Inflammatory diseases of CNS (meningitis, encephalitis).

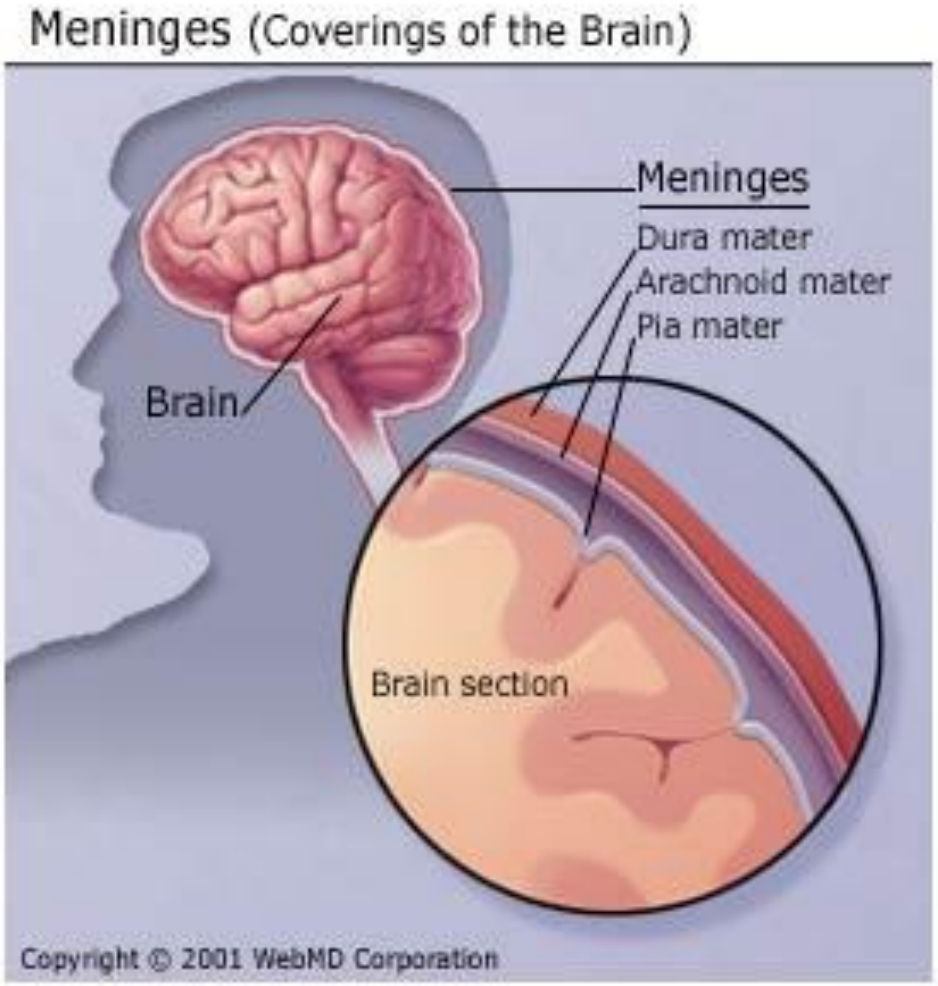
- Meningitis - bacterial, viral and (rare) fungal
  - acute, subacute, chronic
- Encephalitis - viral, bacterial, fungal
  - acute, postinfectious (late), after vaccinations
  - worldwide or endemic
  - endogenous, exogenous, vector-borne
- Brain abscess - bacterial and (rare) fungal
  - localization
- Other: meningoencephalitis, leukoencephalopathy

Definitions of Meningitis

- Inflammation of the meninges
- Abnormal number of WBCs in CSF
- Acute: onset of symptoms over hours to days
- Chronic: symptoms, signs, and CSF remain abnormal for at least 4 weeks

Meningitis

an inflammation of the pia-arachnoid meninges



Meningitis

Clinical manifestations

- headache, fever, neck stiffness
- Brudzinski's sign
- Kernig's sign
- reduced consciousness

