Small Fiber Neuropathies

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Disclosure

- Consultant Independent Contractor: Astra Zeneca, Depomed, Endo Pharmaceuticals, Nektar Therapeutics, Pfizer, Xenoport, Zogenix
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- Stock Shareholder: Depomed, Pfizer
- Other/Royalty: Elsevier
Learning Objectives

- Describe the definition of small fiber neuropathy
- Explain approaches to making the diagnosis of small fiber neuropathy
- Cite current and emerging treatments of small fiber neuropathy
“Discouraging Data on the Antidepressant”
Gabapentin in the treatment of painful diabetic neuropathy*

*Not approved by FDA for this use
† $P < 0.01$; ‡ $P < 0.05$

Which person has pain?
Are Current Common Approaches Diagnosing and Treating Chronic Pain Antiquated?

What are we looking for?

- How often do we encounter a chronic pain state where the degree of damage or inflammation in the PNS or CNS consistently correlates well with the level of pain?
- Do our diagnostic paradigms - and terms we use to describe chronic pain states – suggest otherwise?
- Until recently many assumed that when there was a disparity between peripheral findings and pain, this was primarily due to psychological factors???
- Does this make sense?
- Maybe we need to broaden our evaluation of chronic pain?
Example: Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative

- Chronic widespread pain
- Tenderness in \( \geq 11 \) of 18 tender points
- Final common pathway
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals
**Example: Mechanistic Characterization of Pain**

Any combination may be present in a given individual

<table>
<thead>
<tr>
<th>Peripheral (nociceptive)</th>
<th>Peripheral Neuropathic</th>
<th>Central Neuropathic or Centralized Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Inflammation or mechanical damage in tissues</td>
<td>■ Damage or dysfunction of peripheral nerves</td>
<td>■ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)</td>
</tr>
<tr>
<td>■ NSAID, opioid responsive</td>
<td>■ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA’s, neuroactive compounds) pharmacological therapy</td>
<td>■ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission</td>
</tr>
<tr>
<td>■ Responds to procedures</td>
<td></td>
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</tbody>
</table>

- **Classic examples**
  - Acute pain due to injury
  - Osteoarthritis
  - Rheumatoid arthritis
  - Cancer pain

- **Classic examples**
  - Diabetic neuropathic pain
  - Post-herpetic neuralgia

- **Classic examples**
  - Fibromyalgia
  - Irritable bowel syndrome
  - TMJD
  - Tension headache

- **Mixed Pain States**
Chronic Widespread pain: British Pain Society Guidelines

- CWP including fibromyalgia is highly prevalent
- Diagnosis should be based on the presence and distribution of signs and symptoms in the absence of another defined pathological process
- Comprehensive Assessment
- Goals of guideline include: to reduce variations of standards of care and enable clinicians to help patients accept a diagnosis of CWP
- Use of opioids on chronic basis discouraged

Differential diagnosis - Widespread Pain

- Rheumatic
  - Arthritis (OA, RA)
  - Polymyalgia Rheumatica
  - Osteomalacia
  - Myopathy
  - Spondyloarthropathies
  - Systemic Lupus Erythematosus

- Neurologic
  - Multiple sclerosis
  - Chiari malformation
  - Spinal stenosis
  - Radiculopathy
  - Neuropathy

- Endocrine
  - Hypothyroidism
  - Diabetes
  - IS SMALL FIBER NEUROPATHY OVERLOOKED?
Background

- Peripheral neuropathy is experienced by approximately 40 million people in the US
- Many peripheral neuropathies are mixed neuropathies with both large fiber and small fiber involvement
- Increasingly recognized is the demonstration of specific involvement of small myelinated or unmyelinated fibers, e.g. small fiber neuropathies

Burden of Illness studies - NEUROPATHIC PAIN

- Two observational studies- one regarding HIV related neuropathic pain and the other peripheral neuropathy with small fiber involvement were presented at the APS meeting 2013.
- For both groups, many subjects experienced moderate to severe pain, the economic costs were substantial and the adverse effect on quality of life notable.
What is Neuropathic Pain?

