2021-2022

CNS infections
(2 of 2)

Ali Al Khader, M.D.
Faculty of Medicine
Al-Balqa Applied University
Email: ali.alkhader@bau.edu.jo

We will discuss viral encephalitis and prion diseases

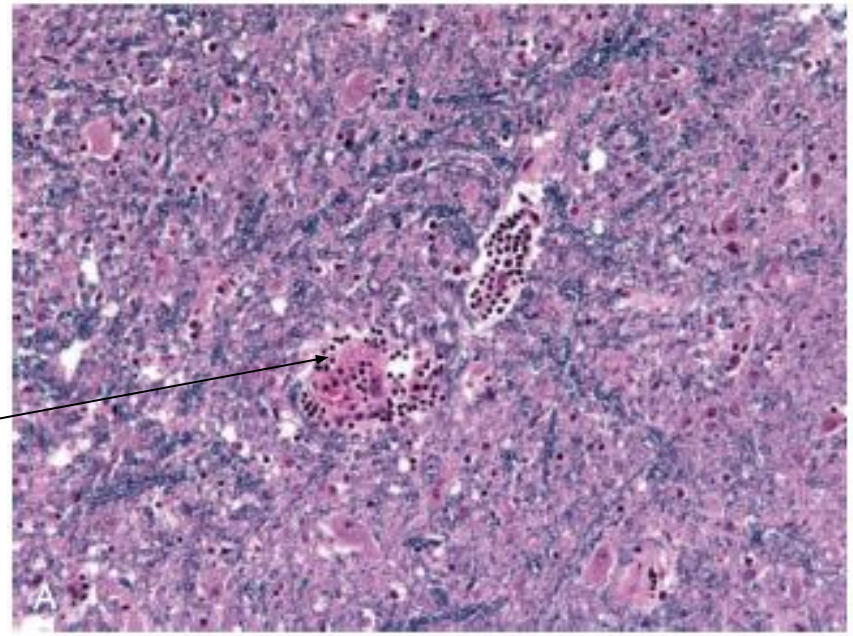
Viral encephalitis, general

- A parenchymal infection of the brain that is almost invariably associated with meningeal inflammation (*meningoencephalitis*)
- The most characteristic histologic features are perivascular and parenchymal mononuclear cell infiltrates, microglial nodules, and neuronophagia (whatever the virus type)
- Certain viruses also form characteristic inclusion bodies
- The nervous system is especially susceptible to certain viruses (rabies and polio)

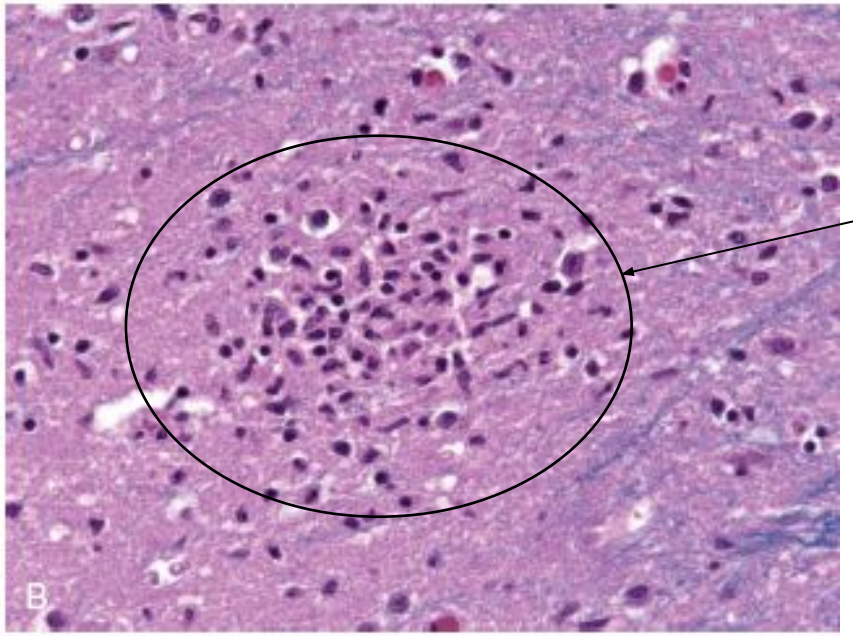
Viral encephalitis, general, cont'd

- Some viruses especially infect certain cell types
- Some other viruses especially affect certain regions, e.g., medial temporal lobes, or the limbic system that lie along the viral route of entry
- Intrauterine viral infection following transplacental spread of rubella and CMV may cause destructive lesions, and Zika virus causes developmental abnormalities of the brain
- In addition to direct infection of the nervous system, the CNS also can be injured by immune mechanisms after systemic viral infections

