Shingles and postherpetic neuralgia

Maria A. Nagel

No disclosures
Learning objectives

- Understand the pathogenesis of Varicella zoster virus reactivation resulting in herpes zoster (shingles) and postherpetic neuralgia (PHN)
- Understand treatment options for PHN
- Understand the role of zoster vaccine for preventing shingles and PHN

Overview

- Cases
- VZV biology
- PHN and ZSH pathogenesis
- Diagnosis
- Treatment options/vaccination
Definitions

Postherpetic neuralgia
Persistent unilateral dermatomal distribution pain more than 3 months after zoster, in the same distribution as zoster

Zoster sine herpete (PHN without rash!)
Unilateral dermatomal distribution pain in the absence of zoster rash

If rash later develops in same dermatome as pain – preherpetic neuralgia

Case 1
preherpetic neuralgia
herpes zoster
PHN
Zoster and PHN

61 yo immunocompetent woman

sudden onset, persistent right T4-T5 radicular pain followed by rash 1 day later

↓

3 months later, pain persisted; exam: allodynia in left T4-T5

↓

trial of oral and topical medications ineffective; nerve ablation ~70% relief

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Case 2

zoster sine herpete

herpes zoster
63 yo immunocompetent woman

sudden onset, persistent right T6-T8 radicular pain without rash

10 months later
right C5-C6 pain/zoster

1 month after zoster with tx, cervical pain resolved but thoracic pain persists

exam: T6-T8 hypalgesia
healing lesions in right C5-C6
cervical and thoracic MRI normal

CSF, 3 months after zoster
acellular
VZV DNA negative
anti-VZV IgG +
Zoster sine herpete, preherpetic neuralgia and zoster

Treatment:
valacyclovir 1 g TID x 4 weeks
no improvement in pain
symptomatic therapy ineffective
or adverse side effects
plan acyclovir IV, 10 mg/kg
x 10-14 days

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Varicella

Latency

cranial nerve ganglia
dorsal root ganglia
autonomic ganglia
Zoster occurs along the entire neuraxis

Characteristic herpesvirus lesions

VZV zoster
HSV-1

dermatomal
patchy
**Zoster epidemiology**

- 1 in 3 individuals will reactivate during their lifetime
- 900,000+ cases of zoster/y in U.S., given current 7% vaccination rate
- Risk factors for reactivation:
  - age
  - HIV/AIDS
  - diabetes
  - immunosuppression

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**Advanced age increases risk of PHN**

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>% PHN</th>
<th>Reference</th>
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<tbody>
<tr>
<td>&gt;18</td>
<td>590</td>
<td>9.0</td>
<td>Ragozzino</td>
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<tr>
<td>&lt;70</td>
<td>756</td>
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<td>&gt;70</td>
<td>160</td>
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<td>&lt;60</td>
<td>333</td>
<td>15.9</td>
<td>Rogers &amp; Tindall</td>
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<td>&gt;60</td>
<td>243</td>
<td>46.9</td>
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</tbody>
</table>

*References:
- de Moragas et al., Arch. Derm., 1957
- Rogers and Tindall, Postgrad. Med., 1971
- Ragozzino et al., Medicine, 1982*
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PHN pathogenesis

- persistent productive VZV infection in sensory ganglia
- excitability of ganglionic neurons altered
Evidence for persistent VZV infection in PHN

- VZV DNA and late glycoproteins in blood MNCs 1-8 years after zoster (Vafai et al., PNAS, 1988)

- VZV DNA in MNCs up to 8 years after zoster in 11/51 PHN patients, but not in MNCs of 19 zoster patients without PHN or 11 age- and gender-matched subjects with no history of zoster (Mahalingam et al., J. Neurovirol., 1995)

- 11-year analysis of immunocompetent elderly woman with PHN: blood MNCs contained VZV DNA, treated with famciclovir and MNCs VZV DNA negative; voluntarily stopped treatment 5 times and pain always recurred within 1 week and blood MNCs VZV DNA+ (Gilden et al., J. Neurovirol., 2003)

- 8/15 patients with PHN reported improvement with acyclovir IV (Quan et al., Arch. Neurol., 2006)

Zoster sine herpete pathogenesis

Initially described in zoster patients who had dermatomal pain distant from rash (Lewis, Brit. Med. J., 1958)

More strict definition:
unilateral dermatomal distribution pain in the absence of zoster rash
Virologically verified cases of chronic pain produced by VZV infection without rash

- thoracic distribution zoster sine herpete no rash, chronic radicular pain, VZV DNA in CSF
  (Gilden et al., Ann. Neurol., 1994)
- chronic sacral distribution pain earlier lumbar zoster, VZV DNA and antibody in CSF
  (Morita et al., J. Neurol. Sci., 2003)

Virologically verified case of chronic pain produced by VZV infection without rash

45-year-old immunocompetent woman

13 months: right facial numbness and "lightning bolt-like" pain in maxillary distribution of the right trigeminal nerve

initially, numbness over right nasal bridge; light touch on face or scalp produced pain (allodynia)

Hevner et al., Lancet Neurol., 2003
Virologically verified case of chronic pain produced by VZV infection without rash

exam: loss of pain sensation in maxillary distribution of the right trigeminal nerve

