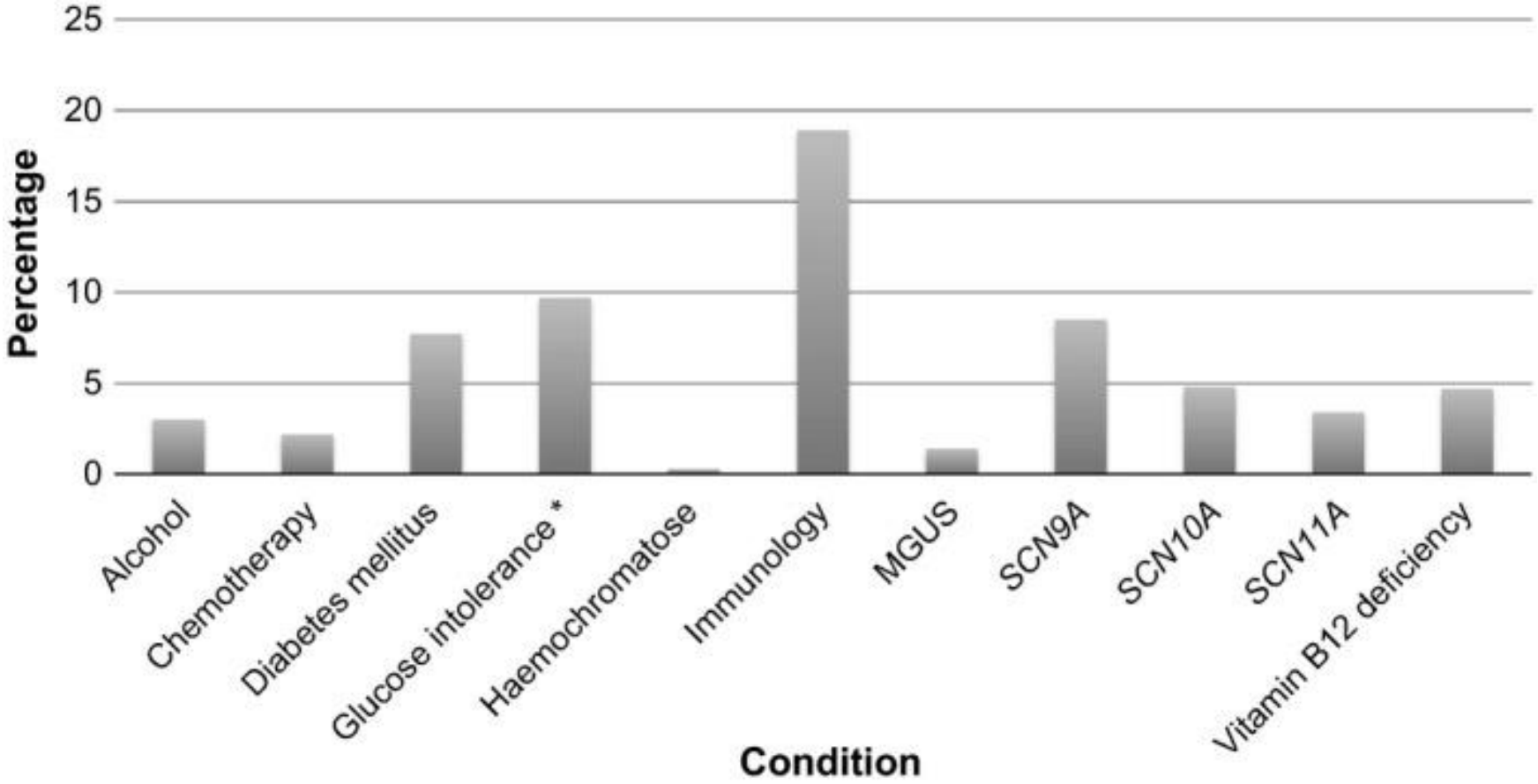
Dutch Cohort 921 Patients



Only 50% were checked for diabetes.

de Greef, B. T. A., Hoeijmakers, J. G. J., Gorissen-Brouwers, C. M. L., Geerts, M., Faber, C. G., & Merkies, I. S. J. (2018). Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. European journal of neurology, 25(2), 348–355. https://doi.org/10.1111/ene.13508

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What About Covid?...Vaccine?

- Association—Yes.
  - Causality--?
- 50% of patients with painful Long-Covid meet criteria for SF-N*
- May underlie fatigue and autonomic symptoms.
- Incidence and prevalence Post-Vaccine is unclear.

*Falco, P., Litewczuk, D., Di Stefano, G., Galosi, E., Leone, C., De Stefano, G., Di Pietro, G., Tramontana, L., Ciardi, M. R., Pasculli, P., Zingaropoli, M. A., Arendt-Nielsen, L., & Truini, A. (2024). Small fibre neuropathy frequently underlies the painful long-COVID syndrome. Pain, 165(9), 2002–2010.

