Small Fiber Neuropathy: More than just burning feet and gabapentin

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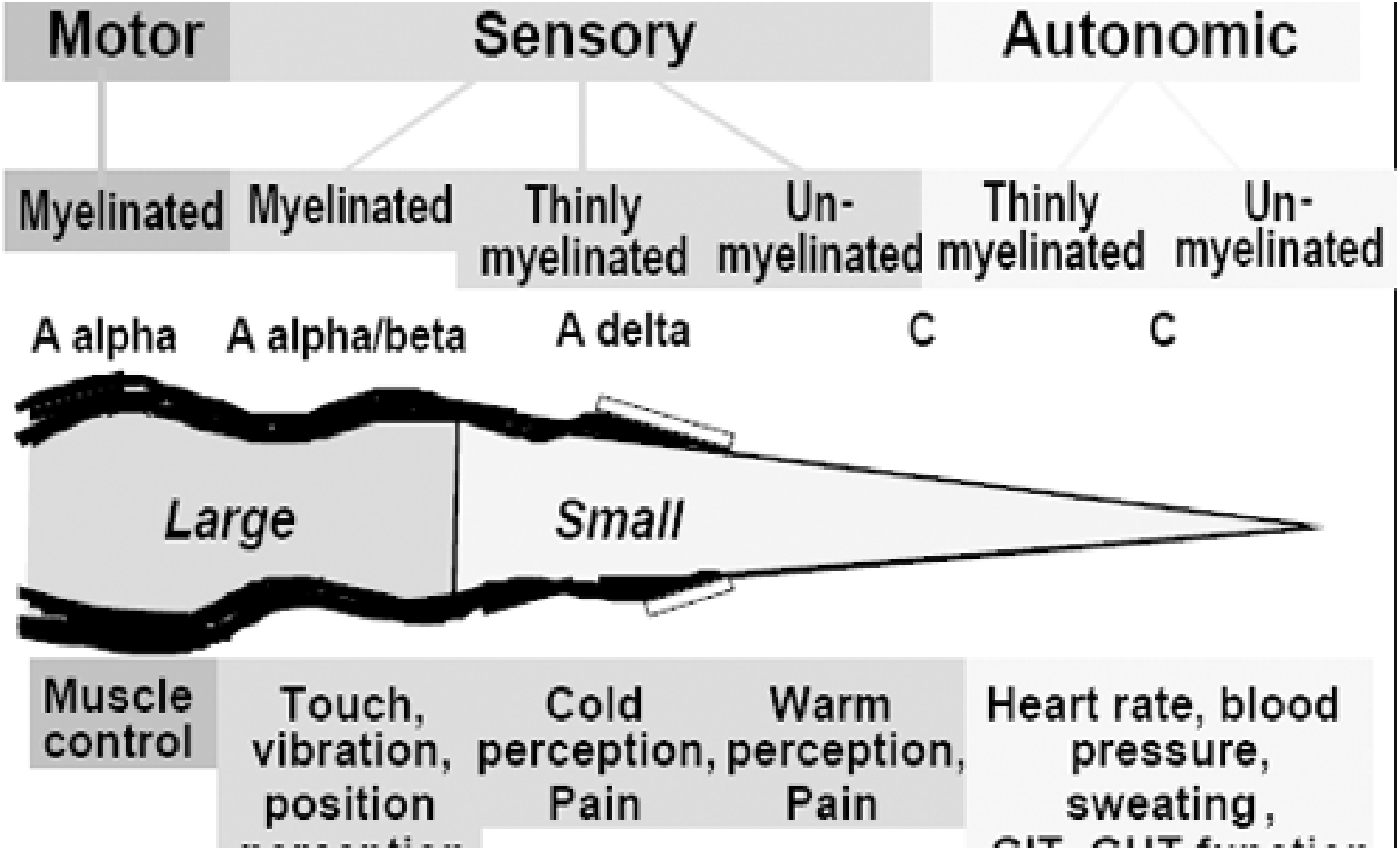
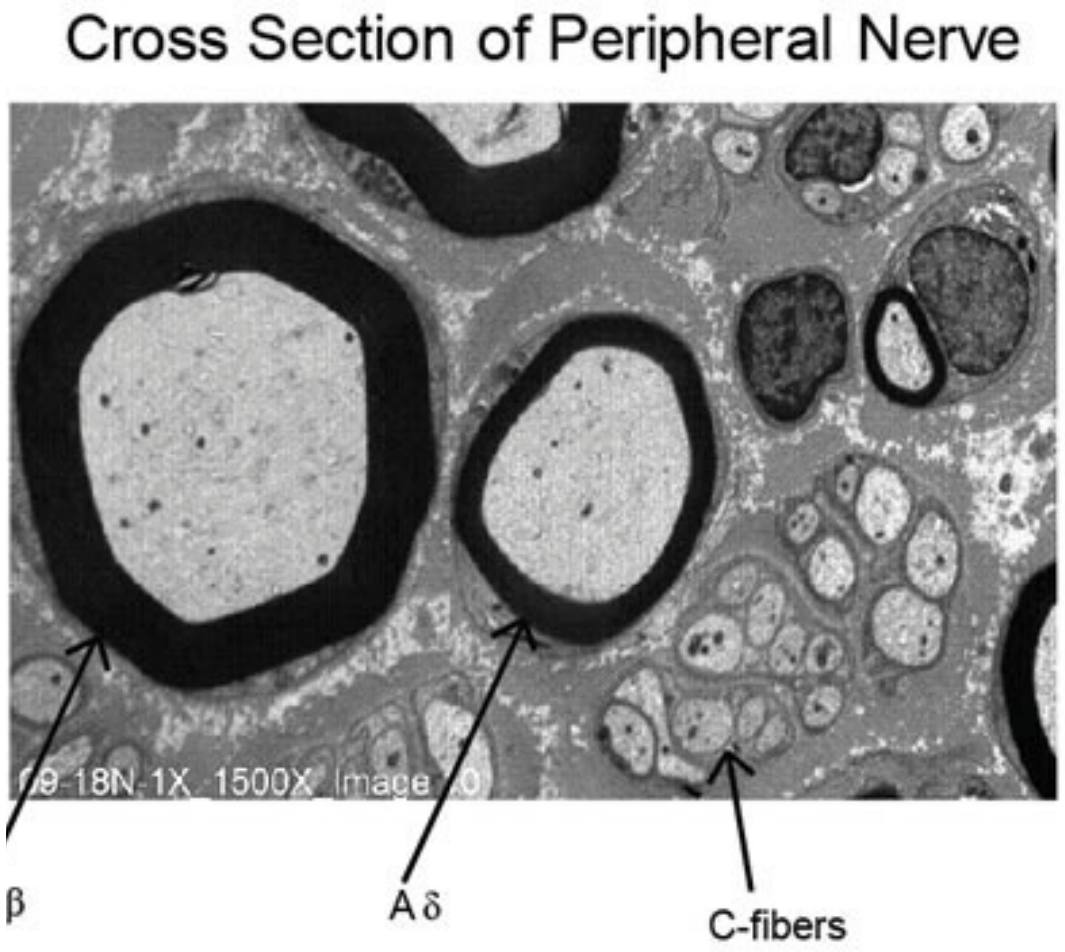
Objectives

