



The Neurological Complications of Varicella Zoster Virus

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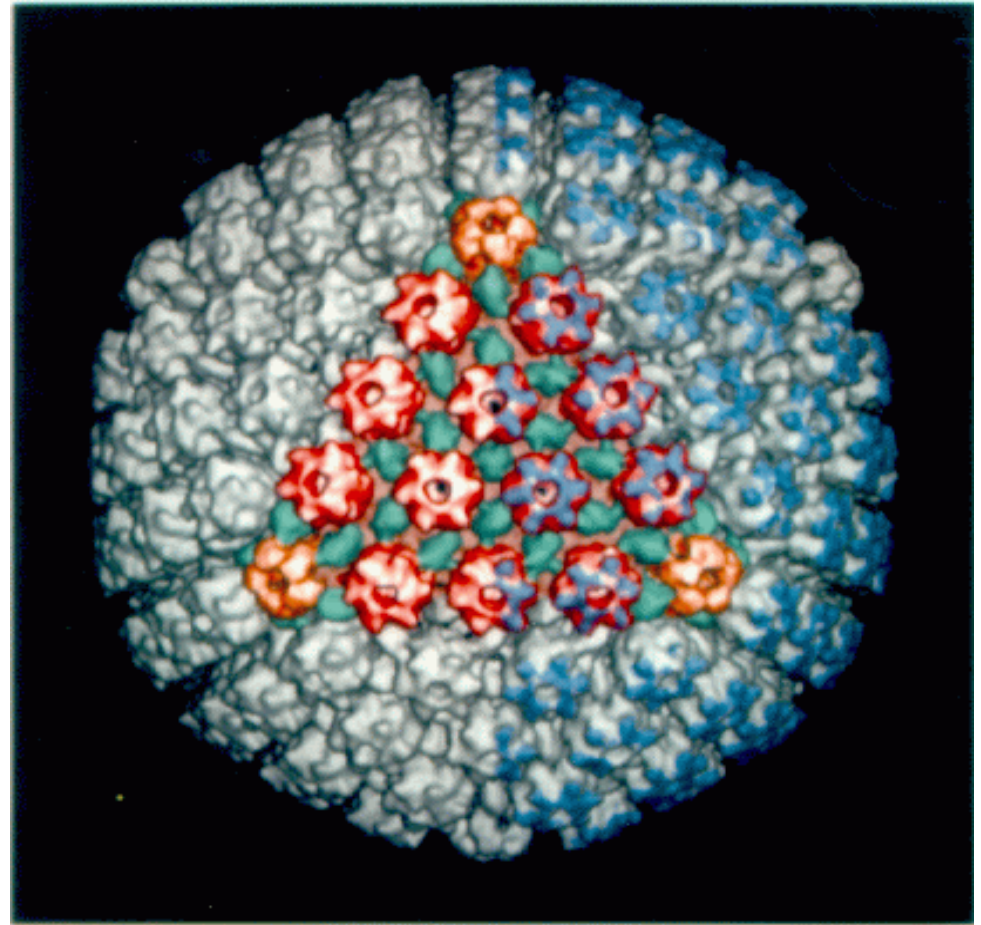
Herpes Viruses