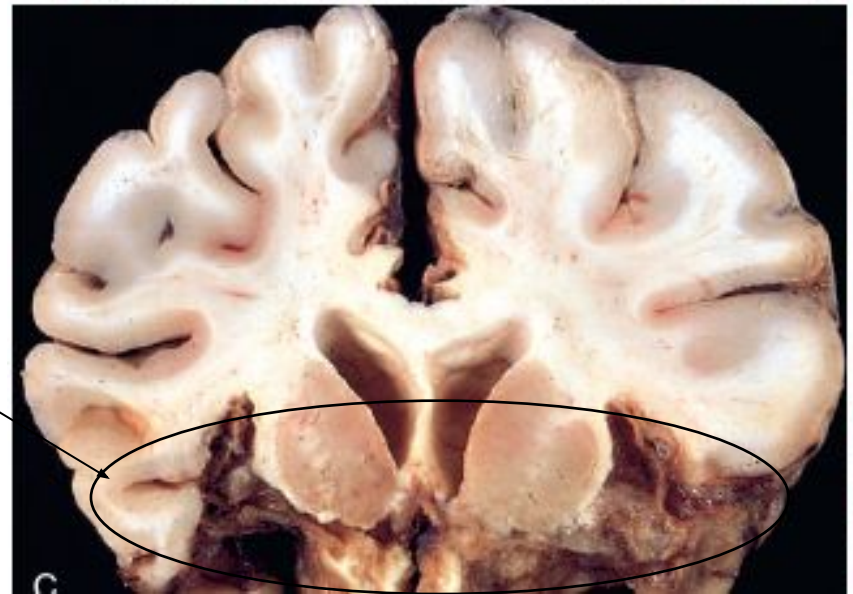
Viral meningoencephalitis, general morphology



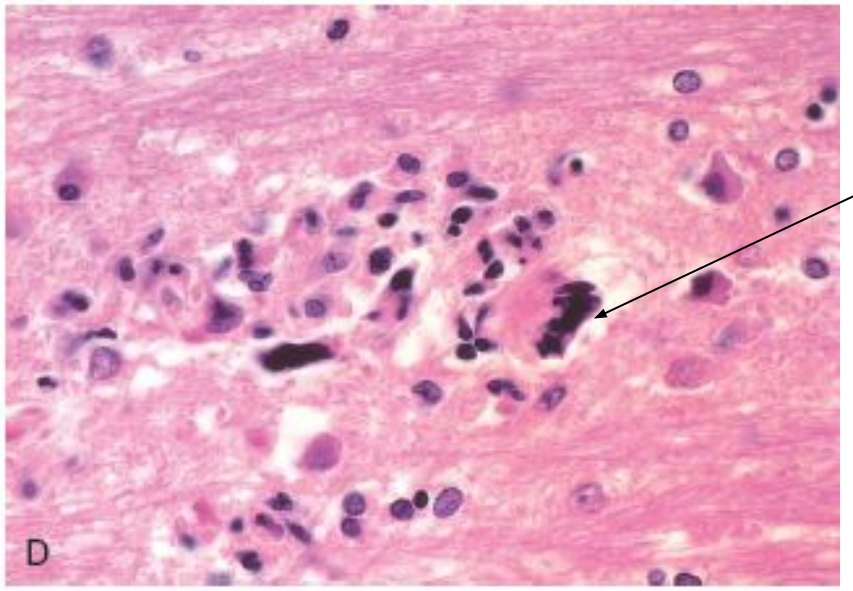
Perivascular cuffing by lymphocytes



Microglial nodule



Destruction of parenchyma



Microglial nodule …including multinucleated Giant cells

Arboviruses

- Usually epidemic in certain tropical areas
- Serious morbidity and high mortality
- Of the common types: Eastern and Western equine encephalitis and West Nile virus infection (in western hemisphere)
- Generalized neurologic symptoms, such as seizures, confusion, delirium, and stupor or coma, as well as focal signs, such as reflex asymmetry and ocular palsies.
- CSF:

-slightly elevated pressure

-early neutrophilic pleocytosis that rapidly converts to a lymphocytosis

-protein concentration is elevated, but the glucose is normal

Herpes viruses

- Regarding HSV-1
  -At any age group but is most common in children and young adults
  -Alterations in mood, memory, and behavior, reflecting involvement of the frontal and temporal lobes

Nuclear inclusions

- TLR3 deficiency…recurrent herpetic encephalitis

- HSV-2 also affects the nervous system, usually in the form of meningitis in adults
  …can cause disseminated severe encephalitis in newborns of women that have active genital disease (normal delivery)