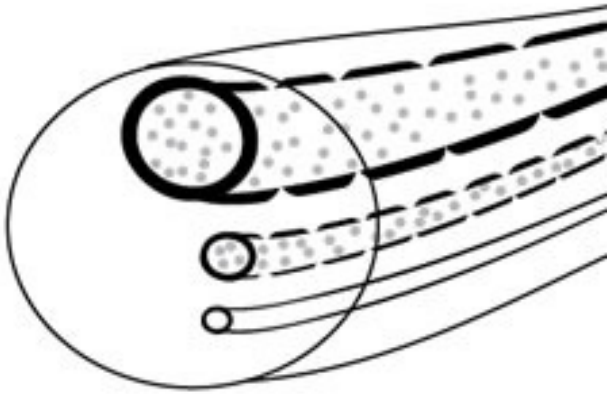
- Understand the neuroanatomical basis of small fiber neuropathies
- Review the clinical symptoms and diverse presentation for small fiber neuropathies
- Discuss the diagnostic tests used in evaluating small fiber neuropathy
- Examine potential treatments of small fiber neuropathy

Assessment of Nerve Fiber Types



Peripheral Pain Nocioceptors

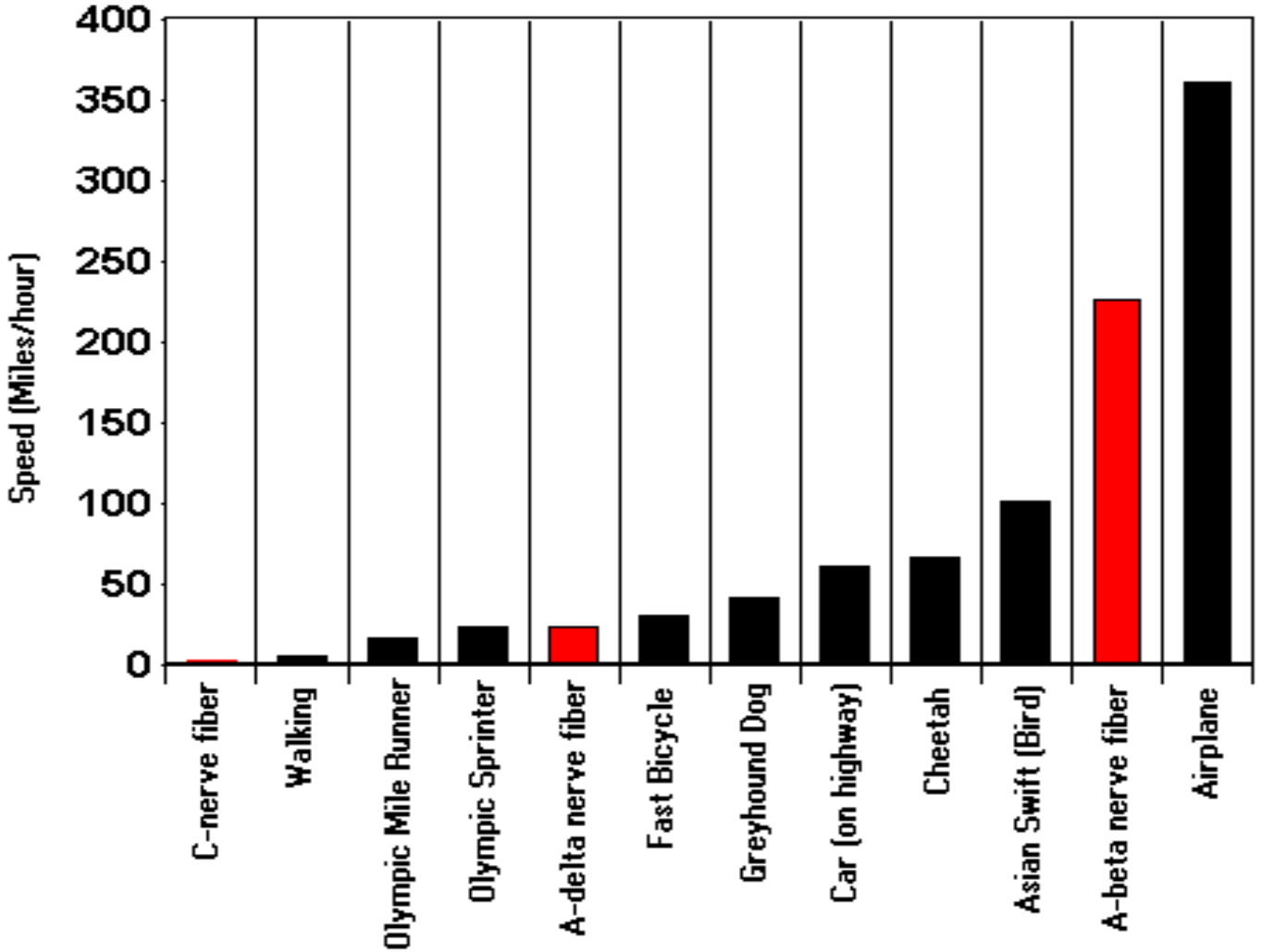




Sensory Nerve Fiber Types

Fiber Type	Diameter (μm)	C.V. (m/s)	Modality
A-alpha	13-20	80-120	proprioception
A-beta	6-12	35-75	touch
A-delta	1-5	5-35	pain, temperature
C	0.2-1.5	0.5-2.0	pain, temperature