- Pain arising as a direct consequence of diseases affecting the somatosensory system.
  - Grading system: definite, probable, possible
- In Plain English: Pain from the nerves, spinal cord, or brain. Not originating in the bones, muscles, organs.

R-D Treede et al. Neurology 2008, Proposed by IASP Neuropathic Pain Special Interest Group
Common Neuropathic Pain Diagnoses

- Diabetic Peripheral Neuropathy*
- Post Herpetic Neuralgia*
- Radicular Pain
- Traumatic Peripheral Nerve Injury
- Complex Regional Pain Syndrome
- Chronic Postop Pain
- Phantom Limb Pain
- HIV related neuropathy
- Spinal Cord Injury*
- Post-stroke pain
- Trigeminal Neuralgia*
- Small Fiber Neuropathies

*FDA approved medications available
Small Fiber Neuropathy Definition

- Small fiber neuropathies (SFN) result from damage to the peripheral nerves affecting small myelinated A-Delta and unmyelinated C fibers.
- The fibers affected include both small somatic as well as autonomic fibers.
- Thermal perception and nociception are subserved by small fibers.
- Enteric function is also subserved by small fibers.

Small Fiber Neuropathy Definition - 2

- Most SFNs occur in a length-dependent fashion – first stocking distribution changes and then later glove distribution.
- Rarely, non-length dependent SFN can result in symptoms involving the face, trunk, proximal limbs, or other more localized areas.
- The pathogenesis of injury to small fibers is not well understood.
- SFN can progress to involve large fibers as well.

Disorders Associated with SFN

- Diabetes
- Impaired Glucose Tolerance
- Metabolic Syndrome
- Sarcoidosis
- Thyroid Dysfunction
- HIV
- Vitamin B12 Deficiency
- Chemotherapy drugs
- Antiviral Agents
- Celiac Disease
- Sjogren’s Syndrome
- Paraneoplastic Syndromes
- Paraproteinemias
- Rheumatoid Arthritis
- Idiopathic (up to 50%!)

Hovagimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy
Disorders Associated with SFN - 2

- Guillain-Barre Syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Restless Leg Syndrome
- Hepatitis C
- Systemic Lupus Erythematosus
- Sjogren’s Syndrome
- Amylodosis
- Fabry’s Disease
- Hereditary Sensory Neuropathies
- Hereditary Autonomic Neuropathies

## DPN involves small and large nerve fibers

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Large-fiber neuropathy</th>
<th>Small-fiber neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Numbness, pins and needles, tingling, poor balance</td>
<td>Pain: burning, electric shocks, stabbing pain, numbness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exam Findings</th>
<th>Reflexes, proprioception Vibration, +/- motor</th>
<th>Thermal, pin-prick sensation, allodynia</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Functional changes</th>
<th>Pressure, balance, fall risk</th>
<th>Nociception; protective sensation</th>
</tr>
</thead>
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<thead>
<tr>
<th>Diagnostic test</th>
<th>EMG/NCV, sural nerve biopsy</th>
<th>QST, nerve biopsy, Intraepidermal nerve fiber density (skin biopsy)</th>
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</thead>
</table>
SFN Pathophysiology - Possible role of Sodium Channel mutations

- Genetic variants in the structure/function of sodium channels may lead to either loss of pain sensitivity or enhanced pain
- Inactivating mutations in SCN9A, which encodes Nav 1.7 is associated with congenital insensitivity to pain
- Gain of function mutations in SCN9A may result in SFN
- Various mutations in TRPA 1 or NAv1.8(SCN10A) and Nav 1.9 (SCN11A) also may lead to SFN
- Might this information lead to new treatments?

SFN Symptoms

- Symptoms vary widely in severity
- Often affected individuals describe a gradual onset of vague distal sensory disturbances
- Examples include feeling like there is sand in the person’s shoe, a sock feeling as if it has pebbles in it, pins and needle sensations, cold painful sensations or tingling.