- 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

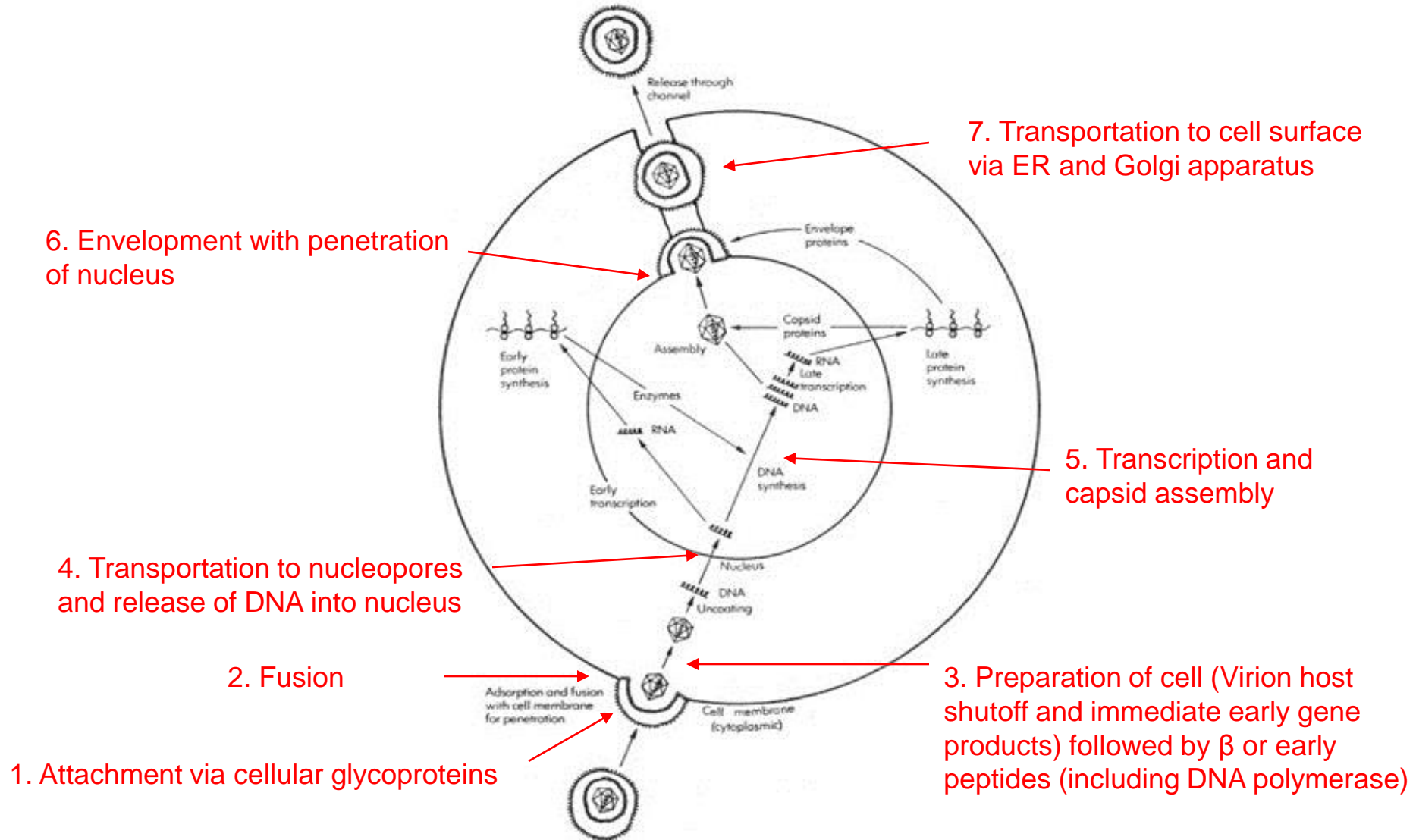
Herpes virus characteristics

- Morphology
 - DS DNA viruses
 - Icosahedral capsule with 162 capsomers
 - Surrounded by tegument (amorphous material)
 - m.w. = 80-150 X 10⁶
- 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