Relative Speed of Sensory Nerve Fibers



Peripheral Neuropathies

- Most are “mixed fiber”
  - Small, medium and large fibers equally affected
  - Electrophysiologically these are detected as axonal sensori-motor neuropathies
- Some neuropathies may start as small fiber and evolve into mixed fiber
  - This can be seen in diabetes where patients have symptoms but no objective evidence of neuropathy for years
- A small percentage remain confined only to small fibers

Small Fiber Neuropathy

Symptoms

- Numbness and tingling
- Pain- primarily neuropathic. However muscle cramps and pain can occur as well
  - Burning
  - Stabbing
  - Shooting
  - Prickly
- Symptoms usually persistent

Small Fiber Neuropathy

- Most commonly distal, “length-dependent” and symmetrical
- May be asymmetrical or non length-dependent
- Normal deep tendon reflexes
- Normal proprioception
- Normal vibratory sensation
- Normal nerve conduction studies/ EMG

Small Fiber Neuropathy

Diagnostic Tests

- Conventional sural nerve biopsy
- Skin biopsy for intraepidermal nerve fiber density
- Quantitative sensory testing (QST)
  - PSSD
  - CASE IV
- Autonomic testing
  - QSART

Quantitative Sensory Testing

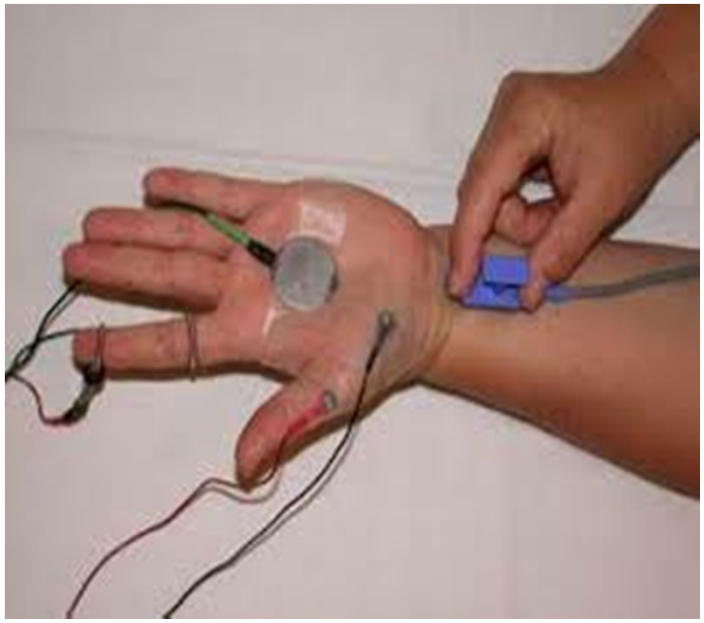
Visual Perception Threshold

Thermal Threshold Testing

Quantitative Sensory Testing

- Provides quantitative information of sensory function, but poor standardization
  - Requires built in trick questions to test for malingering
- Can be used to follow disease progression
- Limited objectivity and reliance on subjective responsiveness
- Not specific for peripheral disorders- can be abnormal in CNS disorders

QSART



QSART

- The test measures resting skin temperature, resting sweat output, and stimulated sweat output.
- Measurements are typically taken on arms, legs or both
- The data is used to determine how well the nerves and sweat glands are functioning.
- Sensitivity is reported to be 80% for small fiber dysfunction
- Limited Availability

Skin Biopsy

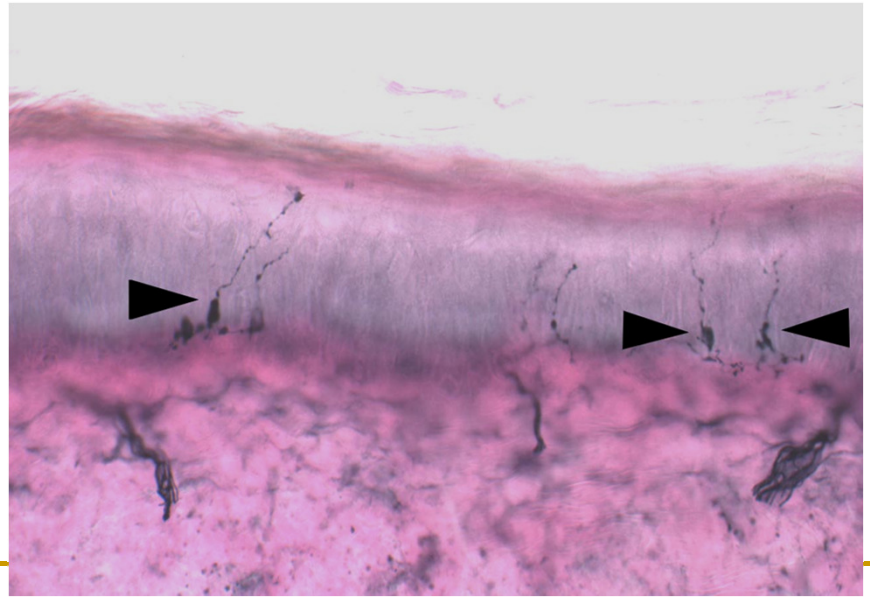
- 2 to 4 3 mm sites are chosen
- No stitches and a small lidocaine injection to numb the area
- Heals up as a scar with no special treatment and in most cases a few months later you can't even see it
- Can be performed by any clinician
- Cannot be processed in regular pathology labs
- Sensitivity is reported to be 92%

