VIRAL INFECTIONS & 
PRION DISEASES

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DISCLOSURE

• The content of this presentation does not relate to any product of commercial interest; therefore, there are no relevant financial relationships to disclose
OBJECTIVES

• Describe the pathologic findings in common viral infections involving the CNS
• Recognize recently emerging viral and immune syndromes affecting the CNS
• Identify other causes of encephalitis
• Discuss the pathologic findings in human prion diseases
INTRODUCTION

TERMINOLOGY

• Cerebritis vs. encephalitis
INTRODUCTION

PATTERNS OF CNS INVOLVEMENT IN VIRAL INFECTIONS

• Meningitis
• Meningoencephalitis
“ASEPTIC” MENINGITIS

- Viral or chemical
- CSF - lymphocytic pleocytosis with moderate protein elevation & normal glucose
- Most common cause - enteroviruses
- Usually self-limited
VIRAL MENINGOENCEPHALITIS

- Infection of brain tissue associated with meningeal inflammation
- Histologic features include perivascular chronic inflammatory cell infiltrates, microglial nodules, neuronophagia, & viral inclusion bodies
VIRAL INCLUSIONS

- DNA viruses – intranuclear inclusions
  - Cowdry type A
- RNA viruses – intracytoplasmic inclusions
CLASSIFICATION OF VIRUSES CAUSING CNS DISEASE

DNA VIRUSES

• Herpesviruses
  – Herpes simplex virus type 1 & 2
  – Varicella-zoster virus
  – Epstein-Barr virus
  – Cytomegalovirus
  – Human herpes virus type 6

• Adenovirus

• Papovaviruses – Polyomaviruses
  – JC virus
  – SV40 virus
CLASSIFICATION OF VIRUSES CAUSING CNS DISEASE

RNA VIRUSES

- Arboviruses (Reoviruses, Togaviruses, Flaviviruses, & Bunyaviruses)
- Retroviruses
  - Human immunodeficiency viruses
  - Human T-cell lymphotrophic virus
- Rubivirus
- Picornaviruses
  - Poliovirus
  - Enteroviruses
CLASSIFICATION OF VIRUSES CAUSING CNS DISEASE

RNA VIRUSES

- Arenavirus – Lymphocytic choriomeningitis virus
- Paramyxoviruses
  - Morbillivirus
  - Henipaviruses – Hendra & Nipah
- Orthomyxoviruses – Influenza virus
- Rhabdovirus
HERPESVIRUSES

- Herpes simplex virus type 1 (HSV-1)
- Herpes simplex virus type 2 (HSV-2)
- Varicella-zoster virus (VZV)
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- Human herpes virus type 6 (HHV-6)
HERPES ENCEPHALITIS
HSV-1

- Produces recurrent infections of epithelial surfaces and establishes latent infection in sensory ganglia
- Most common cause of sporadic, non-seasonal encephalitis
- Highest incidence in adolescence and young adulthood
HERPES ENCEPHALITIS

CLINICAL FINDINGS

• Fever, headache, seizures, personality and mood changes, & mental status changes are characteristic and may rapidly progress to coma and death

• Olfactory or gustatory hallucinations may occur

• Only 10% of patients have a history of previous labial infection

• Radiographic findings - Increased T2 signal in the temporal lobes, insular cortex, and inferior frontal lobes
HERPES ENCEPHALITIS

PATHOLOGY

• Hemorrhagic encephalitis involving the temporal lobes & orbital gyri of the frontal lobes
• Cowdry A nuclear inclusions
GENERALIZED ENCEPHALITIS
HSV-2

- Generalized encephalitis in neonates born by vaginal delivery to women with active primary HSV infection or in immunosuppressed patients
VARICELLA-ZOSTER VIRUS

- Reactivation of latent infection manifests as a painful vesicular skin eruption in the distribution of a dermatome ("shingles")
- May cause an acute meningoencephalitis in immunocompromised patients
- Immunocompetent patients may develop bulbar encephalitis or transverse myelitis
- Vasculopathy/vasculitis can occur during primary infection or after reactivation and may lead to infarcts
EPSTEIN-BARR VIRUS

- Rare cause of encephalitis
- Cause of lymphoma in immunosuppressed patients
CYTOMEGALOVIRUS

- Over 80% of the U.S. population is seropositive by the age of 35 years
- Infections occur in fetuses & immunocompromised patients, especially those with AIDS
- Most common manifestation - retinitis
CYTOMEGALOVIRUS ENCEPHALITIS

