Post Herpetic Neuralgia, Post Herpetic Itch & Trigeminal Neuralgia

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OBJECTIVES:

- Participants will be able to accurately diagnose post herpetic neuralgia, post herpetic itch, and trigeminal neuralgia.
- Participants will be able to explain the pathophysiology and natural history of post herpetic neuralgia, post herpetic itch, and trigeminal neuralgia.
- Participants will be able to select the optimal medication and interventional techniques used for the treatment of post herpetic neuralgia, post herpetic itch, and trigeminal neuralgia.
VARICELLA ZOSTER VIRUS

- Primary infection leads to Chicken Pox
  - A disease affecting immunocompetent children
  - Symptoms include fever, malaise, pharyngitis, generalized vesicular rash
  - Prior to vaccination, 95% of adults experienced Chickenpox
- Usually benign and resulted in long-term immunity

Electron micrograph of Varicella Zoster Virus

CDC Website, Dr. Erskine Palmer; B.G. Partin
CHICKEN POX

Typical diffuse vesicular rash

CDC Website, American Academy of Pediatrics
1995 vaccine introduced

2006, 20% of vaccinees were experiencing breakthrough Chicken Pox
  - Initial vaccine at 12-16 months
  - CDC recommended a booster dose for children 4-6 years old

2007, a shingles vaccination was approved for adults aged 60 years and older

SHINGLES

- Latent virus in neurons of cranial nerve ganglia, dorsal root ganglia, or autonomic ganglia
- Reactivation in immunocompromised individuals and as humans undergo a natural decline in cell-mediated immunity to VZV with age
CHICKEN POX → SHINGLES

VZV Becomes Latent in the Nerve Ganglia

Chicken Pox

Reactivates Years Later

Shingles
SHINGLES

- Hemorrhagic inflammation of the peripheral nerve, dorsal root, and dorsal root ganglion.
- Pain and rash usually occur within days of each other
- Pain is severe and usually burning in quality, but can have lancinating spikes
- Can involve allodynia as well as sensory loss
- Can present without skin eruptions “zoster sine herpete “
  - Radicular/Trigeminal Pain Distribution
  - Confirmed with PCR for VZV in CSF
Typical unilateral painful skin vesicular rash that erupt along the distribution of a nerve in a single dermatome

SHINGLES EPIDEMIOLOGY

- Study of 1019 Patients over 8 years
  - 60% women and 40% were men
  - Mean age of 58 years (range 9-96 years)
  - Prevalence varied between 1.3 and 1.6 per 1000 per year
  - Location
    - Thoracic dermatomes- 56%
    - Cervical dermatomes- 17%
    - Lumbar dermatomes- 10%
    - Sacral dermatomes- 5%
    - Trigeminal nerve- 12%.
  - Most common in the summer and least common in the spring
  - Incidence is 5 to 10 times greater for those older than 80 years

ZOSTER COMPLICATIONS

- Postherpetic neuralgia (PHN) is most common complication
- Postherpetic Itch (PHI)
  - Thought to have similar pathophysiology as PHN
  - Treatment is similar to PHN but PHI can be more resistant to treatment
  - Antihistamines may have a role in the treatment of PHI
  - Topical steroids typically used for pruritus have not proven to be effective

Zoster can also result in:
- Meningoencephalitis
- Myelitis
- Herpes zoster ophthalmicus (acute or progressive outer retinal necrosis)
- Herpes zoster oticus (Ramsay Hunt Syndrome)
  - Hearing loss and facial paralysis
- VZV vasculopathy
  - Transient ischemic attacks, ischemic and hemorrhagic stroke
  - Temporal artery infection mimicking giant cell arteritis
  - Extracranial vasculopathy
  - Aneurysm with and without subarachnoid hemorrhage
  - Arterial dissection
  - Ischemic cranial neuropathies
  - Cerebral venous sinus thrombosis
  - Spinal cord infarction
  - Peripheral thrombotic disease.

