The Neurological Complications of Varicella Zoster Virus

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Herpes Viruses

• History
  • Known since antiquity
  • Herodotus coined term “herpes febrilis”
  • Genital herpes 1st described by French physician, Astruc (1736)

• 8 known Herpes viruses divided in 3 groups
  • α-herpes viruses: HSV-1, HSV-2, VZV
  • β-herpes viruses: CMV, HHV-6, HHV-7
  • γ-Herpes viruses: EBV, KSHV (HHV-8)

• Simian Herpes B can also infect humans
Herpes virus characteristics

• Morphology
  • DS DNA viruses
  • Icosahedral capsule with 162 capsomers
  • Surrounded by tegument (amorphous material)
  • m.w. = 80-150 X 10^6

• Genetics
  • 90 transcriptional units
  • 120,000-230,000 base pairs
  • Viral replication has nuclear and cytoplasmic phases
  • 50% homology between HSV-1 and HSV-2 (most closely related)
  • Herpes viruses infecting humans have unique genomic structures
Herpes Virus
1. Attachment via cellular glycoproteins

2. Fusion

3. Preparation of cell (Virion host shutoff and immediate early gene products) followed by β or early peptides (including DNA polymerase)

4. Transportation to nucleopores and release of DNA into nucleus

5. Transcription and capsid assembly

6. Envelopment with penetration of nucleus

7. Transportation to cell surface via ER and Golgi apparatus
Herpes viruses characteristics

• Alpha HHV Family
  • HSV-1, HSV-2, and VZV
  • Establish latency in the PNS
  • Peripheral sensory ganglia is the reservoir
  • Short reproductive cycle

• Beta HHV Family
  • CMV, HHV-6, HHV-7
  • Establish latency in secretory glands, RES and kidneys
  • Slow reproductive cycle

• Gamma HHV Family
  • EBV and KSHV (HHV-8)
  • Establish latency in lymphoid tissue
Herpes Virus Infection of the Peripheral Sensory Ganglia

• Primary infection
• Access to axon endings within mucocutaneous surface
• Retrograde transportation to PSG
• Maintenance of viral genome within the PSG
• Periodic reactivation
• Antegraded transmission to nerve endings and mucocutaneous surface
Herpes Viruses

1. Primary infection involves mucocutaneous surfaces – portal of entry
2. Primary infection generally occurs in the first 3 decades of life; recurrences throughout a lifetime
3. Primary and recurrent disease typically occurs at the same site
4. Recurrent infection rarely spreads beyond anatomic distribution of a single PSG with immunocompetence
VZV General Features

• First herpesvirus to be entirely genetically sequenced
• High degree of homology with HSV-1
• Replication in culture starts within 8 hrs; maximum titers in 40 hrs
• Extremely labile; cannot persist for long in scabs or fomites
• Cause of chickenpox (varicella)
  • >95% 20-29 year olds with Ab to VZV
  • 99.6% >40 year olds with Ab to VZV
• Latent in cranial nerves and DRGs
  • Cannot be cultured from ganglia (unlike HSV)
  • In situ and PCR demonstrate
  • Present in neurons and satellite cells
VZV Neurologic Complications

Primary infection with varicella–zoster virus (varicella) → Latency → Reactivation → Zoster sine herpete

Zoster (shingles)

Immunocompetent patients
- Myelitis
- Large-vessel granulomatous arteritis

Immunocompromised patients
- Postherpetic neuralgia
- Myelitis
- Small-vessel encephalitis

Gilden NEJM 2000
Varicella (Chickenpox)

• Highly contagious and usually mild
• Spread by direct contact or respiratory transmission
• Incubation period 9-12 days
• Annual U.S. incidence through 1995 was 4,000,000
• Widespread vaccination in 1995
• Characterized by exanthema of macules and papules on trunk spreading centrifugally → vesicles with erythematous halo
• Patients infectious from 2 days before rash until all vesicles crusted
• Subclinical reinfection observed
Zoster (Shingles)

- Affects >300,000 in U.S. annually
  - Chiefly elderly and immunosuppressed
  - Increased risk with varicella < 1 year old
  - 8-10 times as common after age 60 years
  - Recurrent zoster rare in immunocompetent (<5%)
  - Almost all cases of “recurrent zoster” are HSV
Zoster Clinical Features