Skin Biopsy
Processing

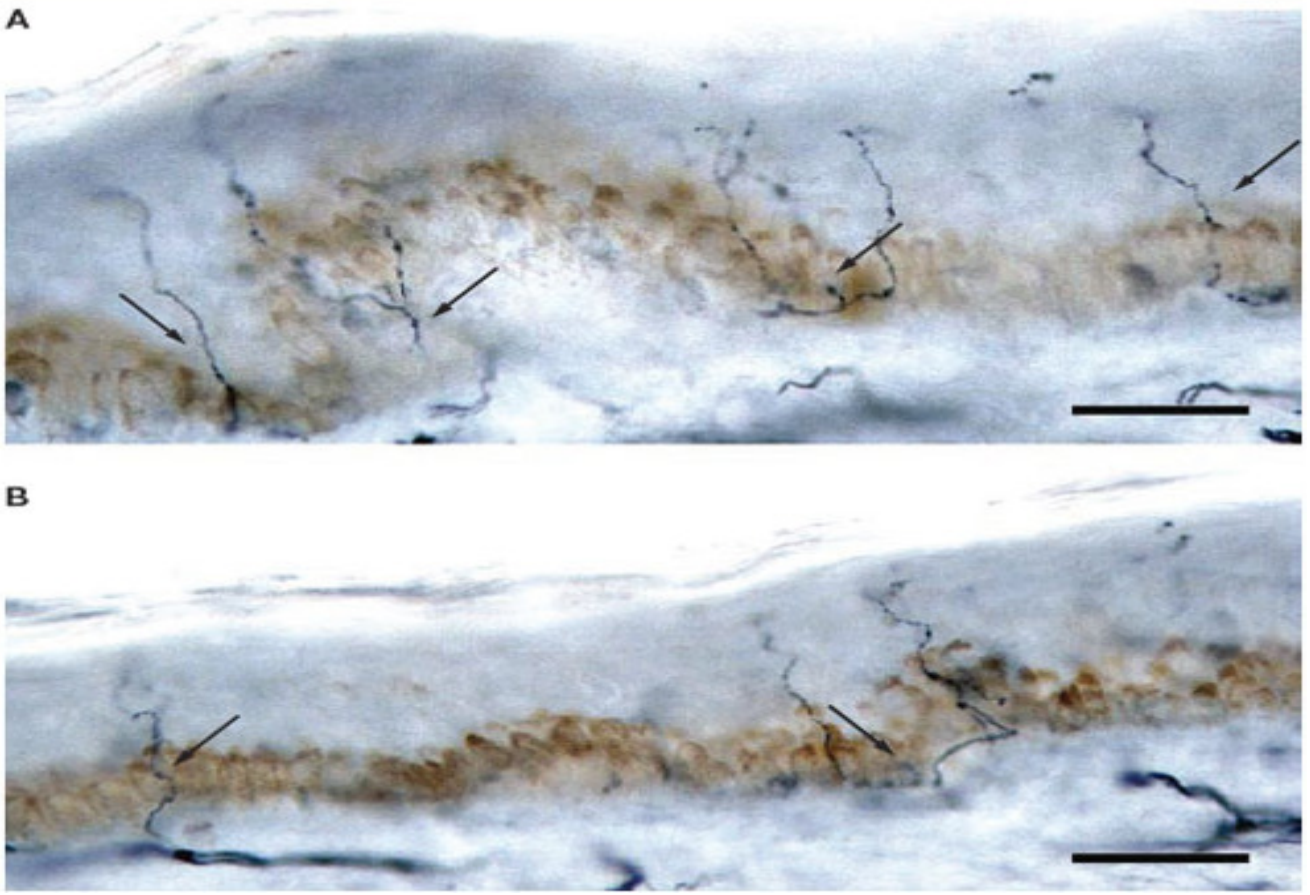
- Fixation
- Cryoprotection
- Sectioning of frozen not paraffin fixed tissue
- Primary & secondary antibodies
- Chromogen
- Mounting, alcohol drying
- Then biopsy is read by trained neuropathologist

Skin Biopsy

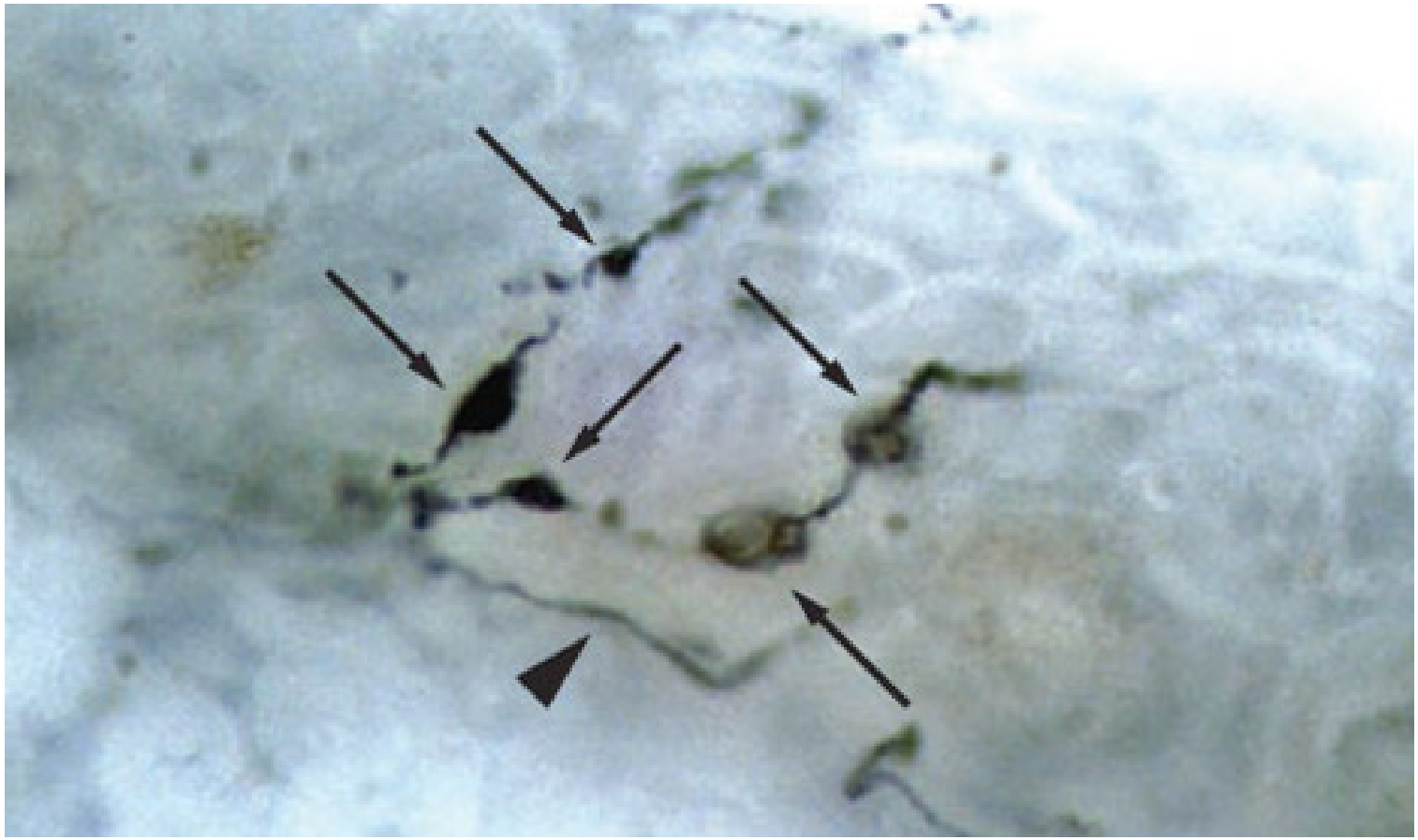
- Well Validated
  - Technique developed by Johns Hopkins and University of Minnesota
  - 100's of articles speak to its reproducibility and acceptance in medical literature



