the Foundation *for* Peripheral Neuropathy

Welcome!

FPN Webinar:

Small Fiber Neuropathy

with Amro Stino, MD

Monday, July 11, 2022

We will begin our presentation shortly.

the Foundation *for* Peripheral Neuropathy

Moderator:

Lindsay Colbert
Executive Director
the Foundation *for* Peripheral Neuropathy

the Foundation *for* Peripheral Neuropathy

Before We Begin

This presentation is being recorded. The recording link will be emailed to you so you can view it again later.

Submit your questions anytime via the Questions Box. We will try to answer them during this webinar.

If you are having trouble with the audio using your computer, you can dial in by phone (check your email for dial-in instructions).

the Foundation *for* Peripheral Neuropathy

Presenter:

Amro Stino, MD
Michigan Medicine

Small Fiber Neuropathy – testing, clinical approach, and research advances

Amro Stino, MD

Assistant Professor,
Neuromuscular Medicine
Director, Peripheral Nerve Center
Co-director, Autonomic Lab

Michigan Medicine

Objectives

- Be aware of both somatic and autonomic testing modalities in SFN evaluation
- Appreciate differential diagnostic considerations in SFN
- Recognize various applications of small fiber testing

Outline

- Why is small fiber neuropathy evaluation important?
- Fiber anatomy
- Testing modalities
  - Somatic
  - Autonomic
- Typical clinical presentations
- Interesting applications
  - Metabolic Syndrome and Diabetic neuropathy research
  - Erythromelalgia
  - Fibromyalgia

Why objective small fiber testing important?

- Certain patients may have early small fiber involvement that precedes large fiber involvement
- Small fiber neuropathy is reversible, whereas large fiber not as much
- Helps objectively separate patients with underlying neuropathy from fibromyalgia and somatization
- **Predicated on a good history and exam**

Anatomy Overview

- **A-beta** – large sensory myelinated (vibration, position). ~100m/s
- **A-delta** – small myelinated (cold temperature). ~20m/s
- **C somatic** – small unmyelinated (hot temperature). ~1m/s
  - Tested for on skin biopsy
- *Unmyelinated: myelinated ratio is >4:1*
- *2/3 myelinated are small diameter*

Nerve composition

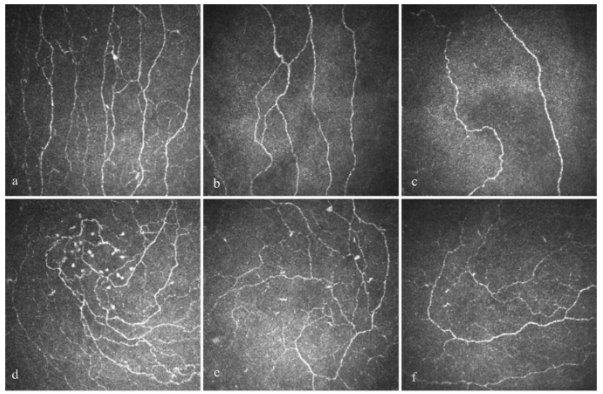
- **C autonomic** – small unmyelinated (sweat). ACh.
  - Pre-ganglionic sympathetic bodies in spine (intermediolateral cell column) – myelinated (as are pre-ganglionic PS)
  - Exit white rami
  - Synapse in para/pre-vertebral sympathetic ganglia
    - Cholinergic fibers synapse on sweat glands (sudomotor)
    - Adrenergic fibers synapse on blood vessels (vasomotor)
      - Peripheral (redness / swelling feet)
      - Splanchnic vasculature (orthostatic hypotension)
  - **Tested on QSART**

SOMATIC SENSORY TESTS

- Corneal confocal microscopy
- Quantitative Sensory Testing (QST)
  - Thermal perception threshold testing
- Skin Biopsy – *gold standard*
  - Intraepidermal Nerve Fiber Density (IENFD)
- Point of Care Devices

Corneal confocal microscopy

- Allows detailed evaluation of the corneal sub-basal nerve plexus
- A rapid, validated, non-invasive and *in vivo* measure of small fiber function in diabetic neuropathy
- Comparable accuracy to IENFD
- Correlates with functional measures of neuropathy severity
- Tracks improvement in diabetic patients after simultaneous pancreas-kidney transplant.



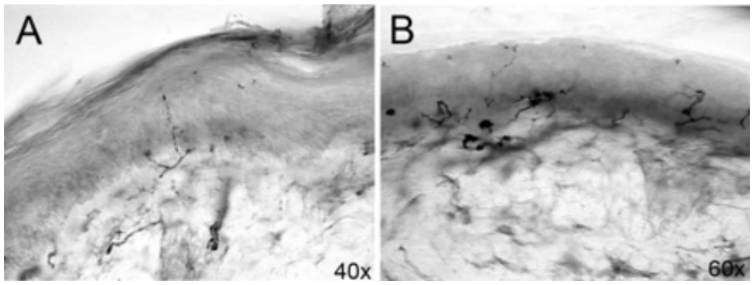
Article | Open Access | Published: 25 February 2020

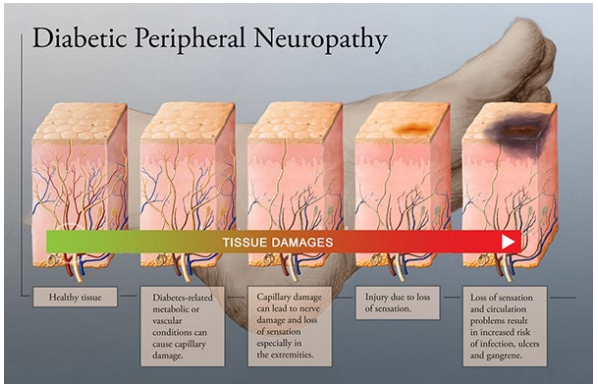
Corneal confocal microscopy detects small nerve fibre damage in patients with painful diabetic neuropathy

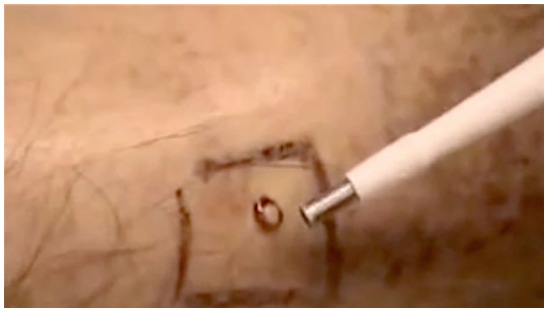
Alise Kalteniece, Maryam Ferdousi, Shazli Azmi, Womba M. Mubita, Andrew Marshall, Giuseppe Lauria, Catharina G. Faber, Handrean Soran & Rayaz A. Malik

Scientific Reports **10**, Article number: 3371 (2020) | Cite this article

Skin biopsy–
intraepidermal nerve fiber density (IENFD)







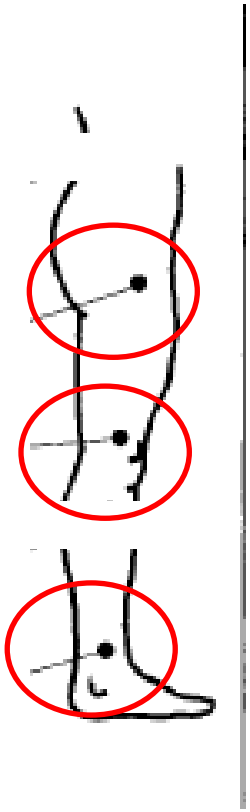
Skin Biopsy

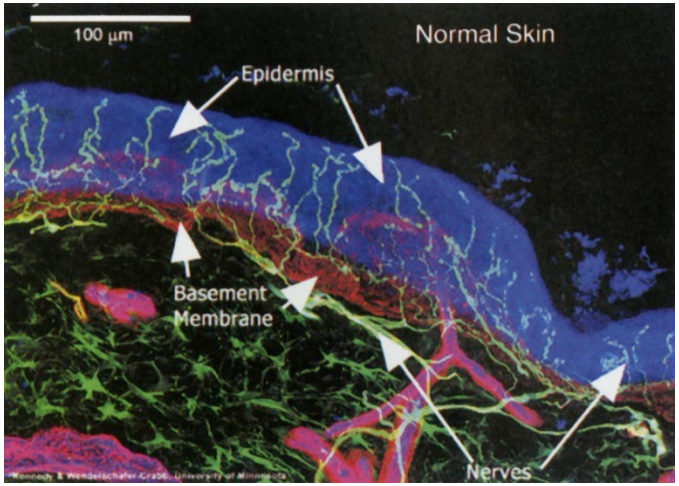
- Assesses **somatic C fiber** nociceptive endings
- **Somatic small fibers** – terminate in ***epidermis (IENFD)****, on hair follicles, and in many encapsulated receptors* – Meissner and Merkel
- **Autonomic small fibers** – terminate in *sweat (sudomotor), blood vessels (vasomotor)*