CLINICAL FINDINGS

• Adults - confusion, gait disturbances, cranial nerve palsies, hyperreflexia, and retinitis
• Neonates – disseminated disease with petechiae, hepatosplenomegaly, jaundice, microcephaly, and chorioretinitis
• Imaging studies - hydrocephalus with periventricular enhancement; calcification in neonates/fetuses
CYTOMEGALOVIRUS ENCEPHALITIS

PATHOLOGY

• Periventricular necrosis & calcification
• Neonates – porencephaly or polymicrogyria
• Diffuse microglial nodules
• Prominent cytomegalic cells with intranuclear & intracytoplasmic inclusions – may occur in any cell type but usually ependymal cells are affected
HUMAN HERPES VIRUS TYPE 6

- Cause of exanthem subitum/roseola infanatum/sixth disease
- Post-transplant limbic encephalitis
- Confirmed with PCR on CSF
ADENOVIRUS

- Encephalitis is a rare complication of infection
- Immunosuppressed patients
- Basophilic intranuclear inclusions
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

• Caused by JC virus, which infects & kills oligodendrocytes
• Approximately 80% of adults are seropositive for JC virus
• Disease occurs most commonly in immunocompromised patients
• Also occurs in those treated with natalizumab, efalizumab, and rituximab
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

CLINICAL FINDINGS

• Focal neurologic deficits, including limb weakness, speech or visual deficits, and cognitive abnormalities

• Multiple sclerosis patients treated with natalizumab - seizures and speech disorders including aphasia

• Imaging studies - hyperintense signal abnormalities of white matter on T2-weighted MRI
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATY

PATHOLOGY

• Demyelination with lipid-laden macrophages
• Nuclear viral inclusions in oligodendrocytes
• Bizarre giant astrocytes
• Presence of viral antigens may be confirmed with immunohistochemistry for JC virus or SV40 virus
ARTHROPOD-BORNE VIRUSES
ARBOVIRUSES

- Reovirus
  - Colorado tick fever virus
- Togaviruses – Alphavirus subgroup
  - Eastern equine encephalitis virus
  - Western equine encephalitis virus
  - Venezuelan equine encephalitis virus
- Flaviviruses
  - Japanese encephalitis virus
  - St. Louis encephalitis virus
  - West Nile virus
  - Tick-borne encephalitis virus
- Bunyaviruses
  - La Crosse virus
  - Toscana virus
ARTHROPOD-BORNE VIRAL ENCEPHALITIS

- Responsible for most outbreaks of epidemic viral encephalitis
- Animal hosts & mosquito or tick vectors
- Generalized or focal neurologic deficits
WEST NILE VIRUS

• Since its introduction to the U.S. in 1999, WNV has emerged as the most common cause of epidemic meningoencephalitis in North America
• It is the leading cause of arboviral encephalitis in the U.S.
Natural transmission cycle of WNV

Mosquito vector

Bird host

Incidental hosts – man & horse

WNV

Natural transmission cycle of WNV
WEST NILE VIRUS
CLINICAL SYNDROMES

- 80% of infections are asymptomatic
- 20% result in a self-limited disease termed West Nile fever
- 1/150 patients develop CNS disease – West Nile neuroinvasive disease
WEST NILE NEUROINVASIVE DISEASE

- Meningitis (40%) – fever, nausea/vomiting, nuchal rigidity, headache, photophobia
- Encephalitis (60%) – fever, diffuse weakness or fatigue, headache, confusion or altered mental status, dizziness/vertigo
- Tremor and myoclonus are common
WEST NILE NEUROINVASIVE DISEASE

ACUTE FLACCID PARALYSIS/POLIOMYELITIS-LIKE SYNDROME

- Acute monoplegia, asymmetric upper or lower extremity weakness, or generalized asymmetric tetraplegia or quadriplegia
- Diminished or absent deep tendon reflexes
- 70% have cranial nerve involvement
- Respiratory failure requiring intubation is a common complication
"We're pretty sure it's the West Nile Virus."
WEST NILE VIRUS

PROGNOSIS AND TREATMENT

- Overall case fatality rate ranges from 2-18%
- Higher in transplant patients (25%)
- 10-20% of patients with encephalitis die
- Up to 70-75% of survivors of neuroinvasive disease experience persistent constitutional and neurological deficits
- Risk factors for fatal disease – intubation, previous stroke, immunosuppression, age > 50 years
- Treatment is largely supportive and includes reduction of immunosuppression
ARBOVIRUSES