Intraepidermal Nerve Fiber Staining



Neuronal Swellings

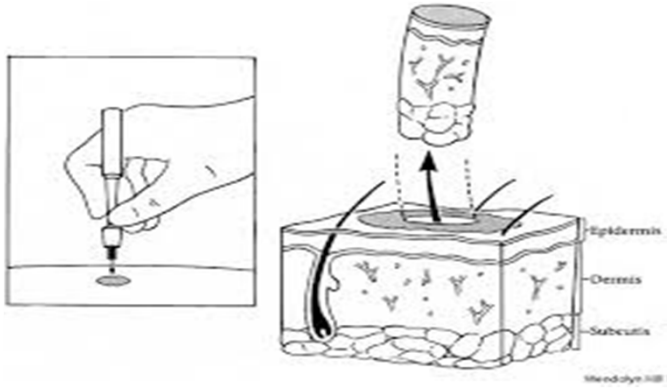


Epidermal Nerve Density (ENFD)

- Normal density varies by region of body
- Ideally should rely on site, age, and gender matched controls
- Lower limit of normal is 2 SD below the median
- Thus 5% of normals may have abnormal results

Where to Biopsy

- Standard sites
  - Distal calf
  - Distal thigh
  - Proximal thigh

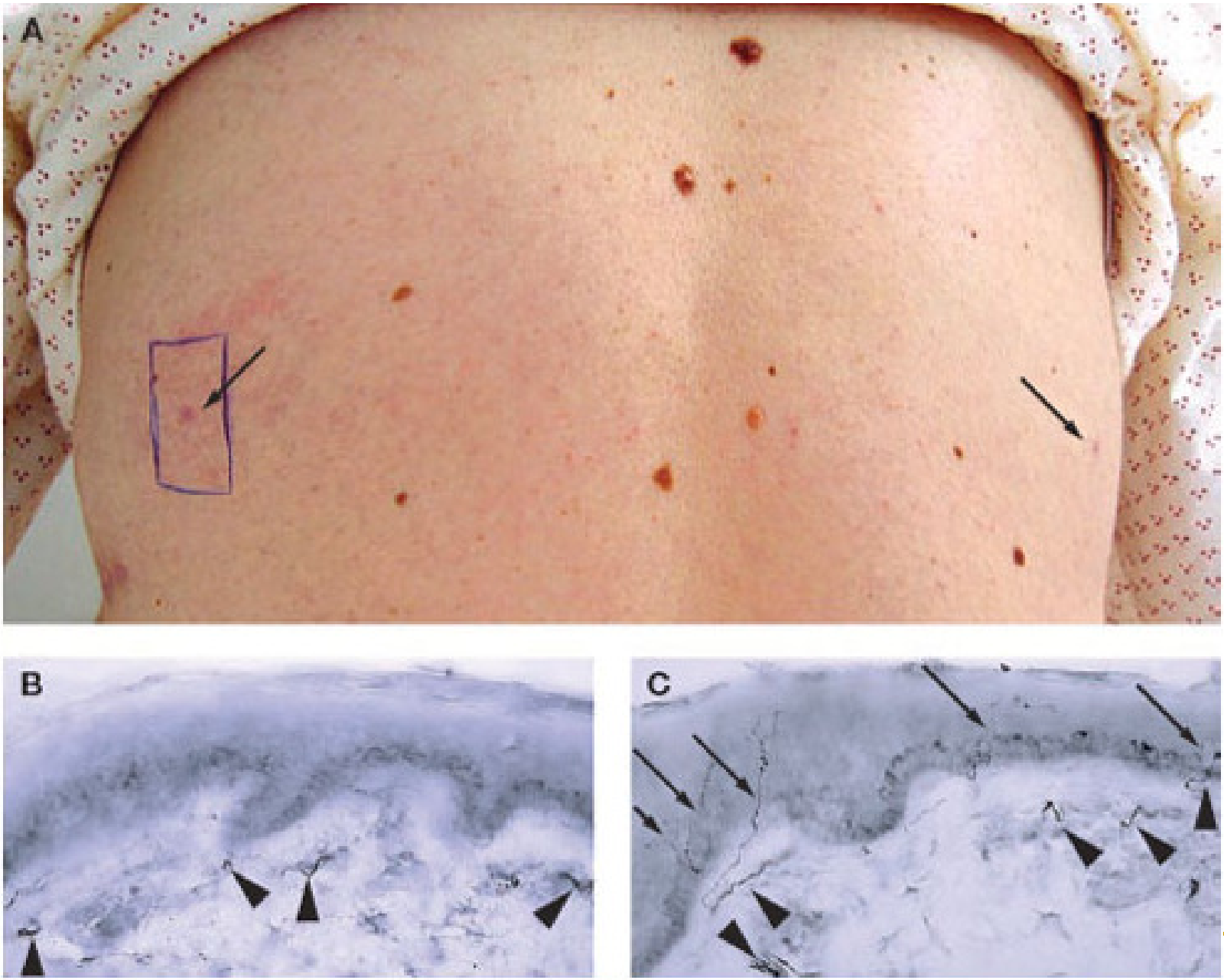


- Other sites – based on symptoms/findings

Length Dependent versus Non-length Dependent Results

Khan S, Zhou L Muscle Nerve 2012 Jan 45(1) 86-91

- Sixty-three patients with NLD-SFSN were compared with 175 patients with LD-SFSN for their demographics and disease associations.
- **RESULTS:**
- Age was younger in those with NLD-SFSN (45.5 ± 13.1 years) than in those with LD-SFSN (55.1 ± 11.4 years, $P < 0.001$).
- Forty-six of 63 (73.0%) patients were women in the NLD-SFSN group, whereas 84 of 175 (48.0%) were women in the LD-SFSN group ($P < 0.001$).
- Disease associations were identified in 26 of 63 (41.3%) patients with NLD-SFSN, including diabetes or prediabetes in 10 (15.9%), connective tissue diseases in 6 (9.5%), thyroid dysfunction in 4 (6.3%), sarcoidosis in 3 (4.8%), vitamin B(12) deficiency in 2 (3.2%), and paraproteinemia in 1 (1.6%).
- Immune-mediated conditions were present in 9 of 63 (14.3%) patients with NLD-SFSN and 6 of 175 (3.4%) patients with LD-SFSN ($P = 0.012$).
- **CONCLUSIONS:**
- NLD-SFSN is more common in women, presents at a younger age, and is more likely to be associated with immune-mediated conditions than LD-SFSN.


A
B
C

Causes of Small Fiber Neuropathy

Causes of Small Fiber Neuropathy	Evaluation
Glucose	HgBA1c, 2 hr OGTT
Sjogren's Syndrome	SS-A, SS-B
Lupus, Connective Tissue Disease	ANA
Immune Mediated	Anti Potassium Channel Aby Anti Nicotinic-Ganglionic Receptor Aby
B12 deficiency	B12, methylmalonic acid,
Sarcoid	ACE
Inherited	SCN9A, SCN10A
Celiac	Gliadin; transglutaminase Abys
Paraprotein/Amyloid	Serum immunofixation, QIgGs
Alcohol/ Chemotherapy/ Drug/Trauma	History
HIV	HIV

Cost Effectiveness analysis of Skin Biopsy

- If you ordered blood tests (not including autoantibodies or genetic testing) on all patients suspected of SFN it would cost $3200 per patient
- Cost for two biopsy sites is $1100
- So if 50% of patients have SFN you save $100,000 for every 100 patients you perform biopsy on before ordering blood tests.

Autonomic function is independent of somatic evaluation of small fiber neuropathy

Thaisetthawatkul P et al J Neurol Sci 2014 Sept 15; 344 (1-2) 51-4

- 122 patients with clinically suspected sensory neuropathy without motor weakness and with normal nerve conduction studies underwent blinded autonomic reflex screening test (ARS), quantitative sensory testing (QST) and skin biopsy (IENFD) for diagnosis of SFN.