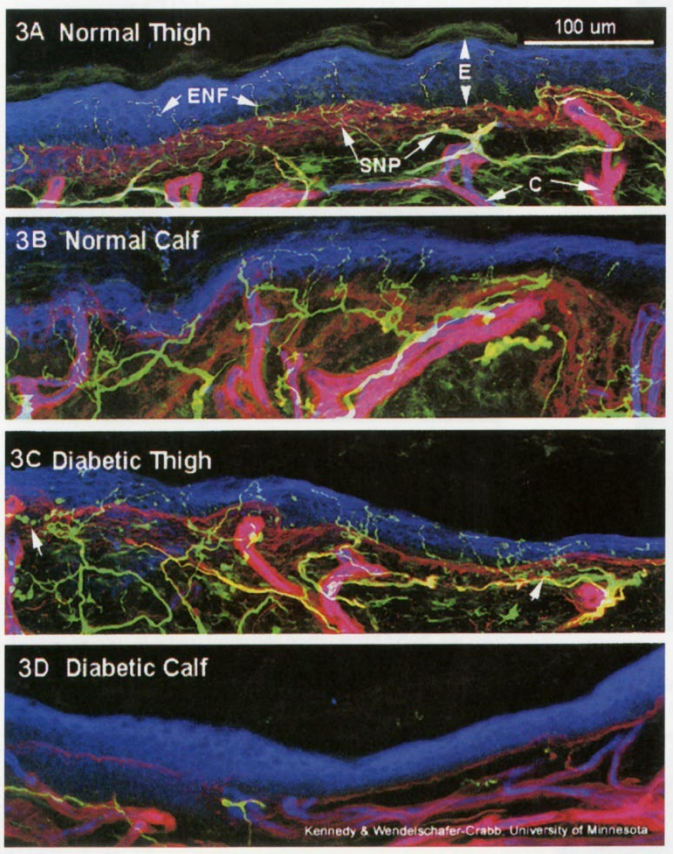
Skin Biopsy Locations

Test of IntraEpidermal Nerve Fiber Density (IENFD)

- **Distal leg:**
  - 10cm above lateral malleolus (most normative data)
- **Distal thigh:**
  - 10cm above lateral aspect of patella
- **Proximal thigh:**
  - 10cm below anterior superior iliac spine
- Stained with **pan-axonal marker protein gene product 9.5 (PMP-9.5)**




100 µm
Normal Skin
Epidermis
Basement
Membrane
Nerves


3A Normal Thigh
100 um
E
ENF
SNP
C
3B Normal Calf
3C Diabetic Thigh
3D Diabetic Calf
Kennedy & Wendelschafer-Crabb University of Minnesota

QST / Nerve Check – Thermal perception threshold

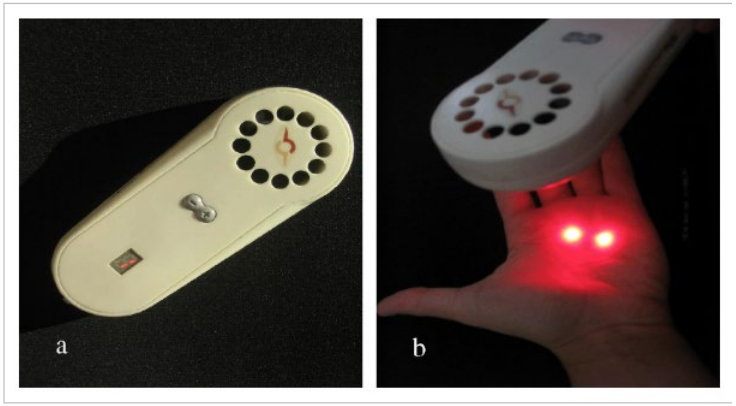
- Uses Quantitative Sensory Testing (QST)
- Captures early diabetic small fiber neuropathy quite well
- Can distinguish healthy patients from those with small fiber neuropathy.
- Can distinguish painful from non-painful SFN
- However, **lack of consensus** on stimulus application, location, and sensations tested hinders it more widespread adoption.
- QST provides relatively consistent inter and intra rater reliability, and is now routinely used as an endpoint in multi-center clinical trials of DPN

Neurometer

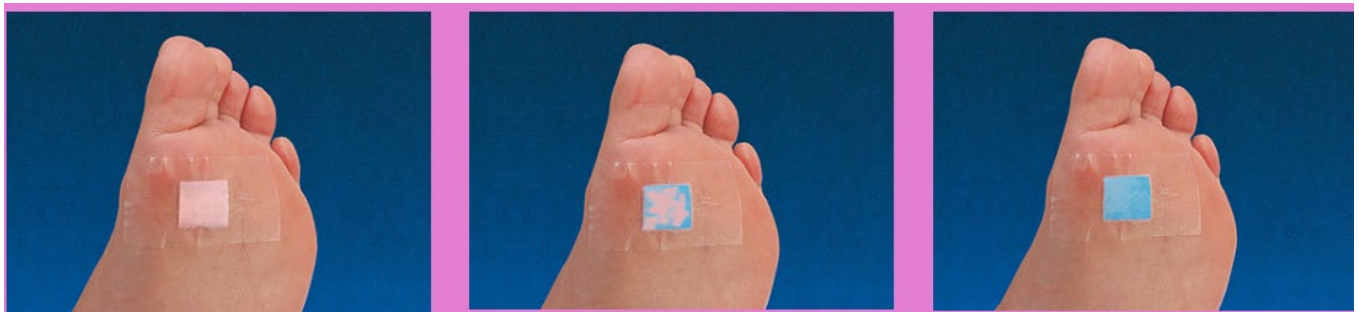
- Applies a constant current via surface electrodes across three currencies – 2000 Hz, 250 Hz, and 5 Hz –
- to selectively stimulate different nerve fiber types

NeuroQuick

- A portable device that assesses **cold perception threshold**.
- In-built fan that emits cold air at velocities of varied intensity onto the dorsum of the foot.
- The NeuroQuick threshold is defined as the airflow at which the subject first recognizes the stimulus



Neuropad / plaster test - *sudomotor*



- Neuropad is sensitive (65-100%) in the diagnosis of DPN and has a high negative predictive value (63-100%),
- Poor specificity (32-78.5%) and positive predictive value (23.3-93.2%)

Sudoscan -

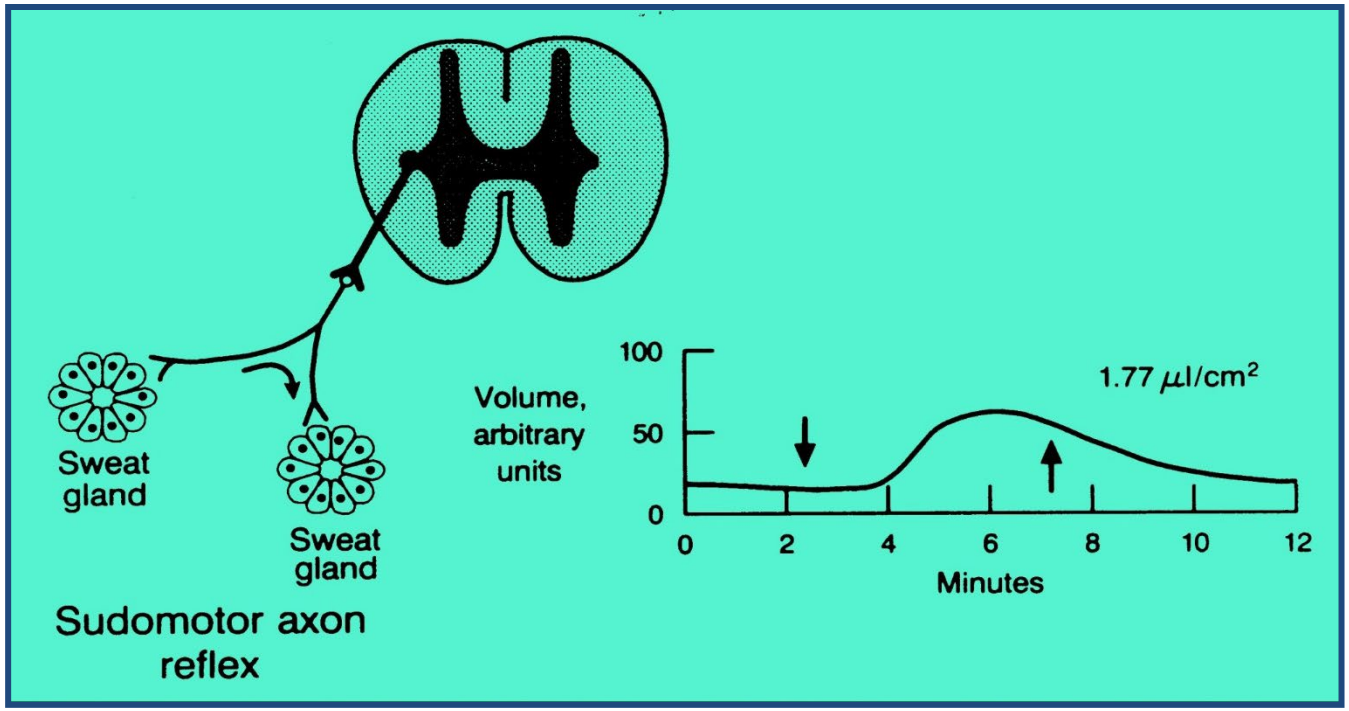
- Uses concept of electrochemical conductance to assess for neuropathy.
- Palms and soles placed on examining electrodes and a low-voltage constant electrical current is applied