POST HERPETIC NEURALGIA
RISK FACTORS

- Risk of PHN after Shingles
  - < 60 years of age $\rightarrow$ < 2 %
  - 60 to 69 years of age $\rightarrow$ 6.9 %
  - >70 years $\rightarrow$ 18.5 %

- Other Risk factors
  - Greater pain
  - Greater rash
  - Immunocompromise


**POST HERPETIC NEURALGIA NATURAL HISTORY**

- Natural history is variable
  - 43 subjects
    - 6 months
      - 14 with PHN
      - Median 3.9 years
      - 2 with PHN
    - 10 subjects assessed at median 7.7
      - 1 with PHN at 6 months developed PHN between 3.9 and 7.7 year follow-up
      - Many subjects had abnormal quantitative sensory testing in the absence of pain
        - Suggestive of some fibrosis and demyelination

Reda H, Greene K, Rice FL, Rowbotham MC, Petersen KL. Natural history of herpes zoster: late follow-up of 3.9 years (n=43) and 7.7 years (n=10). Pain. 2013 Oct;154(10):2227-33.
ACUTE TREATMENT OF SHINGLES

- Antiviral therapy for patients who present within 72 for seven days.
  - Acyclovir 800 mg five times daily
  - Famciclovir 500 mg three times daily
  - Valacyclovir 1000 mg three times daily
  - Medication choice may be driven by cost and convenience

- Benefit less clear after 72 hours
  - New lesion formation means ongoing viral replication
  - All lesions encrusted, likely outside of antiviral treatment window

- Antiviral therapy tends to improve healing time of cutaneous lesions, decrease intensity/duration of neuritis, and reduced tendency to develop post herpetic neuralgia

- Better data for patients >50


ACUTE TREATMENT OF SHINGLES

- Antiviral therapy + Glucocorticoids?
  - Meta-Analysis
    - 5 randomized, double-blind, placebo-controlled parallel group studies
    - 787 participants.
    - Primary outcome: Presence of postherpetic neuralgia six months after rash onset
    - No significant difference between corticosteroid plus antiviral agents and placebo plus antiviral agents groups
    - No significant difference in any serious adverse event (death, acute cardiac insufficiency, rash dissemination, bacterial pneumonia or haematemesis) or non serious adverse event (dizziness, nausea, vomiting, hypertension or hyperglycaemia).
  - Glucocorticoids may increase the risk of secondary skin infections

HERPETIC NEURALGIA
TIME COURSE

- Acute- pain preceding or accompanying rash that persists up to 30 days from its onset
- Subacute- pain that persists after rash but which resolves within four months of onset
- Post Herpetic Neuralgia- pain persisting beyond four months

POST HERPETIC NEURALGIA TREATMENT

- The American Academy of Neurology Quality Standards Subcommittee found the following agents effective in reducing the pain of post herpetic neuralgia
  - Gabapentin
  - Pregabalin
  - Tricyclic antidepressants
  - Lidocaine patch
  - Opioids

POST HERPETIC NEURALGIA
ORAL TREATMENT

• Gabapentin
  – FDA approved
    • 1993: Adjunctive therapy for adult partial seizures
    • 2002: Post-herpetic neuralgia
  – Used for the treatment of pain, alterations of sensation, and pruritus associated with dermatological conditions
  – Dosing typically starts at 100mg HS
  – A dose of 1800 mg/day proved to be effective over 6 randomized clinical trials
  – Dosing can reach 1200mg TID
  – Side Effects: somnolence, peripheral edema, and weight gain
  – Available in an extended release formulation for daily dosing

**POST HERPETIC NEURALGIA ORAL TREATMENT**

- **Pregablin**
  - FDA approved for
    - 2004: Post herpetic neuralgia
    - 2004: Diabetic peripheral neuropathy
    - 2004: Adjunctive therapy for adult partial seizures
    - 2007: Fibromyalgia
  - Dosing typically starts at 25mg HS
  - Doses of 300-600 mg/day have demonstrated efficacy for PHN
    - Usually dosed BID
  - Side Effects: somnolence, peripheral edema, and weight gain
  - Often requires a prior authorization and a failed trial of gabapentin