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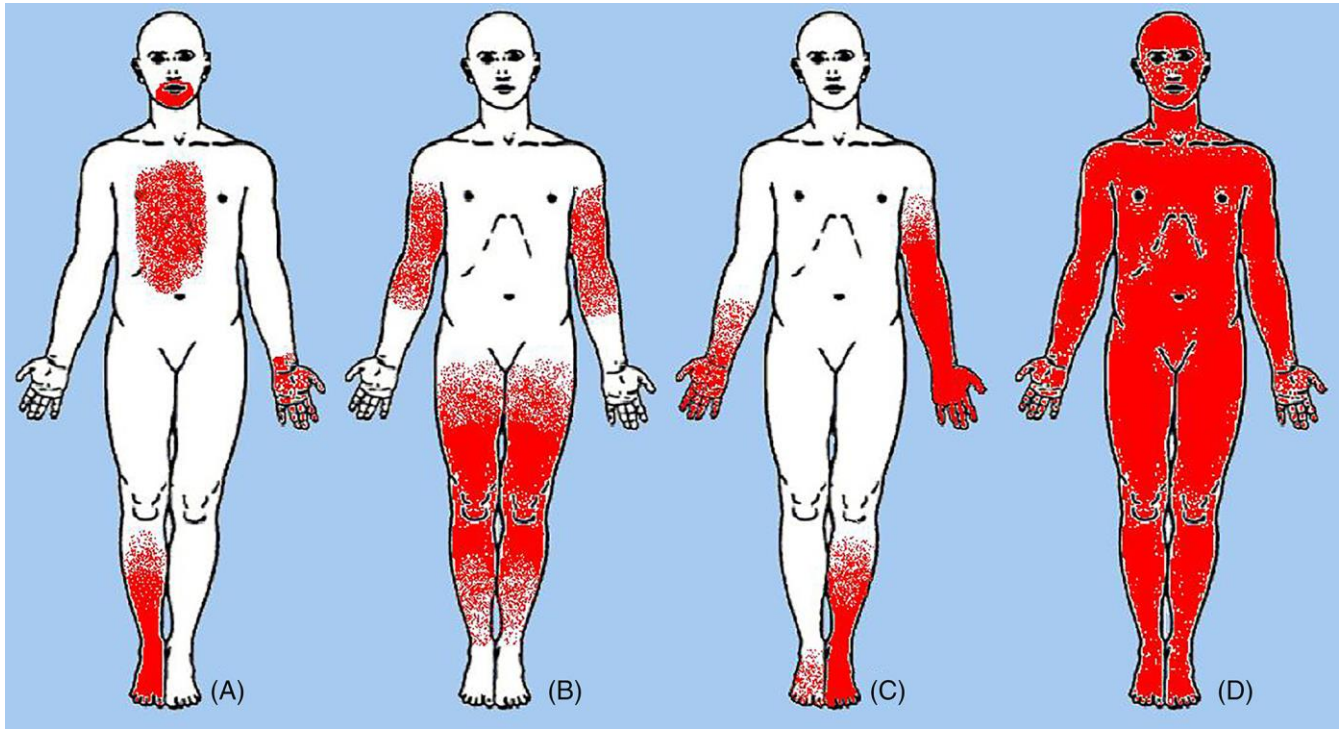
Length-Dependent vs Non-Length Dependent



Muscle and Nerve, Volume: 65, Issue: 1, Pages: 10-28, First published: 09 August 2021, DOI: (10.1002/mus.27379)

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What about the F-Word?

- 50% of patients with fibromyalgia have abnormal skin biopsy.
  - Chicken or Egg? Central sensitization causing excitotoxicity to small fibers or vice-versa?
- 30% of Myalgic Encephalopathy/ Chronic Fatigue Syndrome (ME/CFS) patients found to have reduced nerve fiber density on skin biopsy.
- 50% of patients with Postural Orthostatic Tachycardia Syndrome have abnormal skin biopsy.
  - Patients tend to have less anxiety, better quality of life, but more prominent autonomic symptoms*

*Gibbons, C. H., Bonyhay, I., Benson, A., Wang, N., & Freeman, R. (2013). Structural and functional small fiber abnormalities in the neuropathic postural tachycardia syndrome. *PloS one*, *8*(12), e84716. https://doi.org/10.1371/journal.pone.0084716