Autonomic Testing

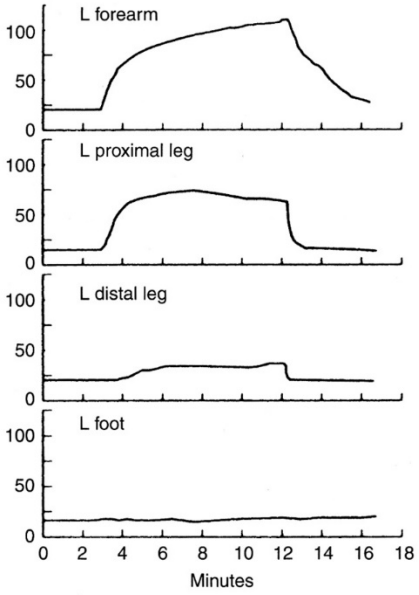
- Often overlaps with small fiber somatic sensory loss
- Can be used as a surrogate or corollary to evaluate for small fiber sensory loss (QSART)

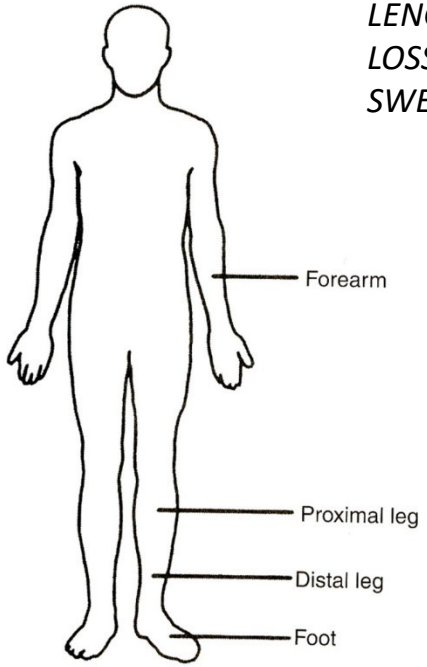
AUTONOMIC TESTS

- Autonomic Reflex Screen (**ARS**)
  - Quantitative Sudomotor Axon Reflex Test *(1)**QSART***
  - **Cardiovagal testing**
    - ***(2) HRDB***
    - **HR variability with *(3) Valsalva***
  - **Adrenergic testing**
    - ***(4) Tilt Study***
    - ***(3) Valsalva*** phase II late and phase IV analysis
- Thermoregulatory Sweat Test (TST)


Sweat gland
Sweat gland
Sudomotor axon reflex
Volume, arbitrary units
100
50
0
1.77 μl/cm²
0
2
4
6
8
10
12
Minutes

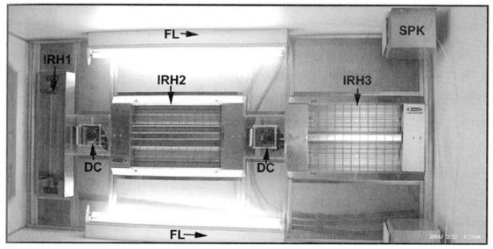
QSART

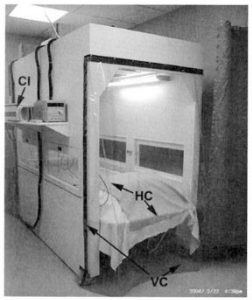


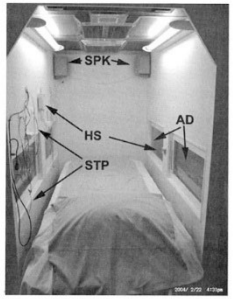


LENGTH DEPENDENT SWEAT LOSS – DISTAL IS < 1/3 PROXIMAL SWEAT VOLUME

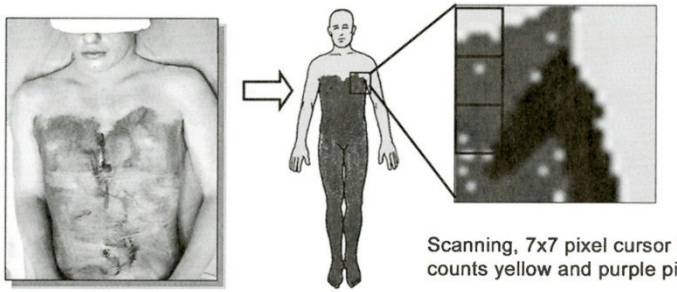
Thermoregulatory Sweat Test







Quantifying the TST (TST%)



Scanning, 7x7 pixel cursor block counts yellow and purple pixels

31402 / 92737

Pixel block count ratio = 31402/92737 x 100

= 34 % anhidrosis

TST

Nicely shows length dependent or independent patterns

Length dependent Patterns – distal-predominant

- Diabetes
- Erythromelalgia
- Fabry

Length independent Patterns - patchy

- Sjogren's syndrome
- Paraneoplastic
- Leprosy –
  - *patchy (cooler) body areas – lepromatous*
  - *Scattered, circular – tuberculoid*

Autonomic impairment in painful neuropathy

V. Novak, MD, PhD; M.L. Freimer, MD; J.T. Kissel, MD; Z. Sahenk, MD, PhD; I.M. Periquet, MD; S.M. Nash, MD; M.P. Collins, MD; and J.R. Mendell, MD

- Prospective evaluation of 92 patients with painful neuropathy, half with abnormal NCS (group 1), half normal NCS (group 2)
- Reported pain, secretory, vasomotor changes, and impotence
- **QSART** – abnormal in 72.8% of patients
- **Cardiac vagal** – impaired in 63%
- **Orthostatic hypotension** – 42%
- *QSART correlated with IENF density (0.86)*
- Patients with abnormal NCS (group 1) had more severe autonomic reflex screen changes

DETECTION OF SMALL-FIBER NEUROPATHY BY SUDOMOTOR TESTING

VICTORIA A. LOW, MS, PAOLA SANDRONI, MD, PhD,
ROBERT D. FEALEY, MD, and PHILLIP A. LOW, MD

Department of Neurology, Mayo Clinic, Guggenheim 811,
200 First Street SW, Rochester, Minnesota 55905, USA

Accepted 27 February 2006

- 125 patients with clinical or pure distal small fiber neuropathy, as per NCS or history
- Included TST and QSART
- Excluded those with significant weakness, large fiber sensory loss, generalized autonomic failure, or motor amplitude reduction

DETECTION OF SMALL-FIBER NEUROPATHY BY SUDOMOTOR TESTING

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Department of Neurology, Mayo Clinic, Guggenheim 811, 200 First Street SW, Rochester, Minnesota 55905, USA

Accepted 27 February 2006

- Length dependence (QSART *or* TST abnormal) seen in 93%
- QSART – 62% met criteria for length dependence – distal sweat output <1/3 proximal
- Distal TST *and* length dependent QSART abnormal in 43%
- Up to 60% had cardiovagal or adrenergic dysfunction
- Etiologies: idiopathic (73%) > hereditary (18%) > diabetes (10%)

Causes of Small Fiber Neuropathy

© 2002 Wiley Periodicals, Inc. *Muscle Nerve* **26:** 173–188, 2002

SMALL-FIBER NEUROPATHY

DAVID LACOMIS, MD

Departments of Neurology and Pathology (Neuropathology), University of Pittsburgh School of Medicine, UPMC Presbyterian, 200 Lothrop Street, F878, Pittsburgh, Pennsylvania 15213, USA

Accepted 3 April 2002

Table 3. Potential causes of small-fiber neuropathy and suggested evaluation.