Herpes Virus Replication

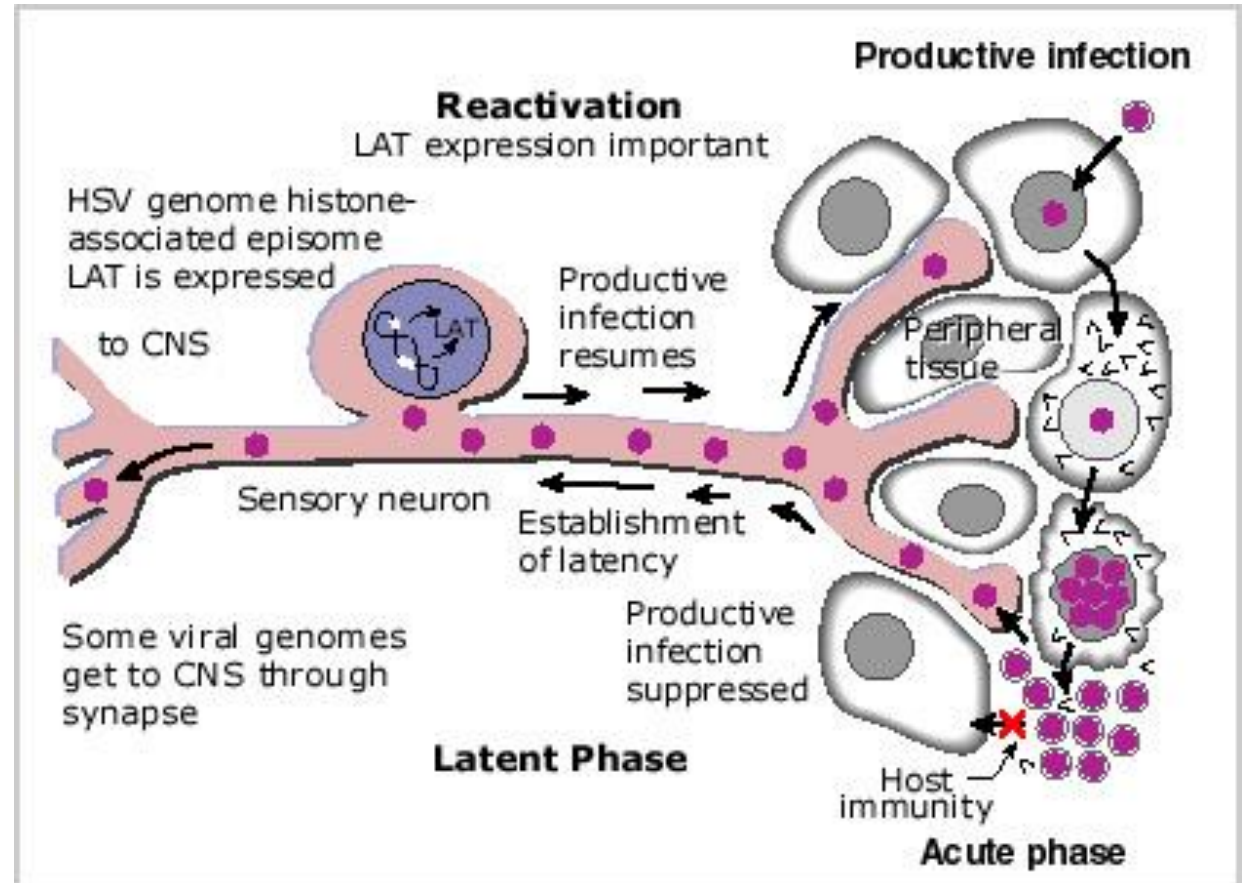


Herpes viruses characteristics

- 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
- Antegrade transmission to nerve endings and mucocutaneous surface