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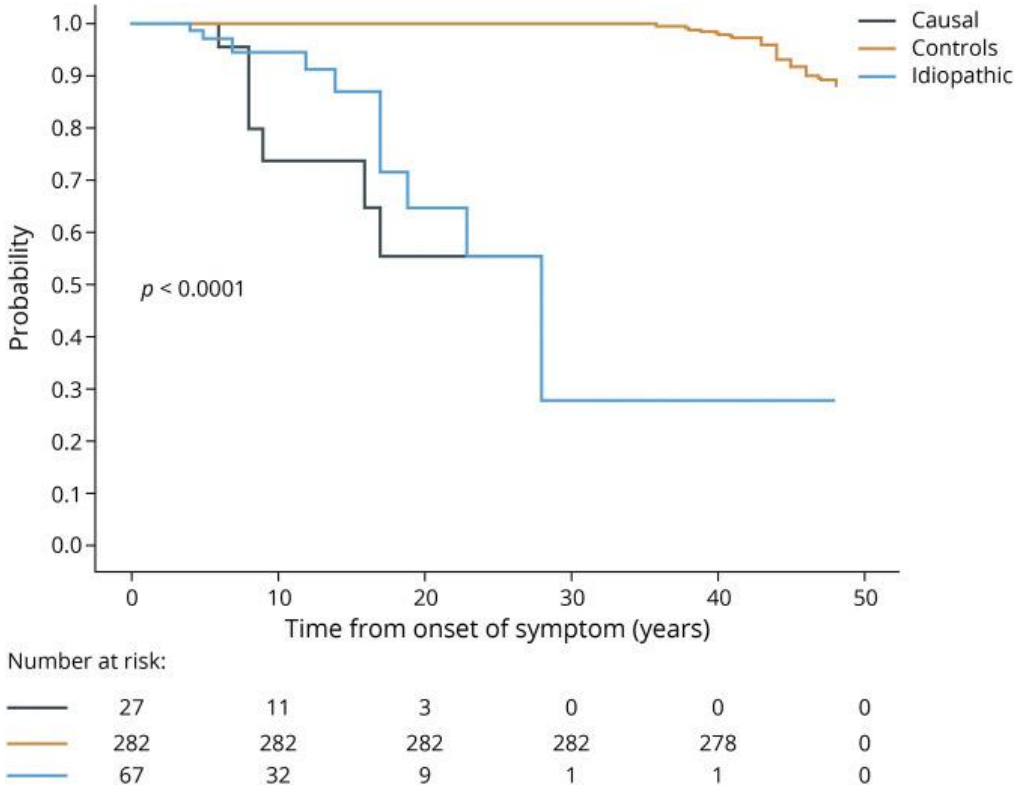
What are these Patients Like?

Klein et al[2] retrospectively analyzed 189patients with isolated small-fiber neuropathy.

- Disability was minimal (Modified Rankin Score=1).
- 89 patients were excluded because of alternative diagnoses (plantar faciitis, rheum conditions).
- Patients were more likely to be female (67%), obese, and have higher triglyceride levels than controls.
- Autonomic symptoms were common, but mild.
- Only two found to have genetic cause.
- Increased risk of death from vascular causes.



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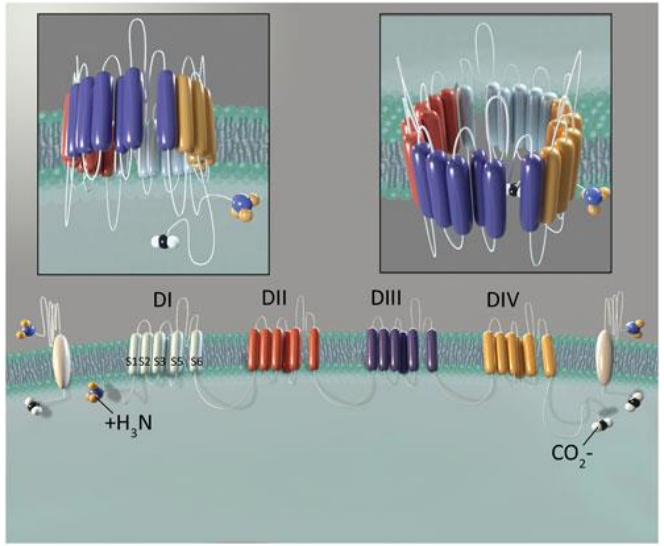
Hot Topic: Voltage-Gated Sodium Channels

- Toxic gain of function of VGSC may lead to hyper-excitability and thus increased pain.
- NaV1.7, NaV1.8, and NaV1.9 are highly expressed in nociceptors and are critical for pain signaling.
- SCN9A(1.7) mutations account for up to 30% of genetic SFN cases, while SCN10A(1.8) and SCN11A(1.9) mutations are less frequent but well-documented.
- In diabetic neuropathy, chronic hyperglycemia and neuroinflammation lead to altered expression, post-translational modification, and sometimes upregulation of these sodium channels in dorsal root ganglion (DRG) neurons.
  - This may explain why only 30% of diabetic neuropathy patients have pain.
- Non-selective sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine, lacosamide, lidocaine, and mexiletine) may be effective in treating neuropathic pain.



Heinle JW, Dalessio S, Janicki P, Ouyang A, Vrana KE, Ruiz-Velasco V and Coates MD (2024) Insights into the voltage-gated sodium channel, NaV1.8, and its role in visceral pain perception . Front. Pharmacol. 15:1398409. doi: 10.3389/fphar.2024.1398409

