Central Nervous System Infections

Infections of Central Nervous System

- ***Meningitis*** **refers to an inflammatory process of the leptomeninges and CSF within the subarachnoid space. Blood and CSF samples are crucial for diagnosis.**
- ***Meningoencephalitis*** **refers to inflammation of the meninges and brain parenchyma.**
- ***Encephalitis*** **refers to inflammation of the brain parenchyma.**

There are four principal routes by which infectious microbes enter the nervous system:

1. ***Hematogenous spread***
   - the most common means of entry
   - infectious agents enter through the arterial circulation
   - retrograde venous spread through anastomotic connections between veins of the face and cerebral circulation.
2. ***Direct implantation of microorganisms:***
   - is almost invariably traumatic or in congenital CNS malformation (Neural tube defect)
3. ***Local extension***
   - occurs secondary to an established infection in an air sinus, most often the mastoid or frontal, an infected tooth or middle ear
4. **Through the *peripheral nervous system into the CNS:***
   - E.g. rabies and herpes zoster.

Infections of Central Nervous System

- **Bacterial**
- **VIRAL**
- **FUNGAL**
  - **(including Candida albicans, Mucor, Aspergillus fumigatus, and Cryptococcus neoformans. In endemic areas, pathogens such as Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatitidis**
- **Protozoal diseases**
  - **(including malaria, toxoplasmosis, amebiasis, and trypanosomiasis), rickettsial infections (such as typhus and Rocky Mountain spotted fever), and metazoal diseases (especially cysticercosis and echinococcosis)**
- **Prion Diseases**

INFECTIOUS MENINGITIS

An inflammatory process of the leptomeninges and CSF within the subarachnoid space

Acute Pyogenic (Bacterial) Meningitis

ACUTE LYMPHOCYTIC (VIRAL) MENINGITIS

Chronic Meningitis: tuberculous, spirochetal, or cryptococcal

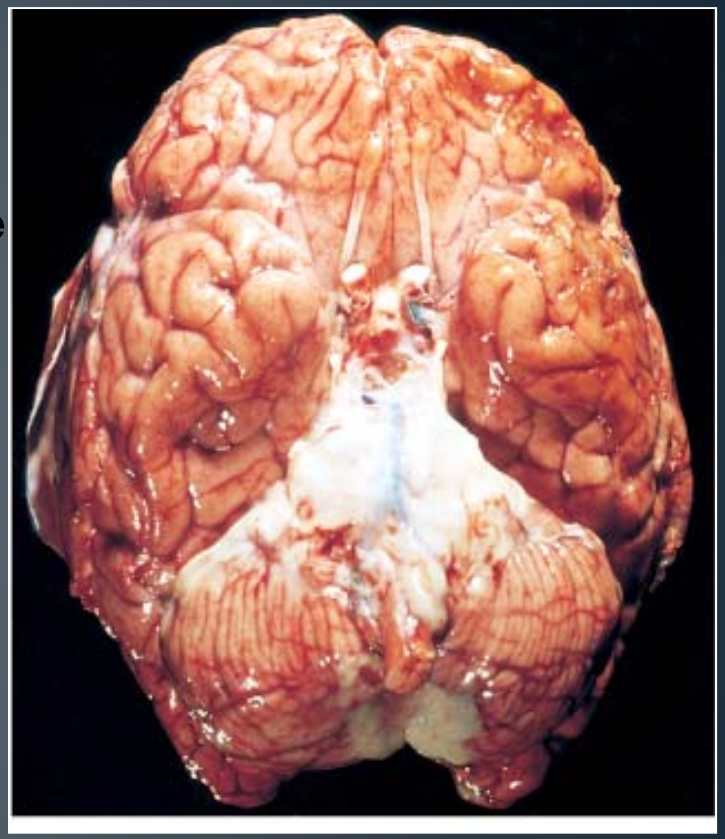
Acute Pyogenic (Bacterial) Meningitis

- **Important cause of morbidity and mortality at any age (Medical emergency)**
- **Pathogen reach CNS via blood after colonizing the nasopharynx**
- **The microorganisms vary with the age of the patient:**
  - **Neonates: *Escherichia coli* and the group *B streptococci***
  - **Old age: *Streptococcus pneumoniae* and *Listeria monocytogenes***
  - **Among adolescents and in young adults, *Neisseria meningitidis***
    - **immunization against *Haemophilus influenzae* has markedly reduced the incidence of meningitis associated with this organism**
- ***S. aureus* and gram negative rods are common after placement of surgical shunts**

Acute Pyogenic (Bacterial) Meningitis

Morphology

- **In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain**
  - **neutrophils fill the entire subarachnoid space in severely affected areas and are found predominantly around the leptomeningeal blood vessels in less severe cases.**



Pyogenic meningitis
CSF Findings in spinal tap

- **cloudy or frankly purulent CSF**
- **as many as 90,000 neutrophils /mm**
- **a raised protein level**
- **a markedly reduced glucose content**
- **Bacteria may be seen on a Gram stained smear or can be cultured**

Acute Pyogenic (Bacterial) Meningitis

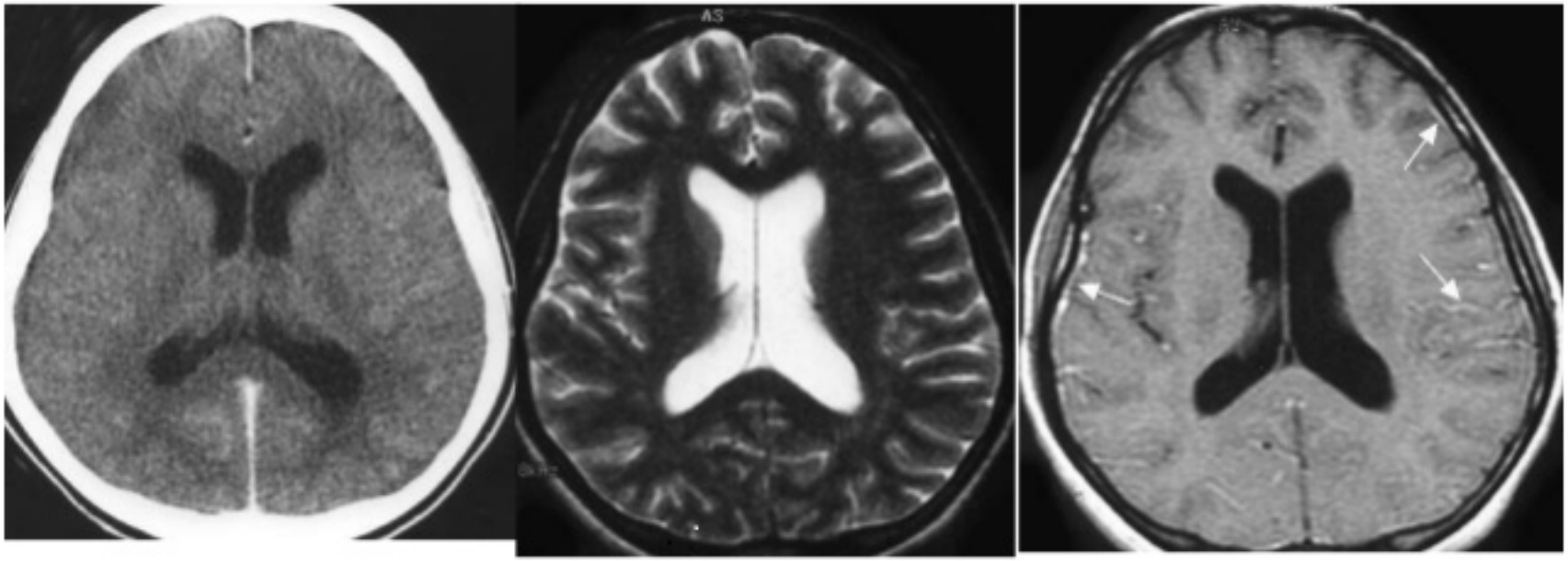
Clinical Features

- Systemic signs of infection superimposed on clinical evidence of meningeal irritation and neurologic impairment, including headache, photophobia, irritability, clouding of consciousness, and neck stiffness.
- Untreated, pyogenic meningitis can be fatal.
- Effective antimicrobial agents markedly reduce mortality associated with meningitis.

Acute Pyogenic (Bacterial) Meningitis

Complications

- **Phlebitis, that may also lead to venous occlusion and hemorrhagic infarction of the underlying brain**
- **Leptomeningeal fibrosis and consequent hydrocephalus**
- **Septicemia with hemorrhagic infarction of the adrenal glands and cutaneous petechiae (known as Waterhouse-Friderichsen syndrome, particularly common with meningococcal and pneumococcal meningitis)**
- **Focal cerebritis & seizures**
- **Cerebral abscess**
- **Cognitive deficit**
- **Deafness**



This axial nonenhanced computed tomography scan shows mild ventriculomegaly and sulcal effacement

Acute bacterial meningitis. This axial T2-weighted magnetic resonance image shows only mild ventriculomegaly.

This contrast-enhanced, axial T1-weighted magnetic resonance image shows leptomeningeal enhancement (*arrows*).

ACUTE LYMPHOCYTIC (VIRAL) MENINGITIS

ACUTE LYMPHOCYTIC (VIRAL) MENINGITIS

Acute Aseptic Meningitis

- Aseptic meningitis is a misnomer, but it is a clinical term referring to the absence of recognizable organisms in an illness with meningeal irritation, fever, and alterations of consciousness of relatively acute onset.
- It may be associated with encephalitis.
- The disease is caused by virus
- Echovirus, coxsackievirus, mumps virus and HIV.