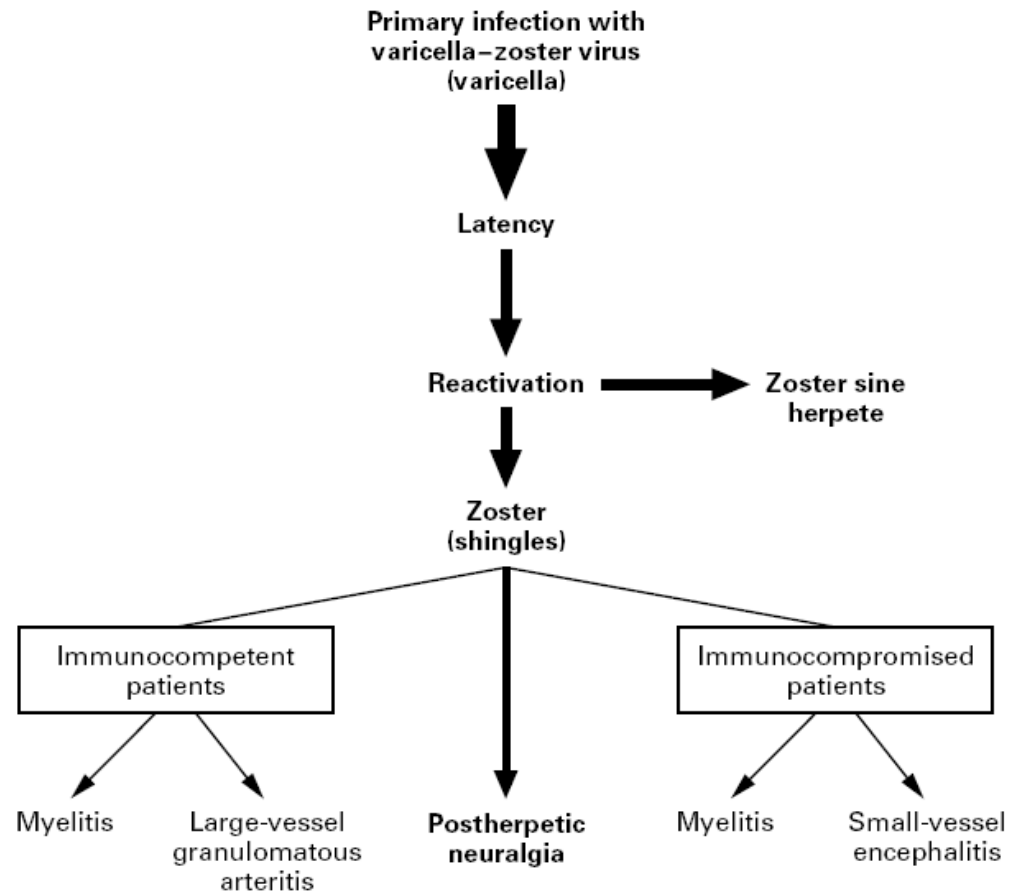
Herpes Viruses

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



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

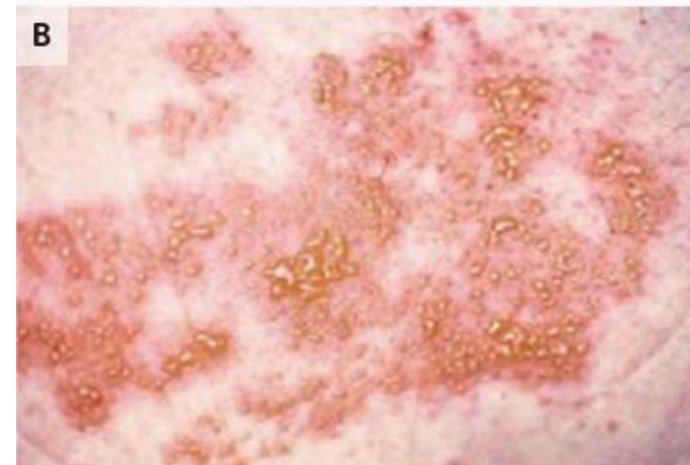


Zoster (Shingles)

- 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 sine herpette*”
- 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