- Varicella-zoster virus (VZV)
  …chickenpox: usually no evidence of neurological involvement
  …latent infection in neurons of dorsal root ganglia
    …reactivation: shingles in 1 or few dermatomes…usually self-limited
    …may cause persistent post-herpetic neuralgia
    …may cause granulomatous arteritis with infarctions
    …may cause encephalitis in the immunocompromized

Cytomegalovirus (CMV)

Nuclear and cytoplasmic inclusions

- Fetuses and the immunocompromized
- All cells within the CNS (neurons, glial cells, ependyma, and endothelium) are susceptible to infection
- Periventricular necrosis…then microcephaly with periventricular calcification
- In adults: subacute, also more in periventricular location

Poliovirus

- An enterovirus
- Most often causes a subclinical or mild gastroenteritis
- In a small fraction of cases, it secondarily invades the nervous system and damages motor neurons in the spinal cord and brain stem (paralytic poliomyelitis)
- Flaccid paralysis with muscle wasting and hyporeflexia in the corresponding region of the body
- Death may occur due to respiratory muscle paralysis
- Post-polio syndrome of weakness in the same distribution may occur 25-35 years after initial illness

Rabies virus

- Incubation period: 9-90 days
- Remember:

  -Dogs, some bat species exposure (even without bite documentation), others

  -paresthesia at site of bite is the earliest symptom
- Initially with nonspecific symptoms of malaise, headache, and fever

  …then extraordinary CNS excitability
- The slightest touch is painful
- Violent motor responses progressing to convulsions
- Contracture of the pharyngeal musculature may create an aversion to swallowing even water (hydrophobia)
- Mania
- Stupor progressing to coma and eventually death, typically from respiratory failure.

Negri bodies

HIV

- CNS is commonly involved in AIDS

- Direct effect (HIV encephalitis) or by opportunistic infections and primary CNS lymphoma

- HAART decreased the incidence of neurological involvement but still there is a problem called:
  *HIV-associated neurocognitive disorder (HAND)
  …ranging from mild to full-blown dementia
  …infection of microglial cells + an innate immune response
  …HIV-derived proteins + cytokines will cause the damage

- 10% of the initial presentation of HIV infection: aseptic meningitis…the virus can be isolated from CSF

- IRIS = immune reconstitution inflammatory syndrome can occur after initiating anti-HIV therapy
  …not fully understood mechanism
  …rapidly developing cognitive impairment and cerebral edema

- What do you know about PML?

Prion diseases

- **The causative agent is an abnormal form of a cellular protein**

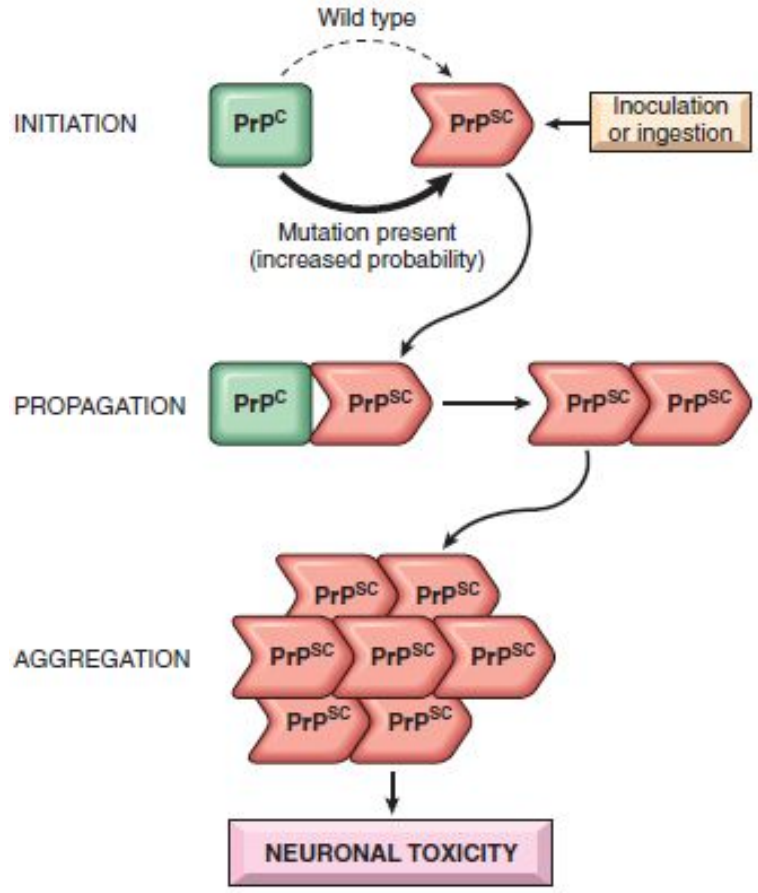
***Several diseases:**

- **Sporadic Creutzfeldt-Jakob disease (CJD)**…the most common
- **Familial CJD**
- **Iatrogenic CJD**
- **Animal diseases such as scrapie in sheep and bovine spongiform encephalopathy in cattle (“mad cow disease”)**
- **Variant Creutzfeldt-Jakob disease CJD (when mad cow disease is transmitted to human)**
- **Others**

