Herpesvirus Infections of the Central Nervous System

- HSV encephalitis
- Herpes B Virus infections
- Varicella-Zoster Virus infections
- Congenital CMV infection

HSV Encephalitis

- HSV-1 is the most common form of sporadic fatal encephalitis in adults
- Estimated incidence of 1 case per 200,000 persons per year
- Focal encephalitis with fever, altered consciousness and behavior, disordered thinking
- The temporal lobe of the brain is most often involved.
- Mortality in untreated patients >70%
- Acyclovir and other anti-herpesviral drugs reduce mortality, but many patients do not regain full mental function

Herpes B Virus

- Cercopithecine Herpesvirus 1
- Common in Old World monkeys, esp. in genus Macaca (e.g., rhesus, cynomologous, and others)
- Infected animals may secrete virus in saliva, other bodily secretions, but don’t necessarily appear ill
- Transmissible by bite or by contact of saliva with mucous membranes
- Highly pathogenic for humans, with a high frequency of fatal encephalitis
- Treatable with high doses of acyclovir and/or ganciclovir

CNS complications of VZV Infection

- Complications of Varicella
  - transient cerebellar ataxia
  - aseptic menigitis
  - cerebral encephalitis
  - transverse myelitis
- Complications of Zoster
  - encephalitis (0.2 – 0.5% of cases)
- Congenital varicella
  - mental retardation, cerebral atrophy
  - Non-CNS abnormalities

Congenital CMV Infection

- 1 – 2% of births have congenital CMV
- 7 – 10% of these have cytomegalic inclusion disease
  - mental retardation, seizures, blindness, deafness, death
- Remainder of cases
significant probability of hearing defects, intellectual impairment

Human Polyomaviruses
- Family: Papovaviridae, Subfamily: Polyomavirinae
- There are 2 Polyomaviruses that are endemic in humans:
  - JC Virus (JCV)
    - Discovered in 1971
    - Associated with Progressive Multifocal Leukoencephalopathy
  - BK Virus (BKV)
    - Discovered 1971
    - Mainly associated with mild upper respiratory disease

Related Animal Polyomaviruses
- Polyomavirus
  - Mouse virus
  - Discovered 1953
  - Causes multiple types of tumors in its natural host
- SV40
  - Monkey virus
  - Discovered 1960
  - Closely related to JCV and BKV
  - Reported to have been isolated from some human tumors

Physical and Biological Characteristics of Polyomaviruses
- Nonenveloped icosahedral virions
- Circular, double-stranded DNA genomes
- Genome size is about 5 kb, containing 6 genes
- Nuclear replicating
- Highly dependent on cellular enzymes for DNA replication and gene expression.

JC Virus
- Prevalent world-wide. Seropositivity rates in adults range from 50 – 75 %
- Mode of transmission is not known
- Primary infections seem to be asymptomatic
- May cause Progressive Multifocal Leukoencephalopathy in immunocompromised individuals

Clinical Features of PML
- Initial symptoms are usually indicative of focal cerebral involvement: personality alterations, intellectual deficits, loss of motor skills, sensory loss
- Less frequently, initial symptoms may indicate cerebellar or brain stem involvement: e.g., difficulty speaking, swallowing, ataxia
Rapid progression. Death usually occurs within 2 – 12 months.
Rare remissions, usually associated with correction or stabilization of immunodeficiency.

Pathogenesis of PML
- Pathological changes may occur in cerebrum, cerebellum or brain stem
- PML lesions are characterized by the loss of myelin.
  - In the cerebrum, this typically occurs in the subcortical region (deep white matter).
  - Cerebral cortex and gray matter appear normal.
- Loss of myelination is due to virus replication in oligodendrocytes.
- Little or no inflammation.

Diagnosis of PML
- PML should be suspected in immunocompromised patients with progressive development of neurological deficits
- MRI imaging for lesions in subcortical and deep white matter
- Brain biopsy to verify presence of JCV and to eliminate other infections which may mimic PML: Toxoplasma gondii, Cryptococcus neoformans, Mycobacterium tuberculosis

Transmissible Spongiform Encephalopathies
- TSEs are caused by a unique type of infectious agent called prions.
- Prions are not viruses and, in fact, do not contain any nucleic acid.
- Prions are defined as small proteinaceous infectious particles
- Transmissible Spongiform Encephalopathies have the following properties
  - They are transmissible, that is, infectious.
  - They produce characteristic vacuolar lesions in the brain giving it a spongy appearance.
  - There is no inflammation of the brain or immune response to the infection

Evidence for the Unusual Nature of TSE Agents
- TSE agents are much more resistant to UV and ionizing radiation than conventional organisms.
- TSE agents are resistant to chemical and enzymatic treatments that attack RNA and DNA
- TSE agents are relatively sensitive to agents that attack protein, e.g., proteases
- Conventional sterilization methods are ineffective against TSE agents
  - Conventional agents are killed by standard autoclaving at 121 C.
  - Inactivation or TSEs requires lengthy autoclaving at 130 C, preferably in 2 N NaOH
Diseases Caused by TSEs

- Human TSEs
  - Kuru
  - Creutzfeldt-Jacob Disease
  - Gerstmann-Sträussler-Scheinker Syndrome
  - Fatal Familial Insomnia

- Animal TSEs
  - scrapie (sheep)
  - transmissible mink encephalopathy
  - bovine spongiform encephalopathy

The PrP Protein is Associated with Scrapie Infectivity

- Scrapie agent copurifies with amyloid fibrils found in scrapie plaques
- Scrapie amyloid consists of PrP-sc, an insoluble, protease-resistant form of PrP-c, a protein normally expressed in the brain
- Accumulation of PrP-sc correlates with pathology
- Intracerebral inoculation of mice with preparations enriched in PrP-sc transfers disease
- PrP null mice are resistant to scrapie
- Transgenic mice expressing foreign PrP have altered species tropism for scrapie
- In humans, PrP mutations are associated with familial TSEs

The Prion Hypothesis for TSEs

- PrP-c, a protein normally found in the brain, has a primarily alpha-helical structure.
- PrP-sc has a primarily beta-sheet structure and is produced by causing Prp-c to undergo a conformation shift.
- Once formed, Prp-sc can catalyze the conversion of Prp-c to Prp-sc.
- Accumulation of PrP-sc in the nervous system causes neuronal damage.