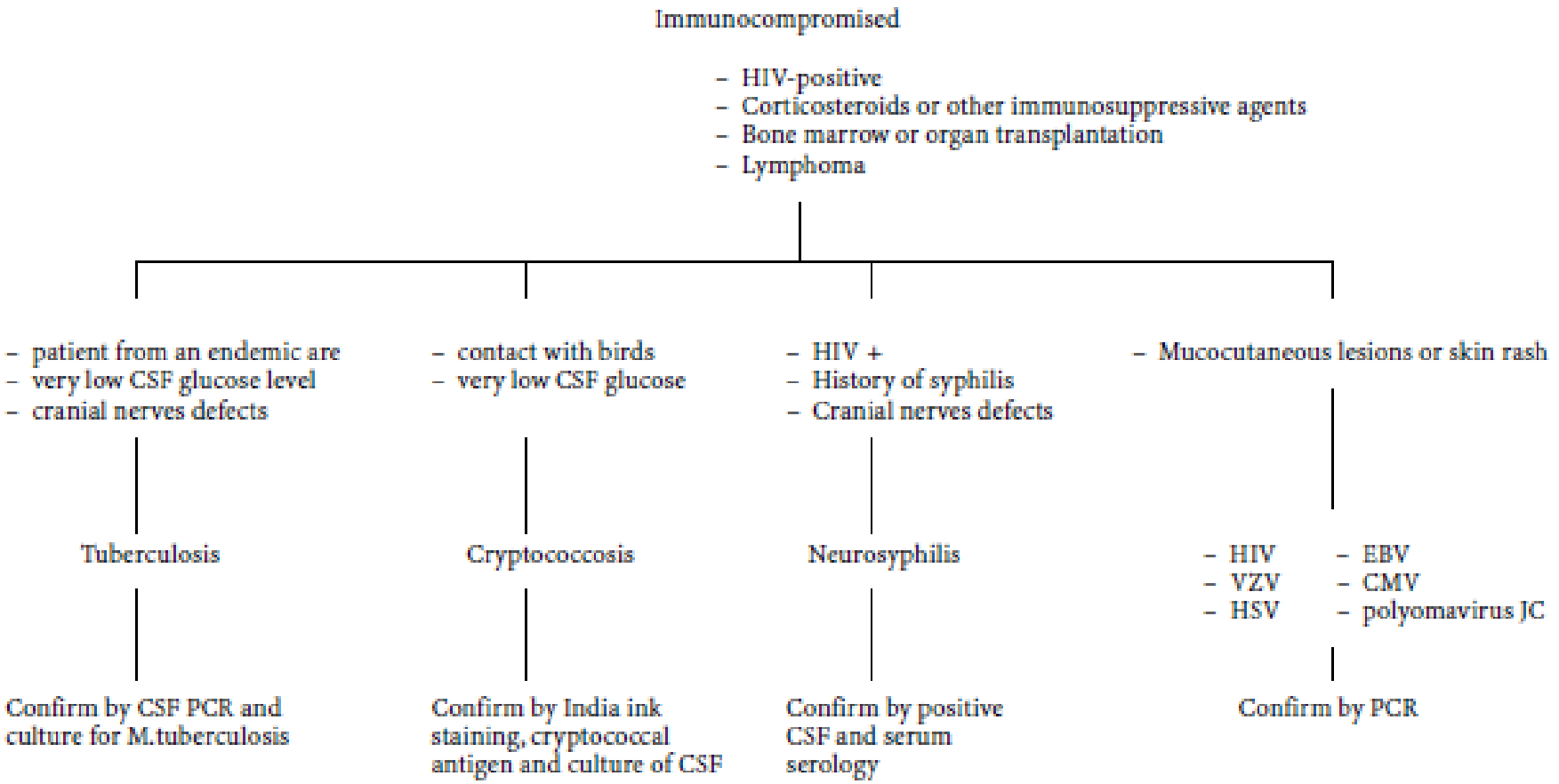
ACUTE LYMPHOCYTIC (VIRAL) MENINGITIS

- The clinical course is less fulminant than that of pyogenic meningitis, and the CSF findings also differ between the two conditions.
- CSF findings in aseptic meningitis:
  - predominant cells are lymphocte
  - the protein elevation is only moderate
  - the sugar content is nearly always normal
- The viral meningitides are usually self-limiting and are treated symptomatically.

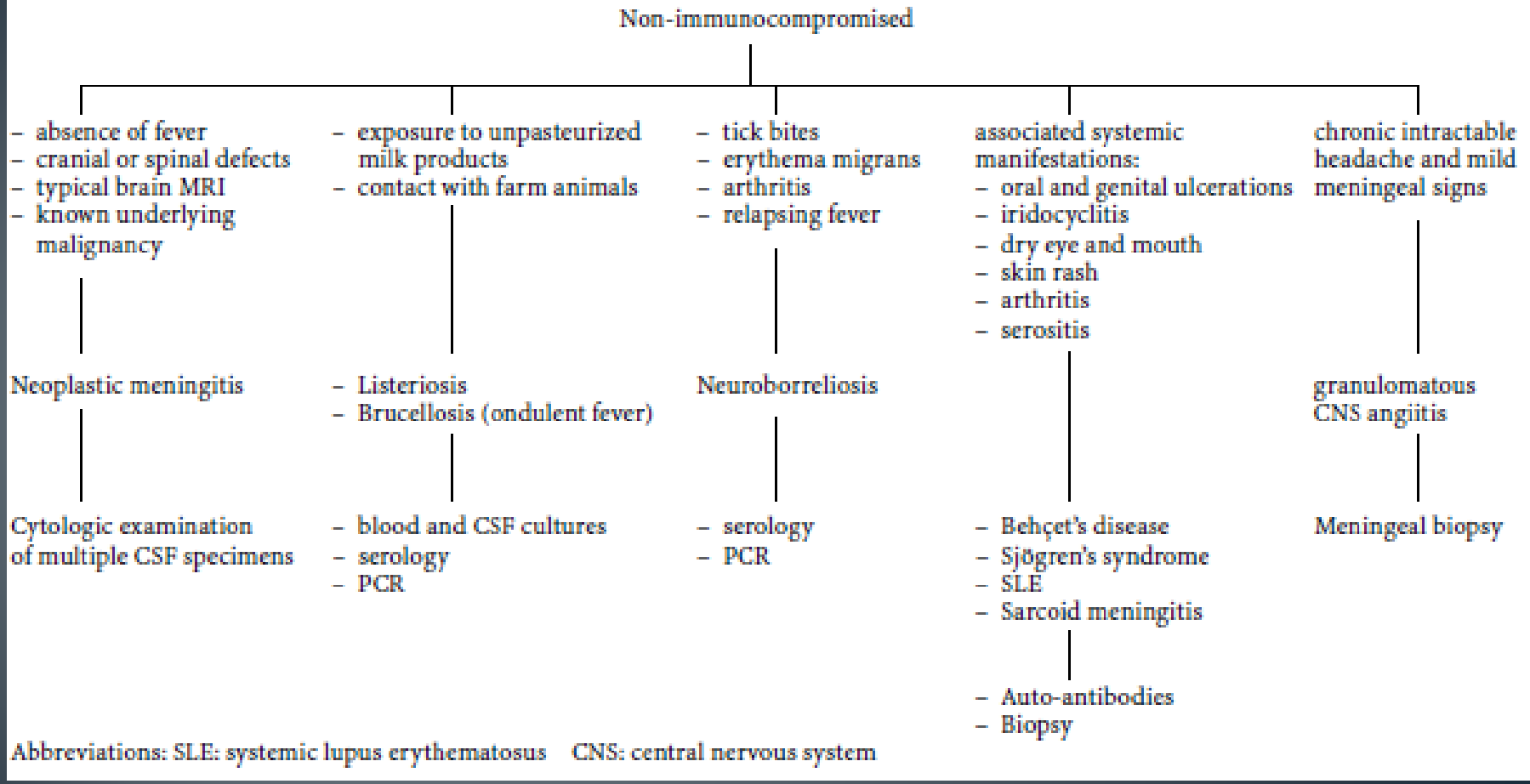
Chronic Meningitis

Bacterial: *Tuberculosis and Neurosyphilis*

Fungal: *Cryptococcus neoformans (in HIV Pt.)*



Abbreviations: PCR: polymerase chain reaction
CSF: cerebral spinal fluid
CMV: cytomegalovirus
HSV: herpes simplex virus
EBV: Epstein Barr virus
VZV: varicella zoster virus


Non-immunocompromised
– absence of fever
– cranial or spinal defects
– typical brain MRI
– known underlying malignancy
Neoplastic meningitis
Cytologic examination of multiple CSF specimens
– exposure to unpasteurized milk products
– contact with farm animals
– Listeriosis
– Brucellosis (ondulent fever)
– blood and CSF cultures
– serology
– PCR
– tick bites
– erythema migrans
– arthritis
– relapsing fever
Neuroborreliosis
– serology
– PCR
associated systemic manifestations:
– oral and genital ulcerations
– iridocyclitis
– dry eye and mouth
– skin rash
– arthritis
– serositis
– Behçet's disease
– Sjögren's syndrome
– SLE
– Sarcoid meningitis
– Auto-antibodies
– Biopsy
chronic intractable headache and mild meningeal signs
granulomatous CNS angiitis
Meningeal biopsy
Abbreviations: SLE: systemic lupus erythematosus CNS: central nervous system

INFECTION OF BRAIN PARENCHYMA

Brain Abscess
Tuberculosis
Toxoplasmosis
Viral Encephalitis
Spongiform Encephalitis

Brain Abscess

Brain Abscess

- may arise by: 1. direct implantation of organisms
  2. local extension (mastoiditis, paranasal sinusitis)
  3. hematogenous spread (from the heart, lungs, or distal bones or after tooth extraction)

- Streptococci and staphylococci are the most common organisms in non immunosuppressed populations

