



The Neurological Complications of the Herpes Viruses

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Herpes Viruses

◆ History

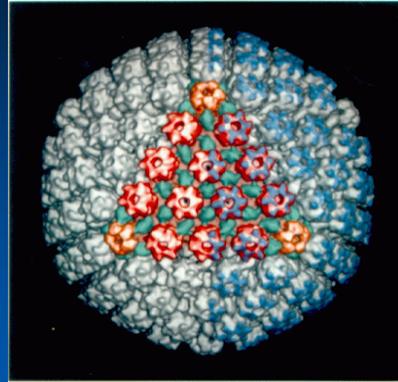
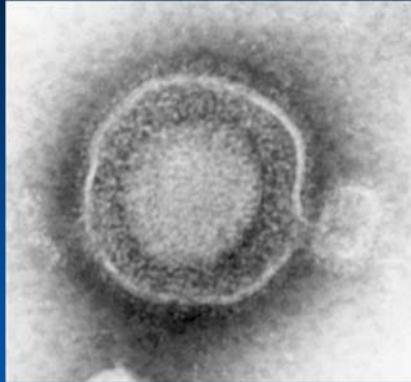
- Greek root is word for “creeping” or “latent”
- Emperor Tiberius banned kissing due to spread of cold sores
- Mentioned in Romeo and Juliet
- Detailed in medical writings by 1713 as “herpes simplex,” “herpes milaris” and “herpes exedens”
- Found to be a family of viruses in the 1940s

◆ 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)



Herpes Virus Icosahedral Structure



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



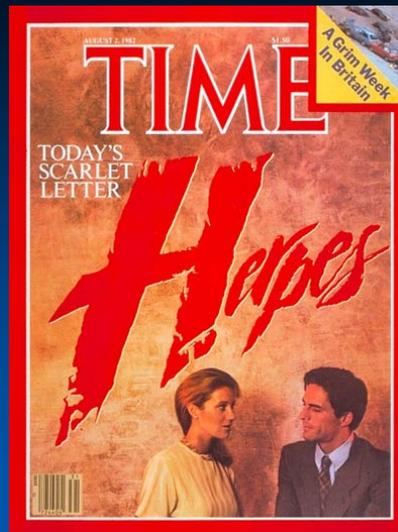
Herpes Viruses

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 post-synaptic ganglion with immunocompetence



Herpes Virus Epidemiology

- ◆ Humans only known reservoir
- ◆ HSV-1
 - >90% of population have HSV-1 Ab by age 50
 - ↑ with age
 - ↓ with higher socioeconomic status
 - Virus typically that carried by mother
- ◆ HSV-2
 - Varies by population
 - Correlates with # of partners, age of sexual debut and other STDs
 - Rate of seroconversion is 2-6% per 100 person years
 - Was not “stigmatized” until Burroughs-Wellcome marketing campaign for Zovirax (acyclovir).



Herpes Virus Epidemiology

- ◆ HSV-1 = HSV-2 as cause of genital herpes in some studies
 - Decrease exposure to HSV-1 in childhood
 - Orogenital sex
- ◆ HSV-2 can be latent in trigeminal ganglia and may cause oral herpetic lesions
 - 44 (3.2%) of 1388 subjects had HSV-2 isolated from their mouths (Wald 2004)
 - Always asymptomatic
 - About ½ the frequency of HSV-1 shedding
- ◆ 1/3 of primary genital herpes and 60% of primary oral herpetic infections are asymptomatic



HSV-1 Neurological Complications



HSV Encephalitis

- ◆ **Three possibilities for viral entry into brain**
 - Reactivation of virus from trigeminal ganglion
 - In situ reactivation in brain
 - Primary infection of CNS
- ◆ **May arise from primary or recurrent infection**
 - 50% due to primary infection
 - 50% due to secondary infection
 - only 10% with history of cold sores
 - DNA of labial and CNS isolates identical in 50%
- ◆ **Pathway to limbic structures either via trigeminal ganglia or olfactory nerve**



