Small Fiber Neuropathy (SFN)

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Terminology

- **Polyneuropathy:** a generalized process affecting many peripheral nerves, with the distal nerves usually affected most prominently.
- **Mononeuropathy**: a focal neuropathy affecting one nerve.
- **Peripheral neuropathy:** a less precise and can refer to any disorder of the peripheral nervous system including polyneuropathy, radiculopathies and mononeuropathies.

Axonal neuropathy : Usually from systemic disorders(DM, HIV, uremia, critical illness), toxins

Demyelinating neuropathy : Usually from Autoimmune and hereditary causes

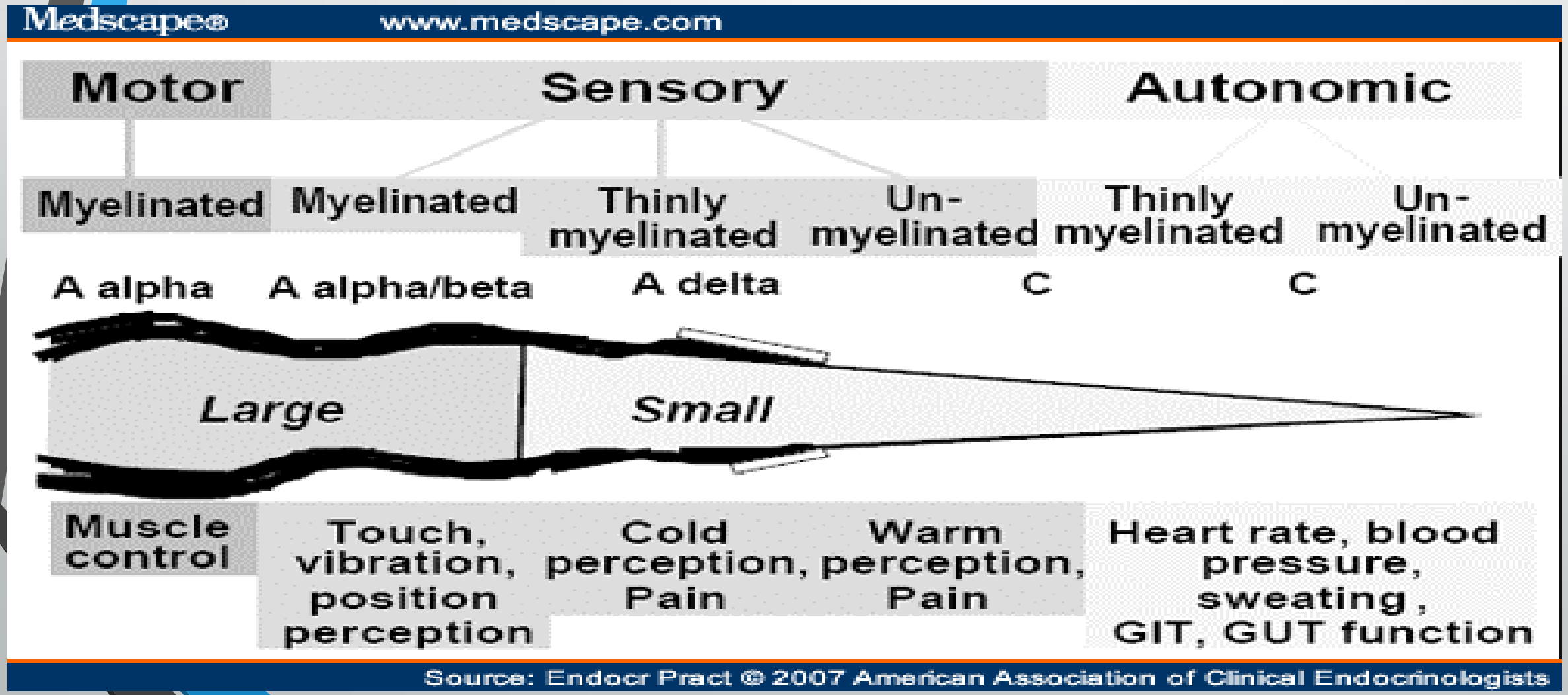
Axonal vs. Demyelinating lesions

	Axonal	Demyelinating
Amplitudes	**Decreased**	Normal
Distal latency	Normal	**Prolonged**
Conduction velocity	Normal	**Slow**

Introduction

- **Most** peripheral neuropathies have mixed involvement of small and large fibers.
- **Small fiber neuropathy (SFN)** refers to a group of neuropathies characterized by a selective or predominant impairment of peripheral afferent thinly myelinated Aδ-fibers and unmyelinated C-fibers.

Peripheral nerves



Small Vs Large fiber neuropathy

Small fiber neuropathy	Large fiber neuropathy
Pain and paresthesia	Impaired vibration
Autonomic signs and symptoms	Loss of position sense
Temperature loss	
No weakness	Wasting and weakness of muscles
Normal deep tendon reflexes	Loss of deep tendon reflexes
Positive Sx	Negative Sx

Epidemiology

- The only study that addressed the incidence of SFN was performed in The Netherlands in 2013
- It reported an incidence of 11.73 cases (15.6 male/8.2 female) per 100,000 population per year, with higher rates in those >65 years of age.
- Prevalence was 52.95 cases (60.9 male/45.4 female) per 100,000/year.

SFN - patterns

- **Length – dependent (LD-SFN) :**
- Most common
- Stocking and glove pattern : starts in feet and moves proximally.
- Pure SFN – usually confined to feet

- **Non-length-dependent (NLD-SFN) :**
- functional impairment of individual or multiple nerves or nerve fibers.
- variable patchy sensory pattern that can affect different parts of the body, including the face, tongue, scalp, upper limb, and trunk, **before the lower limbs.**
- Observed in paraneoplastic, immune mediated, and idiopathic cases of SFN.
- **Burning mouth syndrome:** intraoral burning sensation +/- itching, altered taste sensation. predominantly affects post menopausal-females.

