Small Fiber Polyneuropathy: An Update

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Disclosure

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Learning Objectives

- Describe the definition of small fiber polyneuropathy
- Describe approaches to making the diagnosis of small fiber polyneuropathy
- Explain the range of medical conditions associated with small fiber polyneuropathy
- List current and emerging treatments of small fiber polyneuropathy
“Discouraging Data on the Antidepressant (as well as many other treatments)”
Gabapentin in the Treatment of Painful Diabetic Neuropathy*

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

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>■ Classic examples</td>
<td>■ Classic examples</td>
</tr>
<tr>
<td>■ Acute pain due to injury</td>
<td>■ Diabetic neuropathic pain</td>
<td>■ Fibromyalgia</td>
</tr>
<tr>
<td>■ Osteoarthritis</td>
<td>■ Post-herpetic neuralgia</td>
<td>■ Irritable bowel syndrome</td>
</tr>
<tr>
<td>■ Rheumatoid arthritis</td>
<td>■ Cancer pain</td>
<td>■ TMJD</td>
</tr>
<tr>
<td>■ Cancer pain</td>
<td>■ Classic examples</td>
<td>■ Tension headache</td>
</tr>
</tbody>
</table>

Mixed Pain States
Which person has pain?
Differential Diagnosis - Widespread Pain

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

■ Neurologic
  ■ Multiple sclerosis
  ■ Chiari malformation
  ■ Spinal stenosis
  ■ Radiculopathy
  ■ Polyneuropathy
  ■ Fibromyalgia

■ Endocrine
  ■ Hypothyroidism
  ■ Diabetes
  ■ IS SMALL FIBER POLYNEUROPATHY 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

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.

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 Polyneuropathies

* FDA approved medications available
Small Fiber Polyneuropathy 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.
- LARGE fibers are heavily myelinated and involved in muscle control, as well as touch, vibration and position sense.

Small Fiber Polyneuropathy 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 results 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

Small Fiber Polyneuropathy: BIG impact on quality of life

- Only one study as measured the impact specifically on SFPN on quality of life
- 265 patients enrolled
- SFN-SIQ, VAS, 36 item short form health survey evaluated
- SFPN patients demonstrated a marked overall reduction in quality of life
- Physical and mental measures were decreased

Disorders Associated with SFN

- Diabetes
- Impaired Glucose Tolerance
- Metabolic Syndrome
- Sarcoidosis
- Thyroid Dysfunction
- HIV
- Vitamin B12 Deficiency
- Vitamin B1 Deficiency

- Chemotherapy drugs
- Antiviral Agents
- Celiac Disease
- Sjogren’s Syndrome
- Paraneoplastic Syndromes
- Paraproteinemia
- Rheumatoid Arthritis
- Idiopathic (up to 50%)

Disorders Associated with SFN-2

- Guillain-Barre Syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Restless Leg Syndrome
- Hepatitis C
- Systemic Lupus Erythematosus
- Amylodosis
- Fabry’s Disease
- Ehlers Danlos Syndrome
- Hereditary Sensory Neuropathies
- Hereditary Autonomic Neuropathies
- ? Central post stroke pain (more to follow)

Disorders Associated with SFN-3

- Alcohol use
- Rabies, varicella or Lyme vaccine
- Anti-TNF inhibitors
- Metonidazole
- Linezolid
- Statins
- Sodium channelopathies
- Parkinson disease
- Pompe disease
- Wilson disease
- ALS
- Fragile X
- X linked adrenoleukodystrophy
- Chronic renal disease

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?

Polyneuropathies May Involve Small and Large Nerve Fibers

<table>
<thead>
<tr>
<th></th>
<th>Large-fiber neuropathy</th>
<th>Small-fiber neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Numbness, pins and needles, tingling, poor balance</td>
<td>Pain: burning, electric shocks, stabbing pain, numbness</td>
</tr>
<tr>
<td><strong>Exam Findings</strong></td>
<td>Reflexes, proprioception, Vibration, +/- motor</td>
<td>Thermal, pin-prick sensation, allodynia</td>
</tr>
<tr>
<td><strong>Functional changes</strong></td>
<td>Pressure, balance, fall risk</td>
<td>Nociception; protective sensation</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
<td>EMG/NCV, sural nerve biopsy</td>
<td>QST, nerve biopsy, Intraepidermal nerve fiber density (skin biopsy)</td>
</tr>
</tbody>
</table>
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)
- 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 than non-length dependent)
- 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

Oaklander AL, et al *Pain* 2001
Small Fiber Polyneuropathy- Blood/Other Tests

- Metabolic: thyroid functions, HbA1C, FBS
- Nutritional: CBC, Hepatic Profile, Vitamin B₁ and B₁₂
- Infectious: CRP, HIV, Lyme, HBV, HCV
- Autoimmune: ESR, ANA, Anti-ENA, ANCA, anti-gliadin, RF, serum ACE, ? CXR
- Paraneoplastic: Tumor markers, LDH, Myeloma screen, SPE, anti-Hu and anti-CV₂/CRMP-5 ab

Small Fiber Polyneuropathy- Blood/Other Tests (continued)

- Neurotoxins: urine and blood toxicology, review drug history
- Hereditary: alpha-galactosidase A, globotriaosylceramide levels, renal panel, urine protein, genetic testing for SCN9A or SCN10A
- Lumbar puncture: if you suspect inflammatory, auto-immune or paraneoplastic etiologies

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCA, GBP/PGB, Lidocaine 5% plaster</td>
<td>TCA, GBP/PGB</td>
<td>TCA, SNRI GBP/PGB, Lidocaine 5% (specific circumstances)</td>
</tr>
<tr>
<td>Second line</td>
<td>SNRI (Opioid)</td>
<td>SNRI Lidocaine 5%</td>
<td>Opioid Tramadol</td>
</tr>
<tr>
<td>Third line</td>
<td>Opioid, Lamotrigine, Capsaicin</td>
<td>Opioid (except methadone)</td>
<td>Paroxetine, Bupropion, NMDA antagonist</td>
</tr>
<tr>
<td>Fourth line</td>
<td></td>
<td></td>
<td>Methadone</td>
</tr>
</tbody>
</table>

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 response 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

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

- Limited data for Sjogren’s syndrome- IVIG 2g/kg
- Juvenile onset unexplained widespread pain treated with IVIG in 15 patients by Oaklander et al- treated at 2g/kg/month at least 3 times- 62% demonstrated significant improvement
- In another study, 46 patients with SFPN associated with dysautonomia were treated with one or more IVIG treatment- for patients with pain intensity levels ≥ 3 or with significant dysautonomia, the treatment was helpful

SFPN and Fibromyalgia

- Approximately 50% of patients who have been diagnosed with Fibromyalgia in several published studies have demonstrated findings consistent with SFPN on diagnostic biopsies - studies to be reviewed on subsequent slides
- What does that mean?
- What does that mean about interpreting FM studies that have already been published?
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

CWP, SFPN and Fibromyalgia II (continued)

- 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
SFPN and Central Post Stroke Pain?

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