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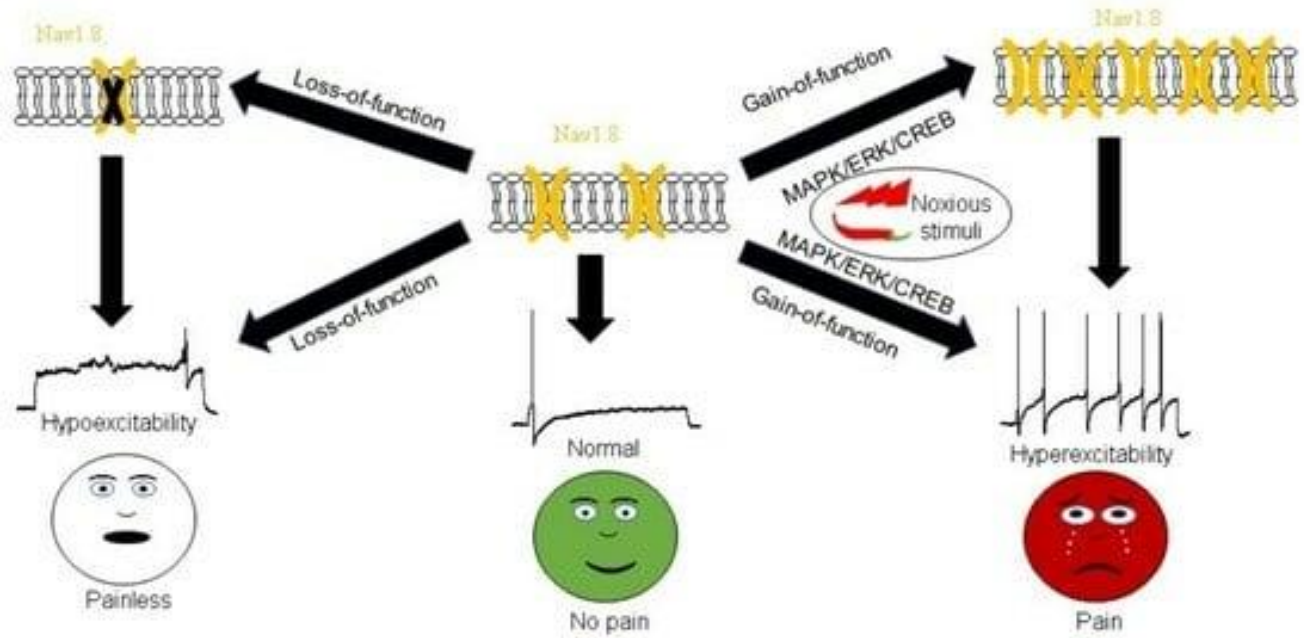
NaV1.8



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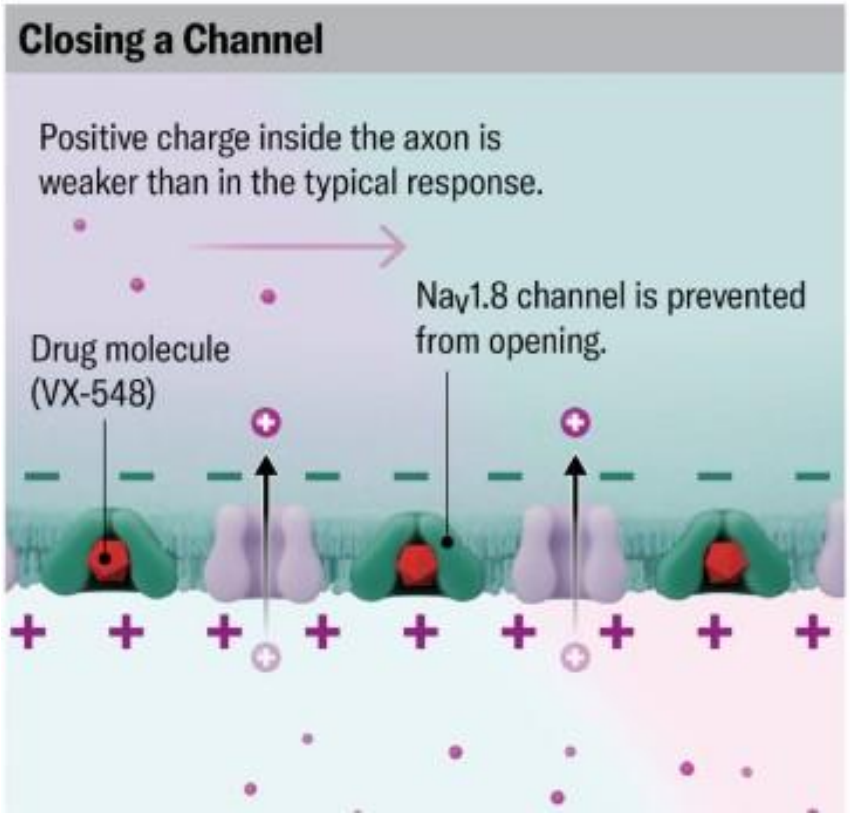
Suzetrigine (Journavx) — A Sodium Channel Blocker for Acute Pain



Cunningham, A. *A New Non-Opioid Painkiller Works by Closing a Channel.* **Scientific American**, Health & Medicine section, December 2024.

- Not studied for more than 14 days.
- Ongoing trials for diabetic neuropathy.

- ANP-230 is a novel agent in clinical development that blocks NaV1.7, NaV1.8, and NaV1.9, showing broad analgesic efficacy in preclinical neuropathic pain models.

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Other Genetic Causes of SF-N

- Transthyretin amyloidosis-6 FDA-approved treatments!
- Fabry's Disease—3 FDA approved treatments
  - Suspect if X-linked inheritance, young onset of episodic severe pain, abnormalities of kidneys, heart, hearing, IBS, blue-black or red lesions in bathing suit distribution.
- Hereditary sensory and autonomic neuropathies (HSAN): Mutations in at least eight genes (e.g., NTRK1, NGFB, SPTLC1, SPTLC2, IKBKAP, WNK1, DNMT1, ATL1.
- COL6A5, TRPA1, TRPV4, Piezo2: These and other ion channel or structural protein gene variants have been associated with SFN and related phenotypes, including neuropathic pain and itch.

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What Role do Antibodies Play?