Table 1. Comparison between length-dependent (LD-SFN) and non–length-dependent small fiber neuropathy (NLD-SFN)

	LD-SFN	NLD-SFN	*P*-value
Symptoms[18]	From distal to proximal	1. Involving proximal regions of the limbs, face, or trunk. 2. Onset of symptoms in the face, scalp, mouth, tongue, trunk, hands, arms, or proximal legs before the feet. 3. Pain that begins in proximal and distal regions of the limbs simultaneously.	
• Demographics			
• Women[14]	48%	73.%	<0.001
• Age at diagnosis[17]	66.0 ± 11.3	53.5 ± 12.2	0.003
• Age at onset[17]	63.3 ± 11.9	50.7 ± 12.9	0.005
• Symptoms			
• Described as itchy[17]	3%	36%	0.010
• Reported touch allodynia[17]	27%	72%	0.012
• Causes/associations			
• DM/IGT[17]	48% 3.4%	9% 14.3%	0.031 0.012
• Immunomediated conditions[14] (lupus, MCTD, RA, psoriasis, sarcoidosis, Sjögren syndrome, scleroderma)			
Prognosis[18]	Satisfactory response with 1 or 2 non-narcotic analgesics.	Limited response to immune therapies; often refractory to aggressive symptomatic pain management with 3 or 4 moderate- to high-dose narcotics.	

Summarized and significant values taken from earlier studies.[14,17,18] DM, diabetes mellitus; IGT, impaired glucose tolerance; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis.

Box 1 | Symptoms of small-fibre neuropathy

For the diagnosis of small-fibre neuropathy, at least two of the following symptoms, not otherwise explained, are required.

Sensory

- Pain (burning, shooting, prickling or itching)
- Paraesthesias
- Allodynia
- Thermal sensory loss
- Pinprick loss
- Sheet or sock intolerance
- Restless legs syndrome

Autonomic

- Sicca syndrome
- Accommodation problems
- Hyperhydrosis or hypohydrosis
- Micturation disturbances
- Impotence and/or diminished ejaculation or lubrication
- Bowel disturbances (constipation, diarrhoea, irritability, gastroparesis, cramps)
- Hot flushes
- Orthostatic dizziness
- Cardiac palpitations

SFN – Clinical features

- **Pain and paresthesia:**

1. burning, prickling, aching, electric-like, or itching sensation, restless leg.
2. Usually worse at night.

However, it can be painless

- **Autonomic symptoms :** dry eyes, dry mouth, palpitations, orthostatic hypotension, constipation, urinary retention, sexual dysfunction, sweating abnormalities, and skin discoloration.

SFN – Examination

- Reduced or absent sensitivity to cold, heat, and noxious mechanical stimuli.
- Sensory loss can occasionally be masked by simultaneous hyperalgesia and allodynia in the affected area.
- Patients might complain of abnormal altered sensations to thermal stimuli (e.g. cold stimuli might be perceived as heat).
- Associated skin changes in affected areas may include dry, cracked, or shiny skin, with decreased moisture on the surface of these affected areas as well.

- **Motor strength, proprioception, vibration, and deep tendon reflexes are usually preserved**

Difficulties when dealing with SFN

1- The course of neuropathy can progress over time from pure SFN to mixed

2- No criteria available for NLD-SFN

3- Most diagnostic tests are time-consuming, require specific expertise, and not readily available.

4- SFN can occur secondary to multiple conditions (e.g. fibromyalgia, motor neuron diseases, Ehlers-Danlos syndrome, Parkinson disease …)

Etiologies

Primary :

- Idiopathic (30-50%)
  - **Idiopathic small fiber neuropathy**
  - **Burning mouth syndrome**

- Hereditary/genetic (suspect especially if young age and/or +ve family history)
  - **Hereditary sensory and autonomic neuropathies**
  - **$Na_v1.7$ mutations**
  - **$Na_v1.8$ mutations**
  - **Familial amyloid polyneuropathy**
  - **Fabry's disease**
  - **Tangier's disease :** decreased/absent HDL → accumulation of foamy macrophages → HSM, accelerated atherosclerosis, neuropathy in 50%.

Etiologies

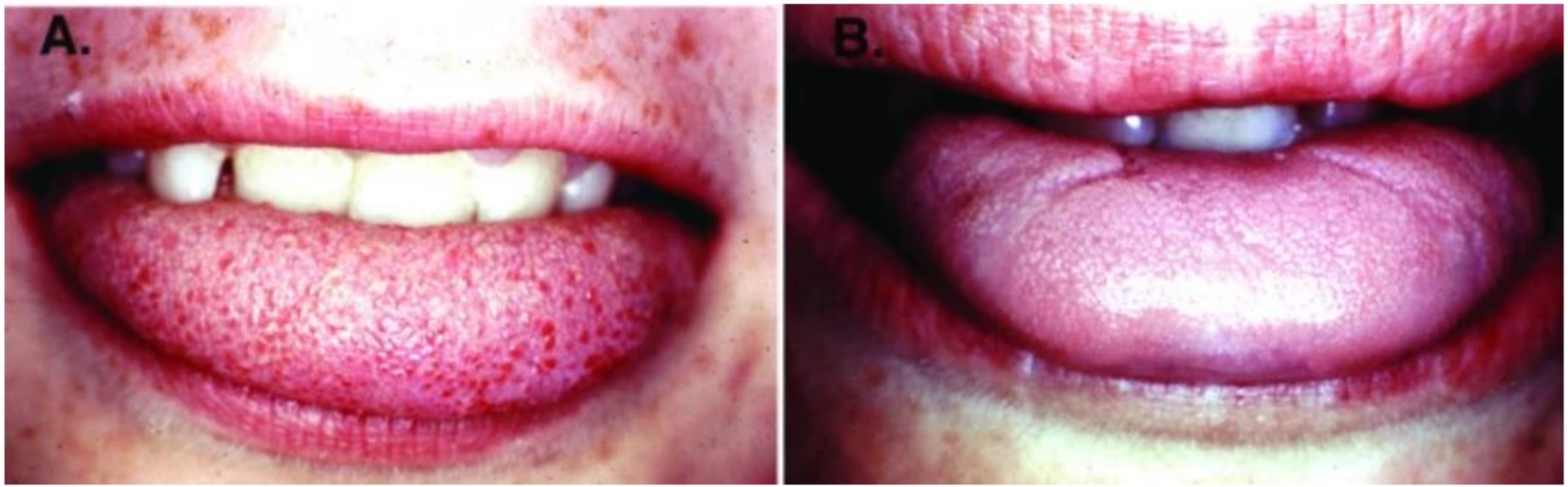
Voltage-gated sodium channelopathies :

- A gain-of-function mutations in *SCN9A, SCN10A , SCN11A,* encoding Nav1.7, Nav1.8, and Nav1.9 α-subunit isoforms of the voltage-gated sodium channels that are preferentially expressed in small-diameter dorsal root ganglion (DRG) neurons, trigeminal neurons.
- The voltage-gated sodium ion channel Nav1.7 is expressed selectively in sensory and autonomic neurons.
- Inactivating mutations in SCN9A, which encodes Nav1.7, result in congenital insensitivity to pain, whereas gain-of-function mutations in this gene produce distinct pain syndromes such as inherited erythromelalgia, paroxysmal extreme pain disorder, **and small-fiber neuropathy.**
- variants of genes coding for the voltage-gated sodium channels Nav1.8 (SCN10A) and Nav1.9 (SCN11A) lead to small-fiber neuropathy and congenital insensitivity to pain, respectively

Hereditary sensory and autonomic neuropathies

- Type 1 : Most common, autosomal dominant, usually in adulthood.
- Type 2: Prominent sensory abnormalities, recurrent digital infections.
- Type III (familial dysautonomia): Characteristic smooth tongue, it is predominantly seen in Ashkenazi Jewish infants.
- Type IV: Severe anhidrosis, and insensitivity to pain.
- Type V: Affected deep pain perception, and thus, severe injuries such as bone fractures and joint injuries.