• Colorado tick fever virus
  – 2nd most common arboviral infection in U.S.
  – Encephalitis occurs primarily in children
• Encephalitis alphaviruses (EEEV, WEEV, & VEEV)
  – Neuroinvasive disease in humans and horses
• Japanese encephalitis virus
  – Most common cause of acute viral encephalitis worldwide
ARBOVIRUSES

• St. Louis encephalitis virus
  – Symptomatic encephalitis occurs most commonly in patients older than 60 years

• Tick-borne encephalitis virus
  – Infection occurs predominantly in Europe and Asia

• La Crosse encephalitis virus
  – Cause of meningitis or encephalitis with seizures

• Toscana virus
  – Common cause of viral meningitis in Europe
HUMAN IMMUNODEFICIENCY VIRUS

- Cause of the acquired immunodeficiency syndrome (AIDS)
- Neurologic dysfunction develops in 40-70% of patients, and neuropathologic findings are seen in up to 90% of brains at autopsy
HUMAN IMMUNODEFICIENCY VIRUS

- Aseptic meningitis
- HIV-associated neurocognitive disorders/HIV encephalitis
- Vacuolar myelopathy - myelin damage
- Disorders related to antiretroviral therapy
- Opportunistic infections/primary CNS lymphoma
HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND)

- HIV-associated dementia (HAD) – AIDS dementia complex, HIV encephalopathy
- Mild neurocognitive disorder (MND)
- Asymptomatic neurocognitive impairment
- Pathologic substrate – HIV encephalitis
VACUOLAR MYELOPATHY

• Leg weakness, spastic paraparesis, ataxia, incontinence
• Vacuolation/myelin loss in white matter tracts of the posterior and lateral columns of the spinal cord
• Defective myelination due to a deficiency of S-adenosylmethionine (vitamin B₁₂ dependent) is a suspected mechanism
IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

- Paradoxical deterioration of clinical status after initiation of combined active antiretroviral therapy
- Thought to be secondary to the sudden activation of and increase in CD4-positive T cells resulting in a heightened immune response with host mediated inflammatory cell damage
- Most common in the setting of AIDS-related opportunistic infections
OPPORTUNISTIC INFECTIONS
TROPICAL SPASTIC PARAPARESIS

- Caused by human T-cell lymphotropic virus (HTLV-1)
  - Aggressive T-cell leukemia
- Endemic in southern Japan, the Caribbean, parts of Africa, & South America
- Slowly progressive weakness of the lower limbs, sensory disturbances, difficulties with bladder control
RUBIVIRUS

- Cause of rubella (German measles)
- Congenital infection may result in neurologic abnormalities including sensorineural deafness and encephalitis
- Pathologic findings include mineralization of vessels in the deep gray nuclei and white matter
POLIOMYELITIS

- Poliovirus - enterovirus that has been controlled by immunization in the U.S. but remains endemic in Afghanistan, India, Nigeria, and Pakistan
- Outbreaks have been attributed to circulating vaccine-derived poliovirus
- Non-specific gastroenteritis in most infected patients
POLIOMYELITIS

- Specifically attacks lower motor neurons producing a flaccid paralysis with muscle wasting & hyporeflexia
- Postpolio syndrome - late neurologic syndrome characterized by progressive weakness associated with decreased muscle bulk & pain
ENTEROVIRUSES

• Typically cause meningitis but may cause a poliomyelitis-like syndrome, brainstem encephalitis, opsoclonus-myoclonus syndrome, Guillain-Barré syndrome, & transverse myelitis

• Enterovirus 71
  – Hand-foot-and-mouth disease
LYMPHOCYTIC CHORIOMENINGITIS VIRUS

- Mouse reservoir
- Acquired by contact with contaminated fomites, via inhalation of aerosolized virus, via organ transplantation, or transplacentally
- Typically causes a viral meningitis
LYMPHOCYTIC CHORIONEUMINGITIS
VIRUS

• Other neurologic illnesses – encephalitis, transverse myelitis, Guillain-Barré syndrome, or hydrocephalus

• Congenital infection – chorioretinitis, macrocephaly secondary to obstructive hydrocephalus, or microcephaly with periventricular calcifications
MEASLES VIRUS

CLINICAL SYNDROMES

• Acute postinfectious measles encephalitis
• Subacute sclerosing panencephalitis
SUBACUTE SCLEROSING PANENCEPHALITIS