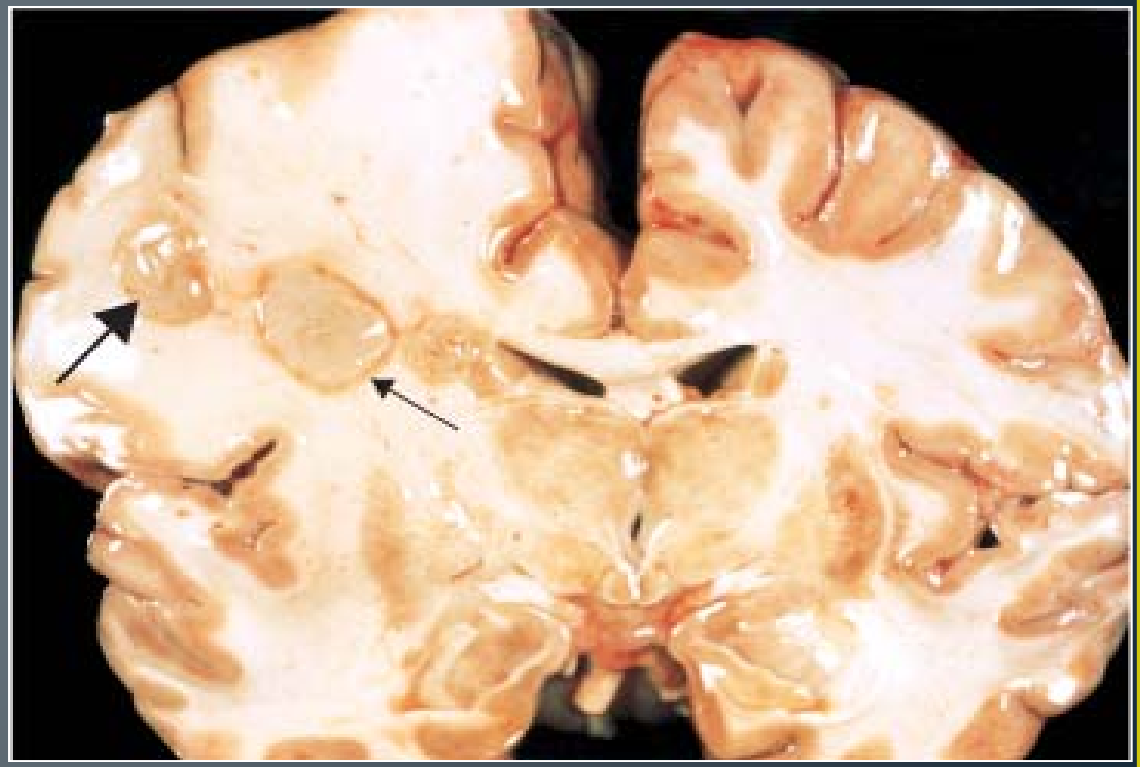
- Predisposing conditions:
  - acute bacterial endocarditis (usually give multiple microabscess)
  - cyanotic congenital heart disease in which there is a right-to-left shunt
  - loss of pulmonary filtration of organisms (e.g. chronic pulmonary sepsis, bronchiectasis)

Brain Abscess

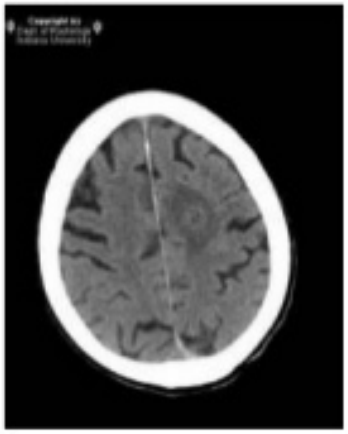
- Most common on cerebral hemispheres
- Liquefactive necrosis

- Clinical presentation: progressive focal deficits in addition to the general signs of raised intracranial pressure

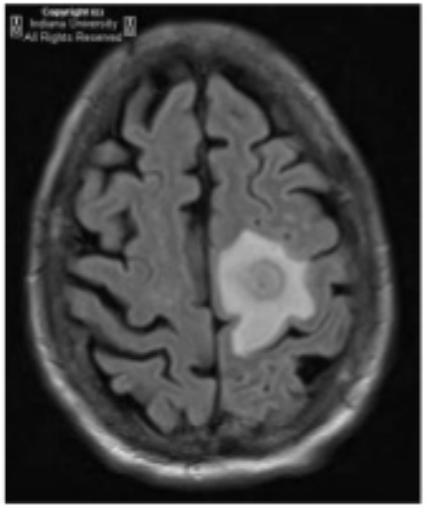
- Complications:
  - Herniation
  - Rupture of abscess into subarachnoid space or ventricle

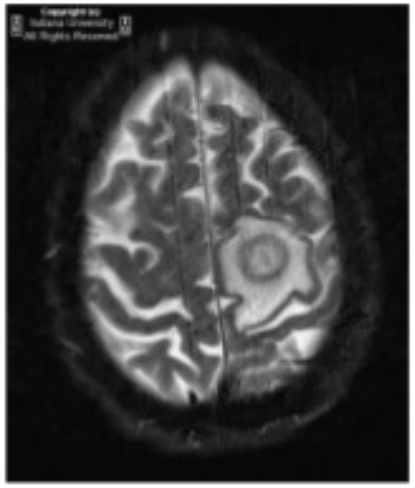


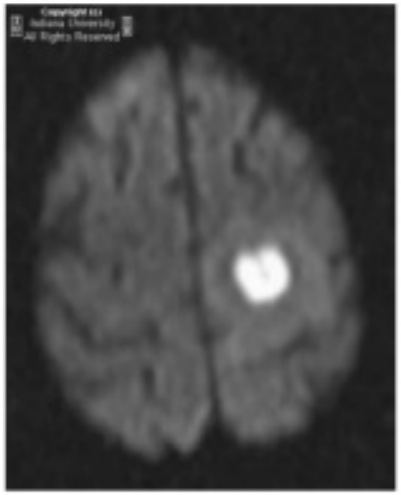
Brain Abscess CT and MRI



Intra-axial mass, located in the posterior left frontal lobe, in the superior frontal gyrus just anterior to the precentral gyrus. There is surrounding vasogenic edema, which expands the left precentral gyrus. Mass shows a well-defined rim on MR, somewhat irregular, consistent with a capsule. Central portion shows pronounced diffusion restriction.







Tuberculosis
Toxoplasmosis

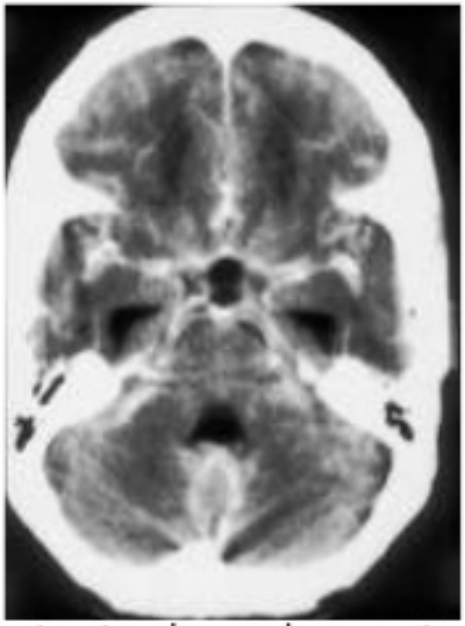
Tuberculosis

- **Tuberculoma** well-circumscribed intraparenchymal mass
- may be associated with meningitis.
- A tuberculoma may be up to several centimeters in diameter, causing significant mass effect.
- **Microscopic examination:**
  - there is usually a central core of caseous necrosis surrounded by a typical tuberculous granulomatous reaction

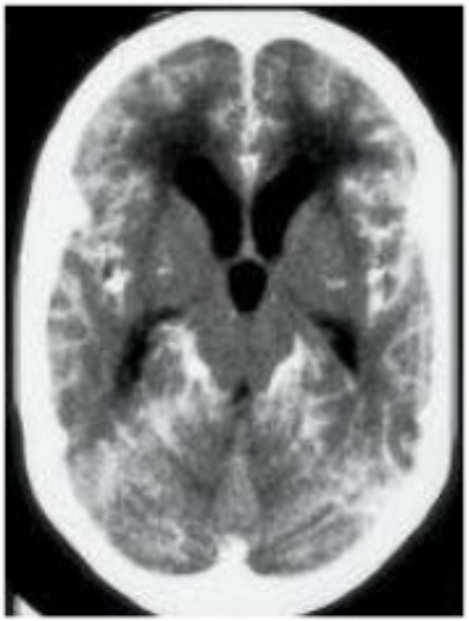
CSF in TB

- There is only a moderate increase in cellularity of the CSF (pleocytosis) made up of mononuclear cells, or a mixture of PMNs and mononuclear cells
- The protein level is elevated
- The glucose content typically is moderately reduced or normal

TB Meningitis



Contrast-enhanced computed tomography (CT) scan in a patient with tuberculous meningitis demonstrating marked enhancement in the basal cistern and meninges, with dilatation of the ventricles.