HSAN	Type I	Type II	Type III	Type IV	Type V
Age of clinical manifestation	Adulthood (2^{nd}–4^{th} decade)	Infancy, early childhood	Birth	Infancy, early childhood	Infancy
Most prominent nerve fiber reduction (sural nerve biopsy)	Small fibers	Myelinated fibers	Small fibers, and significant loss of sympathetic neurons	Absence of unmyelinated fibers, and loss of sudomotor fibers	Selective decrease of small myelinated fibers
Prominent clinical neurological features (history & clinical findings)	Ulcers, mutilations of lowers limbs, lancinating pain, muscle weakness, steppage gait, etc.	Ulcers, mutilations of hands and feet, paronychia, fractures impaired sensory qualities	Ashkenazi Jewish ancestry, diminished deep tendon reflexes, lack of overflow tears, absence of lingual fungiform papillae, no axon flare response to intradermal histamine. Preserved visceral pain	Unnoticed injuries & fractures, episodes of fever with high environmental temperature, dry, hyper-keratotic skin, ulcers, mutilations, Charcot joints, no visceral pain	Repeated unnoticed injuries & fractures, no pain perception
Quantitative sensory testing of thermal (Aδ- and C-fibers) and vibratory (Aβ-fibers) perception	Abnormal warm, cold, heat pain thresholds	Abnormal vibratory thresholds	Highly abnormal warm, cold, heat pain thresholds. Abnormal vibratory thresholds	Abnormal thermal thresholds, absent pain perception	Absent heat pain perception
Nerve conduction studies	Low normal or slightly reduced motor & sensory conduction velocities	Highly abnormal sensory nerve conduction (absent potential). Low normal motor nerve conduction velocities	"Second" motor compound action potential	May be abnormal (no discomfort with high intensity stimulation)	May be normal
Autonomic dysfunction	Hypo-, anhidrosis in distal lower limbs	Episodic hyperhidrosis, apnea, fevers, tonic pupils, bladder dysfunction, oral incoordination, and gastrointestinal dysmotility	Orthostatic hypotension, autonomic crises with vomiting, hyperhidrosis, episodic hypertension	Severe anhidrosis	"mottling" of skin, hyperhidrosis



A. Normal tongue with fungiform papillae present on the tip. B. Dysautonomic tongue. Note the absence of the highly vascularized fungiform papillae from the tongue tip, which gives the appearanc of a smooth tongue.

Etiologies

Secondary:

- **Diabetes** is the most common known cause
- Accounts for around 33% of all SFN cases.
- Might develop insidiously or acutely, as with treatment-induced neuropathy(AKA. Insulin neuritis) caused by fast glycemic control.

Other Etiologies

***Panel 2:* Causes of small fibre neuropathy**

Metabolic causes
- Diabetes, impaired glucose tolerance, and rapid glycaemic control in the setting of chronic hyperglycaemia (treatment-induced neuropathy of diabetes)
- Hypothyroidism
- Hypertriglyceridaemia
- Uraemia

Vitamin deficiency
- Vitamin B12

Neurotoxic exposure or vitamin intoxication
- Alcohol
- Antiretroviral agents
- Chemotherapeutic agents
- Organic solvents
- Pyridoxine B6 intoxication
- Statins
- Anecdotal cases: antiarrhythmic drugs (flecainide), antibiotics (metronidazole, nitrofurantoin, linezolid, ciprofloxacin), ingestion of *Clostridium botulinum* toxin, heavy metals (thallium, lead), and tumour necrosis factor α inhibitors

Infections
- Hepatitis C virus
- HIV
- Influenza
- Leprosy
- Severe sepsis, septic shock, and critical illness
- Anecdotal cases: Epstein-Barr virus, herpes simplex infection, mycoplasma pneumonia, rubella, syphilis, vaccination for rabies, varicella or Lyme disease, and hepatitis B virus

Immunological causes
- Autoimmune autonomic ganglionopathy
- Coeliac disease
- Guillain-Barré syndrome, monoclonal gammopathies, and primary amyloidosis (immunoglobulin light chain associated)
- Paraneoplastic syndrome
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Systemic lupus erythematosus
- Vasculitis

Hereditary causes
- Familial amyloid polyneuropathy (transthyretin amyloidosis)
- Hereditary sensory and autonomic neuropathies
- Fabry disease
- Mutations in COL6A5 and genes encoding voltage-gated sodium channels
- Pompe's disease

Idiopathic small fibre neuropathy

Differential Diagnoses

- Complex regional pain syndrome
- Raynaud phenomenon
- Peripheral vascular disease
- Compressive mononeuropathy
- Porphyrias
- Radiculopathy
- Mononeuritis multiplex

Clinical assessment tools

- **Questionnaires**
- **The Small Fiber Neuropathy and Symptoms Inventory Questionnaire :** includes 13 items, Each item has four response options: 0=never, 1=sometimes, 2=often, and 3=always.
- **The Autonomic Symptom Profile and the Composite Autonomic Symptom Score-31 (COMPASS-31)** : developed specifically for autonomic dysfunctions.