Clinical Features of Creutzfeldt-Jacob Disease (CJD)

- Typical age of onset of “classic” CJD: 50 – 65 years (range: 17 – 83)
- “New Variant” CJD (NV-CJD) – range: 15 - 55
- Survival after onset of disease: 6 – 12 months (range: a few months – 5 years)
- Incubation period
  - sporadic, classical CJD: unknown
  - iatrogenic CJD:
    - via contaminated surgical instruments: 1.5 – 2.0 years, possibly longer
    - via contaminated human growth hormone: average of 13 years
♦ NV-CJD: difficult to say, could range from 3 to 15 years or more

**Clinical Features of Creutzfeldt-Jacob Disease (CJD)**

- Deficits of higher cortical function
  - memory loss
  - impaired judgement
  - decline of intellectual function
  - progression to profound dementia
- Cerebellar deficits (minority of cases)
  - ataxia
  - visual impairment
- myoclonic (jerky) movements

**Neuropathology of CJD**

- spongiform degeneration
- astrocytosis
- cerebral atrophy
- neuronal vacuolization
- amyloid plaques
- lack of inflammation

**Gerstmann-Sträussler Scheinker Syndrome**

- Much rarer than CJD
- Clinical Signs
  - spinocerebellar ataxia
  - dementia (usually later in disease)
  - plaque-like deposits
- Most cases are familial and are linked to a mutation in the PrP-c gene
- Sporadic nonhereditary cases do occur

**Kuru**

- Previously endemic among the Fore tribe of New Guinea
- Spread by ritual cannibalism
- Cerebellar dysfunction
- Dementia in advanced stages
- Death within 1-2 years of onset of symptoms
- Variable incubation time, up to 30 years

**Bovine Spongiform Encephalitis (BSE, Mad Cow Disease)**

- In the 1980’s, a BSE epidemic occurred in cattle in Great Britain
- BSE may have originated from scrapie, a TSE of sheep
  - Scrapie has been known in Great Britain for > 200 years, but was thought not to be transmissible to other animals or humans.
♦ Sheep and cattle offal (waste parts) was used to make meat and bone meal that was added to animal feed as a protein source.
♦ The disease may have been transferred to cattle by contaminated feed, crossing the “species barrier” which makes interspecies transmission of TSEs difficult.

- Alternatively, BSE may have originated by a rare, spontaneous conformational shift of bovine PrP, then spread to other cattle through contaminated feed

**NV-CJD and BSE**

- First case diagnosed in Great Britain in 1996
- Early clinical onset and neuropathology are distinct from “classical” CJD
- Protease Fingerprinting shows that NV-CJD prions resemble BSE prions, not classical CJD prions, strongly suggesting transmission from cattle
  ♦ Protease fingerprinting is a molecular characterization of the PrP fragment resistant to digestion by proteolytic enzymes
- To date >100 cases of NV-CJD have been diagnosed in Great Britain, 3 in France
- Full scope of human outbreak is difficult to estimate.
  ♦ Best case: a few hundred cases
    - This is the prediction if current cases are sensitive responders infected at the peak of the BSE epidemic in 1989-1993.
  ♦ Worst case: several tens of thousands human cases
    - This is the prediction if current cases are fast responders infected at beginning of BSE epidemic in early 1980s.
Study Questions

1) A kidney transplant patient is admitted to hospital suffering from confusion and difficulty walking. His records show that he has been taking immunosuppressive drugs to prevent rejection of his transplant. Which of the following might be responsible:
   A) Creutzfeld-Jacob Disease
   B) New Variant Creutzfeld-Jacob Disease
   C) BK Virus
   D) Progressive Multifocal Leukoencephalopathy
   E) Herpes B Virus

2) NV-CJD is thought to be the result of
   A) Development of a new type of mutation in the PrP gene in the human population.
   B) Infection of humans by the scrapie agent.
   C) Infection of humans by the Bovine Spongiform Encephalopathy agent.
   D) A new type of Alzheimer’s disease.
   E) An occasional long-term consequence of Measles virus infection.

3) An immunologically normal adult patient presents with fever and severe headache. These symptoms have worsened over several days. A physical examination shows no signs of skin lesions or other signs of infection. You suspect encephalitis. Which of the following agents is most likely responsible:
   A) HSV-1
   B) HSV-2
   C) VZV
   D) JCV
   E) BSE
1) D. The fact that the patient is immunosuppressed makes him more susceptible to development of PML, which is the best answer of those listed. CJD and NV-CJD are less common than PML and are not associated with immunosuppression, although they could occur in an immunosuppressed patient. BKV is not associated with CNS disease. Herpes B Virus is acquired from monkeys, and contact with monkeys is not listed as a risk factor here.

2) C. Protease fingerprinting and epidemiological evidence strongly suggests that NV-CJD is the result of infection with the BSE agent.

3) HSV-1 is the most common cause of sporadic encephalitis in adults and so is the best answer to this question. However, further testing (e.g., PCR for HSV DNA in CSF) would be required to verify the diagnosis.