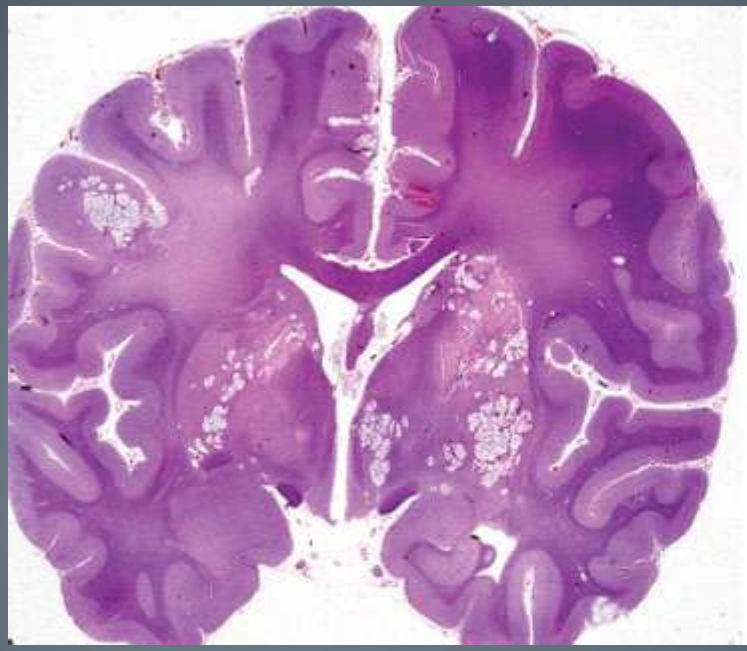


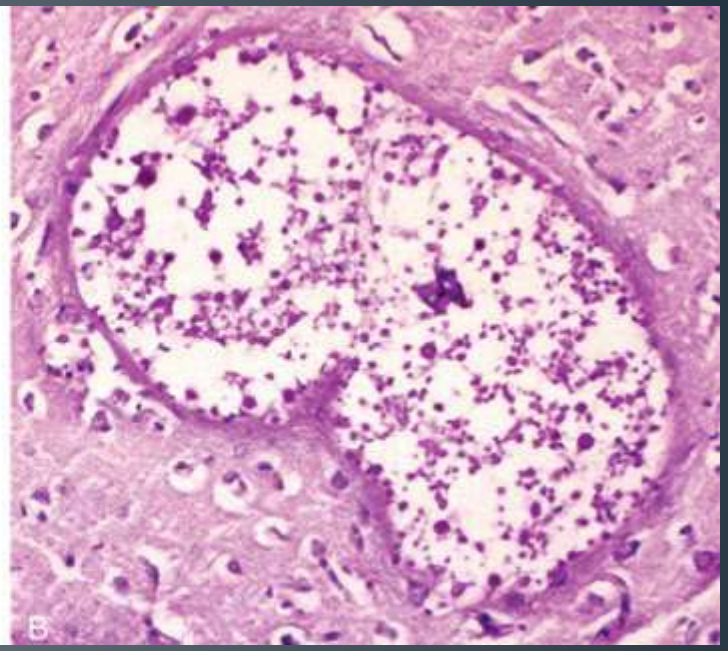
Contrast-enhanced computed tomography (CT) scan of a child with tuberculous meningitis demonstrating acute hydrocephalus and meningeal enhancement.

Fungal infection

- ***Candida albicans, Mucor, Aspergillus fumigatus, and Cryptococcus neoformans are*** **the most common fungi that can cause encephalitis**
- ***Parenchymal invasion, usually in the form of*** **granulomas or abscesses**
- **often coexists with a meningitis**

Cryptococcal meningitis and meningoencephalitis

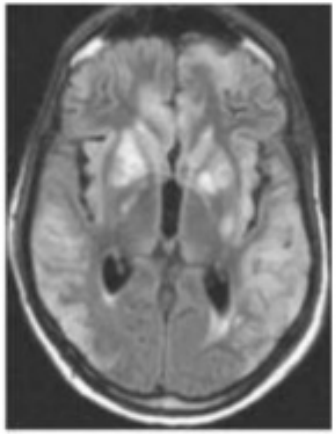




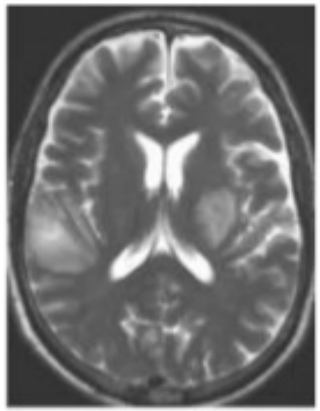
– Observed often in association with AIDS. It can be fulminant and fatal in as little as 2 weeks, or indolent, or it can evolve over months or years

Fungal Infections

On MR images, widened perivascular spaces appear as multiple, bilateral, small round-to-oval lesions in the basal ganglia and midbrain. These show slightly higher signal than cerebrospinal fluid on T1W images and high signal on T2W images.



Cryptococcus neoformans infection of the

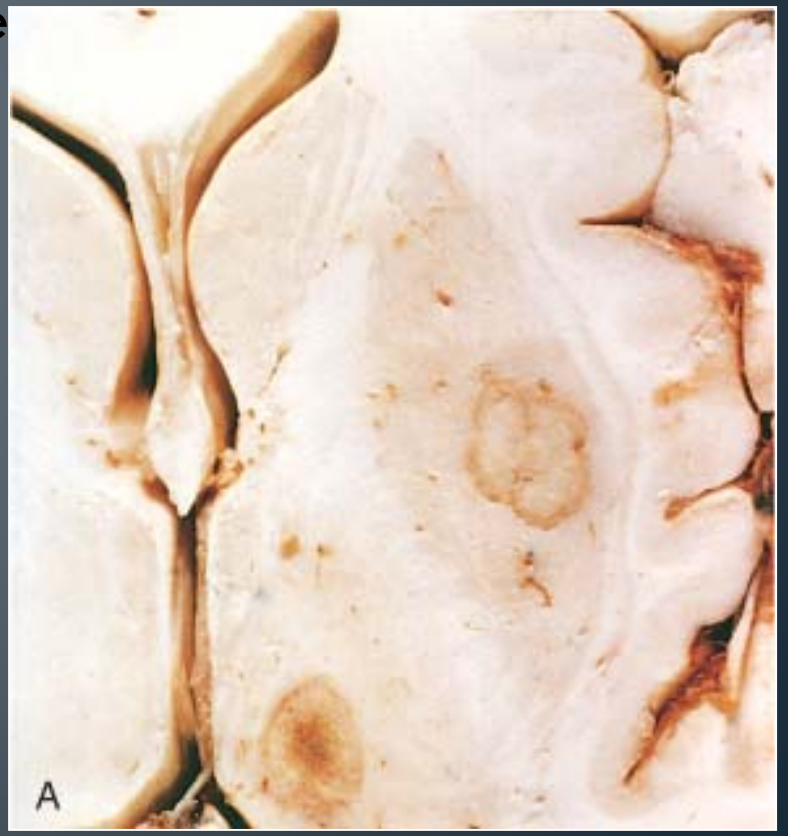


Cerebral aspergillosis in an

Toxoplasmosis

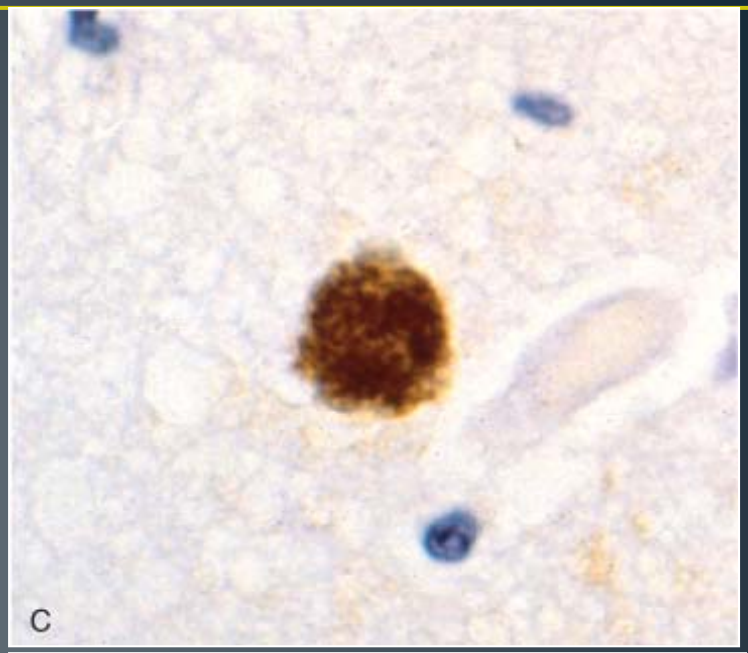
- Infection of the brain by *Toxoplasma gondii* is one of the most common causes of neurologic symptoms and morbidity in patients with AIDS.
- The clinical symptoms are subacute

Toxoplasma abscesses in the putamen and thalamus (multiple abscesses in gray matter

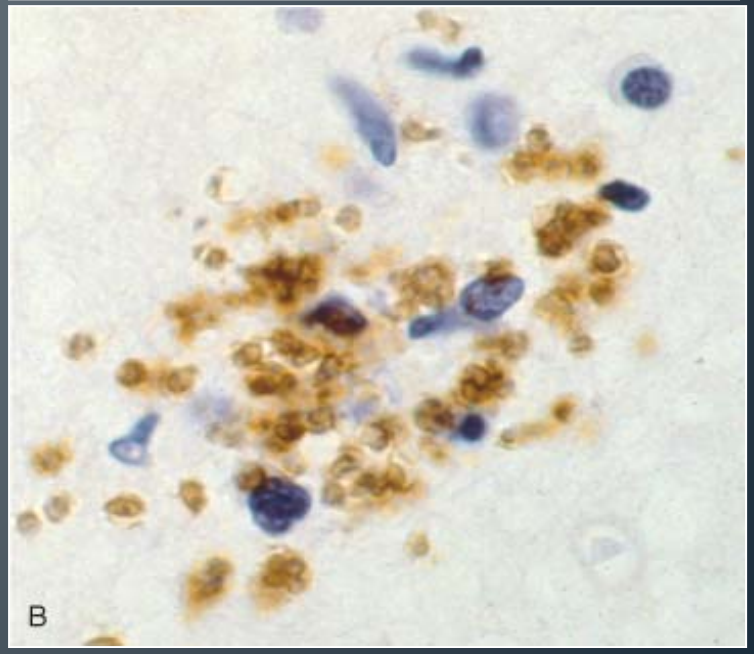


Toxoplasmosis

- *Toxoplasma* pseudocyst with bradyzoites highlighted by immunostaining

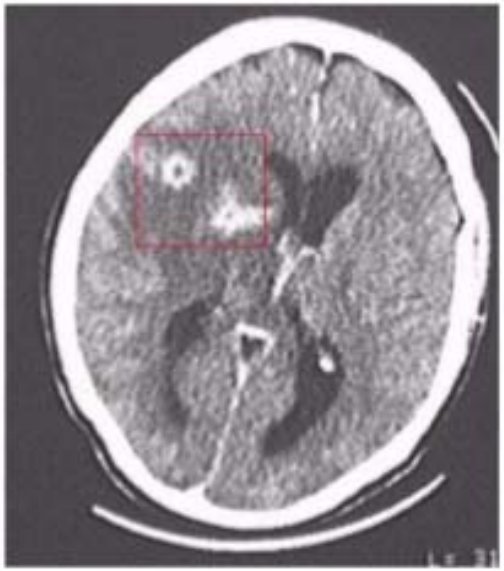


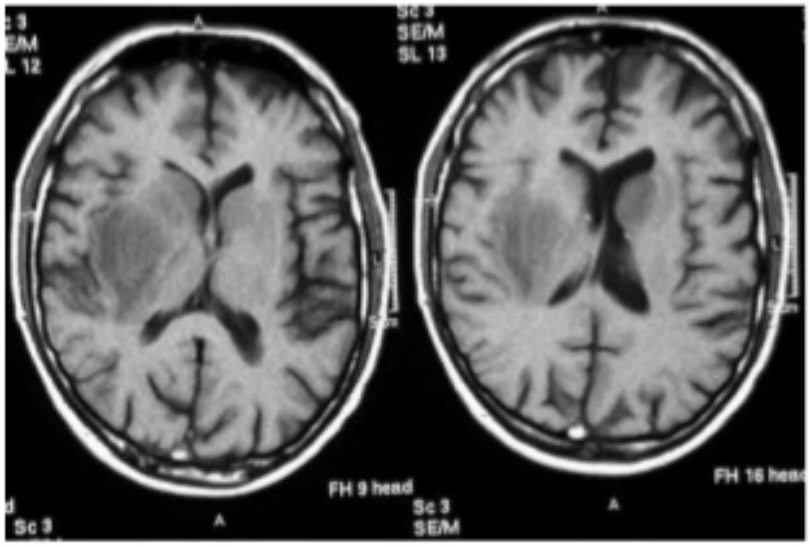
Free tachyzoites demonstrated by immunostaining