Disorder	Evaluation
Diabetes or impaired glucose handling	2-h oral glucose tolerance test
Systemic amyloidosis	Serum and urine protein electrophoresis, consider biopsy of nerve, muscle, abdominal fat, or rectum
Alcohol	History
Sjögren's syndrome	ANA, SS-A, SS-B antibodies, Schirmer tear test, Rose-bengal corneal staining, lip biopsy
Pharmacologic toxins, e.g., metronidazole	History
Environmental toxins	History, specialized toxicologic studies
Acquired immunodeficiency syndrome	HIV antibody
Hyperlipidermia	Fasting lipid panel
Familial "burning feet" neuropathy	History, exclude amyloidosis
Tangier disease	Alpha (high-density) lipoproteins
Familial amyloidosis	Transthyretin gene test, biopsy of affected tissues
Fabry's disease	Alpha-galactosidase assay
Hereditary sensory neuropathies	History, examination, possible DNA study when available
Monoclonal gammopathy	Serum and urine protein electrophoresis, quantitative immunoglobulins

Common Causes

- Workup is generally the same as for large fiber neuropathies –
  - **Diabetes**, IGT, IFG (OGTT)
  - **Alcohol** and thiamine deficiency
  - **Vitamin B12** (and MMA)
  - **MGUS** (Immunofixation electrophoresis)
  - **Chemotherapy**

Diabetic polyneuropathy (DPN) and prediabetic polyneuropathy

- **Diabetes mellitus (DM – type 1 or type 2)**
  - Fasting glucose > 126
  - 2h oral glucose tolerance test > 200
- **Impaired fasting glucose (IFG)**
  - Fasting glucose > 100
- **Impaired glucose tolerance (IGT)**
  - 2h oral glucose tolerance test > 140
  - of IGT population, 30% progress to DM, 25% revert to prandial normoglycemia
- *Do not rely on A1c < 6.5 to 'exclude' diabetic polyneuropathy as potential cause*

Diabetic polyneuropathy management

- Interventions:
  - Moderate aerobic exercise
    - 30 min daily or 60 min three times per week
  - T1DM – glycemic control important
  - T2DM – exercise, diet, and weight control more important
    - Control hypertriglyceridemia
  - alpha lipoic acid 600 mg
    - Trials showed some benefit, but failed to meet primary endpoints (did not get FDA approval)
  - Higher incidence B12 deficiency with metformin –
  - Pain management
  - **Exercise – 30 min daily or 60 min three times a week**

Glucose dysmetabolism + SFN

- Drops > 2% A1c points over 3mo period poses an increased neuropathy risk
  - **Treatment Induced Neuropathy of Diabetes (TIND)**
- 2-6 weeks after glucose improvement
- Length dependent or independent

Chemotherapy-induced polyneuropathy

- Can occur immediately, subacutely, or chronically after exposure
- Certain drugs have stronger associations than others
- Certain drugs are dose-dependent (others are not)
- Most cause sensory (not motor) deficits, and are most disabling due to pain and balance problems
- Depending on severity of neuropathy, oncologist may choose to switch chemotherapy or continue with same chemotherapy and manage symptoms

Vitamin B12 deficiency

- Clinically presents with polyneuropathy or myeloneuropathy (combined polyneuropathy + spinal cord damage)
  - Myeloneuropathy has increased reflexes at knees, absent reflexes at ankles
- Look for systemic features
  - Confusion, memory loss
  - Depression
  - Centrocecal scotomas or unexplained vision loss
  - Tongue changes
- Imaging of brain or cervical spine may be indicated

Vitamin B12 deficiency

- **International** cutoff **400**.
- **US** cutoff of **200** is **likely missing many cases.**
- Check methylmalonic acid **(MMA)**
- If MMA hi and B12 nl = B12 deficiency > treat
- Personally, if **B12<400** then I treat as well
- Always **screen**, and **sometimes preemptively treat**, in **high risk:**
  - Alcoholics
  - Vegans or vegetarians
  - Bariatric surgery or colectomy patients
  - Inflammatory bowel disease
  - Pernicious anemia
  - Metformin use
  - Anorexia or bulimia.
- **Treatment** - 1000mcg IM daily for 1 week then weekly for 1 month then monthly for 1 year. I often also start daily PO 2000mcg indefinitely to cover once IM complete.
- If patients are deficient for one of B12, thiamine (B1), or folate, high chance s/he is deficient for others, so keep broad differential

Alcohol and thiamine (B1)

- How much EtOH is enough to cause polyneuropathy?
  - No good way to quantify
- CAGE questionnaire helpful, but does not always capture
  - If patient has few drinks over decades (even if not dependent or abusive), probably has neuropathy
  - Total lifetime dose EtOH is the only predictive factor
- Use subtle clues on lab work – Mg, Phos, borderline low B12
- Patients at high risk of thiamine (B1) deficiency
  - B1 test not most accurate, so go by clinical suspicion – replace 100 mg PO daily
  - Still send testing if suspecting.
- Thiamine deficiency can also cause hoarseness of voice (recurrent laryngeal nerve). Common in bariatric surgery patients. Lactic acid can be elevated.
  - Wet beriberi – also have congestive heart failure.
  - Dry beriberi – isolated peripheral nerve
  - Can sometimes present subacutely and mimic GBS

Less common (but important) causes

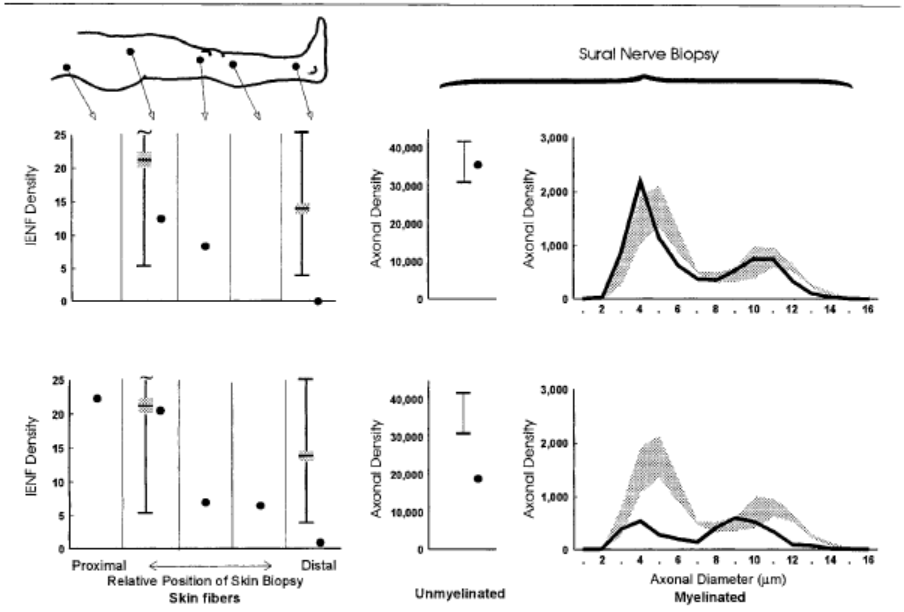
- …with some key exceptions
  - Screen more aggressively for certain causes
    - ***Sjogren's syndrome**, especially if pain and sensory loss onset length independent
    - ***Hereditary transthyretin amyloidosis** (especially if there is strong autonomic involvement)
    - ***Hereditary sensory autonomic neuropathies (HSANs)**
    - **Fabry's disease** (if there are suggestive clinical features)
    - **Treatment induced neuropathy of diabetes (TIND)**

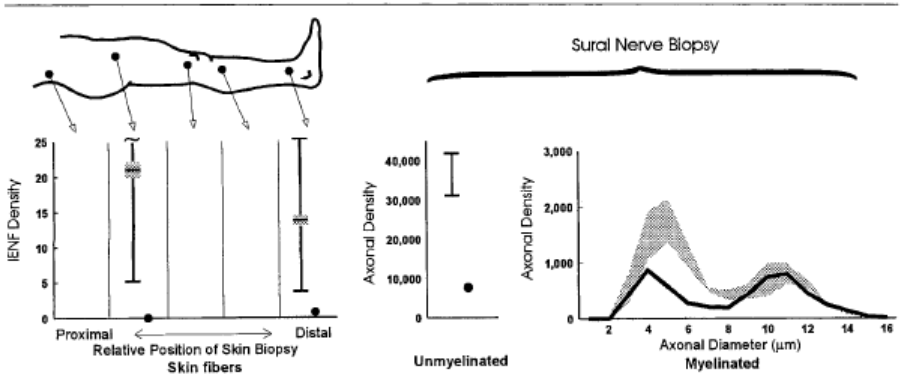
Small-Fiber Sensory Neuropathies: Clinical Course and Neuropathology of Idiopathic Cases