- TS-HDS: IgM against Trisulfated Heparin Disacharide (a complex sugar on the surface of nerve cells).
  - Associated with capillary pathology and complement deposition.
  - Found in 37% of idiopathic SFN patients. Also present without evidence for neuropathy.
- FGFR-3: IgG against fibroblast growth factor receptor-3
  - Found in 15% of idiopathic SFN patients.

Pilot study of 8 patients treated with IVIg found not benefit.

- CASPR2:contactin-associated protein-like 2—clusters proteins in paranodal region.
  - passive transfer of CASPR2 autoantibodies from patients cause increased pain sensitivity and enhanced sensory neuron excitability in mice.
- Novel autoantibodies MX1, DBNL, and KRT8 are found in iSFN.
- Plexin-D1 IgG found in patients with non-length dependent neuropathy and induces pain in animals.
  - Trials currently underway for IVIg. Rituximab suggested to potentially be helpful.

- The clinical significance of these antibodies is unclear.

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What Should the Work-Up Include?

- History:
  - Sensory symptoms, autonomic symptoms, distribution, time course, associated medical conditions.
- Examination:
  - Abnormal examination for pinprick and temperature with normal vibration and reflexes.
- EMG/NCV?
- Autonomic Testing?

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Blood Work

Serologic testing to find the cause of small fiber neuropathy

First-tier studies	Associated conditions
2-hour oral glucose tolerance test, hemoglobin A_{1c}	Diabetes, impaired glucose tolerance
Extractable nuclear antigen testing for Sjögren syndrome A and B antibodies	Sjögren syndrome
Thyroid-stimulating hormone, free T_4, T_3 levels	Hypothyroidism
Vitamin B_{12}, methylmalonic acid, homocysteine levels	Vitamin B_{12} deficiency
Serum and urine monoclonal protein analysis	Paraproteinemia
Tissue transglutaminase, antigliadin antibodies	Celiac disease
Complete metabolic panel	Renal, hepatic impairment
Complete blood cell count	Hematologic abnormalities
Human immunodeficiency virus (HIV) and hepatitis C virus antibodies (may be second-tier tests if no risk factors)	HIV, hepatitis C
Fasting lipid panel	Hyperlipidemia
Erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody	Inflammatory disease
Liver function tests, gamma-glutamyltransferase	Alcohol abuse
Second-tier studies	
Angiotensin-converting enzyme	Sarcoidosis
Thiamine (vitamin B_1)	Vitamin B_1 deficiency
Pyridoxine (vitamin B_6)	Vitamin B_6 deficiency
Copper	Copper deficiency
Serum and urine monoclonal protein analysis, fat pad analysis, nerve biopsy	Systemic amyloidosis
Paraneoplastic autoantibody panel	Paraneoplastic disease
Ganglionic acetylcholine receptor antibody	Autoimmune autonomic ganglionopathy
Genetic studies	
SCN9A and *SCN10A* genes	Hereditary small fiber neuropathy
GLA gene	Fabry disease
Transthyretin gene	Familial amyloidosis
ABCA1 gene	Tangier disease

Office approach to small fiber neuropathy
Jinny O. Tavee, MD
Cleveland Clinic Journal of Medicine October 2018, 85 (10) 801-812; DOI: https://doi.org/10.3949/ccjm.85a.17124

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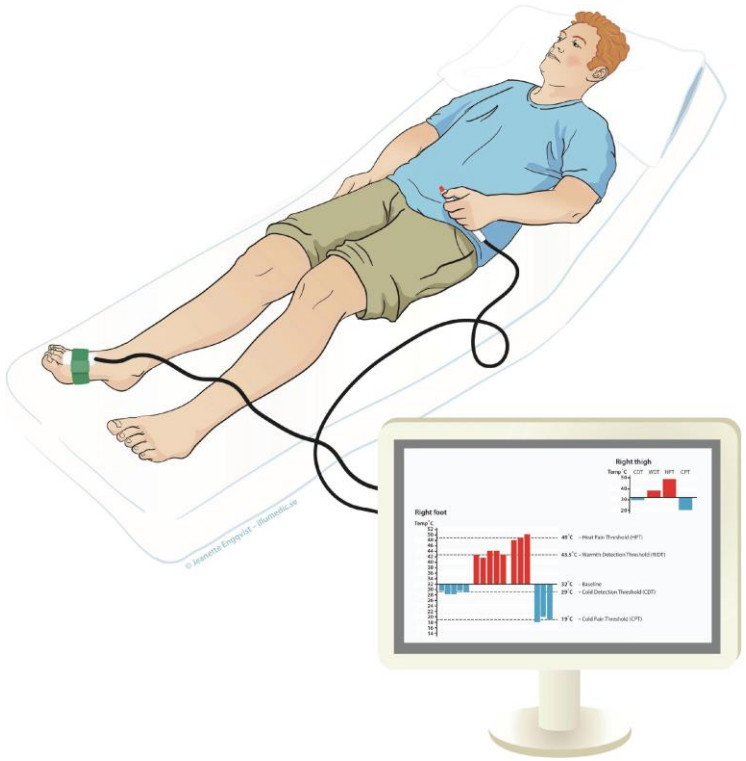
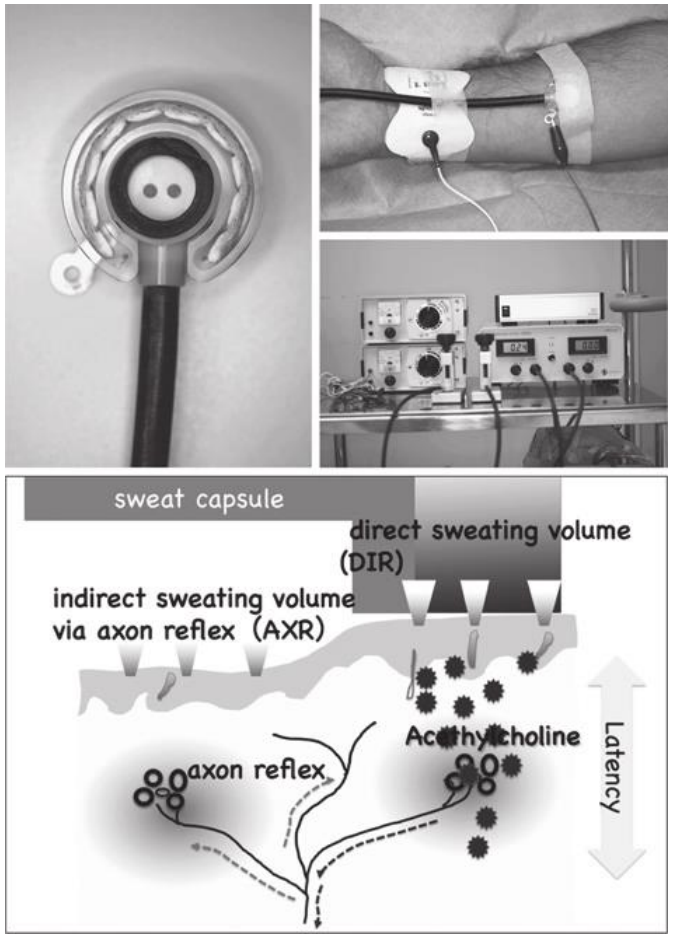
QST vs QSART