- **Examination tools:** The diagnostic accuracy of clinical examination in pure SFN was reported to be 55%
- **Utah Early Neuropathy Scale (UENS):** emphasizes the severity and spatial distribution of pin (sharp) sensory loss in the feet and legs.
- **The composite autonomic scoring scale (CASS):** includes measurements of orthostatic blood pressure, the quantitative sudomotor axon reflex test, heart rate response to tilt, heart rate variability with deep breathing, and changes in blood pressure with the Valsalva maneuver.
- **Thermoregulatory sweat test**

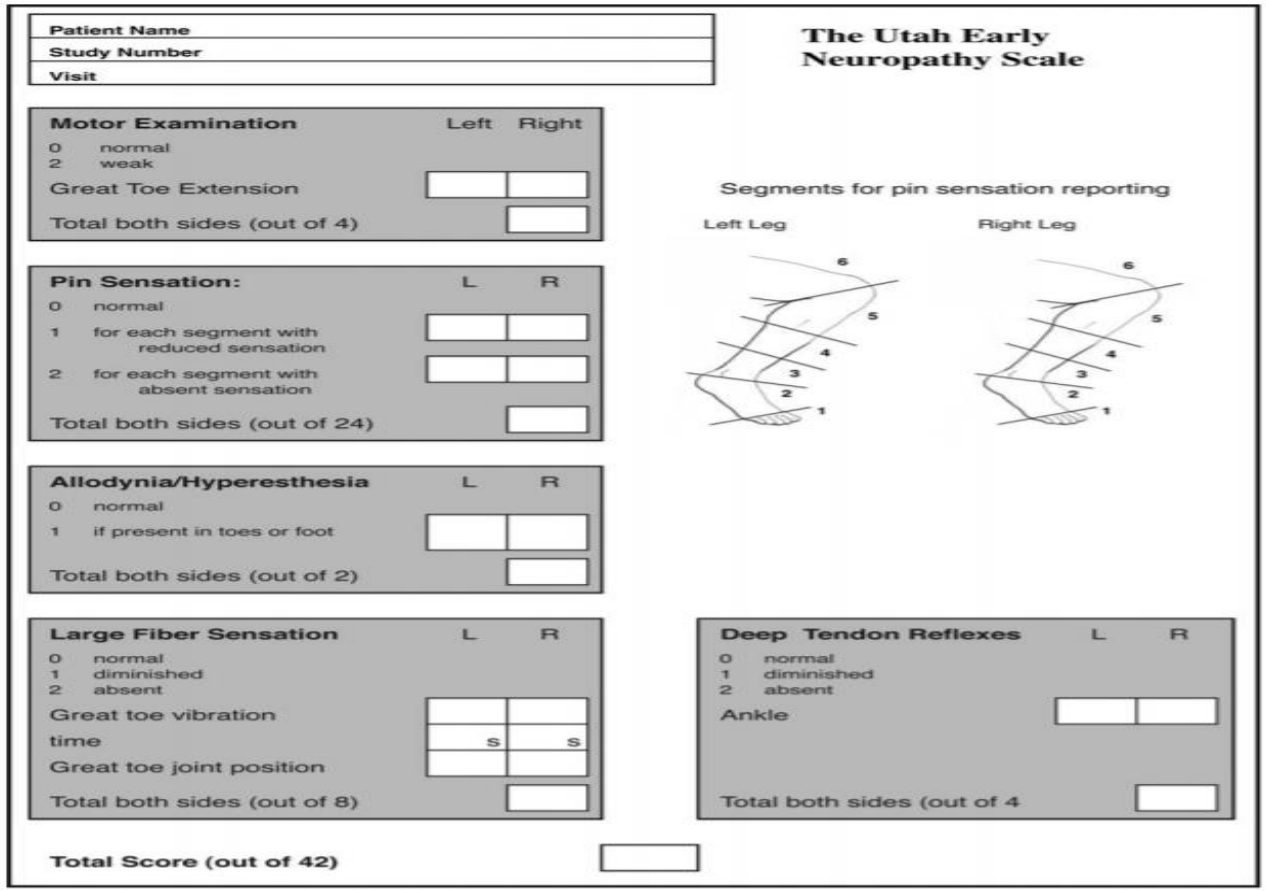
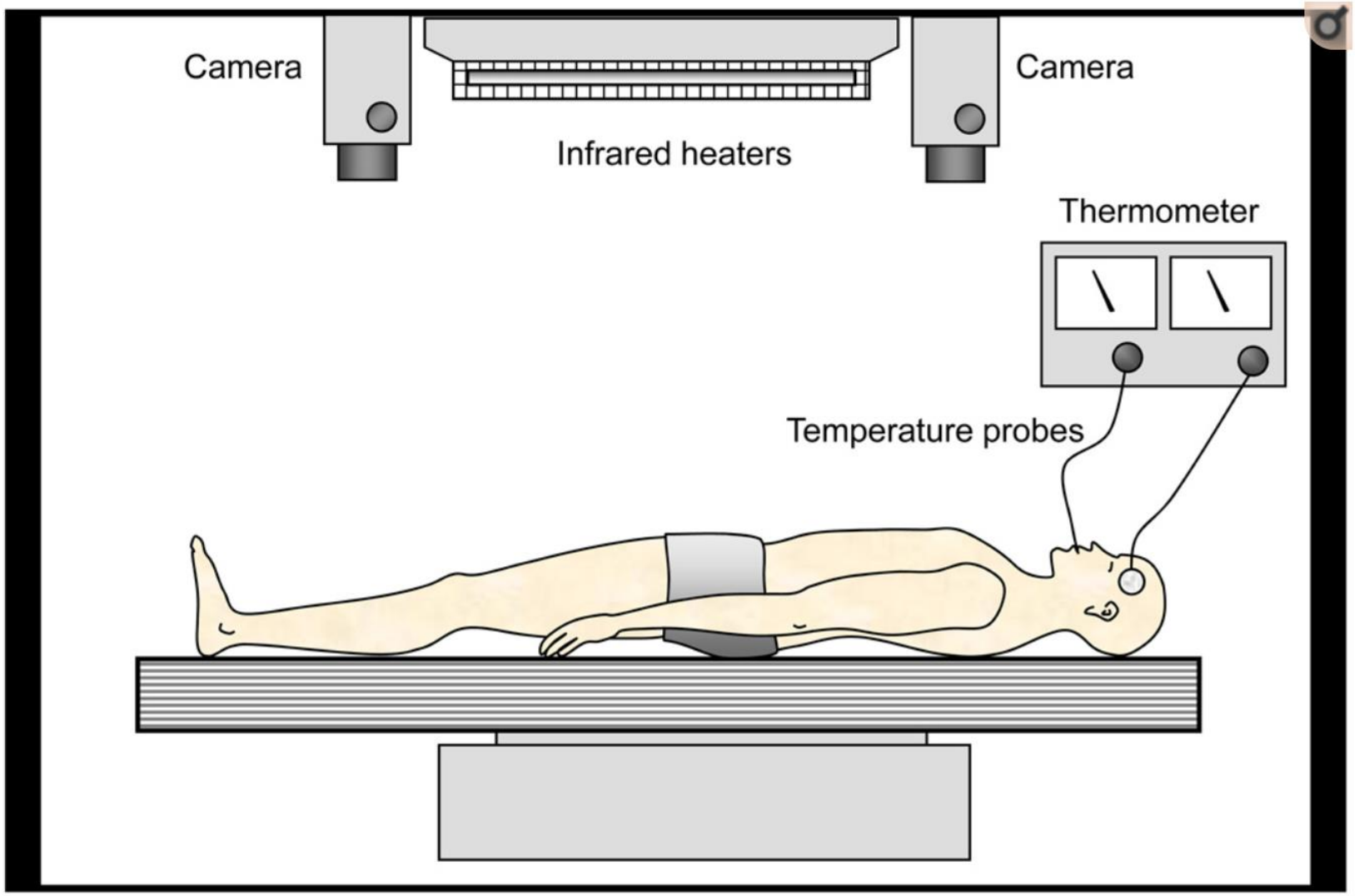