- Severe sharp, lancinating pain
- Pruritus, dysesthesias, allodynia
- Pain precedes rash by 48-72 hrs
- Rash forms over 3-5 days and persists 2-4 weeks
- Radicular or cranial nerve:
  - Thorax 60%
  - Cervical 16%
  - Ophthalmic 15%
  - Sacral 12.5%
- 50% with CSF pleocytosis
Zoster Clinical Features

• Zoster keratitis

• Cranial neuropathies
  • Optic neuritis (may be bilateral)
  • Ophthalmoplegia with III nerve > VI > IV > combinations III, IV, VI
  • Facial palsy
    • Prognosis typically worse than with idiopathic Bell’s palsy
  • Ramsey Hunt syndrome (Herpes zoster oticus)
    • VII and occasionally VIII nerves
    • Tinnitus, deafness, vertigo, N&V, and nystagmus
  • Lower cranial nerves rarely
    • Cranial mononeuritis and polyneuritis in the absence of rash

• Zoster paresis

• Sacral zoster with neurogenic bladder
Zoster Clinical Features

**Hutchinson’s sign**
Involvement of medial nose
(Nasociliary branch of Vth nerve – supraorbital and trochlear branches also typically involved)

**Ramsay Hunt syndrome**
Lesions in external auditory canal and tympanic membrane and anterior 2/3s of ipsilateral tongue and hard palate
Zoster Treatment

- Antiviral medications
  - Famciclovir 500 mg 3 x daily
  - Acyclovir 800 mg 5 x daily
  - Valtrex 1000 mg 3 x daily
- Antiviral Rx ↓ new lesions and pain
- Antiviral Rx in immunocompetent – efficacy has yet to be demonstrated
- Ophthalmic zoster Rx for ≥7 days
Postherpetic Neuralgia

- PHN – pain persisting > 3 months after rash
- Pain may occur in absence of a rash “zoster zine herpete”
- Once pain disappears it does not reappear
- PHN is more common in elderly
  - Rare before age 50
  - > 60 year olds – 40% affected
- Prevention
  - No difference with use of steroids
  - Antiviral agents may reduce frequency
  - VZV vaccine in persons > 60 year old
# Postherpetic Neuralgia Treatment

## Table 2. Treatment Options for Postherpetic Neuralgia.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose</th>
<th>Comments</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Oxycodone, 5 mg orally every 6 hours*</td>
<td>Total dose of 80 mg daily (or higher) potentially necessary for patients with severe pain</td>
<td>Sedation, nausea, dizziness, constipation, tolerance, abuse</td>
</tr>
<tr>
<td>Tricyclic antidepressants&lt;sup&gt;40-43&lt;/sup&gt;</td>
<td>Nortriptyline or desipramine, 10 to 25 mg orally at bedtime*</td>
<td>Total dose of up to 75 to 150 mg daily potentially necessary; amitriptyline also proved effective but may be poorly tolerated by elderly patients; less experience with selective serotonin-reuptake inhibitors</td>
<td>Sedation, confusion, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention)</td>
</tr>
<tr>
<td>Gabapentin&lt;sup&gt;39&lt;/sup&gt;</td>
<td>300 mg orally daily</td>
<td>Titration dose as necessary over a 4-week period, to a total daily dose of 3600 mg (divided into 3 doses)</td>
<td>Somnolence, dizziness, ataxia, nystagmus</td>
</tr>
<tr>
<td>Capsaicin (0.025–0.075% cream)&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Topically 3 to 4 times daily</td>
<td>Apply only to healed, intact skin; patients may start with low-potency preparation, advance to high-potency preparation as tolerated; may take days or weeks to achieve maximal benefit; available without a prescription</td>
<td>Localized skin irritation and burning sensation limit use for many patients</td>
</tr>
<tr>
<td>Lidocaine (5% patch)&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Applied to painful area, up to 3 patches can be used at a time for a maximum of 12 hours</td>
<td>Should be applied only to healed, intact skin; patches may be cut to size; rapid onset of pain relief</td>
<td>Localized skin irritation; systemic toxicity from cutaneous absorption of lidocaine very rare</td>
</tr>
</tbody>
</table>

*Other agents are also available for use.