Neil R. Holland, MB BS,* Thomas O. Crawford, MD,* Peter Hauer, BS,* David R. Cornblath, MD,* John W. Griffin, MD,*† and Justin C. McArthur, MB BS, MPH*‡

Two categories SFN presentation

- chronic progressive SFSN – 28 patients
  - IENFD reduced at both thigh (low normal) + leg (low)
  - QST – 23 of 28 abnormal
    - thermal threshold abnormal in 57%
    - Vibratory abnormal in 30%
- acute generalized hypersensitivity – 4 patients
  - IENFD reduced at both thigh and calf (both low)
  - described feeling ‘sunburned’
  - monophasic followed by slow recovery


Sural Nerve Biopsy
IENF Density
Axonal Density
Axonal Density
Proximal
Distal
Relative Position of Skin Biopsy
Skin fibers
Unmyelinated
Axonal Diameter (µm)
Myelinated

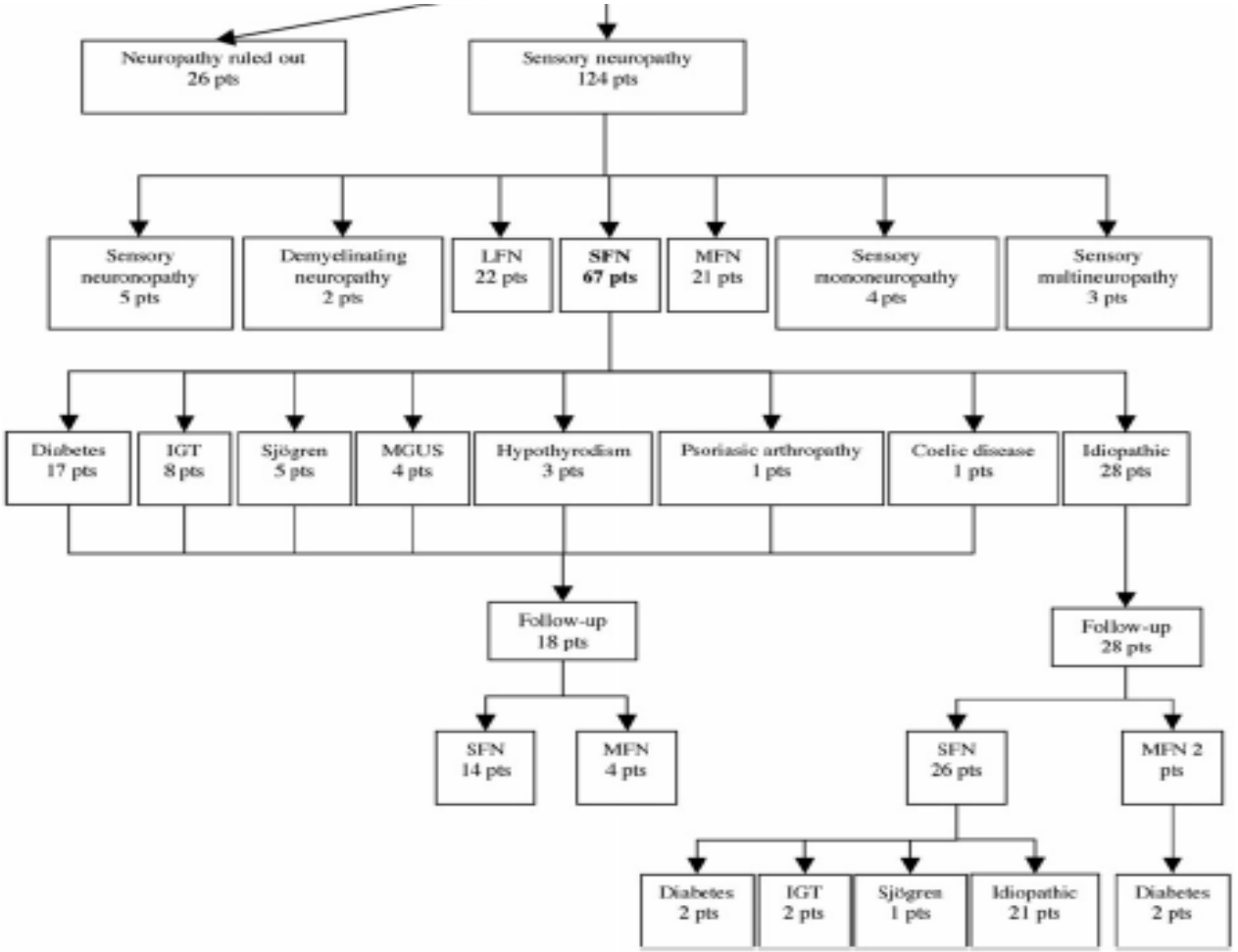

Sural Nerve Biopsy
IENF Density
Axonal Density
Axonal Density
Proximal
Distal
Relative Position of Skin Biopsy
Skin fibers
Unmyelinated
Axonal Diameter (µm)
Myelinated

The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology

Grazia Devigili,[1] Valeria Tugnoli,[2] Paola Penza,[3] Francesca Camozzi,[3] Raffaella Lombardi,[3] Giorgia Melli,[3] Laura Broglio,[4] Enrico Granieri[1] and Giuseppe Lauria[3]

[1]Neurological Clinic, University of Ferrara, [2]Neurophysiological Unit, S. Anna General Hospital, Ferrara, [3]Neuromuscular Diseases Unit, National Neurological Institute 'Carlo Besta', Milan and [4]Neurological Clinic, University of Brescia, Italy

- Identified 68 with **pure SFN** –
  - – needed 2 of the 3 following tests to be abnormal
    - Clinical
    - QST
    - biopsy
- **Etiology - unknown in 41%** of patients
- At **2 year follow up, determined in 25% of those**


Neuropathy ruled out
26 pts
Sensory neuropathy
124 pts
Sensory neuronopathy
5 pts
Demyelinating neuropathy
2 pts
LFN
22 pts
SFN
67 pts
MFN
21 pts
Sensory mononeuropathy
4 pts
Sensory multineuropathy
3 pts
Diabetes
17 pts
IGT
8 pts
Sjögren
5 pts
MGUS
4 pts
Hypothyrodism
3 pts
Psoriasic arthropathy
1 pts
Coelic disease
1 pts
Idiopathic
28 pts
Follow-up
18 pts
Follow-up
28 pts
SFN
14 pts
MFN
4 pts
SFN
26 pts
MFN 2
pts
Diabetes
2 pts
IGT
2 pts
Sjögren
1 pts
Idiopathic
21 pts
Diabetes
2 pts

Sjogren's small fiber ganglionopathy

- Most common is length dependent sensorimotor polyneuropathy
- Can produce sensory polyganglionopathy – large fiber ataxia and areflexia with minimal weakness
- Can also produce a small fiber length dependent neuropathy or ganglionopathy

Painful small-fiber neuropathy in Sjögren syndrome

J. Chai, D. N. Herrmann, M. Stanton, R. L. Barbano, E. L. Logigian

First published September 26, 2005, DOI: https://doi.org/10.1212/01.wnl.0000176034.38198.f9

- 20 consecutive patients with Sjögren neuropathy
- 16 had burning feet
- 12 had non-length-dependent sensory symptoms.
- Leg and thigh skin biopsies (n=13) - 7 showed reduced IENFD
- IENFD loss **frequently non length dependent**
- **Take Home – length independent small fiber onset = Sjogren's until proven otherwise**

Non-length dependent small fibre neuropathy/ ganglionopathy

K C Gorson,[1] D N Herrmann,[2] R Thiagarajan,[2] T H Brannagan,[3] R L Chin,[3] L J Kinsella,[4] A H Ropper[5]

- N = 23 [12 men + 11 women]
- Retrospective chart review
- Patients referred to 4 tertiary centers for 'burning skin syndrome' or non-length dependent pain of unknown cause
  1. Proximal limb, face, or trunk onset
  2. Onset in face, scalp, mouth, tongue, trunk, hands, arm, or proximal legs before feet
  3. Pain in proximal and distal regions concurrently (whole body)

Findings

- Most common diagnosis – **Sjogren's.**
  - **Required minor lip salivary gland biopsy**
- Diagnosis of small fiber ganglionopathy predicated on:
  1. Early proximal involvement – history / exam
  2. Skin biopsy gradient – thigh (+) / calf (–) case
  3. Slow progressive course

Transthyretin Amyloidosis (TTR)