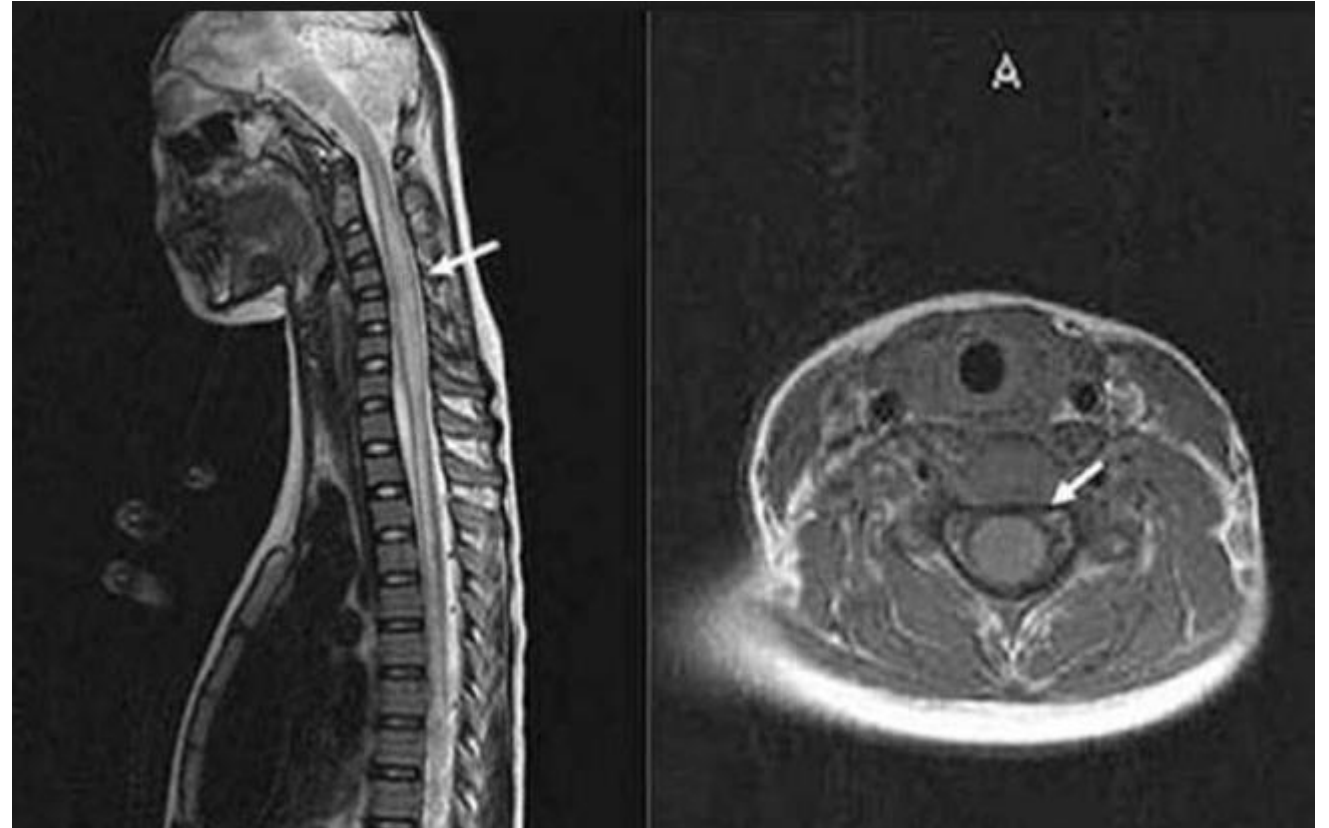
TABLE 2. TREATMENT OPTIONS FOR POSTHERPETIC NEURALGIA.

AGENT	INITIAL DOSE	COMMENTS	POTENTIAL ADVERSE EFFECTS
Opioids ⁴⁰	Oxycodone, 5 mg orally every 6 hours*	Total dose of 80 mg daily (or higher) potentially necessary for patients with severe pain	Sedation, nausea, dizziness, constipation, tolerance, abuse
Tricyclic antidepressants ³⁶⁻³⁸	Nortriptyline or desipramine, 10 to 25 mg orally at bedtime*	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	Sedation, confusion, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention)
Gabapentin ³⁹	300 mg orally daily	Titration of dose as necessary over a 4-week period, to a total daily dose of 3600 mg (divided into 3 doses)	Somnolence, dizziness, ataxia, nystagmus
Capsaicin (0.025–0.075% cream) ⁴¹	Topically 3 to 4 times daily	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	Localized skin irritation and burning sensation limit use for many patients
Lidocaine (5% patch) ⁴²	Applied to painful area; up to 3 patches can be used at a time for a maximum of 12 hours	Should be applied only to healed, intact skin; patches may be cut to size; rapid onset of pain relief	Localized skin irritation; systemic toxicity from cutaneous absorption of lidocaine very rare

*Other agents are also available for use.