SFN Symptoms - 2

- Burning pain in the extremities, sometimes severe
- Allodynia and hyperesthesia
- Socks or bedsheets may be painful
- Symptoms are often worse at night
SFN Symptoms - 3

- Autonomic and enteric dysfunction including: dry eyes, dry mouth, lightheadedness with changes in posture, syncope, abnormalities of sweating, erectile dysfunction, GI symptoms such as nausea and emesis, constipation, diarrhea, changes in urinary frequency including nocturia.

SFN - Diagnosis

- Normal or practically normal basic physical and neurological examination!!!
- However, possible findings include decreased pin prick, diminished thermal sensation, hyperalgesia, dry skin
- A detailed history is vital to making the diagnosis
- Ancillary testing may be helpful as well

SFN – Diagnosis - 2

- Various written tools such as the Neuropathic Pain Symptom Inventory may be helpful.
- Quantitative Sensory Testing - this can detect thresholds of thermal pain, thermal sensation and vibration for example. Contact Heat Evoked Potentials attempts to link peripheral activation to central.
- Quantitative Sudomotor Axon Reflex testing (QSART)

# Diagnostic Studies and Limitations

## Studies
- Blood studies
- X-ray, CT, MRI
- Electromyography (EMG)
- Nerve conduction velocity (NCV)
- Quantitative sensory testing (QST)
- Epidermal skin biopsy

## Limitations of EMG/NCV
- Insensitive in acute injury
- Normal result does not rule out neuropathic pain
- Cannot assess function of small-fiber nerves involved in most neuropathic pain

SFN - Diagnosis - 3

- **Skin Biopsy** - this has become widely accepted as a technique to evaluate the structure of small nerve fibers.
- The standard is a 3-mm skin punch biopsy that can be taken from anywhere over the body.
- Due to the need to compare to normal values the lower extremity is most commonly assessed (also length dependent SFN more common)
- The results are expressed as the number of intraepidermal fibers per mm
- The sensitivity (78-92%) and specificity (65-90%) is fairly high for this technique

Loss of skin nerve fibers in PHN

PGP 9.5 Immunolabeling of Sensory Nerve Endings in Skin Biopsies

Subject without PHN pain
Contralateral site

Subject with PHN pain
Contralateral site

The density of epidermal nerve endings in previously shingles-affected skin

A.L. Oaklander et al., 1998

Oaklander AL, et al Pain 2001
SFN - Treatment

- Treat the treatable! If an underlying cause of SFN can be determined, optimal treatment of the causative condition may lessen the symptoms of SFN.

- Few studies and no guidelines have examined the pharmacologic treatment of the pain associated with SFN.

- In one such study, both gabapentin and tramadol were found to be effective for SFN.

# Neuropathic pain recommendations of various societies

<table>
<thead>
<tr>
<th>First line</th>
<th>EFNS, Europe Neurology</th>
<th>Canadian Pain Society</th>
<th>IASP NeuPSIG</th>
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</thead>
<tbody>
<tr>
<td>TCA</td>
<td></td>
<td>TCA, SNRI GBP/PGB</td>
<td></td>
</tr>
<tr>
<td>GBP/PGB</td>
<td>Lidocaine 5% plaster</td>
<td>GBP/PGB Lidocaine 5%</td>
<td>Opioid</td>
</tr>
<tr>
<td>Second line</td>
<td>SNRI (Opioid)</td>
<td>SNRI Lidocaine 5%</td>
<td>Opioid</td>
</tr>
<tr>
<td>Third line</td>
<td>Opioid</td>
<td>Opioid (except methadone)</td>
<td>Paroxetine</td>
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<tr>
<td></td>
<td>Lamotrigine Capsaicin</td>
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<td>Bupropion</td>
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<td></td>
<td></td>
<td></td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td>Fourth line</td>
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<td></td>
<td>Methadone</td>
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*EFNS, European Federation of Neurological Societies; IASP, International Association for the Study of Pain; NeuPSIG, Neuropathic Pain Special Interest Group*

SFN - Is IVIG (intravenous immunoglobulin) an Emerging Treatment?