POST HERPETIC NEURALGIA
ORAL TREATMENT

- Tricyclic Antidepressants
  - Amitriptyline, Nortriptyline, and Desipramine are the most commonly used agents
  - Amitriptyline FDA approved in 1961 for Depression
  - Cochrane 21 study analysis
    - No supportive unbiased evidence for a beneficial effect
    - Decades of successful treatment of neuropathic pain and fibromyalgia
    - There is no good evidence of a lack of effect
  - Dosing typically starts at 10mg HS
  - Doses of 150mg HS have demonstrated some efficacy for neuropathic pain of many types including PHN
  - Depression dosing can reach 300mg HS
  - Side Effects: Sedation, Weight Gain, Dry Mouth, Dry Eyes, Glaucoma Exacerbation, QT prolongation

POST HERPETIC NEURALGIA
TOPICAL & SYSTEMIC TREATMENT

- PHN patients tend to be elderly or immunocompromised
  - Multiple medical conditions
    - Hepatic and renal issues affect pharmacokinetics
    - Psychiatric co-morbidities may increase chances of adverse events
  - Multiple medications

- Topical therapies lack systemic side effects and can be used in place or in addition to oral systemic agents

- Refractory cases may require oral polypharmacy in addition to topical agents

POST HERPETIC NEURALGIA
TOPICAL TREATMENT

- Capsaicin
  - Stimulates the transient receptor potential cation channel subfamily V member 1 (TrpV1)
  - Derived from chili peppers
  - Initial stimulation causes intense burning, but prolonged exposure leads to desensitization of local pain fibers
    - Initial dose normally placed for 60 minutes under local anesthesia
    - Can cause first to third degree chemical burns at application site
  - Benefits typically last for about 12 weeks
    - Repeated as needed

POST HERPETIC NEURALGIA
TOPICAL TREATMENT

• Capsaicin
  – Four studies involving 1272 participants with PHN
    • High concentration patch (8%) demonstrated significant improvement of pain over placebo and low concentration capsaicin at 8 and 12 weeks
  – Over the counter patch has a typical concentration of 0.025%

The appropriate treatment of PHN neuropathic pain with a capsaicin patch

The inappropriate treatment of “pain not otherwise specified” with aerosolized capsaicin (pepper spray)
TOPICAL TREATMENT

- Topical 5% Lidocaine
  - Patches applied for 12-24 hours at a time
  - Can be costly and insurance coverage can be difficult
  - Trials have yielded mixed results
  - 102 subjects
    - 10 dropped out due to lack of efficacy
    - 9 dropped out due to treatment-related adverse events
    - 56 left the study for non-treatment-related reasons
    - 27 still under treatment after 4 years
      - 80% reported continued improvement of clinical global impression of change (CGIC) and patients' global impression of change (PGIC) scores
  - Treatment overall found to be safe and well tolerated over years

POST HERPETIC NEURALGIA INJECTABLE TREATMENT

• Botulinum Toxin (BTX) Injections
  – 30 subjects with PHN randomized BTX vs. Control
    • 13/15 in BTX arm had a 50% reduction in visual analogue pain scores
    • Benefit persisted for a median of 16 weeks
    • 0/15 in control arm had a 50% reduction in visual analogue pain scores
    • Safe and well tolerated
  – 60 subjects with PHN randomized BTX vs. lidocaine 0.5% vs. saline
    • BTX significantly decreased pain and reduced opioid use compared with lidocaine and placebo at 3 months post-treatment.

**POST HERPETIC NEURALGIA INJECTABLE TREATMENT**

- **Intrathecal glucocorticoids**
  - Intrathecal 3 ml of 3 percent lidocaine with 60 mg of methylprednisolone Vs. Lidocaine Vs. No Treatment Control
    - 270 Subjects per group
    - 2/3 subjects received injections once per week x 4 weeks
    - Use of pain medication decreased by 70% in mixed group
  - Intrathecal found to be superior to epidural injections

POST HERPETIC NEURALGIA
OTHER TREATMENT OPTIONS

- Opioids are typically adjunctive therapy and not first line
  - Tramadol, morphine, oxycodone, and methadone used with mixed results
  - Physical dependence, tolerance, addiction, and overdose

- NMDA receptor antagonists
  - IV Ketamine provided some pain relief
  - Limited by IV access, sedation, dysphoria, and dissociative episodes