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

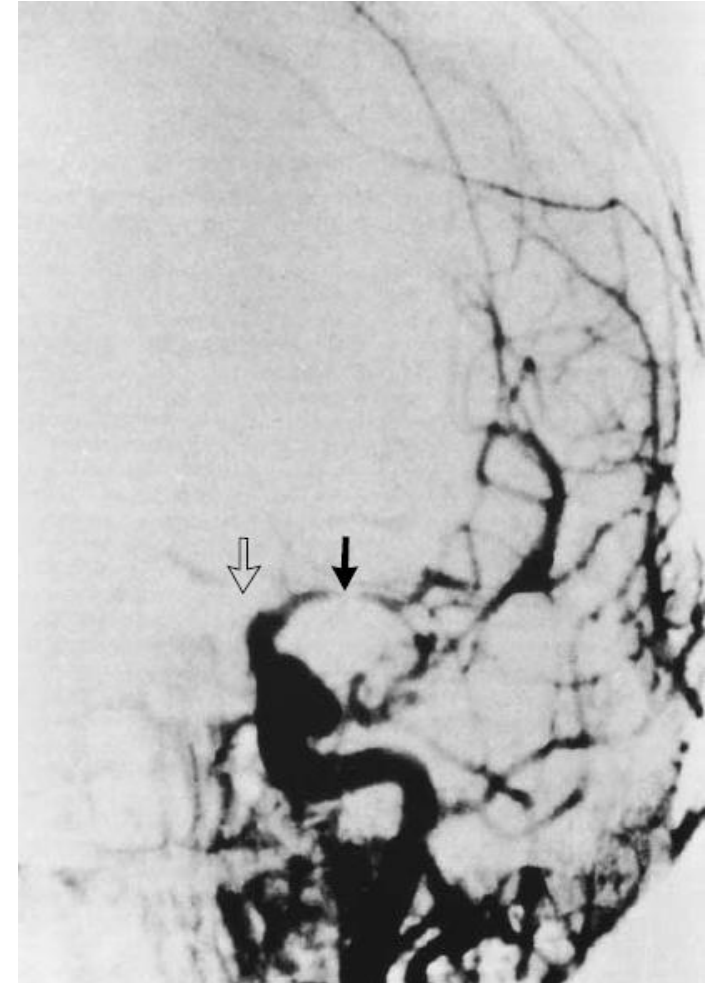


VZV CNS Vasculitis

- 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

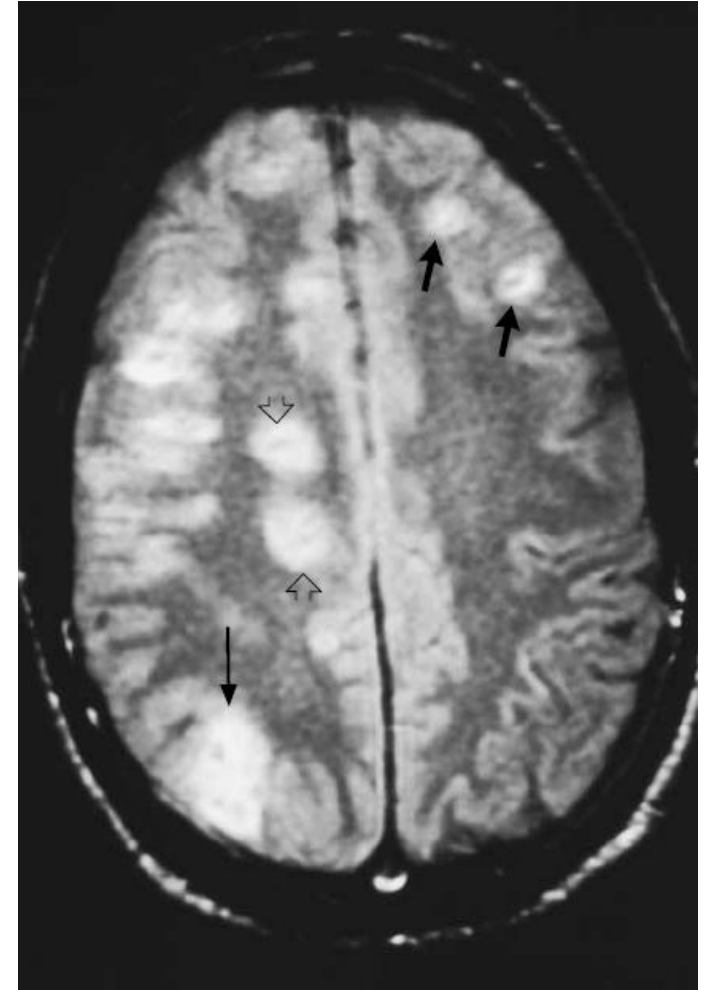
VZV Large Vessel CNS Vasculitis

- 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