HSVE General Features

- ◆ Occurs in 1/250,00 to 1/500,000
- ◆ Accounts for 10-20% of viral encephalitides
- ◆ HSV-1 encephalitis occurs in all ages
 - 30% <20 years old but over 6 months
 - 50% >50 years old
 - Male = female
- ◆ Beyond neonatal period – almost always HSV-1
- ◆ Rarely observed in immunosuppressed
 - Except BMT patients



HSVE Clinical Features

- ◆ Generally subacute (< 1 week) in onset
- ◆ Fever and headache is extremely common
- ◆ Often preceded by URI symptoms
- ◆ Acute psychiatric changes at onset common
- ◆ Cortical features predominate
 - Personality change, confusion, disorientation
 - 1/3 with focal neurological features



HSVE Neuroimaging

◆ Computed tomography

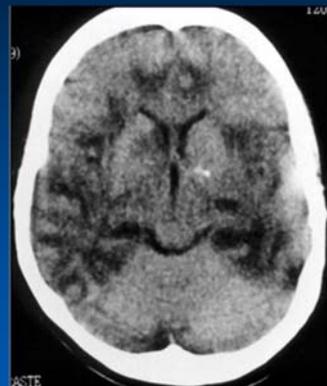
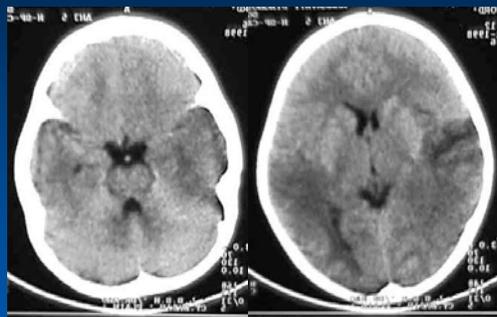
- May be normal or subtly abnormal early
- Temporal lobe low density lesions with mass effect
- Hemorrhage highly suggestive of HSVE
- Ill-defined patchy and gyriform CE

◆ MRI

- More sensitive than CT
- Gyral edema on T1WI
- High signal of temporal lobes, insula and cingulate on T2WI and FLAIR
- CE and petechial hemorrhage rare in early disease

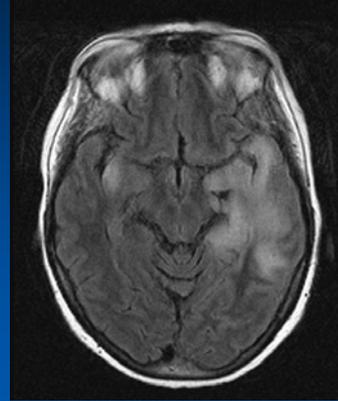
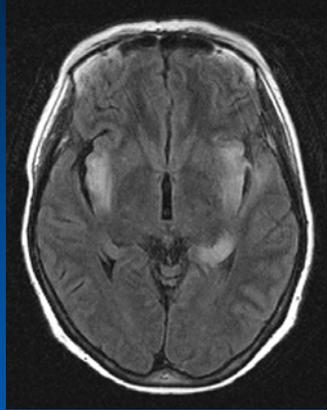


HSVE Neuroimaging CT Scan





HSVE Neuroimaging MRI



HSV Encephalitis CSF and other diagnostic studies

- ◆ CSF is abnormal in 95%
 - Moderate pleocytosis (50-100 lymphocytes)
 - Up to 3000; PMNs may be seen early
 - Red blood cells (40%); Xanthochromia (11%)
 - Moderate increase in protein (50-90 mg/dl); 25% normal
 - Hypoglycorrhachia is rare
- ◆ CSF PCR
 - Sensitivity 98% and specificity 94%
 - False negative typically in first 2 days



HSVE Treatment

- ◆ Acyclovir 10 mg/kg q 8 h for 2 weeks
 - Phosphorylated by viral thymidine kinase
 - Inhibits viral DNA polymerase in infected cells
- ◆ Demonstration of viral DNA in CSF may dictate an additional 1-2 weeks of ACV Rx
- ◆ Other measures
 - Prophylactic anticonvulsant Rx
 - Respiratory assistance
 - ICP monitoring



HSV-2 Neurological Complications



HSV-2 Neurological Complications

- ◆ Neonatal Encephalitis
- ◆ Aseptic meningitis (Mollaret's meningitis)
- ◆ Adult meningoencephalitis
- ◆ Adult encephalitis
- ◆ Acute myelitis
- ◆ Myeloradiculitis
- ◆ Radiculopathy and polyradiculopathy
- ◆ Bell's palsy
- ◆ Acute retinal necrosis