- **RESULTS:**
- There was no association between autonomic function measures (QSART volume, CASS_QSART, CASS_vagal, CASS_adrenergic or total CASS) and small fiber sensory measures (IENFD, cooling or heat-pain thresholds). Weak correlations were noted among some modalities of QST (vibration and cooling thresholds) and IENFD.
- **DISCUSSION:**
- Autonomic and sensory outcomes are independent (complementary) measures of distal SFN, and should where feasible be used concurrently in the evaluation of SFN.

Who Should be Tested for Small Fiber Neuropathy

The Clinical Phenotype Continues to Expand….

Would we look for reversible causes of SFN in these patients without a biopsy

SFN Associated with Postural Orthostatic Syndrome

Haensch CA et al Muscle Nerve 2014 Dec 50(6) 956-61

- Postural tachycardia syndrome (POTS) is a disorder of orthostatic intolerance characterized by excessive tachycardia of unknown etiology.
- Objective: evaluate the correlation between C-fiber involvement as shown by skin biopsy and adrenergic cardiac metaiodobenzylguanadine (MIBG) uptake in POTS patients.
- Methods: Skin biopsies of 84 patients with POTS were examined by Protein Gene Product 9.5 (PGP9.5) immunohistochemistry and were compared with MIBG myocardial scintigraphy imaging data.
- Results: Mean intraepidermal nerve fiber (IENF) density was below the normal range in 45% of POTS patients. Low IENF density correlated with reduced cardiac MIBG uptake ($r = 0.39$, $P = 0.001$).
- A subset of neuropathic POTS patients may harbor small fiber neuropathy with abnormalities of unmyelinated nerve fibers in the skin associated with reduced myocardial postganglionic sympathetic innervation.

Muscle Cramps and SFN

Lopate G etal Muscle Nerve 2013 Aig 48(2) 252-55

- Methods: Skin biopsies were performed on consecutive patients with cramps but without neuropathic complaints. Twelve patients were biopsied, 8 with normal small-fiber sensation.
- Results: Seven patients had decreased intraepidermal nerve fiber density (IENFD), 2 with non-length-dependent loss. A cause for neuropathy was found in 1 patient with cramp-fasciculation syndrome. Creatine kinase was elevated in 8 patients, 4 with decreased IENFD. Muscle biopsy, performed in 8 patients, but was diagnostic in only 1, with McArdle disease.
- Conclusion: Our data show that 60% of patients with muscle cramps who lack neuropathic complaints have SFN, as documented by decreased IENFD. Cramps may originate as local mediators of inflammation released by damaged small nerve that excite intramuscular nerves.

Small fiber neuropathy in fibromyalgia

Oaklander AL1, Herzog ZD, Downs HM, Klein MM. Pain. 2013 Nov;154(11):2310-6.