- Liver produces mutated TTR protein
- Results in unstable tetramers > dissociate into monomers > form oligomers > form fibrils > deposit in multiple end organs
  - autonomic and somatic sensory nerves
  - heart, kidney, gastrointestinal tract
  - vitreous fluid, spinal canal, and carpal tunnel.
- Family history of unexplained peripheral neuropathy or recurrent carpal tunnel syndrome suggests
- Most common worldwide mutation = Val30Met mutation (screen for Portuguese, Brazilian, Swedish, Japanese ethnicity).
  - African Americans = Val122Ile mutations most common.
- TTR further subdivided into early onset (<50y) and late onset (>50y)
  - Most autonomic manifestations are in early onset, not late onset TTR

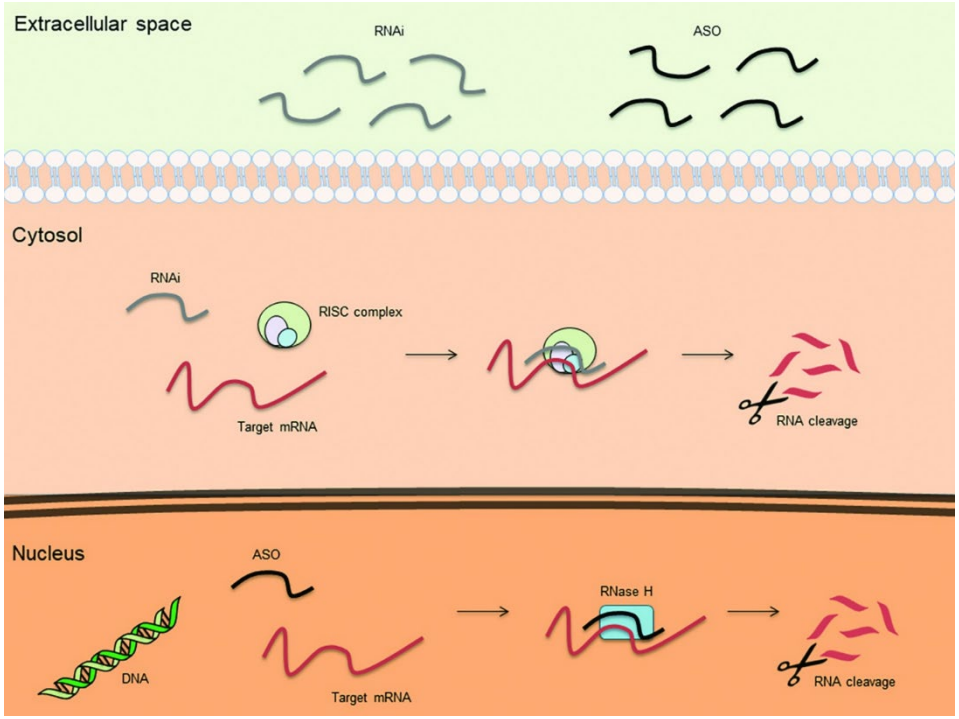
TTR Amyloid Neuropathy

- Next Generation sequencing of mutation now commercially available
- Technetium-99 pyrophosphate cardiac imaging now precludes need for endocardial biopsy

TTR Amyloid Neuropathy

- Two new FDA-approved gene therapies
- **Patisiran**, an RNA interference therapy, is administered intravenously once every 3 weeks
  - Not only halts, but also reverses neuropathy.
  - Lessens autonomic impairment in TTR amyloid patients as compared to untreated patients.
- **Inotersen**, an antisense oligonucleotide (ASO) administered intravenously once weekly, inhibits hepatic production of transthyretin by binding to TTR mRNA and targeting it for degradation via RNAase.

TTR Amyloid Neuropathy



RNAi (Patisiran) acts in cytosol

ASO (Inotersen) acts in nucleus

Hereditary Sensory Autonomic Neuropathy

IN THE LAB

A mysterious disease has plagued this family for generations. They may be on the verge of answers

By KAREN WEINTRAUB / AUGUST 14, 2017

Hereditary Sensory Autonomic Neuropathy (HSAN)	Onset	Inheritance	Sensory	Motor	Autonomic	Allied Features
HSAN I	**Juvenile to adult**	**AD**	**Marked**	**Minimal**	**Minimal**	**Foot ulcers or amputations; bone deformities and osteomyelitis; hearing loss occurs occasionally**
HSAN II	Childhood	AR	Marked	Minimal	Absent or minimal	Some patients develop ulcers, atrophy, and hyporeflexia
HSAN III/ Familial dysautonomia	Congenital	AR	Modest Decreased sensitivity to pain and temperature	Absent	Marked Autonomic crises	Recurrent pneumonias; absence of tears
HSAN IV	Congenital/ childhood	AR	Modest Congenital sensory loss affecting perception of pain and temperature	Absent	Modest Anhidrosis	Oral self-mutilation; fingertip biting; repeated bone fractures and joint trauma
HSAN V	Early childhood to adult	AR	Modest Congenital reduced pain and anhidrosis	Absent	Minimal Sweating normal or reduced	Charcot joints and fracture

Interesting Applications SFN testing

- **Metabolic syndrome and T2DM research** on nerve regeneration
- **Erythromelalgia**
- **Fibromyalgia**

Interesting Application # 1

Metabolic Syndrome (MetS) / Type 2 Diabetic Neuropathy (T2DM) Research

NCEP ATP III Proposed Diagnostic Criteria of Metabolic Syndrome	
Diagnostic Criteria (any 3 below)	**Defining Points**
Elevated waist circumference[a]	Men: >102 cm (>40 in) Women: >88 cm (>35 in)
Elevated TG	≥150 mg/dL *OR* Drug treatment for elevated TG
Reduced HDL-C	Men: <40 mg/dL Women: <50 mg/dL *OR* Drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mmHg systolic blood pressure *OR* ≥85 mmHg diastolic blood pressure *OR* Drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dL *OR* Drug treatment for elevated glucose

Interesting Application # 1 – MetS and T2DM Research

Lifestyle Intervention for Pre-Diabetic Neuropathy

A. Gordon Smith, MD[1,2]
James Russell, MD[3]
Eva L. Feldman, MD, PhD[3]
Jonathan Goldstein, MD[4]
Amanda Peltier, MD[3]
Sheldon Smith, BS[1]
Jouhaina Hamwi, BS[1]
Donald Pollari, BS[1]
Billie Bixby, BS[1]
James Howard, BS[1]
J. Robinson Singleton, MD[1]

- 32 subjects with IGT
- 3-mm skin biopsies with measurement of IENFD at the distal leg and proximal thigh at baseline and after 1 year
- Each received individualized diet and exercise counseling as a standard of care

Interesting Application # 1 – MetS and T2DM Research

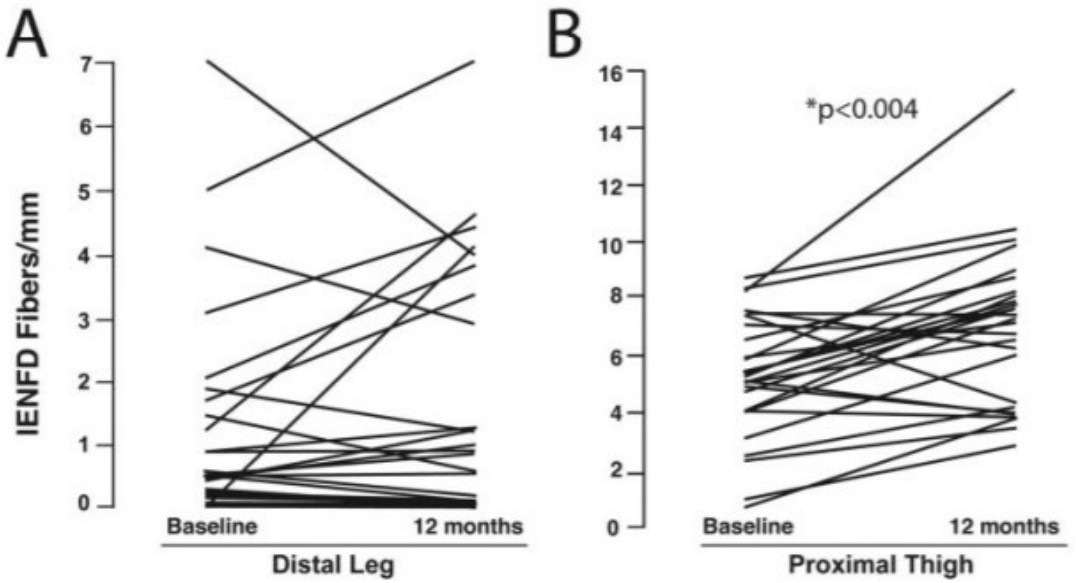


Figure 1—*The change in IENFD for each patient from the baseline visit to the 12-month visit is displayed for the distal leg (A) and the proximal thigh (B). Distal IENFD improved 0.3 ± 1.1 fibers/mm, and the proximal IENFD improved 1.3 ± 2.2 fibers/mm (*P < 0.004). Improvement in proximal thigh IENFD was observed in 70% of subjects compared with 31% for the ankle.*