HSV-2 Ascending Myelitis

- ◆ Likely to be underrecognized
- ◆ Typically thoracic or lumbosacral myelopathy
- ◆ May be necrotizing with poor prognosis
- ◆ May be recurrent

Enlargement of conus in a case of recurrent HSV-2 myelitis in a 70 year old woman



Nakajimi et al: *Rinsho Shinkeigaku*, 1993

Gobbi et al: *Eur Neurol*, 2001



Varicella Zoster Virus Neurological Complications

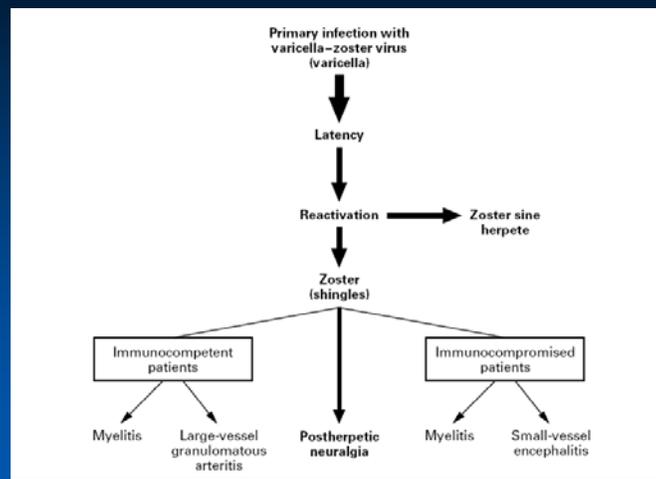


VZV General Features

- ◆ High degree of homology with HSV-1
- ◆ 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 viral DNA
 - Present in neurons and satellite cells



VZV Neurologic Complications



Gilden NEJM 2000



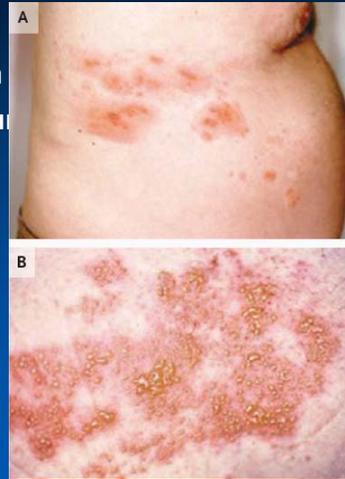
Zoster (Shingles)

- ◆ 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 hours
- Rash forms over 3-5 days and persists 2-4 weeks
- Radicular or cranial nerve:
 - Thorax 60%
 - Cervical 16%
 - Ophthalmic 15%
 - Sacral 12.5%



Kumar Ind J Dermatol
2005



Zoster Clinical Features

- ◆ Zoster keratitis
- ◆ Cranial neuropathies
 - Optic neuritis
 - Ophthalmoplegia with III nerve
 - 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
- ◆ Zoster paresis
- ◆ Sacral zoster with neurogenic bladder



Zoster Clinical Features



Hutchinson's sign
Involvement of medial nose



Ramsay Hunt syndrome



Zoster Treatment

- ◆ Antiviral medications
 - Famciclovir 500 mg 3 x daily
 - Acyclovir 800 mg 5 x daily
 - Valacyclovir 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 > 6 weeks
- ◆ 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.



VZV Myelitis

- ◆ Develops 1-2 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
- ◆ T2 WI MRI with hyperintense lesion
- ◆ Rx with high dose Acyclovir



VZV Large Vessel Encephalitis

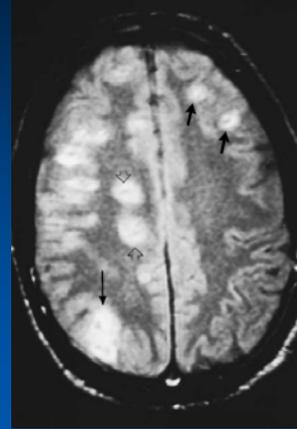
- ◆ Chiefly in immunocompetent
 - Most affected > 60 years old
- ◆ Clinical features
 - Acute stroke weeks or months after contralateral trigeminal zoster
 - TIAs and confusion
 - Mortality – 25%
- ◆ CSF with pleocytosis (<100 mono cells); OCBs; and ↑IgG
- ◆ Angiogram with focal and segmental narrowing
- ◆ Rx – ACV and corticosteroids