- Occurs in children or young adults following infection with measles virus
- Cognitive decline, spasticity of the limbs, and seizures
- Loss of myelin and gliosis
- Nuclear and cytoplasmic viral inclusions
HENDRA AND NIPAH VIRUSES

• Cause of outbreaks of infection in Australia & Asia, respectively
• Natural host – fruit bat
• Direct bat-to-human transmission or transmission via intermediate hosts – horse & pig
HENDRA AND NIPAH VIRUSES

CLINICAL FINDINGS

- Hendra virus – produces pulmonary disease or a neurological syndrome consisting of confusion, motor deficits, and seizures
- Nipah virus – reduced deep tendon reflexes, segmental myoclonus, nuchal rigidity, seizures, cerebellar ataxia, and brainstem signs
HENDRA AND NIPAH VIRUSES

PATHOLOGY

• Vasculitis with thrombosis and foci of necrosis
• Perivascular chronic inflammation, microglial nodules, and neuronophagia
• Neuronal intranuclear and intracytoplasmic inclusions
INFLUENZA VIRUSES
CNS MANIFESTATIONS

- Influenza-associated encephalopathy
- Febrile seizures
- Reye syndrome
- Postinfluenzal encephalitic Parkinson disease
- Encephalitis lethargica
INFLUENZA-ASSOCIATED ENCEPHALOPATHY

• Occurs most commonly in children and is associated with typical flu symptoms
• Signs & symptoms include seizures, alterations in consciousness, decreased cognitive function, abnormal behavior, & changes in mental status
• Imaging studies – necrotizing encephalopathy with cerebral edema
INFLUENZA VIRUSES

H1N1

• Risk factors for severe disease – age less than 2 years, pregnancy, chronic pulmonary disease, immunosuppression, & metabolic disorders including diabetes & obesity
RABIES

• Usually transmitted by the bite of a rabid animal, and the virus enters the CNS by ascending along the peripheral nerves from the wound site
• May rarely be transmitted by aerosols in labs or caves with large numbers of bats and by organ transplantation
• Death results from respiratory center failure
RABIES

CLINICAL FINDINGS

• Encephalitic (furious) form - generalized arousal or hyperexcitability, disorientation, bizarre behavior, hallucinations, and hydrophobia

• Paralytic (dumb) form - motor weakness, often beginning in the bitten extremity, which progresses to quadriplegesis with associated facial weakness
RABIES
PATHOLOGY

• Negri bodies - cytoplasmic eosinophilic inclusions in pyramidal neurons of the hippocampus & cerebellar Purkinje cells
• Lyssa bodies - more irregular, less sharply demarcated inclusions
OTHER ENCEPHALITIDES

- Rasmussen encephalitis
- Paraneoplastic disorders
  - Encephalomyelitis
  - Limbic encephalitis
- Autoimmune encephalitis
  - Nonparaneoplastic limbic encephalitis (Anti-LGI1)
  - Anti-NMDA receptor encephalitis – ovarian teratoma
**RASMUSSEN ENCEPHALITIS**

- Medically intractable focal epilepsy in association with chronic encephalitis
- Epilepsia partialis continua
- Progressive disease with hemiparesis, homonymous hemianopia, & mental retardation
- Imaging studies - atrophy of the affected hemisphere and areas of increased T2 and FLAIR signal within the cortex
- Autoantibodies to the glutamate receptor GluR3
RASMUSSEN ENCEPHALITIS

PATHOLOGY

• Perivascular and leptomeningeal chronic inflammation, microglial cell proliferation, & cortical atrophy with gliosis
• CD8-positive T-cells
## PARANEOPLOPLASTIC ANTIBODIES

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Associated Syndrome</th>
<th>Most Frequent Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu (ANNA1)</td>
<td>Paraneoplastic encephalomyelitis (PEM), paraneoplastic sensory neuronopathy, paraneoplastic cerebellar degeneration (PCD), limbic encephalitis</td>
<td>Small cell lung cancer (SCLC), other neuroendocrine tumors</td>
</tr>
<tr>
<td>Yo (PCA1)</td>
<td>PCD</td>
<td>Ovary, breast</td>
</tr>
<tr>
<td>CV2/CRMP5</td>
<td>Limbic encephalitis, PCD, chorea, uveitis, optic neuritis, retinopathy, sensorimotor neuropathy</td>
<td>SCLC, thymoma, other</td>
</tr>
<tr>
<td>Ri (ANNA2)</td>
<td>Ataxia, opsoclonus myoclonus, brainstem encephalitis</td>
<td>Breast, gynecologic, SCLC</td>
</tr>
<tr>
<td>Ma2a</td>
<td>Limbic, diencephalic, brainstem encephalitis, myelopathy</td>
<td>Testicular, lung, breast, other</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Stiff person syndrome, PEM, limbic encephalitis</td>
<td>Breast, SCLC</td>
</tr>
</tbody>
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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
PRION DISEASES

