Neuropathic Pain

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Educational Objectives

1. Utilizing a case vignette approach, describe the clinical presentation of multiple neuropathic pain states
2. Review the assessment of multiple neuropathic pain states
3. Describe the general as well as specific treatment of multiple neuropathic pain states

References

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Complex Regional Pain Syndrome

- 45 yo female complains of persistent pain in her left forearm and wrist following routine phlebotomy (left antecubital fossa) 3 months ago
- PMH notable only for congenital right brachial plexopathy
- Married, has 2 children, had been working as a physical therapist but not able to at present
- Since the phlebotomy she has experienced severe pain which radiates to her left hand and has experienced persistent painful burning and allodynia in the left forearm and hand
- Her left forearm and hand feel cool at times and then hot, she notes that the hand turns red at times
- Given her congenital right brachial plexopathy, she has extremely limited function of either her dominant (left) or non-dominant (right) upper extremity.

Which of the following next steps would you consider and in what order?

- Physical Therapy referral
- EMG/NCV testing of the left upper extremity
- MRI of the Cervical Spine and Left Brachial Plexus
- Initiate gabapentin
- Topical Lidocaine Patch
- Topical Capsaicin
- Stellate Ganglion Block
- Other?

Classification and Diagnosis of CRPS

- The diagnosis of CRPS can be made clinically using the IASP (Budapest) criteria
- When evaluating a person with CRPS, Type 1 (no obvious nerve lesion) should be distinguished from Type 2 (verifiable nerve lesion)
- Spontaneous CRPS is rare and nearly always there is a history of trauma
- One must consider an often wide differential diagnosis asnper the diagnositc criteria, one must know that “There is no other diagnosis that better explains the symptoms.”

Budapest diagnostic Criteria for CRPS

- Continuing pain which is disproportionate to any inciting event
- Must report at least 1 symptom in at least 3 of the 4 following categories:
- **1. Sensory**: Hyperalgesia and/or allodynia
- **2. Vasomotor:** Temperature asymmetry and/or skin color changes/asymmetry
- **3. Sudomtor:** edema and/or sweating changes/asymmetry
- **4. Motor/trophic:** Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails and skin)

Must report at least 1 sign when evaluated in 2 or more of the following categories:

1. Sensory: Hyperalgesia (pin-prick) and/or allodynia (light touch, deep pressure, joint movement)
2. Vasomotor: Temperature asymmetry and/or skin color changes and/or asymmetry
3. Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
4. Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor and dystonia) and/or trophic changes (hair, nails and skin.
5. THERE IS NO OTHER DIAGNOSIS THAT BETTER EXPLAINS THE SIGNS AND SYMPTOMS

Treating CRPS

- Medical and non-medical treatments- including neuromodulation (acute and chronic)
- PT, OT
- Anti-inflammatory treatment (acute)
- Multimodal treatment with emphasis on reducing/managing pain catastrophizing
- Sympathetic blocks
- Dystonia treatment

Treating CRPS (cont.)

- Some advocate the use of oral prednisolone acutely (100mg /day then tapered)- IV steroids have been used as well
- Bisphosphonates have been used with success
- No clear evidence of the efficacy for medications used in other NP disorders for CRPS- it is worthwhile considering gabapentin, pregabalin and the sedative TCAs
- Intravenous ketamine
- SCS/DRG stim may be effective in treating CRPS pain BUT not improve function- some studies suggest DRG may be superior

Treating CRPS (cont.)

- PT and OT are extremely important! Patients should be encouraged to use the affected extremity even if this increases pain and other symptoms
- Mirror therapy involves learning to adapt the mirror image of the healthy extremity as the affected limb. This can reduce pain and later improve movement. Best with acute CRPS and post CVA CRPS
- Graded motor imagery can be considered a further development of mirror therapy
- Other approaches including the use of opioids, IV lidocaine, topical therapies and IT analgesic therapy have been considered as well

Painful Diabetic Neuropathy

- 67 year old male with painful diabetic neuropathy
- 10 year history of Type 2 DM
- Currently on Metformin 500mg twice daily and dulaglutide
- Last Hgb A1C: 7.8 (was 10)
- Presents with numb, distal lower extremities, hates to have anything touch his ankles or feet as any time something touches these areas, his pain increases.
- Exam is notable for reduced knee and ankle reflexes, poor balance and diminished pin prick sensation to the calves bilaterally

Which of the following would you do next?