QST:



QSART:



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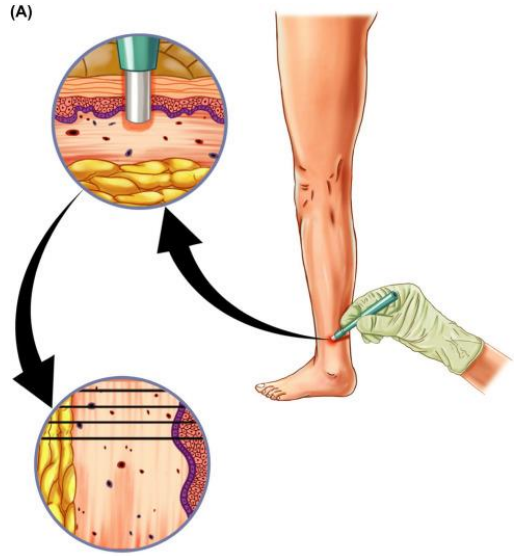
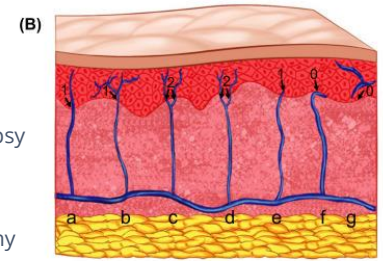
Skin Biopsy?

- 3mm punch biopsy-different fixatives and processing
  - Recent studies looking at standard FFPE protocols so most labs can do.
- Radiolabeled with PGP9.5
- Bright –field microscopy vs immunofluorescence microscopy, but different references.
- Reference values differ between labs –reliability?
- Fiber density is higher in females, declines with age.
- Does not indicate cause of reduced small fiber density.
- Amyloid detection?
- Some use biopsy to exclude small-fiber neuropathy rather than confirming suspected cases.





Chapter:
Chapter 5 Skin biopsy analysis in diabetic neuropathy
Book:
Diabetic Neuropathy
Author:
Páll Karlsson
Publisher:
Elsevier
Date:
2022