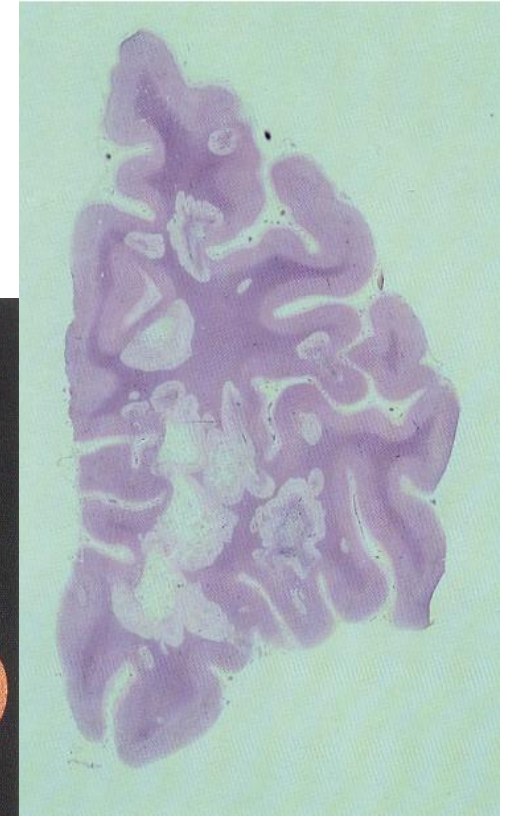
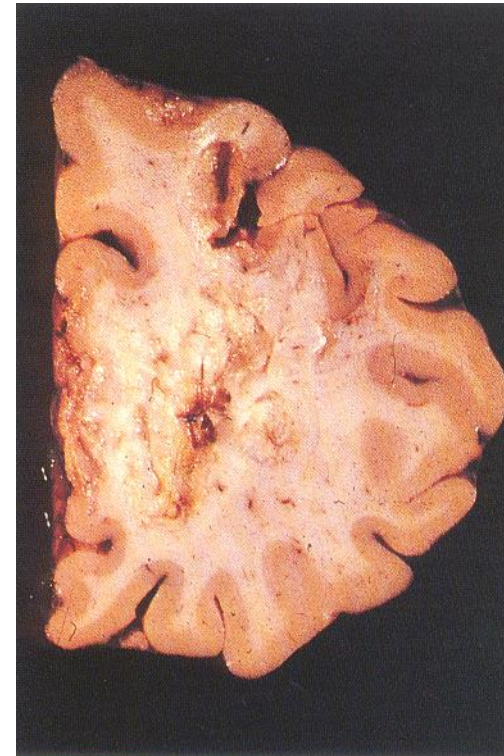
- Immunocompromised hosts, chiefly AIDS
- Clinical manifestations
 - Meningoencephalitis
 - Ventriculitis with gait abnormality
 - Necrotizing vasculitis involving chiefly meninges
- Diagnosis is by
 - CSF PCR
 - CSF/serum VZV antibody (more sensitive)