Interesting Application # 1 – MetS and T2DM Research

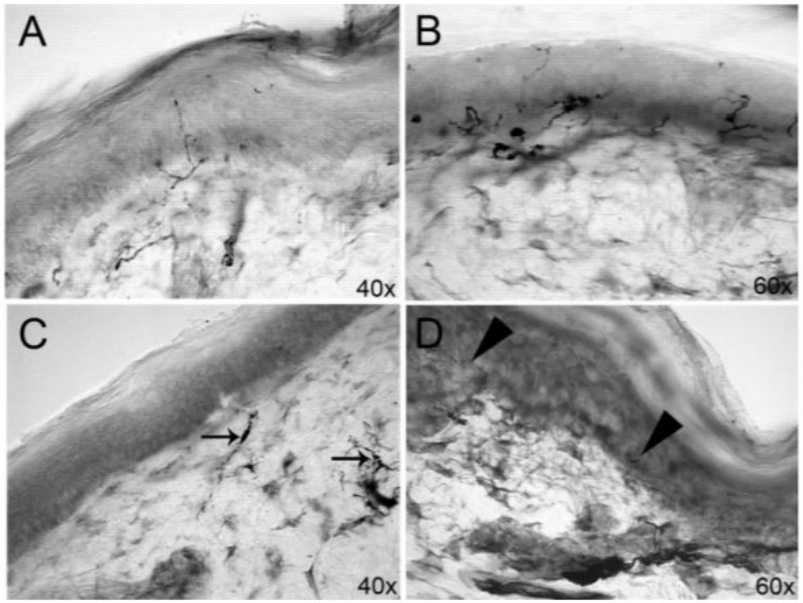


Figure 2—*Reinnervation was observed at the proximal site in most subjects. In the subject shown in A, at baseline the IENFD was 8.2 fibers/mm. At 12 months, IENFD at the same site had increased to 15.1 fibers/mm and frequent axonal swellings and dystrophic appearing axons were observed in both the dermis and the epidermis (B). A subject with absent epidermal fibers but preserved dermal nerve fibers at baseline (C) (arrows) did experience epidermal reinnervation after 12 months (D) (arrowheads, 4.4 fibers/mm). Subjects with absent dermal and epidermal fibers typically did not experience epidermal reinnervation.*

Obesity A Research Journal

THE OBESITY SOCIETY

ORIGINAL ARTICLE

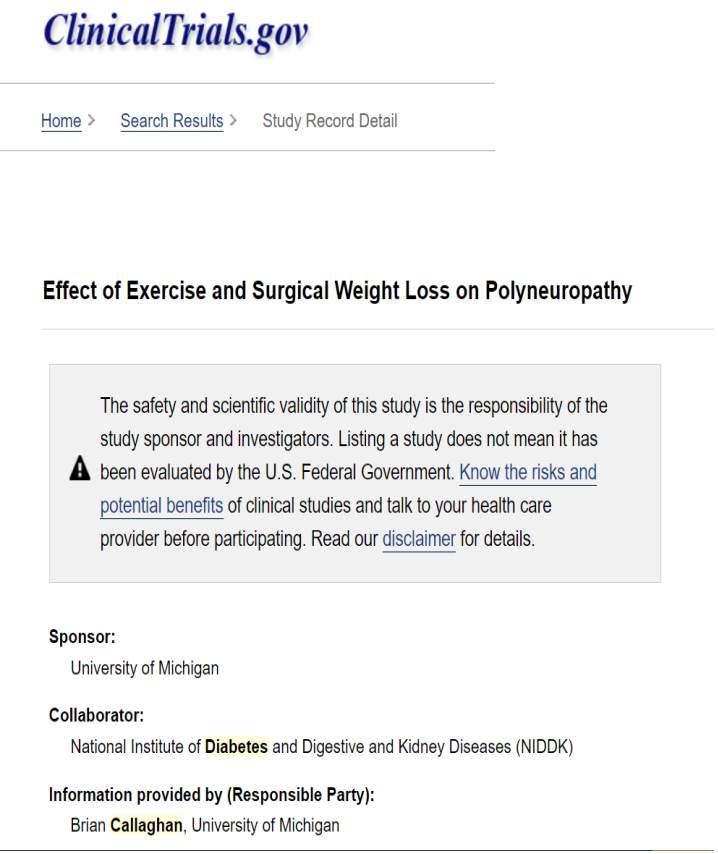
Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology

Brian C. Callaghan, Evan L. Reynolds, Mousumi Banerjee, Gulcin Akinci, Ericka Chant, Emily Villegas-Umana, Amy E. Rothberg, Charles F. Burant, Eva L. Feldman ... See fewer authors

First published: 07 November 2021 | https://doi.org/10.1002/oby.23246 | Citations: 1

--**Aim**: Determine the effect of dietary weight loss on neuropathy outcomes in people with severe obesity.
--**Design**: Prospective cohort study. Meal replacement of 800kcal/day for 12 weeks, then transition to 1200-1500kcal/day diet.
Outcome measures: IENFD change at distal leg and proximal thigh, with secondary outcome measures
--**Results**: 131 patients. 2 year follow up. Patients lost 12 kg. All MetS components improved, except for BP. IENFD at distal leg and proximal thigh stabilized. MNSI, QoL, and QST improved.
--**Take Home**– natural history of IENFD shows decline over time. *Weight loss may be a stabilizing intervention.*

Effect of Surgical Weight Loss and High Intensity Interval Training



ClinicalTrials.gov

Home > Search Results > Study Record Detail

Effect of Exercise and Surgical Weight Loss on Polyneuropathy

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
University of Michigan

Collaborator:
National Institute of **Diabetes** and Digestive and Kidney Diseases (NIDDK)

Information provided by (Responsible Party):
Brian **Callaghan**, University of Michigan

High Intensity Interval Training (HIIT) – *"a form of exercise in which short periods of extremely demanding physical activity are alternated with less intense recovery periods."*

Four arms

Arm 1

- **Bariatric surgery + HIIT** –
  - Underwent surgery + HIIT for 24mo
  - HIIT involves 2 supervised + 1 unsupervised sessions / wk

Arm 2

- **Surgery + routine exercise** – standard regimen for 24mo

Arm 3

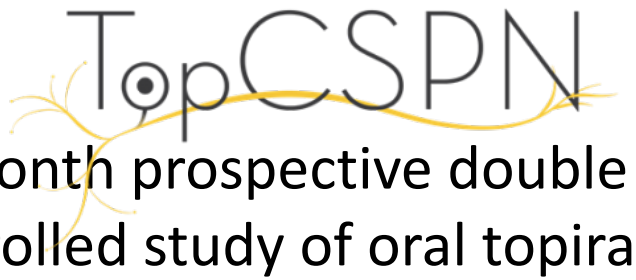
- **No bariatric surgery + HIIT** – HIIT for 24mo

Arm 4

- **No surgery + routine exercise for 24mo**

Primary outcome: Change in IENFD at proximal thigh

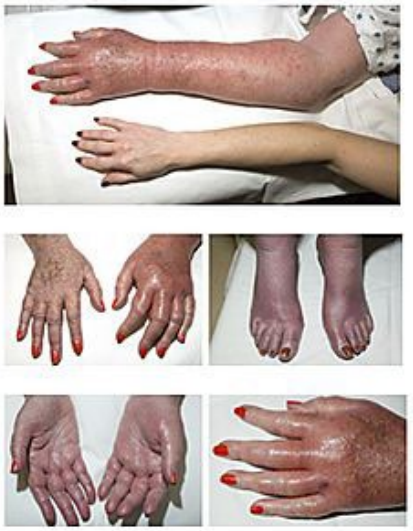
Inclusion Criteria: BMI > 35



- 24 month prospective double blinded randomized placebo controlled study of oral topiramate as a potential disease modifying therapy for cryptogenic sensory peripheral neuropathy (CSPN)
- Inclusion: Metabolic Syndrome without secondary cause
- Co primary outcome measures
  - change in the Norfolk Quality of Life - Diabetic Neuropathy (NQOL-DN) Scale
  - **Intraepidermal nerve fiber density (IEFND) at the distal thigh.**

→ **<u>Primary Endpoint not met</u>**

Interesting Application #2
Erythromelalgia



- Red, hot painful extremities
- Intermittent
- Normal at presentation
- Red or hot after provocation
- Hands affected in 25%
- Types
  - Primary – no underlying disorder
  - Secondary – myeloproliferative (aspirin-responsive)
- Pathophysiology
  - AV anastomosis contribute to blood maldistribution causing skin hypoxia

Interesting Application #2
Erythromelalgia
Neuropathy or Vasculopathy?