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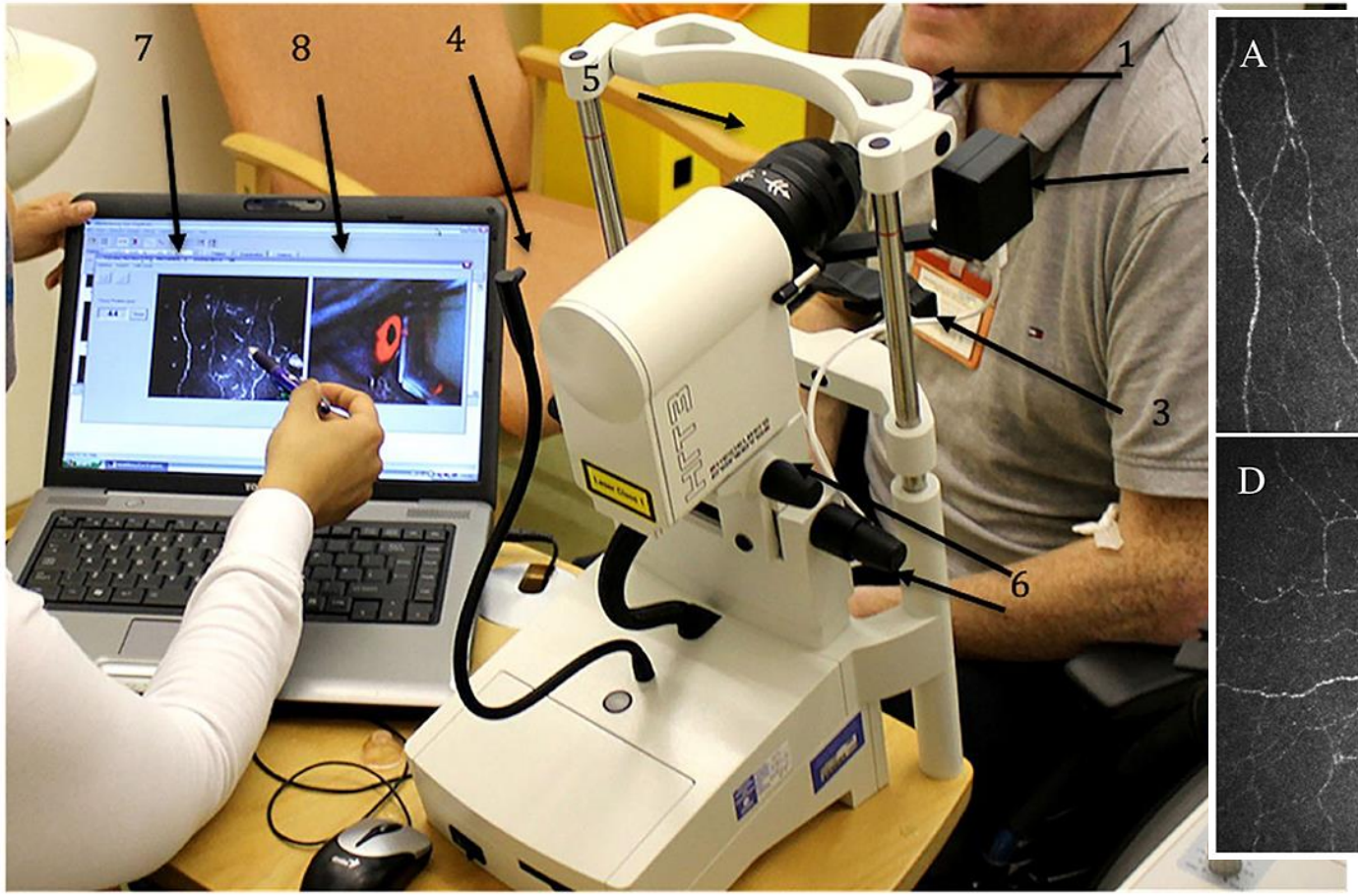
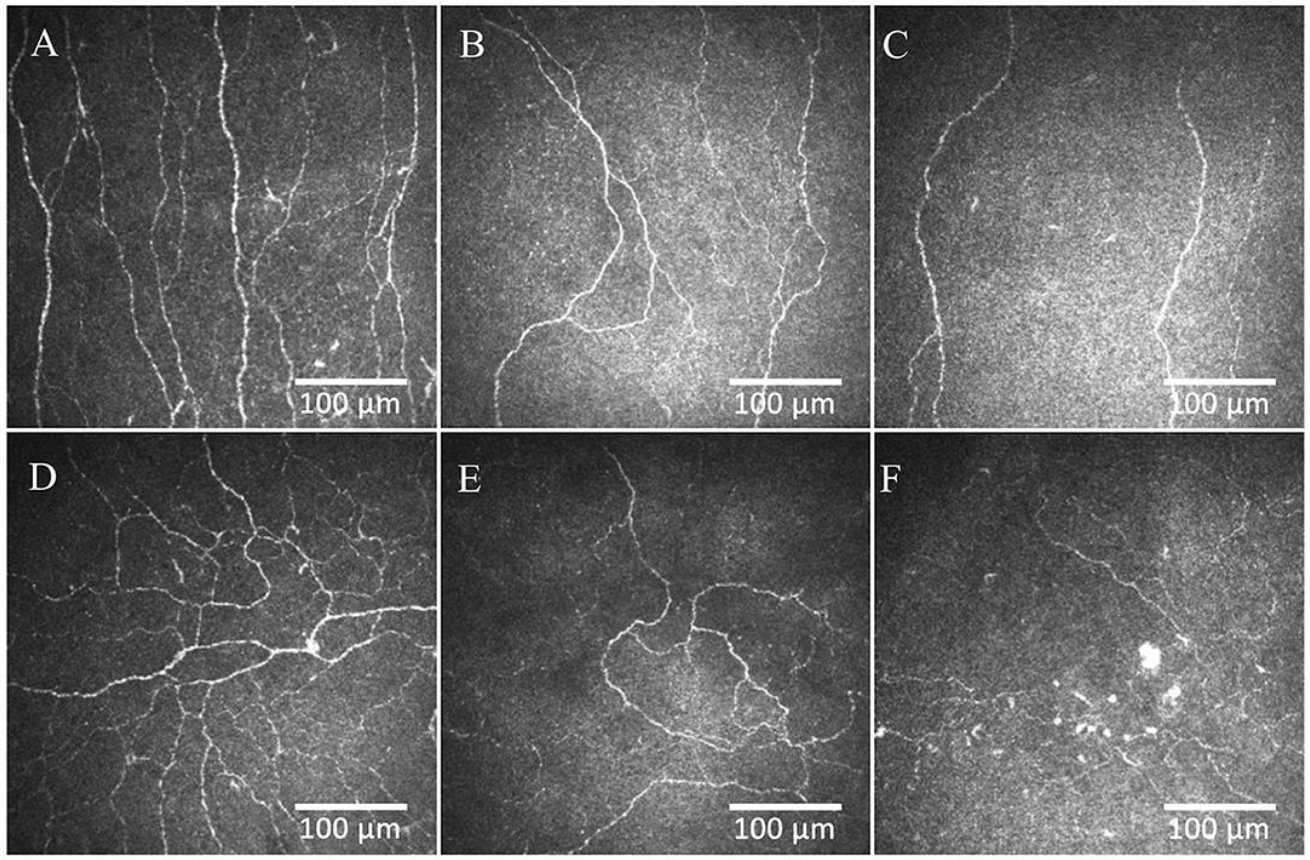
Corneal Confocal Microscopy