CSF, brain CT and MRI: normal

treated with gabapentin, 900 mg tid,
but pain increased

1 year later, brain imaging revealed homogeneously enhancing mass at base of right brain at site of the trigeminal ganglion

Mass at site of right trigeminal ganglia
Biopsy of right trigeminal ganglia mass

Cowdry type A inclusion bodies

T cells

B cells

Trigeminal ganglia contains VZV

VZV  HSV-1  NRS

Hevner et al., Lancet Neurol., 2003
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Diagnosis algorithm

PHN

↓

Symptomatic treatment

chronic radicular pain without rash

↓

MRI to rule out structural lesion

↓

CSF analysis for VZV DNA and anti-VZV IgG antibody

↓

Antiviral therapy

Symptomatic treatment
Antiviral treatment

- Valacyclovir, 1 g PO TID x 14 days
  if effective, maintenance dose of 1 g PO daily
  x 6-12 months
- Acyclovir, 10 mg/kg IV TID x 14 days

Symptomatic treatment

- TCAs: nortriptyline, desipramine, amitriptyline
- Gabapentin, pregabalin
- Lidocaine patches
- Opioids
- Tramadol
- Capsaicin cream
- Capsaicin 8% patch
- Combination therapy
- Botulinum toxin
- Sympathetic blockade
- Spinal cord stimulators
- Peripheral nerve field stimulators
Capsaicin 8% dermal patch

- NGX-4010, Qutenza
- One hour application at UCH Pain Clinic every 3 months
- 32.3% reduction in numeric pain rating scale score over 3 months
- Side effects:
  - application site erythema (63%)
  - pain (42%)
  - transient HTN

Mechanism of pain reduction

**TRPV1 agonist:** reduces transient receptor potential vanilloid 1 (TRPV1) expression

**Neurolytic:**
eliminates ~80% of epidermal nerve fibers within 1 week; reinnervation by 24 weeks
Percutaneous peripheral nerve field stimulation

- Stimulating electrodes placed in painful areas without respect to a particular nerve's location
- Unclear mechanism: large myelinated fiber stimulation may result in release of putative inhibitory neurotransmitters
- Unlike SCS, can be used for PHN pain in the head
- Used to treat refractory PHN in the ophthalmic, occipital, and thoracic distribution with reduced pain and concomitant medication 8 weeks to 3 years after implantation

Zoster vaccination

- Zostavax contains live, attenuated virus that boosts waning cell-mediated immunity to VZV ($t_{1/2}$ at least 5 years)
- Recommended for individuals ≥ 60 yo; contraindicated in individuals with h/o immunodeficiency, malignant neoplasm infecting the bone marrow or lymphatic system, AIDS, and in pregnant women
- Subjects with Zostavax ($n = 19, 270$) and placebo ($19, 276$) followed for 3 years:
  - **Zostavax reduced incidence of zoster by 51%
  - **Fewer cases of PHN
- Side effects: a injection site; erythema (34%), pain/tenderness (33%), swelling (25%), hematoma (1.4%), pruritis (6.6%), warmth (1.5%); headache (1.4%)
Special considerations

- Consider vaccination of elderly patients
- When you first see a patient with a diagnosis of intractable PHN, confirm the diagnosis by previous records, exam, and MRI
- Consider diagnosis of zoster sine herpete in patients with dermatomal distribution rash with normal MRI
- If patient has “recurrent” zoster rash and persistent dermatomal distribution pain between outbreaks, most likely HSV-1 or HSV-2. Scrape the lesion and PCR for VZV, HSV-1, and HSV-2.

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NIH
NINDS K08 067070
NIA RO1 AG006127
NIA PO1 AG032958

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<th>Medication</th>
<th>Maintenance dose</th>
<th>Cost per dose (8)*</th>
<th>Cost per 90 days (8)*</th>
<th>Level of evidence in PHN(^{3})</th>
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<tr>
<td>Topical patches</td>
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<tr>
<td>Capsaicin 8% topical patch</td>
<td>1 to 4 patches every 3 months as</td>
<td>810.00–3240.00</td>
<td>810.00–3240.00</td>
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<td>(Quinexa)</td>
<td>needed</td>
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<tr>
<td>Lidocaine 5% topical patch</td>
<td>1 to 3 patches for up to 12 hours</td>
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<td>694.80–2084.40</td>
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<td>(Lidoderm)</td>
<td>in a 24-hour period</td>
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<td>Anticonvulsants</td>
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<td>Gabapentin (generic)</td>
<td>600 to 1200 mg TID</td>
<td>0.10–0.19</td>
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<td>(Lyrica)</td>
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<tr>
<td>Gabapentin (generic)</td>
<td>150 to 300 mg BID or 100 to 200 mg</td>
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<tr>
<td>(Lyrica)</td>
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*Lowest listed AWP of currently marketed dosage forms was used. Costs listed are for the medications only, and do not include the cost of office visits or related expenses.

\(^{3}\)Levels of evidence descriptors: A = Established as effective for the given condition; B = Probably effective for the given condition; C = Possibly effective for the given condition.

AAN = American Academy of Neurology; BID = twice daily; EFNS = European Federation of Neurological Societies; PHN = postherpetic neuralgia; QHS = at bedtime; TID = three times daily.

Jones et al., J Pain Palliat Care Pharmacother, 2011