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

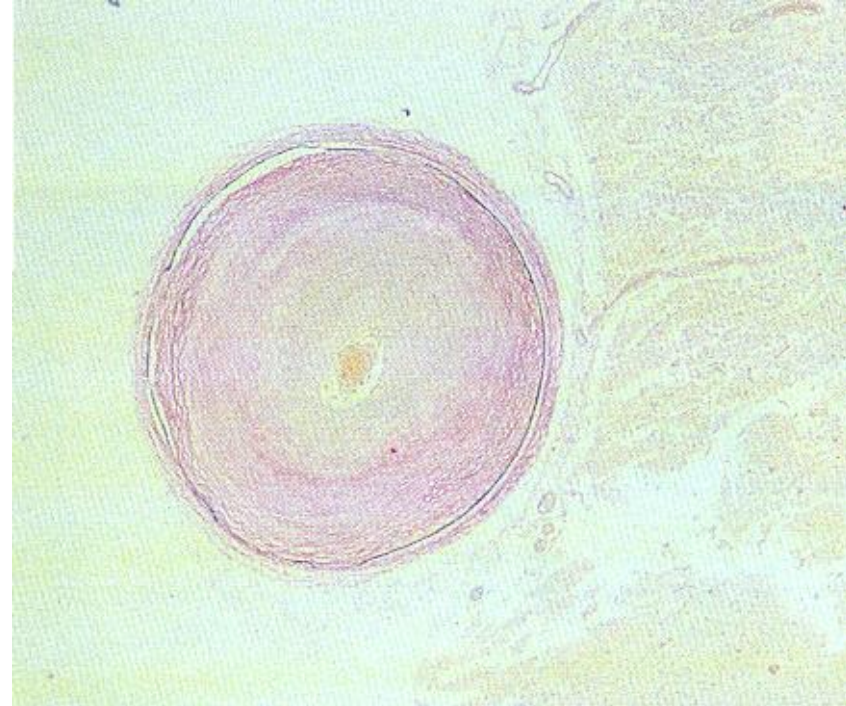


VZV Myelitis

- 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

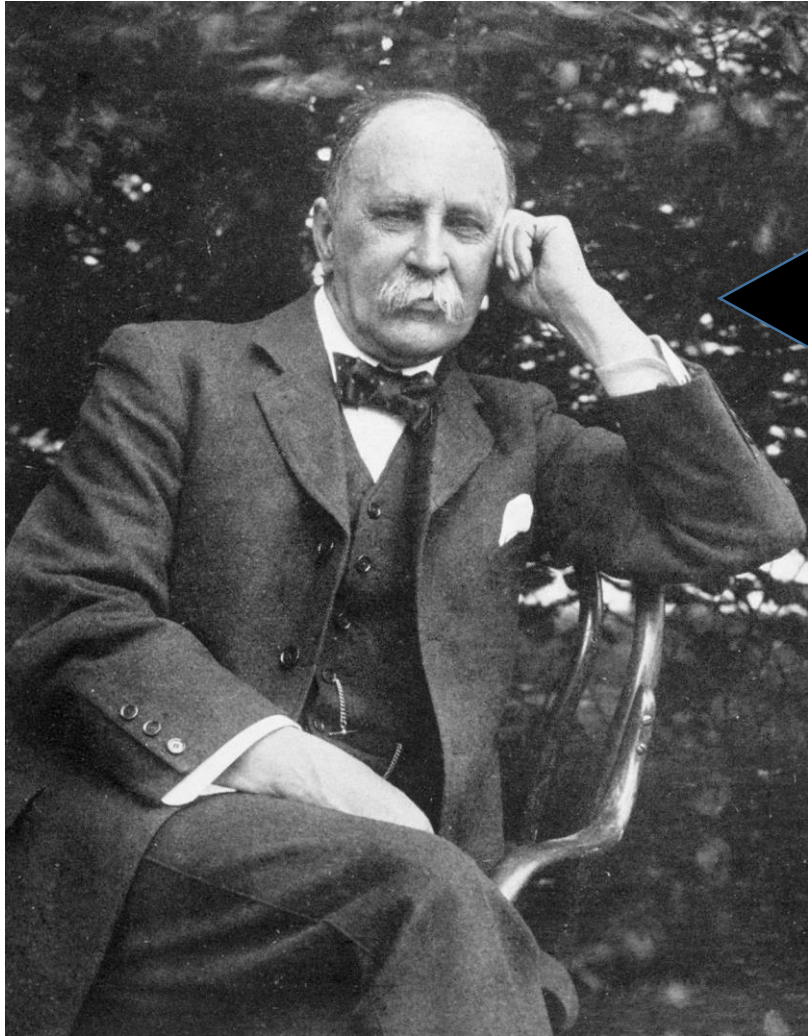
- May involve large or small vessels
- may be inflammatory or bland
- often preceded by zoster ophthalmicus or cranial zoster
- interval up to one year
- associated VZV encephalitis or meningomyelitis not uncommon



Leptomeningeal artery with intimal fibrosis and almost complete luminal occlusion.

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)



Sir William Osler
(1849-1919)

*Humanity has but three
great enemies; Fever,
famine and war; of these
by far the most terrible is
fever.*