- EMG/NCV
- Initiate duloxetine
- Initiate pregabalin
- Initiate tramadol
- Initiate amitriptyline
- Refer to Physical Therapy
- Skin Biopsy
- Lumbar epidural steroid injection
- Optimize his diabetic regimen, lifestyle changes
- Initiate topical lidocaine
- Other?

Treatment of PDN

- Optimize management of DM
- Consider supplements
- Pharmacological manageament
- Non-pharmacological management

Oral and Topical Treatment of Painful Diabetic Polyneuropathy: AAN Practice Guideline Update

- This guideline addresses the following questions:
- In people with painful diabetic polyneuropathy, what is the efficacy of using oral pharmacologic interventions to reduce pain compared with placebo or an active comparator?
- In people with painful diabetic polyneuropathy, what is the efficacy of using topical pharmacologic interventions to reduce pain compared with placebo or an active comparator?

AAN Guideline (cont)

- **Conclusion—Gabapentinoids/Gabapentinoid Class Effect**
- Gabapentin is probably more likely than placebo to improve pain (SMD 0.53; 95% confidence interval [CI], 0.22–0.84; medium effect, moderate confidence; 1 Class I study).
- Pregabalin is possibly more likely than placebo to improve pain (SMD 0.29; 95% CI, 0.13–0.45; small effect, low confidence; 8 Class I and 7 Class II studies).
- Mirogabalin is possibly more likely than placebo to improve pain (SMD 0.21; 95% CI, 0.02–0.40; small effect, low confidence; 2 Class II studies).
- Gabapentinoids are probably more likely than placebo to improve pain (SMD 0.44; 95% CI, 0.25–0.63; small effect, moderate confidence; 8 Class I studies and 8 Class II studies).

AAN Guideline (cont)

- **Conclusion—Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)/SNRI Class Effect**
- Duloxetine is probably more likely than placebo to improve pain (SMD 0.50; 95% CI, 0.26–0.74; moderate effect, moderate confidence; 2 Class I and 5 Class II studies).
- Desvenlafaxine is possibly more likely than placebo to improve pain (SMD 0.25; 95% CI, 0.07–0.43; small effect, low confidence; 1 Class II study).
- Three Class I16-18and 6 Class II19-24studies were included for medications of this class, including 1 for venlafaxine, 1 for desvenlafaxine, and 7 for duloxetine. SNRIs are probably more likely than placebo to improve pain (SMD 0.47; 95% CI, 0.34–0.60; small effect, moderate confidence; 3 Class I and 6 Class II studies).

AAN Guideline (cont)

- **Conclusion—Tricyclic Antidepressants (TCAs)/TCA Class Effect**
- In addition to 1 new study, 2 Class I or Class II studies were identified for amitriptyline from the systematic review of the prior 2011 guideline.11 Amitriptyline is possibly more likely than placebo to improve pain (SMD 0.95; 95% CI, 0.15–1.8; large effect, low confidence; 1 Class I study and 2 Class II studies).
- No Class I or Class II studies were found for other TCAs; therefore, the best estimate for the class effect is based solely on amitriptyline studies. TCAs are possibly more likely than placebo to improve pain (SMD 0.95; 95% CI, 0.15–1.8; large effect, low confidence; 1 Class I study and 2 Class II studies).

AAN Guideline (cont).