- A recent report described 3 patients with sarcoidosis and SFN who were experiencing severe pain as well as dysautonomia
- Each patient had biopsy proven SFN
- Each patient had failed to respond to “conventional” analgesic/symptomatic approaches
- Each patient received an initial dose of IVIG 2g/kg followed by 1g/kg doses at regular intervals - each with dramatic resolution of pain and autonomic symptoms
- Further larger studies are warranted

CWP, SFPN and Fibromyalgia I

- 27 patients with fibromyalgia who satisfied the 2010 ACR criteria were compared to 30 matched controls
- 41% of skin biopsies from fibromyalgia subjects compared to 3% from controls were diagnostic for SFPN
- The Michigan Neuropathy Screening Instrument and Utah Early Neuropathy Scale scores were higher in fibromyalgia patients

CWP, SFPN and Fibromyalgia II

- 25 patients with fibromyalgia were compared to 10 depressed patients and controls
- Small fiber evaluation included QST, pain-related evoked potentials and quantified intraepidermal nerve fiber density and regenerating IENF of the lower leg and upper thigh
- Compared with control subjects fibromyalgia patients BUT not depressed patients had impaired small fiber function

Skin biopsy findings demonstrated that total and regenerating IENFs at the lower leg and upper thigh were reduced in patients with fibromyalgia compared with controls.

A reduction in unmyelinated nerve fiber bundles was seen in patients with fibromyalgia compared with depressed and control subjects.

The authors concluded that the results point towards a neuropathic nature of fibromyalgia.

CWP, SFPN and Fibromyalgia III

- At the ACR annual meeting in 2012, 56 patients who met the 2010 ACR diagnostic criteria for fibromyalgia underwent skin punch biopsies at proximal and distal lower limb sites

- 61% of these had findings consistent with SFPN using PGP 9.5 immuno labeling

Levine T and Saperstein D. ACR 2012
Four Recent patients - 1

- 67 year old male with history of Sjogren’s syndrome and progressively severe burning pain in both lower extremities and less severe complaints over upper body.
- Strength full, DTRs present, PS/VS ok in both distal lower extremities, mild allodynia over dorsal aspect of feet and
- 3mm skin punch biopsy of left leg and thigh demonstrates reduced intraepidermal nerve fiber density
Four Recent patients - 2

- 50 year old female complaining of chronic widespread pain following cholycystectomy one year prior.
- Initial complaints localized to RUQ
- Detailed evaluation revealed no specific etiology
- Skin punch biopsies demonstrate reduced IENF density
Four Recent patients - 3

- 48 year old female with 10 year history of fibromyalgia
- Symptoms flared while being treated for localized thoracic radicular complaints
- Skin punch biopsy revealed reduced IENF density at both lower extremity sites
Four Recent patients - 4

- 29 year old female with multiple surgical procedures performed for treatment of endometriosis who develops in addition to chronic pelvic pain, more widespread complaints
- Referred for “pain management.”
- Skin punch biopsies demonstrate reduced IENF density in lower extremity
Pathologies in Vascular Innervation Associated with Fibromyalgia

Excessive Peptidergic Sensory Innervation of Cutaneous Arteriole-Venule Shunts (AVS) In the Palmar Glabrous Skin of Fibromyalgia Patients: Implications for Wide-Spread Deep Tissue Pain and Fatigue
Phillip J. Albrecht, Quanzhi Hou, Charles E. Argoff, James R. Storey, James P. Wymer, Frank L. Rice
Pain Medicine (2013) in press
Females With Fibromyalgia Have Excessive Innervation of Cutaneous Arteriole-venule Shunts (AVS)

AVS profiles labeled with anti-PGP in sections of hypothenar skin biopsies from control subjects (A, C, E, G, I) and from comparable age FM patients (B, D, F, H, J).
Summary

- Multiple medical conditions are associated with SFN
- The mechanism(s) of SFN are not completely understood and may vary depending on the individual/specific associated disorder
- Recognizing SFN and its existence in perhaps more conditions than previously recognized may lead to improved treatment approaches