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 miliaris” 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

- 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

HSV Encephalitis
**HSVE General Features**

- Occurs in 1/250,000 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
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
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
- Ramsey 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

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**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*</td>
<td>Oxycodeone, 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*</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; antidepressants also proved effective but may be poorly tolerated by elderly patients, less experience with selective serotonin-reuptake inhibitors</td>
<td>Sedation, confusion, amitryptiline effect (dry mouth, blurred vision, constipation, urinary retention)</td>
</tr>
<tr>
<td>Gabapentin*</td>
<td>300 mg orally daily</td>
<td>Titration of 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)*</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 limits use for many patients</td>
</tr>
<tr>
<td>Lidocaine (5% patch)*</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.
**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

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**VZV Unusual Neurological Complications**

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

Gilden NEJM 2000
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 paresthesiaes
- 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

- 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

- 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?