POST HERPETIC NEURALGIA
OTHER TREATMENT OPTIONS

- Cryotherapy with liquid nitrogen
- Thalamic stimulation
- Electrocoagulation of the dorsal root
- TENS
- Intravenous lidocaine
- Acupuncture
- Peripheral Nerve Stimulation
TRIGEMINAL NEURALGIA (TN)
DIAGNOSTIC CRITERIA

- A) At least three attacks of unilateral facial pain fulfilling criteria B and C
- B) Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
- C) Pain has at least three of the following four characteristics:
  - Recurring in paroxysmal attacks lasting from a fraction of a second to two minutes
  - Severe intensity
  - Electric shock-like, shooting, stabbing or sharp in quality
  - At least three attacks precipitated by innocuous stimuli to the affected side of the face (some attacks may be, or appear to be, spontaneous)
- D) No clinically evident neurologic deficit
- E) Not better accounted for by another ICHD-3 diagnosis

TRIGEMINAL NEURALGIA FEATURES

- Triggered by trivial stimuli including washing, shaving, smoking, talking and/or brushing the teeth (trigger factors) and frequently occurs spontaneously.
- Usually involves the second or third divisions with first division involvement in <5% of patients.

TRIGEMINAL NEURALGIA FEATURES

- Between attacks the patient is usually pain free, but a dull background pain may persist in some long-standing cases.
- Between attacks, trigger zones remain inactive during refractory period.

TRIGEMINAL NEURALGIA FEATURES

- In some cases a paroxysm can be triggered from somatosensory stimuli outside the trigeminal area, such as a limb, or by other sensory stimulation such as bright lights, loud noises or tastes.

- Attack periods can last for weeks to months followed by remissions, but the pain usually returns.

- Usually responsive, at least initially, to pharmacotherapy.

TRIGEMINAL NEURALGIA FEATURES

- Pain can trigger a facial spasm hence the name tic douloureux
- TN does not typically involve unilateral autonomic features that can be seen with Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA)
- Based on this image President Vladimir Putin is more likely to have SUNCT than TN

TRIGEMINAL NEURALGIA

EPIDEMIOLOGY

- Annual incidence of TN is 4-13 per 100,000 people
- Incidence increases with age, and most idiopathic cases occur to those over the age of 50
- Male to female ratio of TN is about 1:1.7
- Hypertension may be a risk factor


“CLASSIC” TRIGEMINAL NEURALGIA

- **Idiopathic**
  - Patients with possible compression not revealed on imaging or confirmed with surgery

- **Vascular Compression**
  - Artery or vein near root entry zone of pons
  - Some estimates as high as 91% have vascular compression
  - Chronic compression thought to cause focal demyelination and aberrant sensory impulses


TRIGEMINAL NEURALGIA
RED FLAGS

- According to the AAN and EFNS
  - Structural causes in up to 15% of patients
  - Features that increase risk of underlying lesion
    - Trigeminal sensory deficits
    - Bilateral involvement of the trigeminal nerve
    - Younger age

TRIGEMINAL NEURALGIA

- TN due to secondary causes = Painful Trigeminal Neuropathy
  - Acute herpes zoster/Postherpetic neuralgia
    - Most commonly affects V1
  - Post-traumatic trigeminal neuropathy
  - Multiple Sclerosis
  - Vestibular schwannoma/acoustic neuroma
  - Cerebellopontine Meningioma
  - Epidermoid or other cyst
  - Saccular aneurysm
  - Arteriovenous malformation

According to the AAN and EFNS

- Carbamazepine (Level A, Established as effective)
  - 100mg daily → 600mg BID
  - Test for HLA-B*1502 allele in patients of Asian ancestry
    - Stevens-Johnson syndrome and/or toxic epidermal necrolysis
- Oxcarbazepine (Level B, Probably effective)
  - 300mg daily → 900mg BID
- Baclofen (Level C, Possibly Effective)
  - 5 mg PO q8hr → 80 mg/day
- Lamotrigine (Level C, Possibly Effective)
  - 50mg daily → 400mg daily
- Phenytoin, Valproic acid, Gabapentin, Pregabalin, and Topiramate have small study support

TRIGEMINAL NEURALGIA PHARMACOTHERAPY

- Other potentially agents with IV formulations, which may be useful in intractable cases and/or the ED
  - Levetiracetam
  - Phenytoin
  - Valproic Acid