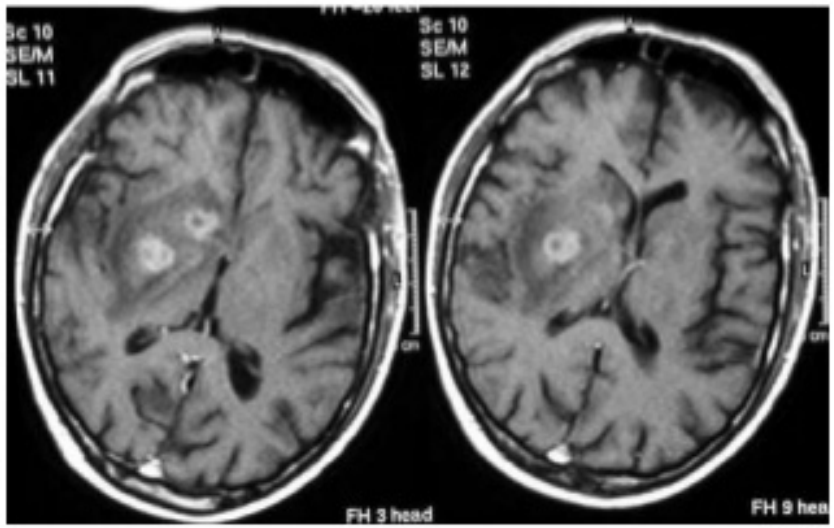
CNS Toxoplasmosis

- CT- The typical lesion is an hypodense focal area with **ring contrast-enhancement** and edema





Nonenhanced T1-weighted images in a patient infected with human immunodeficiency virus and cerebral toxoplasmosis. These images show hypointense, asymmetrical, bilateral periventricular/basal ganglial lesions.



T1-weighted axial gadolinium-enhanced magnetic resonance images. These images show 2 complex**, ring-enhancing** lesions in the basal ganglia on the right, with surrounding notable white matter edema. This appearance is typical of central nervous system toxoplasmosis, which has **the propensity for involvement of the basal ganglia.**

VIRAL ENCEPHALITIS

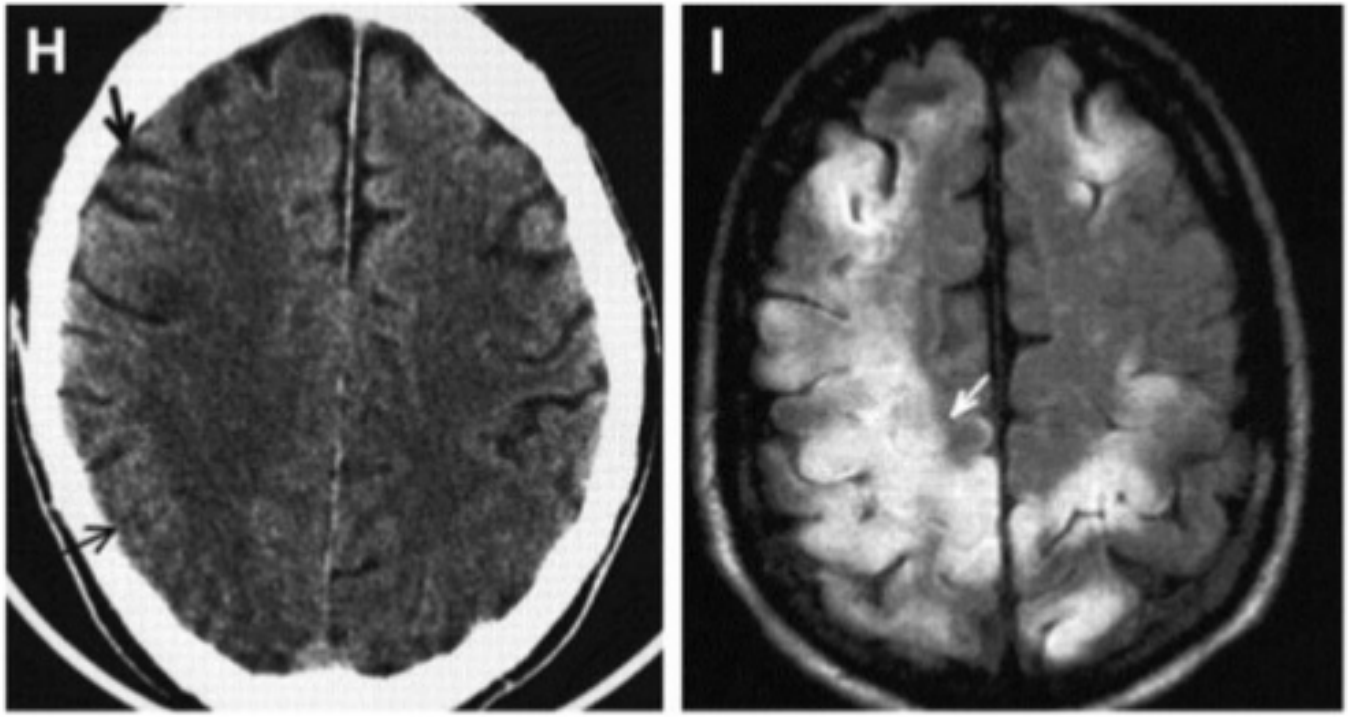
VIRAL ENCEPHALITIS

- The most common cause of encephalitis
- Almost invariably associated with meningeal inflammation
- General features:
  - Perivascular inflammatory infiltrates(mononuclear cells)
  - Microglial nodules
  - Inclusion bodies

VIRAL ENCEPHALITIS

- Arthropod-Borne Viral Encephalitis (Arboviruses)
- *Herpes Simplex Virus Type 1 (HSV-1)*
- *Varicella-Zoster Virus (Herpes Zoster)*
- *Cytomegalovirus*
- *Poliomyelitis*
- *Rabies*
- Subacute sclerosing panencephalitis
- HIV encephalitis
- *Progressive Multifocal Leukoencephalopathy*

Viral Encephalitis



- Brain imaging is frequently normal in viral encephalitis. Occasionally, nonspecific changes consist of either sulcal effacement (H) (thin arrow), compared with normal sulcal spaces (thick arrow); or increased signal (I) (arrow), reflecting increased water content in the mildly swollen brain of the same patient
- These changes developed in a patient with probable enterovirus encephalitis but can be produced by many viruses, as well as after head injury and in various metabolic encephalopathies.