Figure 1. Performing the Utah Early Neuropathy Scale (UENS) examination. The UENS requires a number 2 (1¾ inch) safety pin and a 128 Hz tuning fork. Pin sensation is tested by first reviewing normal sharp sensation to pin on an unaffected portion of the skin. Once this is established, touch the dorsal surface of the foot and leg with the pin, working centripetally from the great toe in 1–2 cm increments while asking the subject to respond when they first feel "any sharpness," and again more proximally when the pin feels "as sharp as they would expect." Repeat to firmly establish these levels. On each side, 2 points are scored for each region in which the patient fails to feel any sharpness. One additional point is scored for each additional region in which the pin feels less sharp than expected. Only distal sensory loss is scored. So, for instance, a person who reported absent pin sensation to the mid foot dorsum (4 points) and reduced sensation to the low ankle (1 point) bilaterally would score a total of 10 points for this portion of the UENS. Vibration is tested by first acquainting the subject with vibration (as opposed to pressure) sensation, then holding the maximally vibrated tuning fork to the dorsum of the great toe at the distal interphalangeal joint. Extinction of vibration in less than 10 s is considered "diminished," while "absent" requires that the patient cannot detect the maximally vibrating tuning fork at the toe. The motor examination is limited to great toe dorsiflexion. Other aspects are as typically performed in neurological examination.



Thermoregulatory sweat testing (TST)

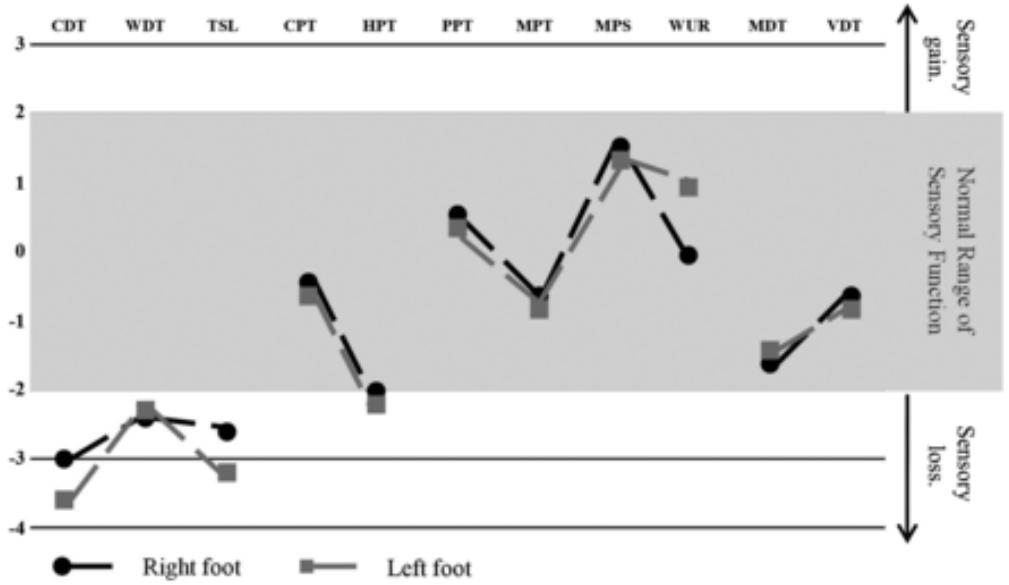
Diagnostic tools

Neurophysiological and pathological techniques

- Nerve biopsy[36]
- Skin biopsy[24]
- Quantitative sensory testing[37]
- Quantitative sudomotor axon reflex test[38]
- Corneal confocal microscopy[39]
- Microneurography[40]
- Electrical-evoked potentials
- Laser-evoked potentials[41]
- Contact heat-evoked potentials[42]

Quantitative sensory testing (QST)

- QST is a is a non-invasive method that can evaluate both gain and loss of sensory function can be used to assess the functional impairment of sensory nerve fibers.
- QST is a psychophysical method used to quantify somatosensory function
- It is based on measurements of responses to calibrated, graded innocuous or noxious stimuli (generally mechanical or thermal)
- Limitations :
- (1) QST is a psychophysical test and is thus open to bias
- (2) abnormal results do not have a localizing value in terms of the identification of peripheral versus central lesions
- (3) it is time-consuming and only available at specialized centers.