- 27 patients with fibromyalgia and 30 matched normal controls were studied
- They found that 41% of skin biopsies from subjects with fibromyalgia vs 3% of biopsies from control subjects were diagnostic for SFPN
- 8 subjects had dysimmune markers, 2 had hepatitis C serologies, and 1 family had apparent genetic causality.
- These findings suggest that some patients with chronic pain labeled as fibromyalgia have unrecognized SFPN

SFN and Fibromyalgia

Levine, TD, Saperstein DS. Clinical Rheumatol Dec 2014

- 34 of 56 patients with ACR criteria for FM (61%) had SFN as indicated by reduced IENFD.
- 24of 34 patients with SFN (71%) had laboratory evidence that revealed an underlying etiology for the SFN.
  - Glucose dysmetabolism, Sjorgen's syndrome, MCTD, vitamin B6 toxicity, Vitamin B12 deficiency, and Fabry's disease.
  - These underlying conditions were not previously detected

Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. Oaklander AL, Klein MM Pediatrics 2013 Apr;131(4) 1091-100

- Objective: Evaluate presence of acquired small-fiber polyneuropathy (SFPN), in unexplained pediatric widespread pain syndromes.
- Methods: Forty-one consecutive patients evaluated for unexplained widespread pain beginning before age 21 had medical records comprehensively analyzed regarding objective diagnostic testing for SFPN (neurodiagnostic skin biopsy, nerve biopsy, and autonomic function testing),
- Results: Sixty-eight percent were chronically disabled. Objective testing diagnosed definite SFPN in 59%, probable SFPN in 17%, and possible SFPN in 22%. Only 1 of 41 had entirely normal SFPN test results. Ninety-eight percent of patients had other somatic complaints consistent with SFPN dysautonomia (90% cardiovascular, 82% gastrointestinal, and 34% urologic), 83% reported chronic fatigue, and 63% had chronic headache.
- Exhaustive investigations for SFPN causality identified disordered immunity in 89%. Treatment with corticosteroids and/or intravenous immune globulin objectively and subjectively benefited 80% of patients (12/15).

Inherited forms of SFN

- 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.
- Heterozygous mutations in TRPA1, which encodes the transient receptor potential cation channel, can cause familial episodic pain syndromes, and 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..

SFN and SCN9A mutations

Faber et al, Ann neurol 2012 Jan 71(1) 26-39

- Patients referred with possible Idiopathic SFN, who met the criteria of ≥2 SFN-related symptoms, normal strength, tendon reflexes, vibration sense, and nerve conduction studies, and reduced intraepidermal nerve fiber density (IENFD) plus abnormal quantitative sensory testing (QST) and no underlying etiology for SFN, were assessed for SCN9A mutations
- **RESULTS:**
- 28 patients with biopsy-confirmed SFN were analyzed, 8 were found to carry novel mutations in SCN9A. Functional analysis revealed multiple gain of function changes in the mutant channels; each of the mutations rendered dorsal root ganglion neurons hyperexcitable.
- **INTERPRETATION:**
- We show for the first time that gain of function mutations in sodium channel Na(V)1.7, which render dorsal root ganglion neurons hyperexcitable, are present in a substantial proportion (28.6%; 8 of 28) of patients meeting strict criteria for SFN.

So they have SFN…So What?

Can we treat them or is it just gabapentin

What Skin Biopsies Can Tell Us

Likelihood of responding to pain medication

Abnormal biopsy predicts a 85% likelihood of responding to traditional neuropathic pain medications.

	Small fiber neuropathy	Normal	P value
Gabapentin/Lyrica /Cymbalta/ amytriptiline	85% (n=62)	37% (n=31)	P<0.001

Levine, TD et al Poster Presentation, American Academy of Neurology, Seattle 2009

Does IVIG have a role in SFN

- No large studies to date
- However if there is an immune mediated disease and SFN, IVIG is a reasonable treatment option as a therapeutic trial
  - Like in mixed fiber neuropathies probably 10-20% are immune mediated. How do we identify
    - Serologic Evaluation
    - If severe consider LP
    - Therapeutic trial
- Very expensive and difficult to get insurance to cover

IVIG in Sarcoid mediated SFN

Parambil JG et al Respir Med. 2011 Jan;105(1):101-5

- Background: Small fiber neuropathy (SFN) can be associated with sarcoidosis
- Results: They described three patients with biopsy-proven sarcoidosis who developed intractable neuropathic pain and/or symptoms related to associated autonomic dysfunction despite treatment with various immunosuppressive medications and narcotic analgesics. Painful neuropathic symptoms, as well as symptoms related to dysautonomia from SFN responded significantly to treatment with intravenous immunoglobulin (IVIG).
- Conclusion: IVIG appears to be effective in relieving symptoms from SFN associated with sarcoidosis, suggesting an underlying immune mechanism.

IVIG in Celiac Mediated SFN

Souyah N, et al Eur J Neurol 2008 Dec 15(12) 1300-3

- Case report of three patients with biopsy-proven CD who developed cerebellar ataxia and neuropathic pain despite strict adherence to a gluten-free diet.
- A small fiber neuropathy was diagnosed by skin biopsy findings.
- All patients' symptoms, including small fiber neuropathy symptoms, responded to treatment with intravenous immunoglobulin (IVIG).
- Discontinuation of IVIG in two patients resulted in worsened ataxia that reversed after resumption of IVIG.
- **CONCLUSION:**
- Intravenous immunoglobulin may be effective in treating cerebellar ataxia and small fiber neuropathy associated with CD, suggesting an immune pathogenesis.

Ganglionic Antibody Mediated SFN

Iodice V, et al Neurology 2009 Jun 9(72) 2002-6

- Methods: Six patients with Autoimmune Autonomic ganglionopathy AAG, underwent autonomic function tests and completed two validated questionnaires, to assess autonomic symptoms before and after immunomodulatory treatment. Patients were treated with standard doses of IVIg, PE, or immunosuppressants
- Results: Of the six patients (all women, mean ages 49.3 +/- 10.6 years), four patients were ganglionic AChR autoantibody positive and two were autoantibody negative. All patients showed clinical improvement after treatment. Sudomotor function assessed by quantitative sudomotor axon reflex test and thermoregulatory sweat test improved in four patients after treatment.
- Conclusions: Immunomodulatory treatment can be effective in both seropositive and seronegative putative autoimmune autonomic ganglionopathy. Plasma exchange or combined therapy with immunosuppressive agents should be considered in patients who do not benefit from i.v. immunoglobulin alone.