Front. Pain Res., 18 August 2021
Sec. Neuropathic Pain
Volume 2 - 2021 |
https://doi.org/10.3389/fpain.2021.725363

Cost, time, user-dependent, standardization, sensitivity, specificity?

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The Gorilla in the Room?

What about IVIg?

- Geerts et al. studied 60 patients with idiopathic small fiber neuropathy with standard IVIg for CIDP and found no difference compared to placebo on pain scales.
- Gibbons et al. treated 16 patients (1/2 placebo) with FGFR-3 and TS-HDS antibodies and found no difference.
- Some are using retrospective Class IV evidence to rationalize use (Oaklander et al.)
- Retrospective study of small-fiber neuropathy in Sarcoidosis showed 62/115 patients felt improvement with IVIg (Tavee et al.)
- Small case series (12 or fewer patients) suggest global improvement in patients with confirmed Sjogren's.
  - Immunosuppressive treatment in these patients may provide modest improvement.
- How do we select patients with lack of inflammatory biomarkers and how do we justify to insurance?

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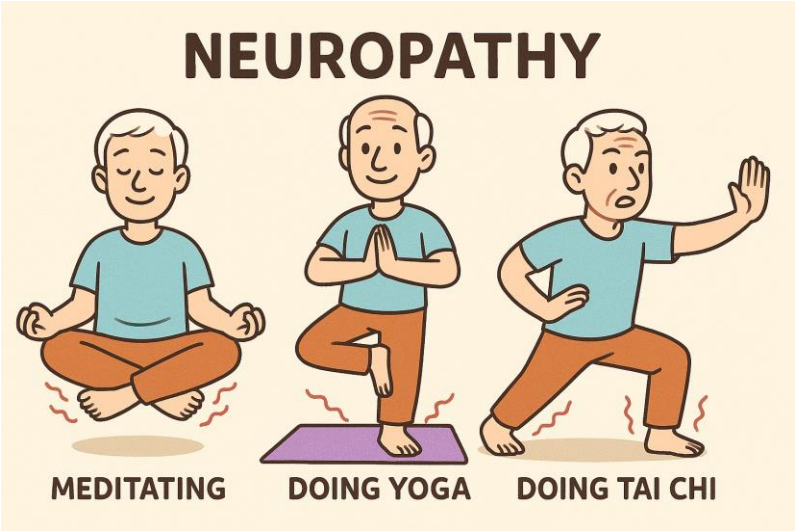
Symptomatic Treatment

- Treat vascular risk factors!
- Weight loss
- Physical Therapy
- Meditation, Cognitive Behavioral Therapy, Yoga, Tai Chi may be beneficial
- Careful about supplements particularly B6 and Zinc



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Neuropathic Pain Prescription Meds

- Opiates as last resort
- Combinations of different classes may work better than single agent
- Gabapentinoids: gabapentin, pregabalin
- Tricyclic antidepressants: amitriptyline, nortriptyline, desipramine
- SNRI's: duloxetine, venlafaxine
- Sodium channel inhibitors: mexiletine, oxcarbazepine, lamotrigine, zonisamide—Suzetrigine?
- Tramadol
- Topicals: lidocaine, capsaicin

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Future Directions

- New, more broadly available FFPE-based technique for skin biopsy
- Better biomarkers for inflammation (immunohistochemistry-staining?)
  - Identify patients who might benefit from immunomodulation
- Selective sodium channel inhibitors for chronic pain
- Better management of autonomic symptoms
- Improve understanding of post-viral mechanisms and relationship to COVID and vaccines.

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Small Fiber Neuropathy: 5 Key Takeaways

- SFN is common but often underdiagnosed – up to 70% of cases are idiopathic.
- Clinical clues: Positive sensory symptoms with preserved reflexes; autonomic involvement in ~50%.
- Associated conditions: Diabetes, autoimmune disease (Sjogren's, Sarcoid), post-viral syndromes (including Long-COVID), and genetic variants.
- Treatment challenges: Limited evidence for immunotherapy; focus on symptom control and risk factor management.
- Future directions: Better biomarkers, selective sodium channel blockers, and improved understanding of post-viral mechanism

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