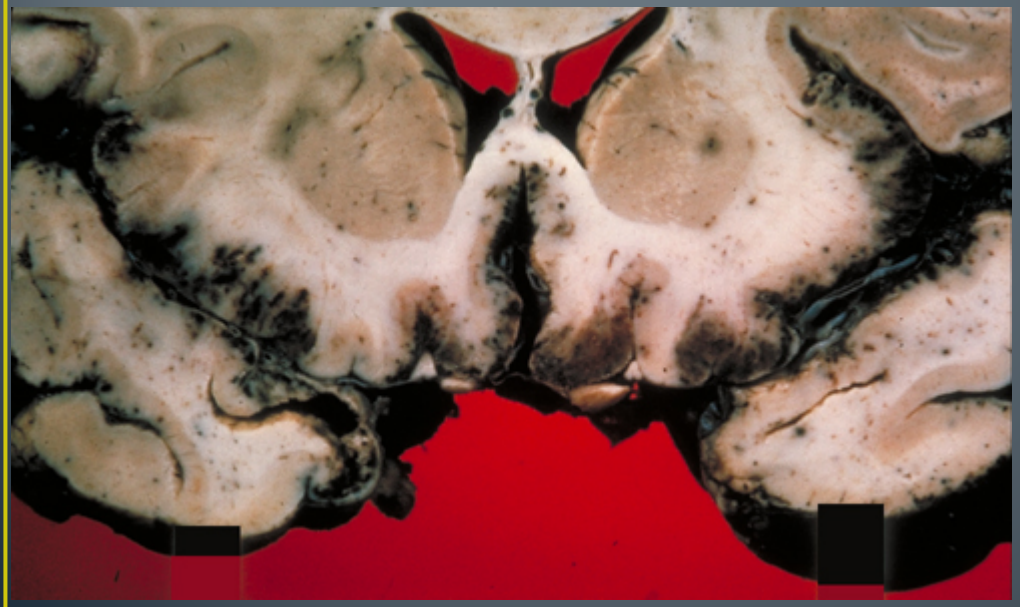
VIRAL ENCEPHALITIS

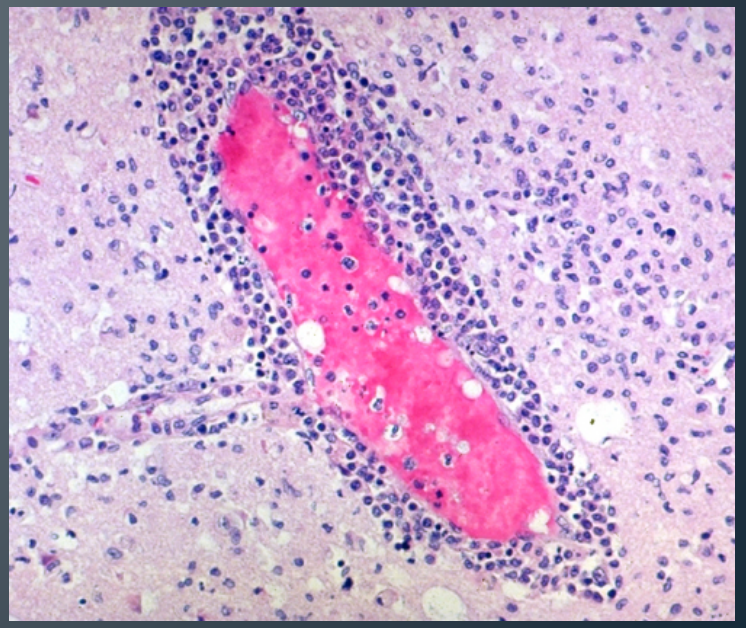
- The CSF Finding:
  - is usually colorless but with a slightly elevated pressure and, initially, a neutrophilic pleocytosis that rapidly converts to lymphocytes
  - the protein level is elevated
  - sugar content is normal

VIRAL ENCEPHALITIS

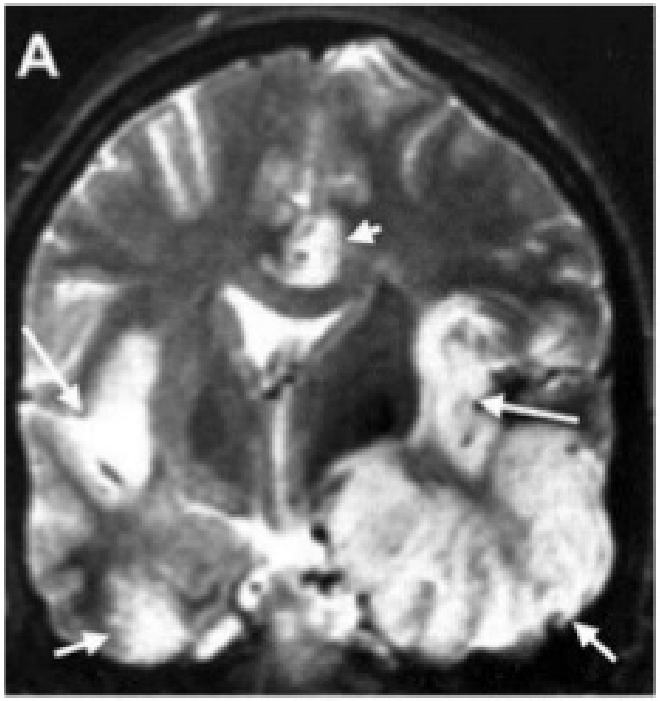
Herpes Simplex Virus Type 1 (HSV-1)

- HSV-1 produces an encephalitis that occurs in any age group but is most common in children and young adults.
- Clinical symptoms: alterations in mood, memory, and behavior





Herpes simplex virus encephalitis



. Abnormal signal and edema in the left temporal lobe (short bottom arrow), insula (long arrow) and cingulate gyrus (arrowhead), sparing deep nuclear structures with mass effect compressing the left lateral ventricle and uncal herniation; also not increased signal in the right inferomedial temporal lobe (short bottom arrow) and insular cortex (long arrow).

HIV encephalitis (Subacute Encephalitis)

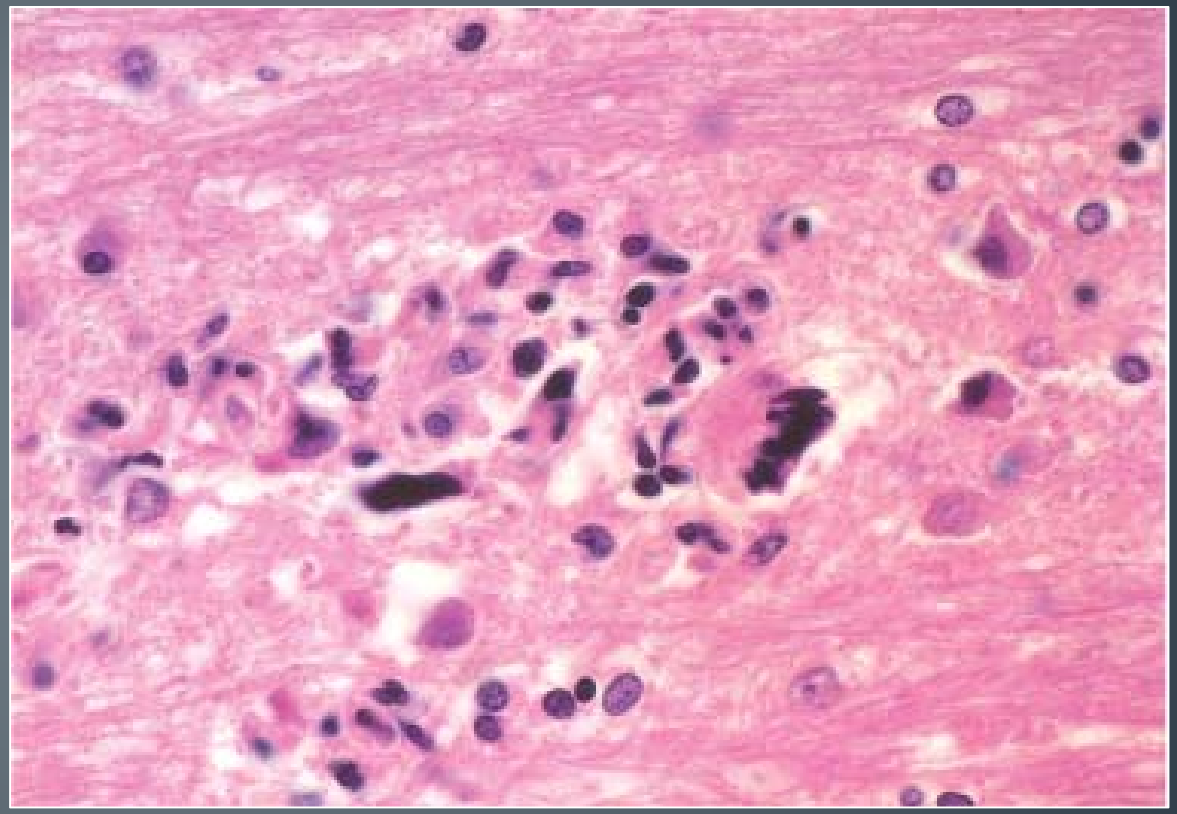
- Patients affected with this remarkable neurologic disorder with dementia referred to as AIDS-dementia complex (ADC)
- The dementia begins insidiously, with mental slowing, memory loss, and mood disturbances, such as apathy and depression.
- Motor abnormalities, ataxia, bladder and bowel incontinence, and seizures can also be present.

HIV encephalitis (Subacute Encephalitis)

Morphology

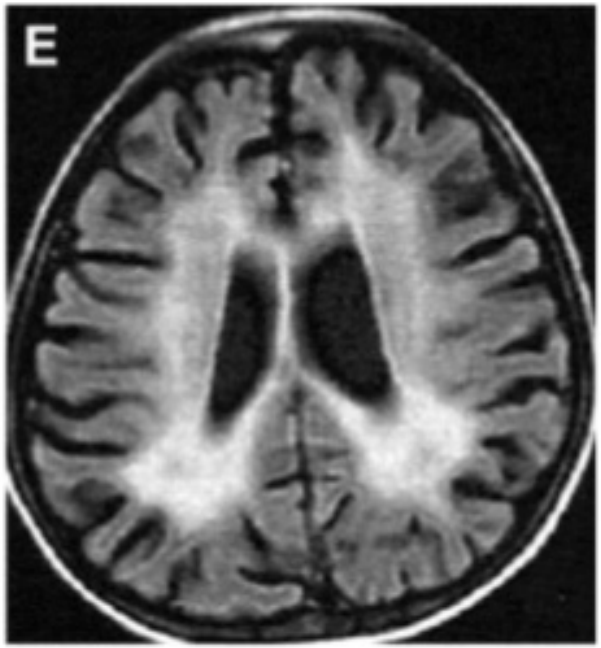
- On macroscopic examination
  - the meninges are clear, and there is some ventricular dilation with sulcal widening but normal cortical thickness.
- Microscopically:
  - a chronic inflammatory reaction with widely distributed infiltrates of microglial nodules, sometimes with associated foci of tissue necrosis and reactive gliosis

HIV encephalitis (Subacute Encephalitis)



An important component of the microglial nodule is the macrophage-derived **multinucleated giant cell**

HIV infection of CNS

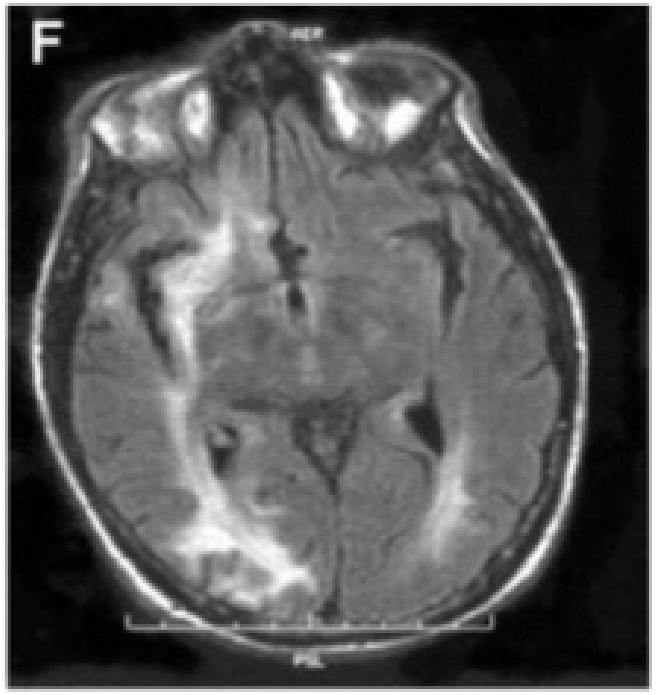


- Characteristic abnormalities are brain atrophy and diffuse white matter attenuation

Progressive Multifocal Leukoencephalopathy

- is a viral encephalitis caused by the JC polyomavirus
- demyelination is its principal pathologic effect because the virus preferentially infects oligodendrocytes
- occurs almost invariably in immunosuppressed individuals in various clinical settings, including:
  - chronic lymphoproliferative or myeloproliferative illnesses
  - immunosuppressive chemotherapy
  - granulomatous diseases
  - AIDS

JCV infection- PMLE



- Progressive Multifocal Leuco Encephalopathy
- Typical multifocal and confluent subcortical nonenhancing white matter hyperintensities extending to the cortical gray matter.