VZV Small Vessel Encephalitis

- ◆ 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 - Acyclovir



VZV Unusual Neurological Complications

- ◆ Immunocompromised hosts, chiefly AIDS
- ◆ Clinical manifestations
 - Meningoencephalitis
 - Ventriculitis with gait abnormality
 - Necrotizing vasculitis involving chiefly meninges



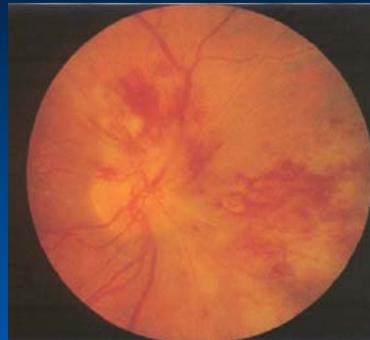
Cytomegalovirus Neurological Complications



Cytomegalovirus Systemic Manifestations



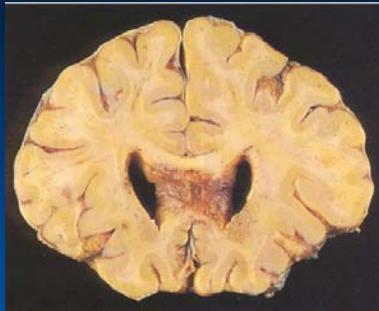
CMV Pneumonia



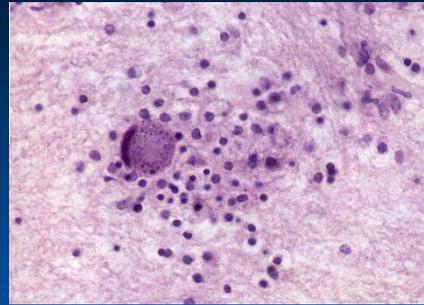
Hemorrhagic CMV retinitis



Cytomegalovirus Encephalitis



Corpus callosum and frontal horns of both lateral ventricles are necrotic



Microglial nodule with cytomegalic cell (Nissl stain)



CMV Polyradiculomyelitis

- ◆ Lower extremity and sacral paresthesias
- ◆ Rapidly progressive paraparesis
- ◆ Areflexia
- ◆ Ascending sensory loss
- ◆ Occasional thoracic sensory level
- ◆ Urinary retention
- ◆ CSF polymorphonuclear pleocytosis
- ◆ MRI with Gd enhancement of cauda equina
- ◆ CMV in blood, urine, and CSF



HHV-6 Neurological Complications



HHV-6

- ◆ Etiology of roseola
- ◆ May directly invade the CNS
- ◆ HHV-6 detected in CSF of febrile sz patients
- ◆ Complications include:
 - Encephalitis after BMT
 - Limbic encephalitis
- ◆ Implicated in pathogenesis of MS
 - Found in only a minority of MS patients
 - ↑ HHV-6 Ab found with other illnesses



Epstein-Barr Virus Neurological Complications



Epstein-Barr Virus

- ◆ Infects B and T cells of > 90% of population before adulthood
- ◆ Replicates in oropharynx
- ◆ Transmitted by oral secretions
- ◆ Acute infection results in transient viremia
- ◆ EBV associated with variety of tumors
 - nasopharyngeal carcinoma
 - Burkitt's lymphoma
 - Hodgkin's disease
 - Lymphoproliferative disorders in immunocompromised



EBV Neurological Disorders

Neurological disease develops in 5-8% of infectious mononucleosis cases

Spectrum of Neurological Disorders

- Aseptic meningitis
- Encephalitis
- GBS
- Cranial nerve palsies
- Transverse myelitis
- Cerebellar ataxia
- Psychiatric manifestations and Alice in Wonderland syndrome
- Acute hemiplegia
- PCNSL



Questions?