- EMG/NCS showed PN pattern in 21/54
- ARS (retrospective)– 17/24 showed sudomotor dysfunction (QSART)
- ARS (prospective) – 46/57 showed **abnormal QSART**
  - 15 – abnormal adrenergic function
  - 15 – abnormal cardiovagal function
- **TST – 28/32 had abnormal findings**
  - 19 – distal type (alone or with proximal sites)
  - 8 – global – areas affected by erythromelalgia anhidrotic
- **IENFD – 13/16 – lower than normal in affected areas**

Interesting Application #3
Fibromyalgia

FIBROMYALGIA SYNDROME AND SMALL FIBER, EARLY OR MILD SENSORY POLYNEUROPATHY

VICTORIA H. LAWSON, MD,[1] JESSIE GREWAL, MD,[2] KEVIN V. HACKSHAW, MD,[3] PHILLIP C. MONGIOVI, MD,[4] and AMRO M. STINO, MD [2]

[1] Dartmouth-Hitchcock Medical Center Department of Neurology, One Medical Center Drive, Lebanon, New Hampshire, 03766, USA
[2] Ohio State University Medical Center Department of Neurology, Columbus, Ohio, USA
[3] Ohio State University Medical Center Department of Internal Medicine, Division of Rheumatology, Columbus, Ohio, USA
[4] University of Rochester Department of Neurology, Rochester, New York, USA

Accepted 17 March 2018

- 155 FMS patients with neuropathic symptoms completed a Short Form McGill Questionnaire and visual analog scale
  - Identified those with Fibromyalgia syndrome only (**FMS**)
  - Identified those with fibromyalgia AND small fiber sensory polyneuropathy (**FM-SFSP**N) as proven on skin biopsy at distal leg site
- Does **pain quality** discriminate **FM-SFSPN** from **pure FMS**?
- Do **distal nerve action potential amplitudes** correlate with **IENFD**?

Interesting Application #3
Fibromyalgia

- Quality and Quantity of Pain Did Not Distinguish FM-SFSPN from FMS
- Pain Intensity Did Not Correlate Well with Reduced ENFD
- Patients with **FM-SFSPN - have more glucose dysregulation and MetS**
- **Lower Extremity Sensory Nerve Action Potential Amplitudes Correlated Well with IENFD**

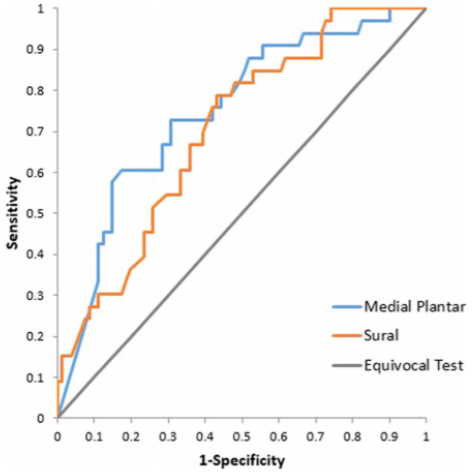


FIGURE 1. Sensitivity, specificity, positive predictive value, and negative predictive value of MP nerve action potential amplitude as predictor for reduced ENFD in FMS patients. An ROC curve is demonstrated for both MP and sural nerve action potential amplitudes, indicating better performance of MP amplitudes. [Color figure can be viewed at wileyonlinelibrary.com]

Polyneuropathy Pain Management

- ***GABANOIDS***
  - Gabapentin* – TID dosing. Doses > 1800 mg typically not needed.
    - Start 300 mg TID.
  - Pregabalin – TID dosing. Doses > 300 mg typically not needed. Start 75 mg TID or BID.
- ***TRICYCLICS***
  - Amitriptyline
  - Nortriptyline* *Start at 25 mg.*
- ***SNRIs***
  - Duloxetine - 60mg once daily. Start at 30 mg once daily
  - Venlaxafine – 150mg/d.
- ***SODIUM CHANNEL BLOCKERS***
  - Mexiletine
  - Topiramate
  - Oxcarbazepine

Pain Management Principles

<u>Guiding Principles:</u>

- Start **low and go slow**
- **Give the drug at least 6-8 weeks** of maximal dose before assessing pain responsiveness.
- **Set expectations:** the goal is pain reduction, and may not necessarily be complete pain elimination
- If a patient say s/he cannot tolerate the drug, **ascertain the side effect exactly** (Drowsiness? Rash? Cost?). Can the drug be used at a low dose or is it not feasible to try?
- Ensure there are **no major drug-drug interactions.**

First

- I usually start with a Gabapentinoid – **Pregabalin or Gabapentin**.
  - **Gabapentin**:
    - Increase in 300 mg weekly increments to necessary target dose
    - Some can be at 600 mg TID, some at 900 mg TID
    - Some can be variations (e.g. 300 mg morning, 300 mg afternoon, and 900 mg at night)

First

- **Pregabalin** is a good alternate first line option
  - Cost can be a limiting factors
  - Start at 75 mg twice or three times daily
  - Uptitrate to target dose, which can be 100 mg three times daily or 150 mg three times daily

Second

- As a next option, I often use a Tricyclic Antidepressant – **Nortriptyline or Amitriptyline**.
- Personal preference – **Nortriptyline**
  - Titrate in 25 mg increments up to target dose of 75 mg at night
  - Lower side effect profile.
  - Minimize/avoid drug-drug interactions with other psychotropic drugs (especially if there is risk of QTc prolongation; but I do not routinely get an EKG).
  - Good option for those with insomnia, have migraines, or cannot tolerate drowsiness of Gabapentinoids

Third

- As a next option, I often use an SNRI –
  - **Duloxetine or Venlafaxine** –
  - **Duloxetine**
    - Start at 30 mg daily for week 1, then titrate up to 60 mg daily week two.
    - Can go up to 60 mg twice daily by week 3
    - Be careful of serotonin syndrome if multiple other offending agents on board
  - **Venlafaxine Extended Release** is another good option
    - Start at 37.5mg daily for week 1, then 75 mg daily week 2
    - Can monitor or increase to 150 mg week three onwards.

Fourth

- As a next option, I will often use a **Sodium channel blocker** –
  - **Mexiletine**.
    - Always obtain a baseline EKG to ensure no arrhythmia (if present, avoid use).
    - Titrate slowly
      - Week 1 - 150 mg at night
      - Week 2 – 150 mg twice daily
      - Week 3 onwards – 150 mg three times daily

Sodium Channel Blockers

- **Topiramate** –
  - Ensure no baseline history of kidney stones.
  - Titrate as follows –
    - Week 1 – 25 mg at night.
    - Week 2 – 25 mg twice daily.
    - Week 3 – 25 mg in morning, and 50 mg at night
    - Week 4 onwards – 50 mg twice daily.
  - Can cause drowsiness
  - Good option for those with concomitant migraines

<u>Sodium Channel Blockers</u>

- **Oxcarbazepine**
  - Unique titration schedule
    - *300 mg at night*
    - *Days 3-8 – 300 mg BID*
    - *Days 8-15 – 300 mg QAM / 600 mg QHS…*
    - *Max dose is 900 mg twice daily*
  - Monitor for hyponatremia
- **Lamotrigine**
  - Titration schedule:
    - Weeks 1-2: 25 mg/d
    - Weeks 3-4: 50 mg/d
    - Week 5: 100 mg/d
    - Target dose: 150-250 mg/d
  - Monitor for Stevens Johnson Syndrome

Where to go from here

- Careful, focused history and physical
  - Pinprick
  - Temperature
- Go through small fiber checklist

  (varies from large fiber)
- Evaluate for underlying risk factors but recognize that oftentimes idiopathic
- Recognize that minimal large fiber changes are allowed

Where to go from here

- Skin biopsy is the gold standard
- Recognize that autonomic fibers serve as excellent surrogates for somatic fiber testing
  - QSART
  - Thermoregulatory Sweat Testing
  - Cardiovagal – diabetic mortality
- Do Sjögren's screen on idiopathic cases, especially when length-independent
  - Mino lip salivary gland biopsy

Thank You

Questions?

the Foundation *for* Peripheral Neuropathy

Thank You for Watching!

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Do you like us? Please consider supporting us so that we can continue to fulfill our mission of improving the lives of people living with Peripheral Neuropathy. You can give securely online, via mail or via phone. Every dollar matters!

Can we help with anything else? Call 847-883-9942 or email info@tffpn.org. You may also mail inquiries and donations to *the* Foundation *for* Peripheral Neuropathy at 485 E. Half Day Road, Suite 350, Buffalo Grove, Illinois 60089.