Progressive Multifocal Leukoencephalopathy

- **Morphology**
  - The lesions consist of patches of irregular destruction of the white matter

Transmissible Spongiform Encephalopathies

(Prion Diseases)

Transmissible Spongiform Encephalopathies (Prion Diseases)

- group of diseases includes:
  - in humans:
    - Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia, and kuru
  - in sheep and goats: scrapie
  - mink transmissible encephalopathy
  - chronic wasting disease of deer and elk
  - bovine spongiform encephalopathy (BSE)

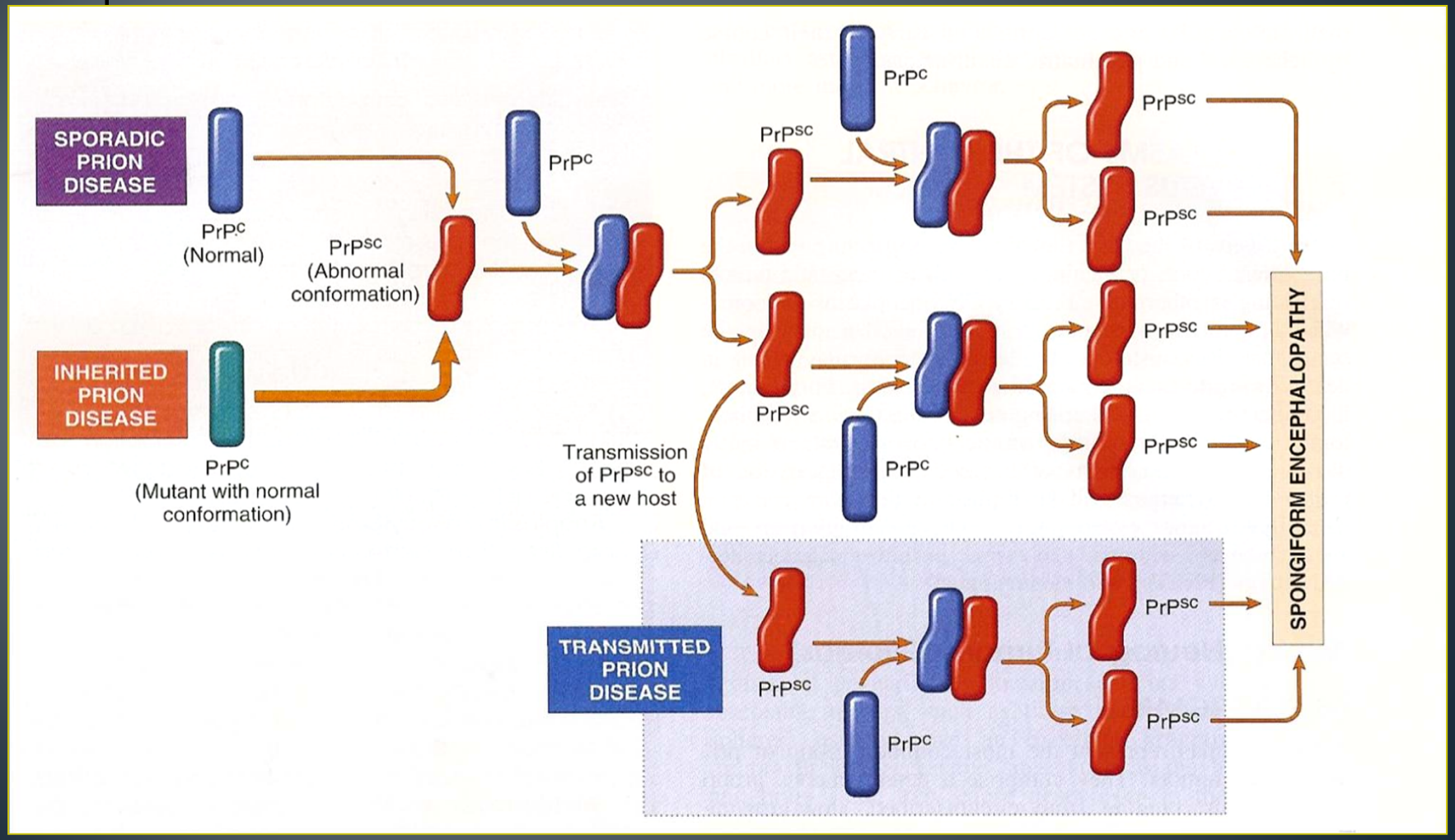
They are all associated with abnormal forms of a specific protein, termed prion protein (PrP),

Pathogenesis and Molecular Genetics of Prion Diseases

- Disease occurs when the prion protein undergoes a conformational change from its normal α-helix-containing isoform (PrP^{c}) to an abnormal β-pleated sheet isoform, usually termed either PrP^{sc} (for scrapie) or PrP_{res} (for protease resistant)
- The conformational change resulting in PrP^{sc} may occur spontaneously at an extremely low rate (resulting in sporadic cases) or at a higher rate if various mutations are present in PrP^{c}, such as occurs in familial forms of CJD and in GSS and fatal familial insomnia.
- PrP^{sc} then facilitates, in a cooperative fashion, comparable transformation of other PrP^{c} molecules

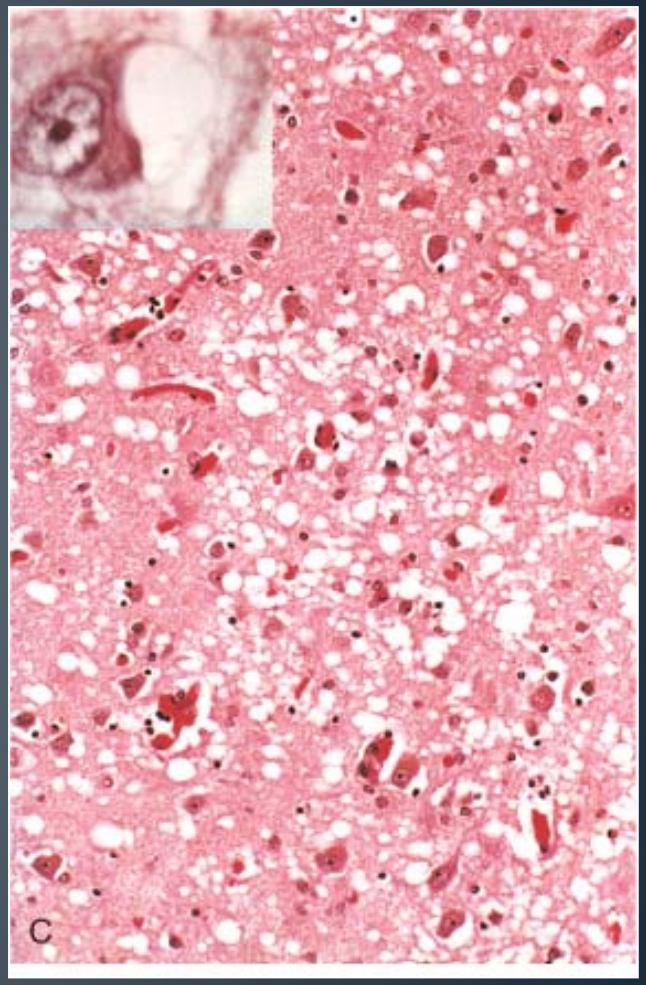
Molecular Genetics of Prion Diseases

- The infectious nature of PrP^{sc} molecules comes from this ability to disrupt the integrity of normal cellular components through conformational



Transmissible Spongiform Encephalopathies (Prion Diseases)

- **Morphology**
  - The pathognomonic finding is a **spongiform** transformation of the cerebral cortex and, often, deep gray matter structures (caudate, putamen)
  - In advanced cases, there is severe neuronal loss, reactive gliosis, and sometimes expansion of the vacuolated areas into cyst like spaces
  - No inflammatory infiltrate is present



- Accumulation of PrP^{sc} in neural tissue appears to be the cause of the pathology in these diseases but how this material causes the development of cytoplasmic vacuoles and eventual neuronal death is still unknown

Creutzfeldt-Jakob Disease

- a rare but well-characterized disease that manifests clinically as a rapidly progressive dementia and diffuse atrophy of the brain.
- It is primarily sporadic (about 85% of cases) in its occurrence, with a worldwide annual incidence of about 1 per million
- familial forms also exist
- The disease has a peak incidence in the seventh decade.
- There are well-established cases of iatrogenic transmission, notably by corneal transplantation, deep implantation of neural electrodes, and contaminated preparations of human growth hormone.