TRIGEMINAL NEURALGIA
BOTULINUM TOXIN INJECTIONS

• Randomized controlled trial with 42 subjects with TN
  – 22 subjects received 75 units of BTX
  – 20 subjects received saline injections
  – Significant reduction in pain frequency at week 1 and intensity at week 2
  – More responders in BTX group (68.18%) than in the placebo group (15.00%).
  – BTX was well tolerated, with few treatment related adverse events at the end of 12 weeks

In cases resistant to pharmacotherapy, there are multiple procedures that can be used for the treatment of TN:

- Microvascular Decompression
- Denervating/Destructive Procedures
  - Percutaneous Trigeminal Rhizotomy
  - Radiofrequency, Glycerol, or Balloon
  - Stereotactic Radiosurgery
  - Gamma Knife
MICROVASCULAR DECOMPRESSSION

- 2 inch craniotomy exposes area posterior to ear
- Under microscope, the superior cerebellar artery is decompressed from nerve, and teflon felt is placed in between
- More invasive than other procedures, but no nerve destruction
- Faster results and longer lasting
- If no compression found, open denervation (microsurgical rhizotomy) could be performed
- Destructive procedures could be considered in MVD failure

RISKS OF NEUROSURGERY

- Highest rates of permanent cranial nerve deficit
- Meningitis/Encephalitis
- Intracranial Hemorrhage/Stroke
- Cranial Nerve Deficits/Neuralgias
- CSF Leaks
TRIGEMINAL NEURALGIA

- First denervating/destructive procedures were peripheral trigeminal neurectomies
  - Caused dense numbness
  - Earlier recurrence of pain
  - Treated focused, small, superficial branch of TN

- Proximal treatment (rhizotomy, root exit zone) has better results
  - Longer lasting
  - Less or no facial numbness
    - Worst case is anesthesia dolorosa
TRIGEMINAL NEURALGIA

- Percutaneous Trigeminal Rhizotomy
  - Needle inserted through cheek one inch from angle of the mouth
  - Needle advanced through foramen ovale using fluoroscopy
TRIGEMINAL NEURALGIA

- Percutaneous Trigeminal Rhizotomy Via
  - Radiofrequency Ablation (heat) → 6205 patients
    - Stimulation is performed prior to ablation to ensure correct target
    - Only selective technique
    - If V1 involved, caution to not over-numb corneal sensation, which risks keratophathy
    - Highest rates of initial pain relief and the lowest rates of pain recurrence
  - Glycerol (chemical) → 1217 patients
    - CSF coming from needle is a good finding before bathing nerve
    - Highest recurrence rate
  - Balloon (mechanical) → 759 patients
    - More likely to affect mastication

TRIGEMINAL NEURALGIA

- Stereotactic Radiosurgery
  - Used for treatment of tumors, vascular lesions, and functional disorders like TN
  - Highly focused beams of ionizing radiation with high precision
  - Useful for targets that are inaccessible for open surgery
  - Immediately outside of target there is a steep drop in radiation so surrounding tissues are relatively spared
- Not useful for large targets
TRIGEMINAL NEURALGIA

- Stereotactic Radiosurgery
  - 497 patients presenting with TN underwent GKS
    - No clear vascular compression or history of multiple sclerosis
  - Results
    - 169 patients became pain free within the first 48 hour
      - Pain recurrence in 66 patients (39%)
      - Postoperative hypesthesia in 18 patients (13.7%)
    - 194 patients became pain free within post treatment Day 3-30
      - Pain recurrence in 71 patients (36.6%)
      - Postoperative hypesthesia in 30 patients (19%)
    - 91 patients became pain free 30 days post-GKS
      - Pain recurrence in 27 patients (29.7%)
      - Postoperative hypesthesia in 22 patients (30.6%)

CONCLUSIONS OF PHN, PHI, TN

- There are many treatments for these 3 conditions
- Medication trials should start at a low dose, and titrations should be fast/slow based on patient preference and side effects
- Combination therapies should be considered
- Do not hesitate to refer patients to another provider for treatments that you may not provide
- With so many treatment options, there is little reason for our patients to not have their pain addressed
THANK YOU!!!

FELLOWS AND STAFF
2015-2016