Prion diseases, pathogenesis

- Prion protein (PrP)…the causative agent
- If a conformational change occurred from its normal shape (PrPc) to an abnormal conformation called PrPsc (sc for scrapie)
- PrP normally is rich in α-helices, but PrPsc has a high content of β-sheets

  …so it becomes resistant to proteolysis (hence an alternative term for the pathogenic form, PrPres—i.e., protease-resistant)



CJD

Spongiform transformation of the cerebral cortex and deep gray
matter structures…the characteristic microscopic feature

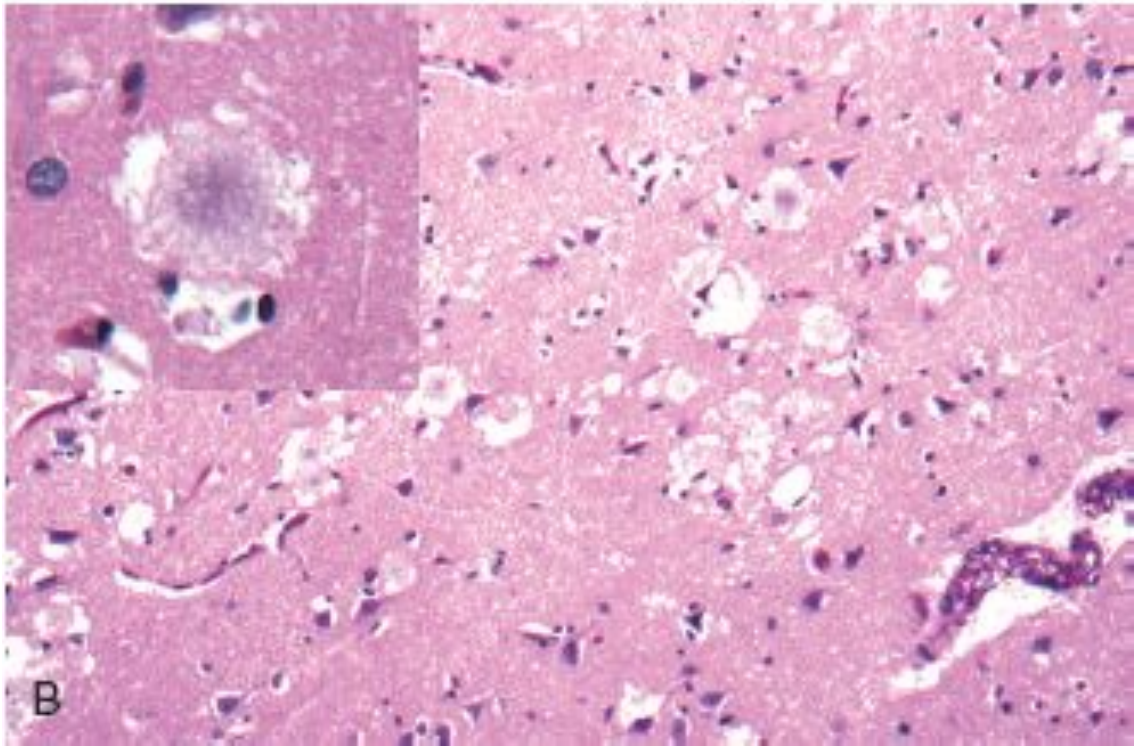
- A rapidly progressive dementing illness
- First onset of subtle changes in memory and behavior to death in only 7 months
- Sporadic in approximately 85% of cases and has a worldwide annual incidence of about 1 per million
  …usually older than 70 years
- Familial forms caused by mutations in *PRNP* may present in younger individuals

In advanced cases, there is severe neuronal loss, reactive gliosis, and sometimes expansion of the vacuolated areas into cystlike spaces ("status spongiosus")

*No inflammation
*Immunostaining for PrPsc is positive

Variant CJD

- Started to appear in 1995
- Younger age of patients
- Earlier behavioral manifestations
- Slower progression
- Amyloid deposition



Transmission?!

Thank You