- The disease is uniformly fatal, with an average duration of only 7 months

Creutzfeldt-Jakob Disease

- Diagnosis of CJD with the CSF protein 14-3-3 assay. This test is not very sensitive (~50%) or specific (e.g., caused by subacute and acute neuronal injury, as in encephalitis, stroke, vasculitis and paraneoplastic limbic encephalitis). A negative test does not rule out the diagnosis, and a positive test supports the diagnosis but is not diagnostic.
- Diffusion-weighted abnormalities in the cerebral cortex and basal ganglia are fairly common in this disease, much more common than the classic EEG abnormality of diffuse delta slowing and periodic sharp waves.
-

Variant Creutzfeldt-Jakob Disease (vCJD)

- Starting in 1995, a series of cases with a CJD-like illness came to medical attention in the United Kingdom
- It has been linked to the ingestion of tissues from cattle with bovine spongioform encephalopathy
- The disease affected young adults with behavioral disorders and the neurologic syndrome progressed more slowly than in patients with other forms of CJD
- The neuropathological findings and molecular features of these new cases were similar to those of CJD

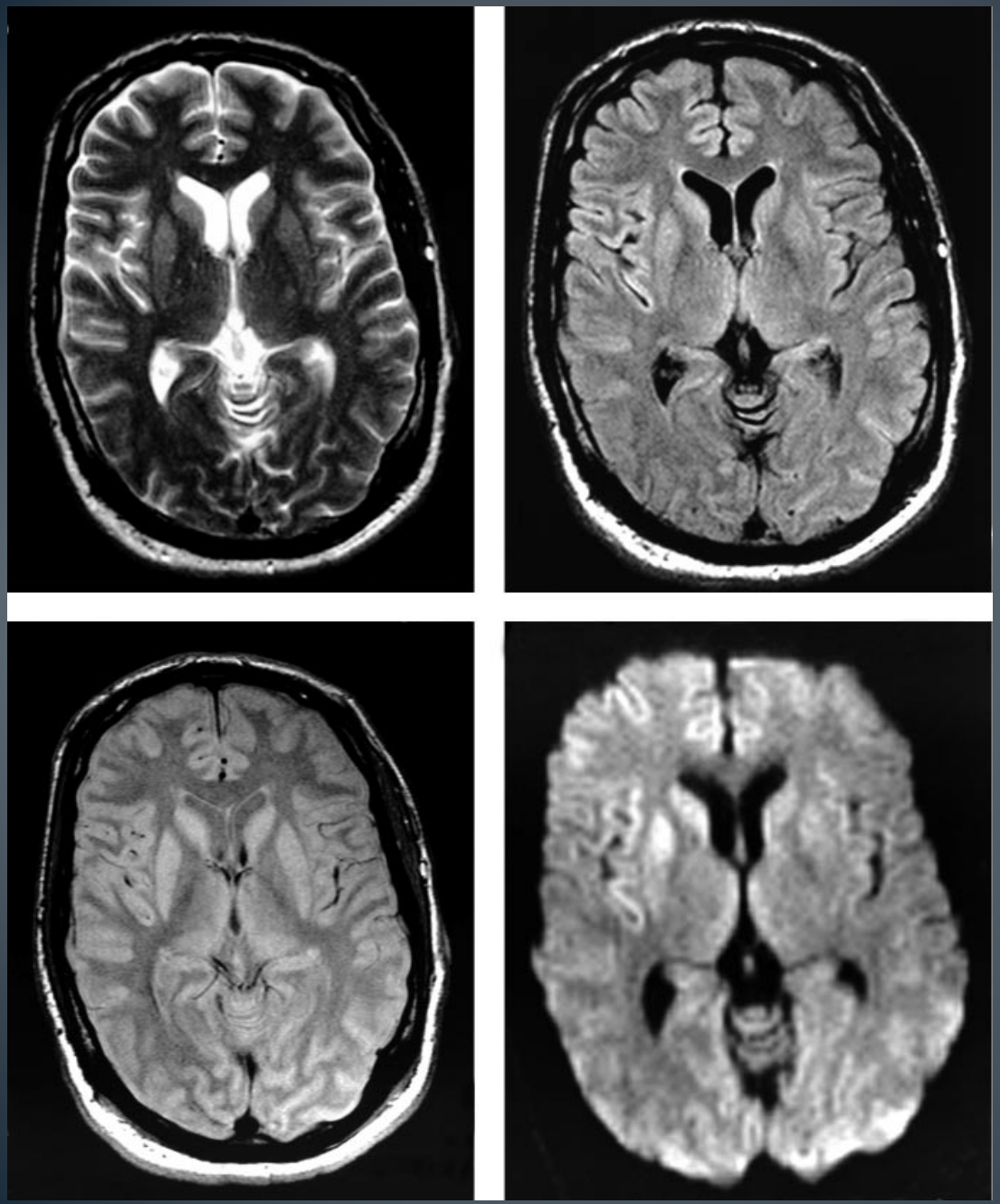
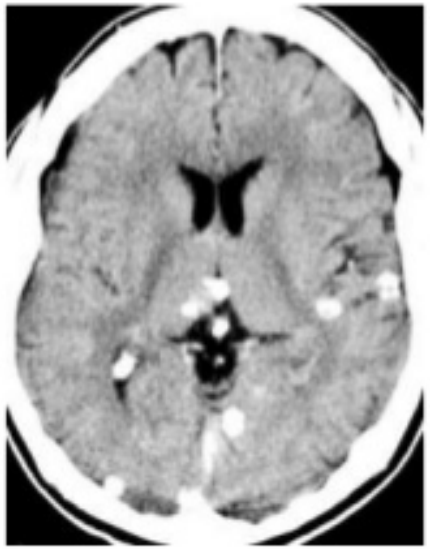
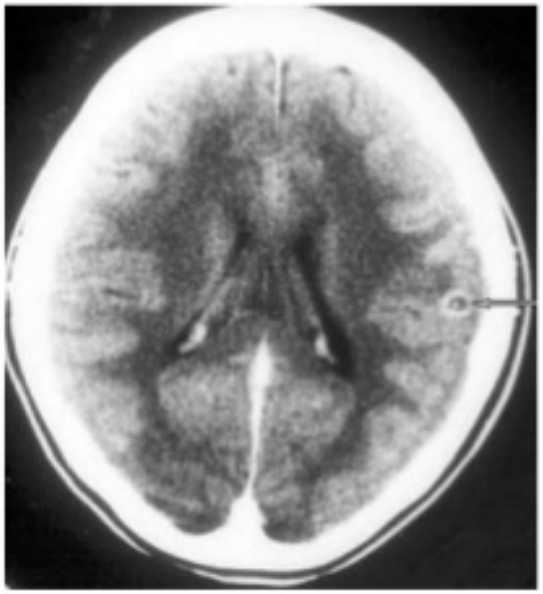


Fig. 1 T2-Weighted (A), FLAIR (B), PD-Weighted (C) and DW (D) sequences of a patient with autopsy-proven sCJD. The MRI was rated as ‘typical for sCJD’ by all three observers. Scans show high signal in the caudate nucleus and putamen bilaterally. In the DW sequence (D) a predominance of the right striatum and additionally increased signal in the right frontal and insular cortex is discernible.

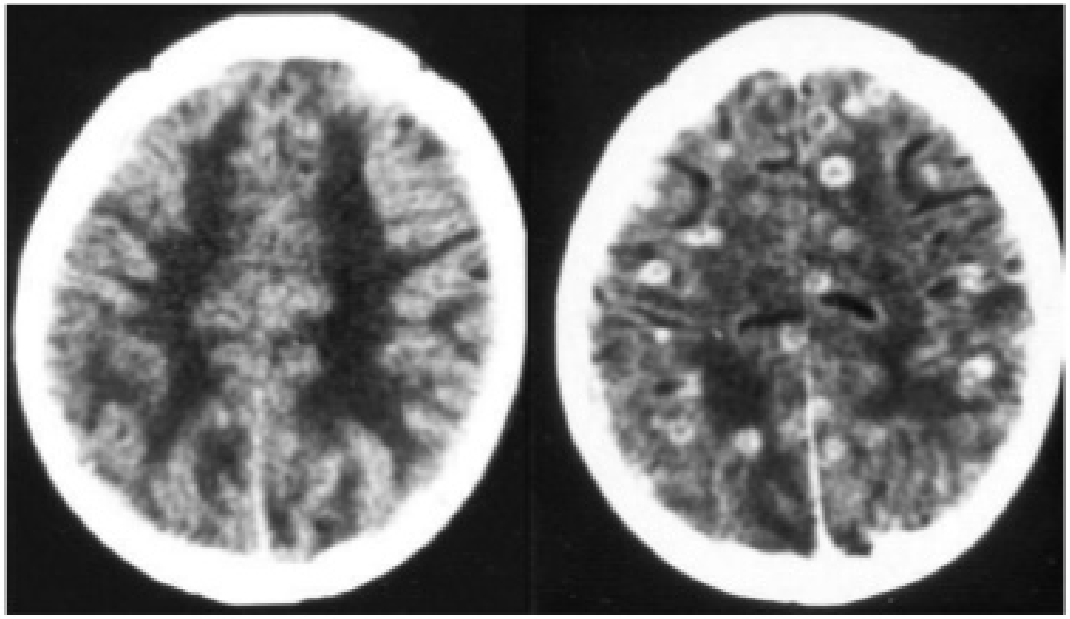
THE END



Nonenhanced CT scan of the brain demonstrates the multiple **calcified** lesions of **inactive** parenchymal neurocysticercosis



Enhanced CT scan of the brain in a patient with neurocysticercosis demonstrates a live cyst with a ***minimally*** **enhancing** wall and an eccentric hyperattenuating scolex.



44 year old lady with acute fever/confusion

- She was a healthy and a teacher before this. She went camping on a riverside 2 weeks prior to admission and got multiple mosquito bites there. Due to fever and mild headache 5 days ago, she was admitted to a local hospital. CSF had 15 WBC. West Nile virus antibodies were sent, and a brain CT was read as “negative”. She began exhibiting memory loss 3 days ago.

Continued

- According to the patient's husband, after 4 days of work-up, nothing particular could be found. She was sent here.
- Neurology was consulted to see this "aphasic" lady with suspected "stroke".

Continued

- On exam, she was awake but totally disoriented to time, person and place. Her temperature was 39 C. She could not spell world. She understood simple commands only (e.g., raise you hand), could not repeat, and could not name simple objects.
- She did not have weakness and could walk with supervision.

What is your diagnosis?