Improvement in Small Fiber Neuropathies Following Immunomodulatory Therapy

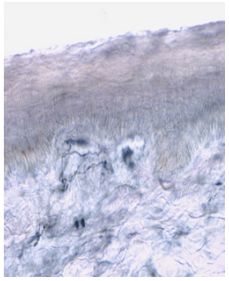
Todd D Levine, MD and David Saperstein, MD
Phoenix Neurological Associates

Abstract

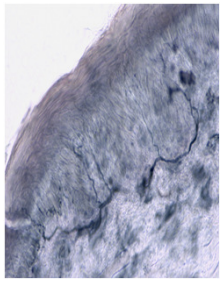
Objective: Patients with isolated small fiber neuropathies may have evidence for immune dysregulation such as Sjogren's syndrome. While these laboratory abnormalities do not definitively identify the immune dysregulation as a cause for the small fiber neuropathy, we have treated a series of patients with immunomodulatory therapy with these abnormalities.

Background: Small fiber neuropathies are being recognized with increasing frequency as the availability of epidermal nerve fiber testing has become more widespread. These patients often have relatively normal neurologic examinations but can be severely affected in terms of sensory complaints such as dysesthesias and pain. While 50-60% of these patients have no identifiable cause, specific etiologies can be identified in many patients. Disorders of glucose metabolism represent the largest identifiable cause followed by B12 deficiency. Patients with evidence for immune dysregulation such as Sjogren's disease or monoclonal gammopathies or paraproteins can be found in 5-10% of patients with small fiber neuropathy. There is however no large controlled study of the efficacy of immunomodulatory therapy in these patients.

Results: The five patients reported here all responded rapidly to either IVIG or plasmaphresis. In addition repeated skin biopsies after six months of therapy showed an increase in epidermal nerve fiber density.



Patient 2 before therapy



Patient 2 after therapy

Methods

Patients with neuropathic symptoms who had normal EMG/NCV underwent skin biopsy to look for evidence for a small fiber neuropathy. Patients with abnormal skin biopsies underwent a serologic evaluation looking for reversible causes for neuropathy. Those patients who had evidence for immune dysregulation with severe enough symptoms to warrant therapy were treated as noted below.
A repeat skin biopsy 3-6 months after therapy was initiated was performed to look for objective evidence of improvement.

Conclusions

1) **A thorough search for potential causes of small fiber neuropathies should entail a serologic screen for underlying signs of immune dysregulation including sarcoid, sjogrens, and monoclonal gammopathies.**
2) **Small fiber neuropathies associated with underlying immune dysregulation may respond to immunomodulatory therapy with IVIG or plasmaphresis**
3) **Repeat skin biopsies provide an objective measure of improvement in small fiber neuropathies and can show significant changes in as little as three months.**

	Clinical Symtpoms	Abnormal labs	Pre-Rx Biopsy	Post-Rx Biopsy	Treatment	Clinical Response
Patient 1	Length dependent numbness and pain. Thermal sensitivity	Elevated lambda light chains	Calf: 3.8/mm (>5) Thigh: 4.7/mm (>8)	Calf: 11.8/mm (>5) Thigh: 11.8/mm (>8)	IVIG 1 gm/kg/month for six months	Decreased pain Improved energy
Patient 2	Length dependent numbness and pain. Allodynia	IgM MGUS	Calf: 0/mm (>5) Thigh: 2.3/mm (>8)	Calf: 6.3/mm (>5) Thigh: 9.0/mm (>8)	IVIG 2 gm/kg/month for six months	Improved pain and decreased numbness
Patient 3	Length dependent pain. Allodynia. Orthostasis	+ SS-A	Calf: 1.2/mm (>5) Thigh:1.9/mm (>8)	Calf: 6.3/mm (>5) Thigh:1.0/mm (>8)	IVIG 2 gm/kg/month for six months	Improved pain. Improved energy. Decreased orthostasis
Patient 4	Distal foot pain and dysesthesias	IgG MGUS	Calf:0/mm (>5) Thigh: 4.7/mm (>8)	Calf: 5.7/mm (>5) Thigh:9.8/mm (>8)	Plasmaphresis 2/ week for three months	Improved pain
Patient 5	Proximal and distal pain Facial numbness	+SS-A +SS-B	Calf: 6/mm (>5) Thigh:1.6/mm (>8)	Calf:7.2/mm (>5) Thigh:11.2/mm (>8)	IVIG 2 gm/kg/month for six months	Improved numbness and pain

Potential novel therapies

Dahan et al, Mol Med 2013 Nov 8:19 334-45

- Small nerve fiber loss and damage (SNFLD) is a frequent complication of sarcoidosis that is associated with autonomic dysfunction and sensory abnormalities.
- Current therapy of sarcoidosis-associated SNFLD consists primarily of immune suppression and symptomatic treatment; however, this treatment is typically unsatisfactory.
- ARA 290 is a small peptide engineered to activate the innate repair receptor that antagonizes inflammatory processes and stimulates tissue repair. Here we show in a blinded, placebo-controlled trial that 28 d of daily subcutaneous administration of ARA 290 in a group of patients with documented SNFLD significantly improves neuropathic symptoms.
- ARA 290 administration was also associated with a significant increase in corneal small nerve fiber density, changes in cutaneous temperature sensitivity, and an increased exercise capacity as assessed by the 6-minute walk test.
- On the basis of these results and of prior studies, ARA 290 is a potential disease-modifying agent for treatment of sarcoidosis-associated SNFLD.

OK.. Now the gabapentin part

- Anti-Convulsants
  - Gabapentin
  - Pregabalin
  - (Sodium Channel Blocking drugs theoretically)
- SNRI's
  - Tricyclics
  - Duloxetine
  - Savella (Fibromyalgia pain not Neuropathic Pain)
- Topical Agents
- Narcotics

As Neurologists shouldn't we localize the lesion?

- Skin Biopsies can tell us that
  - Small nerve fibers are affected
  - Small fiber damage is probably causing the patients pain
- Whether or not length-dependent
- Who might respond to treatments for pain
- Direct physicians to look for underlying cause
- Start to study specific treatments