- Group of uniformly fatal neurodegenerative disorders occurring in humans and animals
- Caused by the accumulation of an abnormally aggregated, protease-resistant form of the mammalian prion protein (PrP)
- Misfolded form of prion protein may seed the progressive conversion of normal protein
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

PRION DISEASES

• Sporadic, hereditary, and iatrogenic forms
• Susceptibility to and clinical characteristics of these disorders are influenced by a polymorphism at codon 129 of PRNP, the gene encoding prion protein
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

PRION DISEASES

- Creutzfeldt-Jakob disease
- Kuru
- Gerstmann-Straüssler-Scheinker syndrome
- Fatal familial insomnia
- Variant Creutzfeldt-Jakob disease
CREUTZFELDT-JAKOB DISEASE

EPIDEMIOLOGY

• Most common prion disease – incidence of 1 case/million population/year
• Most patients between 50-70 years of age
• Usually sporadic – familial form with autosomal dominant inheritance in 10-15% of cases secondary to mutations in PRNP gene
• Iatrogenic transmission – dural/corneal grafts, pooled human pituitary growth hormone injections, contaminated neurosurgical instruments
CREUTZFELDT-JAKOB DISEASE

CLINICAL FINDINGS

• Rapidly progressive dementia with startle myoclonus
• EEG - periodic, triphasic sharp-wave complexes which are superimposed on a slow background rhythm
• MR - increased signal in affected gray matter on T2-or diffusion-weighted images
• Elevated levels of protein 14-3-3 and total tau protein in the CSF
CREUTZFELDT-JAKOB DISEASE

PATHOLOGY

• Atrophy
• Spongiform change, neuronal loss, and gliosis
• Kuru plaques – approx. 10% of cases
• No significant inflammation
• Antibodies directed against the protease-resistant prion protein
KURU

• Acquired prion disorder confined to the Fore tribe of Papua New Guinea
• Transmitted via ritualistic cannibalism
• Pure cerebellar ataxia with relatively preserved cognition
Do you kuru?

Smart cannibals don’t eat brains!
(A public service announcement from the Association for Informed Anthropophagy and the Cannibal Anti-Defamation Society)
GERSTMANN-STRAÜSSLER-SCHEINKER SYNDROME

- Inherited, progressive ataxic and/or parkinsonian disorder
- Considerable phenotypic variation, even in patients with identical mutations
- Limbic hyperintensities on FLAIR and DWI MR images
- Amyloid plaques in brain and cerebellum
FATAL FAMILIAL INSOMNIA

• Inherited, progressive insomnia with hallucinations and dysautonomia
• Caused by a single *PRNP* point mutation
• FDG-PET imaging reveals hypometabolism in thalamus and cingulate gyrus
• Neuronal loss and gliosis in thalamus
VARIANT CJD

• First recognized in 1995 in the United Kingdom
• Associated with bovine spongiform encephalopathy (BSE, mad cow disease)
• Codon 129 polymorphism is an important susceptibility factor - nearly every case reported has been found to be 129MM
“Mad Cow?!...BULL! I wasn’t even the least bit angry until I laid on this leather couch of yours!”
VARIANT CJD

CLINICAL FINDINGS

• Younger age of onset, more prominent behavioral disturbances, and a longer clinical course than typical CJD cases

• “Pulvinar sign” – pulvinar is brighter than the anterior putamen on T2-weighted or DWI MR images
VARIANT CJD

PATHOLOGY

• Prion protein can be found in the lymphoreticular system, including tonsillar tissue

• “Florid plaques” – amyloid/kuru plaques surrounded by a halo of spongiform vacuoles
TAKE-HOME POINTS

• Most viral infections in the CNS are characterized by the histologic triad of perivascular chronic inflammation, microglial nodules, and neuronophagia

• In general, DNA viruses produce intranuclear inclusions, and RNA viruses produce intracytoplasmic inclusions
TAKE-HOME POINTS

• Autoimmune/paraneoplastic disorders may mimic viral encephalitis both clinically and pathologically

• Pathologic findings in prion disorders include spongiform change, neuronal loss, gliosis, and amyloid plaques; there is no significant inflammation
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SELECTED REFERENCES