- Valproic acid is possibly more likely than placebo to improve pain (SMD 0.86; 95% CI, 0.38–1.33; large effect, low confidence; 3 Class II studies).
- Five Class II studies were included formedicationsof this class: 1 lamotrigine,252 lacosamide,26,271 oxcarbazepine,28and 1 valproic acid.29Sodium channel blockers are probably more likely than placebo to improve pain (SMD 0.56; 95% CI, 0.25–0.87; medium effect, moderate confidence; 5 Class II studies).

AAN Guideline (cont)

- Nabilone, a synthetic cannabinoid, is probably more likely than placebo to improve pain (SMD 1.32; 95% CI, 0.52–2.13; large effect, moderate confidence; 1 Class I study). Ginkgo biloba is possibly more likely than placebo to improve pain (SMD 0.83; 95% CI, 0.48–1.18; large effect, low confidence; 1 Class II study).
- •Ginkgo biloba is possibly more likely than placebo to improve pain (SMD 0.83; 95% CI, 0.48–1.18; large effect, low confidence; 1 Class II study).
- Tocotrienols, which belong to the vitamin E family, are possibly no more likely than placebo to improve pain (SMD 0.09; 95% CI, −0.14 to 0.32; low confidence; 1 Class II study).

AAN Guideline(cont)

- Nutmeg extract is possibly no more likely than placebo to improve pain (SMD –0.01; 95% CI, –0.46 to 0.44; low confidence; 1 Class II study).
- Metanx, consisting of L-methylfolate calcium, algae-S powder, pyridoxal-59-phosphate, and methylcobalamin, is possibly no more likely than placebo to improve pain (SMD –0.43; 95% CI, –0.86 to 0.001; low confidence; 1 Class II study).
- There is insufficient evidence to determine whether dextromethorphan/quinidine is more or less likely than placebo to improve pain (SMD 0.69; 95% CI, –0.03 to 1.41; very low confidence; 1 Class II study). The reason for insufficient evidence is that there was only 1 Class II study with a large CI.

AAN Guideline (cont).

- Capsaicin is possibly more likely than placebo to improve pain (SMD 0.30; 95% CI, 0.14–0.47; small effect, low confidence; 1 Class I study of 8% and 1 Class II study of 0.075%).
- •Nitrosensepatch is possibly more likely than placebo to improve pain (SMD 0.59; 95% CI, 0.03–1.15; medium effect, low confidence; 1 Class II study).
- •Citrullus colocynthis is possibly more likely than placebo to improve pain (SMD 0.91; 95% CI, 0.36–1.45; large effect, low confidence; 1 Class II study).
- •Glyceryl trinitrate spray is possibly more likely than placebo to improve pain (SMD 1.19; 95% CI, 0.55–1.83; large effect, low confidence; 1 Class II study).
- •Topical clonidine is possibly no more likely than placebo to improve pain (SMD 0.29; 95% CI, –0.01 to 0.58); low confidence; 1 Class II study).
- •Buprenorphine transdermal patches are possibly no more likely than placebo to improve pain (SMD 0.23; 95% CI, –0.09 to 0.55; low confidence; 1 Class II study).

Neuromodulation

- **Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial: Peteresen EA, et al.** JAMA Neurol.2021 Jun 1;78(6):687-698. doi: 10.1001/jamaneurol.2021.0538
- **Objective:** To determine whether 10-kHz spinal cord stimulation (SCS) improves outcomes for patients with refractory painful diabetic neuropathy (PDN).
- **Results:** The primary end point assessed in the intention-to-treat population was met by 5 of 94 patients in the CMM group (5%) and 75 of 95 patients in the 10-kHz SCS plus CMM group (79%; difference, 73.6%; 95% CI, 64.2-83.0; P < .001).
- **Conclusions and relevance:** Substantial pain relief and improved health-related quality of life sustained over 6 months demonstrates 10-kHz SCS can safely and effectively treat patients with refractory PDN.