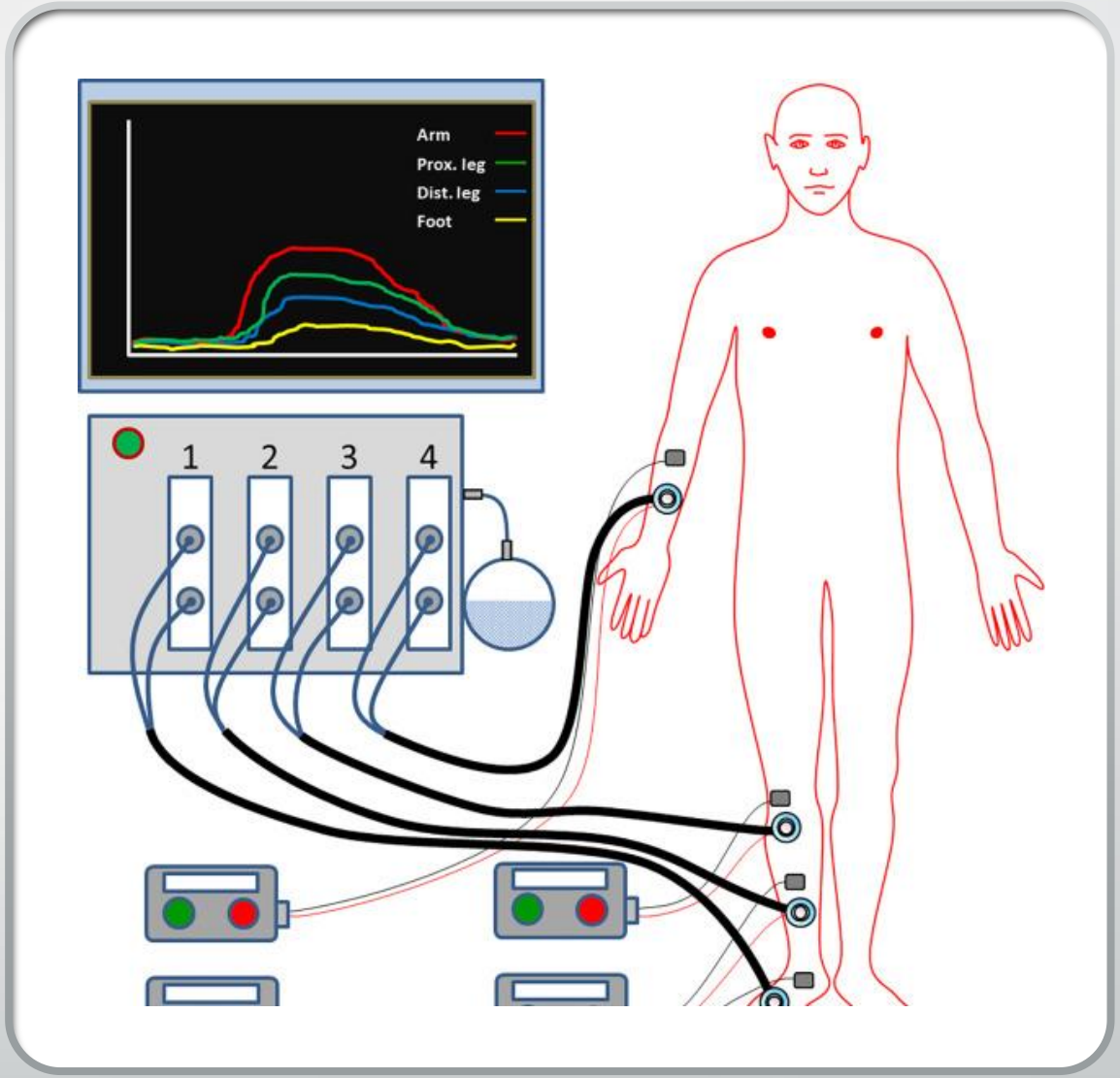


Nerve conduction studies

- Usually normal in SFN.
- Done to exclude large fiber involvement.
- However, the involvement of large fibers does not exclude SFN, and overlap is common.

Quantitative sudomotor axon reflex test (QSART)

- Assesses the postganglionic sympathetic cholinergic sudomotor function in the extremities.
- Acetylcholine 10% is iontophoresed into the skin to stimulate unmyelinated C-fibers. And sweating is measured and quantified by a sudorometer.
- Can provide early diagnosis of sudomotor dysfunction and can be used to monitor disease progression or recovery



Skin biopsy

- Highest diagnostic accuracy, Considered to be the Gold standard.
- The procedure is fast and simple, and the resultant wound heals within a few days.
- Disease progression can therefore be followed up over time by repeated skin biopsies.
- Skin biopsy can also distinguish between somatosensory and autonomic nerve fibers.

Skin biopsy

- Quantitative assessment of intraepidermal nerve fiber density(IENFD)
- Sensitivity and specificity > 90%.
- Other measures :
- Quantification of axonal swellings : especially in painful neuropathies. Could represent pre-degenerative changes.

- The correlation between IENFD and functional test measures, such as QST, is still unclear, because the quantification of intraepidermal nerve fiber density reveals structural changes, but does not predict the degree of functional changes. The remaining fibers can thus be sensitized, hypofunctional, or normal.
- For example, Patients with erythromelalgia can have altered small fiber function without loss of intraepidermal nerve fibers.

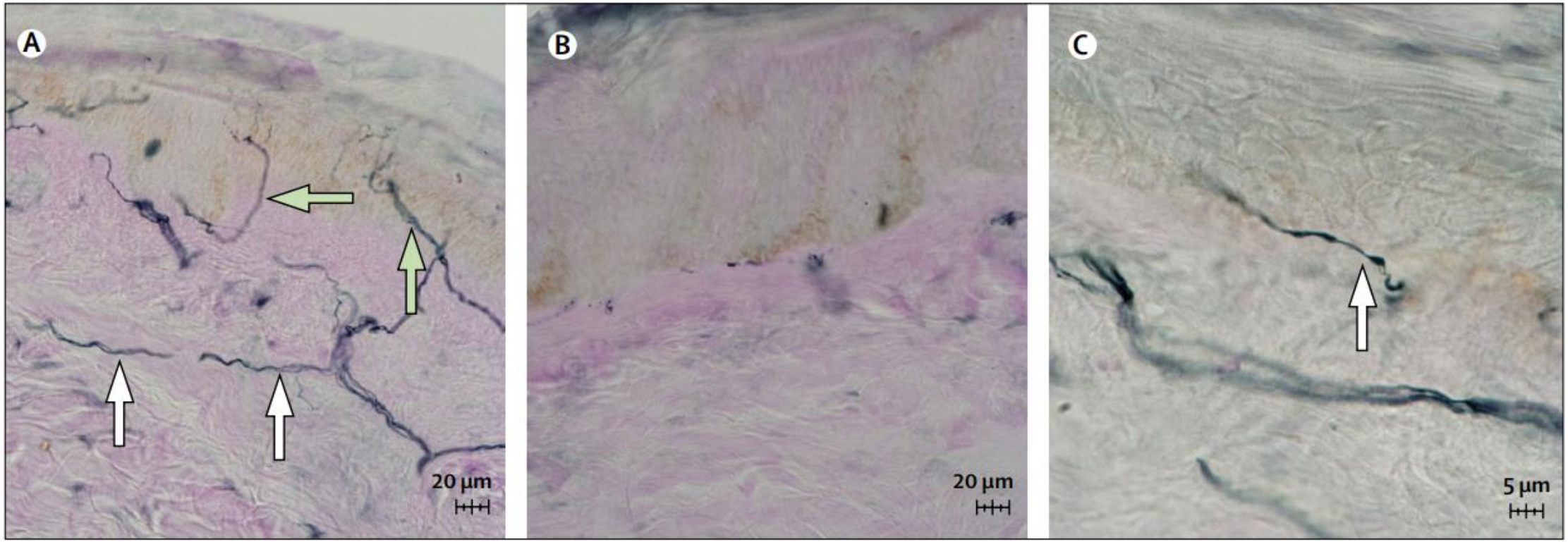


***Figure* 2: Skin nerve fibres**

In a punch skin biopsy, a sample that is usually 3 mm in diameter is removed. After overnight fixation, the sample is frozen and cut into 50-µm thick cryosections (vertically to the direction of the epidermis) and then immunostained with PGP9.5 antibody, to visualise the fibres and estimate their density. (A) Intraepidermal nerve fibres (green arrows) and dermal nerve fibres (white arrows) in a healthy individual. (B) Loss of skin nerve fibres in a patient with painful diabetic neuropathy. (C) Axonal swelling of intraepidermal nerve fibres (white arrow) in a patient with painful diabetic neuropathy.