Gnann NEJM 2002
Post-infectious Myelopathy with VZV

- Typically immunocompetent individuals
- Days to weeks after varicella or zoster
- CSF with mild increased lymphocytes and protein
- Improves with steroids

LETM in child following chickenpox
VZV Myelitis

• Develops during infection to 2 weeks after rash
  • More insidious with ↓ immunity
  • Long term steroids may predispose
• Paraparesis with sensory level and sphincter dysfunction
• CSF normal or ↑ cells and protein
  • Cultures for VZV negative
  • Demonstration in CSF by PCR or VZV Ab
• T2WI MRI with hyperintense lesion
  • May cause longitudinally extensive lesion
• Rx with high dose ACV
VZV CNS Vasculitis

• Results from transaxonal spread of VZV to the adventitia of cranial arteries with subsequent transmural spread

• May present as
  • TIA
  • Ischemic stroke
  • Hemorrhagic stroke
  • Chronic headache
  • Altered mental status

• 30% without rash

• CSF VZV PCR positive in small percentage

• Diagnose by CSF/serum VZV antibody

• Treat with Acyclovir 10-15 mg/kg 3 x day for 14 days
VZV Large Vessel CNS Vasculitis

• Chiefly in immunocompetent
  • Most affected > 60 years old

• Clinical features
  • Acute stroke weeks or months after contralateral trigeminal zoster
  • TIAs and confusion
  • Mortality – 25%

• CSF with pleocytosis (<100 mono cells); OCBs; and ↑IgG

• Angiogram with focal and segmental narrowing

• Rx – ACV and corticosteroids
VZV Small Vessel Vasculitis

• Typically in AIDS or other immunocompromised

• Zoster precedes encephalopathy by weeks or months
  • May develop in absence of antecedent rash

• Clinical features
  • Headache, confusion, seizures and focal deficits
  • MRI with WM lesions
  • CSF with ↑ monos, normal or ↑ protein

• Rx - ACV
VZV Encephalitis

• Usually days after rash; but sometimes weeks before or after
  • Sometimes occurs in the absence of rash
• Increased risk in immunocompromised
• Cranial zoster and disseminated zoster associated with increased risk
• Clinical features: H/A, seizures, encephalopathy, ataxia, meningismus, fever
• EEG diffusely slow
• CT and MRI findings variable
• CSF with pleocytosis; PCR typically positive
• Mortality ~10% (0-25%)
• Uncertain whether infectious or autoimmune
  • Intranuclear viral particles at brain at autopsy
  • Demyelination
  • Inflammatory infiltrate
VZV Unusual Neurological Complications

• Immunocompromised hosts, chiefly AIDS

• Clinical manifestations
  • Meningoencephalitis
  • Ventriculitis with gait abnormality
  • Necrotizing vasculitis involving chiefly meninges

• Diagnosis is by
  • CSF PCR
  • CSF-serum VZV antibody (more sensitive)
Varicella-Zoster Virus in AIDS

• VZV radiculitis common in AIDS and may herald AIDS
• VZV in AIDS brain at autopsy 2-4.4% in pre-HAART era
• 5 CNS clinico-pathological patterns:
  • multifocal encephalitis
  • ventriculitis
  • acute meningomyelitis with necrotizing vasculitis
  • focal necrotizing myelitis
  • vasculopathy with cerebral infarction
VZV Encephalitis in AIDS

• 30-40% without history of cutaneous zoster
• Leukoencephalitis chiefly affecting PV area and GW junction
• Subacute encephalopathy
  • headache, fever, cognitive change, lethargy, seizures, and focal findings
• Evolves over weeks but may be acute or more chronic
• MRI may show WM plaque-like lesions
• Dx: CSF PCR and CSF/serum Ab for VZV
• Often progressive deterioration and death despite Rx
VZV Myelitis

- Temporal association with cutaneous eruption
  - may occur months after eruption or myelitis may precede eruption
- Acute or subacute evolution of myelitis
- Polyradicular features may mimic CMV
- Extensive hemorrhagic necrotizing myelitis with vasculitis and thrombosis in DRG
VZV cerebral vasculopathy

• May involve large or small vessels
• may be inflammatory or bland
• often preceded by zoster ophthalmicus or cranial zoster
• interval up to one year
• associated VZV encephalitis or meningomyelitis not uncommon
CNS VZV Treatment in AIDS

• no randomized prospective clinical trials
• progression of encephalitis and myelitis despite treatment with ACV or GCV
  • ~50% will recover (de la Blanchardiere 2000)
• famciclovir anecdotally helpful
• high doses for indefinite periods of time
• foscarnet recommended for ACV-resistant cutaneous zoster, however, no evidence of CNS efficacy
• prophylactic Rx with ACV (1600-4000 mg/d) when CD4<50 recommended by some (Leautez 1999)
Humanity has but three great enemies; Fever, famine and war; of these by far the most terrible is fever.