Small Fiber Neuropathy

- 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.
- 50 year old female complaining of chronic widespread pain following cholycystectomy one year prior.
- 48 year old female with 10 year history of fibromyalgia
- 29 year old female with multiple surgical procedures performed for treatment of endometriosis who develops in addition to chronic pelvic pain, more widespread complaints

Which of the following would you consider when assessing a person with possible SFN?

- EMG/NCV
- MRI of the Lumbar Spine
- Lumbar Puncture
- QST
- Skin Biopsy
- Bone Scan
- Corneal confocal microscopy
- GTT

Small Fiber Neuropathy

- Small fiber neuropathy is characterized by sensory and autonomic symptoms and signs associated with neural damage selectively or predominantly involving peripheral thinly myelinated Aδ fibers and unmyelinated C nerve fibers
- Skin biopsy and quantitative sensory testing are widely acknowledged as confirmatory diagnostic tests
- Diagnostic criteria are available for clinical practice and research
- Variants in genes encoding for sodium channels have been discovered as novel cause of small fiber neuropathy
- Current symptomatic treatment for neuropathic pain is based on a "trial-and-error" approach, though new studies suggested that genotype might influence the response to specific drugs
- Deep phenotyping and genotyping of patients could contribute to achieve concrete steps towards personalized management
- Epidemiological data on SFN have come from only one epidemiological study conducted in the Netherlands that reported an incidence of 12 cases per 100,000/year and a prevalence of 53 cases per 100,000 [

How do you evaluate for SFN?

- Patients with SFN present different patterns: length-dependent polyneuropathy (i.e. first affecting the feet with later proximal involvement), non-length-dependent neuropathy, and asymmetric mono/multiplex neuropathy (i.e. affecting one or more sensory peripheral nerve)
- Non-length-dependent SFN presents with proximal, diffuse or patchy distribution involving different parts of the body
- SFN patients can also complain of restless leg, intolerance to bed sheets, shoes and clothes causing dysesthesia or allodynia.
- Autonomic nervous system disturbances add complexity and heterogeneity to the assessment
- The quantification of IENFD can be considered the “gold standard” for the diagnosis of SFN when associated with clinical signs

Etiologies of SFN

- There is a growing number of associations between SFN and systemic diseases, some supported by strong evidence others reported in small case series or as anecdotal cases - up to 50% of cases remain idiopathic
- Laboratory screening is crucial to unravel the most common causes among metabolic, infectious, immune-mediated, toxic and genetic diseases
- Diabetes accounts for about 20% of cases, but the prevalence increases if impaired fasting glucose (IFG) and oral glucose tolerance test (OGTT) are included
- SFN has been reported in patients with HIV infection, immune-mediated disorders such as Sjogren's syndrome, celiac disease and sarcoidosis, and after exposure to neurotoxic drugs.
- One major advance has been the identification of gain-of-function sodium channel mutations which now include SCN9A, SCN10A and SCN11A genes encoding Nav1.7, Nav1.8 and Nav 1.9 α-subunits and β-subunits. Most variants in VGSCs genes have been associated with distal pain in SFN patients

Etiologies of SFN (cont)

- SFN has been also described in association with disorders characterized by widespread pain such as fibromyalgia, and EhlersDanlos syndrome, and in neurodegenerative diseases like Parkinson's disease
- Other genetic conditions associated with SFN include presymptomatic stage of familial amyloidosis due to TTR gene mutations and Fabry's disease and in patients with Gaucher disease

Clinical Presentation of SFN

- 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
- Burning pain in the extremities, allodynia and hyperesthesia - symptoms are often worse at night
- 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

Treatment of SFN

- In SFN related to a known etiology, therapeutic strategy should be focalized to the management of the underlying condition
- Current pharmacological and non-pharmacological treatment of neuropathic pain is still unclear
- In patients with immune-related SFN, the use of immunomodulatory drugs as corticosteroids has been considered
- In a few studies in Sjogren syndrome, systemic lupus erythematosus and sarcoidosis IVIG has been used successfully
- In SFN associated with sodium channel disorders, peripheral sodium channel blockade may improve sensory symptoms