Nerve biopsy

- Usually of sural nerve
- Virtually never done for pure SFN
- May be used to detect demyelination with associated inflammation in patients with vasculitis or infiltrating diseases as amyloidosis.

Corneal confocal microscopy

- The cornea is innervated by Aδ-fibers and C-fibers that originate from the ophthalmic division of the trigeminal nerve. **It is the most densely innervated part of the human body** and offers a unique window to small fiber innervation.
- A promising new technique, quantification of small fibers located near the center of the cornea.
- It is non-invasive and fast, and thus might be a useful method to confirm small nerve fiber pathology.
- Multiple parameters measured: nerve fiber length density, nerve fiber branch density, and nerve fiber tortuosity.

- The diagnostic sensitivity and specificity of this technique in diabetic polyneuropathy are 91% and 93%, respectively.
- Can be used to follow up progression and treatment response.

Other tests : research

- Laser-evoked potentials
- Contact heat-evoked potentials
- Microneurography

Biochemical tests

Panel 3: Biochemical markers of small fibre neuropathy

Initial screening in polyneuropathy

Glucose dysmetabolism

- Fasting plasma glucose
- Glycosylated haemoglobin (HbA_{1c})
- Oral glucose tolerance test in selected cases with normal HbA_{1c}

Renal, thyroid, and liver function

Vitamin deficiency

- Cobalamin
- Homocysteine
- Folate
- Methylmalonic acid

Haematological disease

- Serum protein electrophoresis with immunofixation electrophoresis

Other causes

- Erythrocyte sedimentation rate
- Complete blood count
- IgM, IgA, IgG

Biochemical screening in definite small fibre neuropathy

Acute or subacute development of autonomic dysfunction

- Ganglionic acetylcholine receptor antibodies
- Onconeuronal antibodies (anti-Hu antibodies, anti-CV2 antibody, voltage-gated calcium channel antibody, voltage-gated potassium channel antibody, Purkinje cell cytoplasmic antibody type 2)

Autoimmune or connective tissue disorder

- Rheumatoid factor
- Antinuclear antibody
- Antineutrophil cytoplasmic antibody screening
- Cryoglobulin
- Interleukin-2 receptor antibody
- Total and free calcium ion
- Serum and urine protein immunofixation electrophoresis
- CSF analysis

Sjögren's syndrome

- Anti-RO (SSA), anti-La (SSB)

Infection

- HIV tests
- Fluorescent treponemal antibody absorption test
- Hepatitis B and C
- CSF analysis

Diseases of the gut

- Antibodies for coeliac disease (gliadin, transglutaminase, and endomysial)
- Vitamin B and E concentrations

Porphyria

- Blood, urine, and stools for porphyrins

Neurotoxins

- Urine and blood toxicology

Hereditary causes

- Leucocyte α-galactosidase A enzyme activity in men and genetic tests in women for suspected Fabry disease when systemic features of the disease are present
- Genetic testing for *SCN9A* and *SCN10A* in patients with suspected Nav1.7α, 1.8α, or 1.9α sodium channelopathies
- Genetic testing for familial transthyretin amyloidosis

Diagnostic criteria for LD-SFN

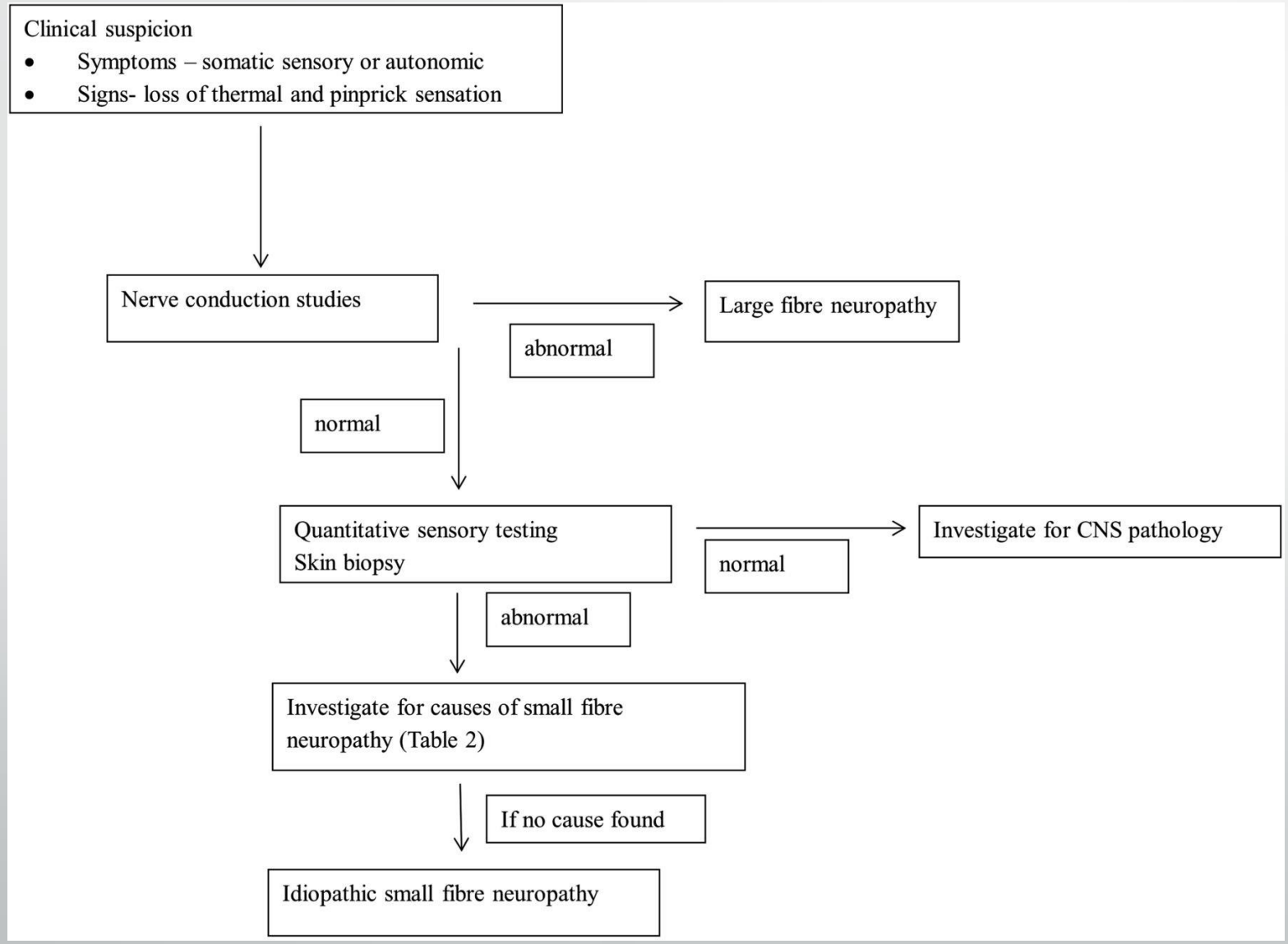
- From the Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB)

1) possible : presence of length-dependent symptoms or clinical signs of small fibre damage, or both)

(2) probable as possible + **a normal sural nerve conduction study)**

(3) definite : as probable + **abnormal QST thresholds at the foot or reduced intraepidermal nerve fiber density at the ankle, or both).**

Diagnostic approach



Management

- Currently, There are no treatments that can prevent or reverse SFN.

- Treatment of underlying cause

- Tighter glycemic control in DM
- Thyroid replacement in hypothyroid…
- Avoid toxic substances

Treatment for specific conditions

- Enzyme replacement for Fabry Disease
- Some case reports supporting effectiveness of IVIG on sarcoidosis, celiac, Sjogren syndrome.
- Liver transplant for hereditary amyloidosis
- Selective Nav1.7 blockers are currently under development, and might prove effective, especially in patients with *SCN9A* mutations.

Symptomatic management

Summary of Guidelines

Medication Class	Neuropathic Pain Special Interest Group (NeuPSIG) (2010)	Expert Panel Recommendations for the Middle East Region (2010)	European Federation of Neurological Societies (EFNS)[1] (2010)	Guidelines for the Diagnosis and Management of Neuropathic Pain: Consensus of a Group of Latin American Experts[2] (2009)	Canadian Pain Society (2007)
Tricyclic Antidepressants	First Line	First Line	First Line for PPN and PHN	First Line	First Line
SNRIs	First Line	Second Line	First Line for PPN	Third Line	Second Line[3]
Anticonvulsants	First Line	First Line	First Line for PPN and PHN	Second Line	First Line
Topical Lidocaine	First Line for localized peripheral NP	First Line for PHN with focal allodynia	First Line for PHN for the elderly	First Line for localize peripheral neuropathies	Second Line for localized peripheral NP[4]
Opiods Analgesics	Second line except in selected Circumstances[5]	Second Line	Second line for PHN and Third Line for PPN	Second Line	Third line
Tramadol	Second line except in selected Circumstances[5]	Second Line	Second Line for PPN[6]	Second Line	Third line

[1]Based on recommendations for painful polyneuropathy and postherpetic neuralgia
[2]Based on the recommendations for localized and diffuse peripheral neuropathies
[3]Duloxetine was not available in Canada per the authors at the time of this guideline
[4]The lidocaine patch was not available in Canada per the authors at the time of this guideline, however lidocaine gel was.
[5]Opioid analgesics and tramadol can be used as first-line options for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.
[6]Tramadol can be used as a second line agent for patients with painful polyneuropathy and painful exacerbations or patients with predominant coexisting non-neuropathic pain

NP=Neuropathic pain

PPN = painful polyneuropathy

PHN = postherpetic neuralgia

	First-line drugs			Second-line drugs			Third-line drugs	
	Serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine	Tricyclic antidepressants	Pregabalin, gabapentin, gabapentin extended release or enacarbil	Tramadol	Capsaicin 8% patches	Lidocaine patches	Strong opioids	Botulinum toxin A
Quality of evidence	High	Moderate	High	Moderate	High	Low	Moderate	Moderate
Balance between desirable and undesirable effects								
Effect size	Moderate	Moderate	Moderate	Moderate	Low	Unknown	Moderate	Moderate
Tolerability and safety*	Moderate	Low-moderate	Moderate-high	Low-moderate	Moderate-high	High	Low-moderate	High
Values and preferences	Low-moderate	Low-moderate	Low-moderate	Low-moderate	High	High	Low-moderate	High
Cost and resource allocation	Low-moderate	Low	Low-moderate	Low	Moderate-high	Moderate-high	Low-moderate	Moderate-high
Strength of recommendation	Strong	Strong	Strong	Weak	Weak	Weak	Weak	Weak
Neuropathic pain conditions	All	All	All	All	Peripheral	Peripheral	All	Peripheral

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.

***Table 3*: Summary of GRADE recommendations**

Symptomatic management

Pharmacotherapy for painful diabetic neuropathy: Relevant comorbidities for drug selection

Drug class	Comorbidities favoring use	Comorbidities favoring avoidance
Serotonin-norepinephrine reuptake inhibitors (SNRIs) ▪ Duloxetine* ▪ Venlafaxine	Depression Anxiety	Restless legs syndrome Sexual dysfunction (for venlafaxine) Angle-closure glaucoma
Tricyclic antidepressants (TCAs) ▪ Amitriptyline ▪ Nortriptyline ▪ Desipramine	Depression Anxiety Insomnia	Cardiac disease Prolonged QTc Orthostatic hypotension Sexual dysfunction Urinary retention Angle-closure glaucoma
Gabapentinoid anticonvulsants ▪ Pregabalin* ▪ Gabapentin	Restless legs syndrome Essential tremor Insomnia	Substance abuse Peripheral edema Chronic obstructive pulmonary disease

* Approved by the US Food and Drug Administration for diabetic neuropathy.

Nonpharmacologic options

- Use of cool or warm soaks, soft socks
- TENS
- Acupuncture
- Physical therapy and massage also have been used

Prognosis

- Most patients experience a slowly progressive course with symptoms and signs spreading proximally over time.
- Large fibers can be eventually involved.

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