- Seizures (small children)
- cranial nerve palsies
- hydrocephalus
- vasculitis

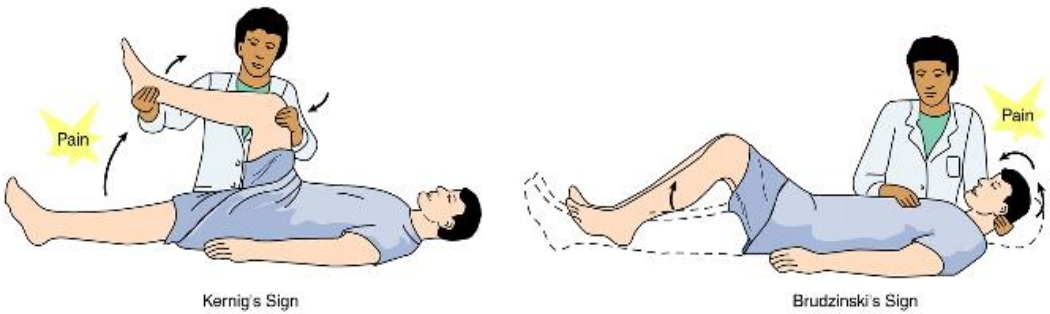
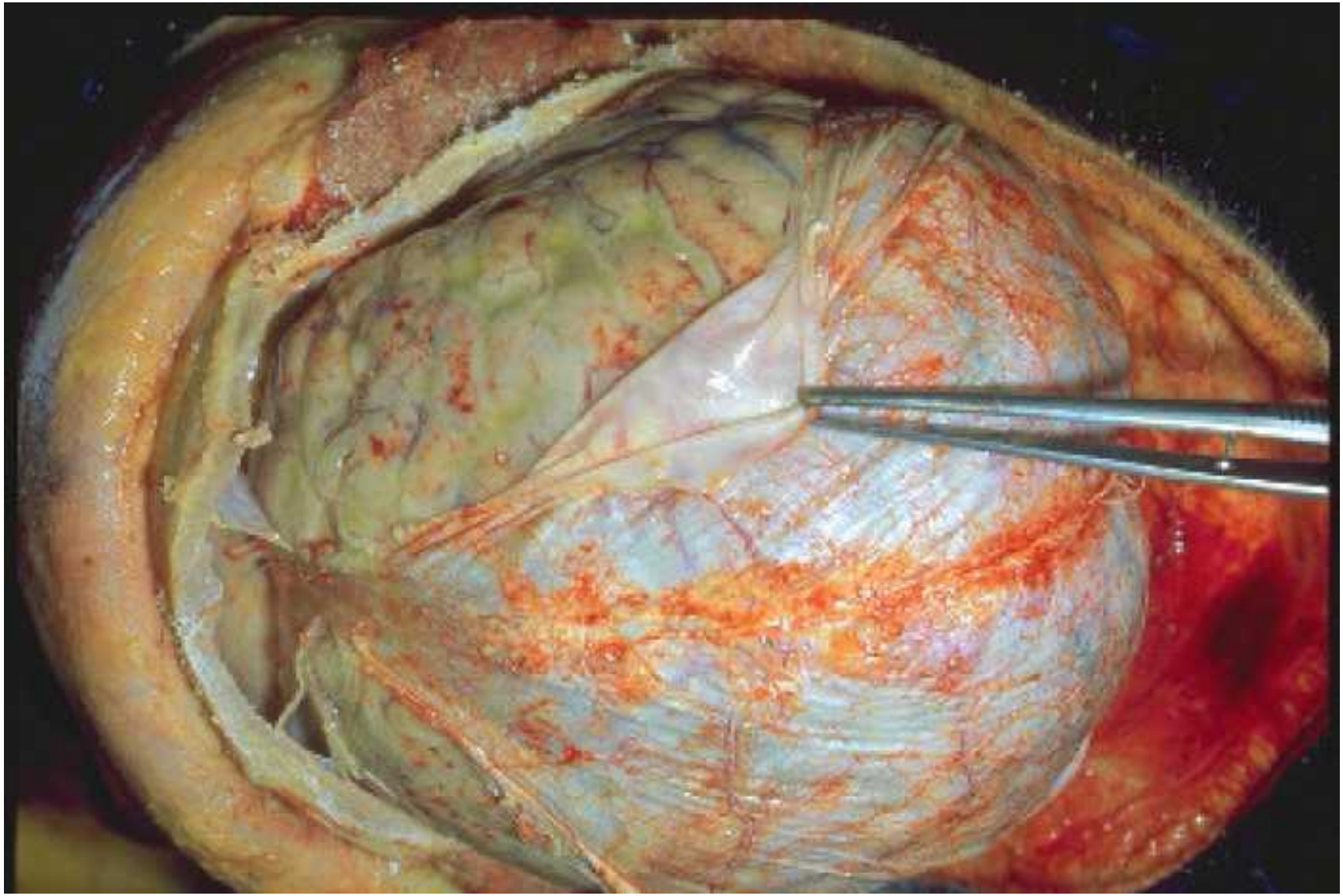


Figure 64-1 Testing for meningeal irritation. (A) Kernig's sign. (B) Brudzinski's sign.

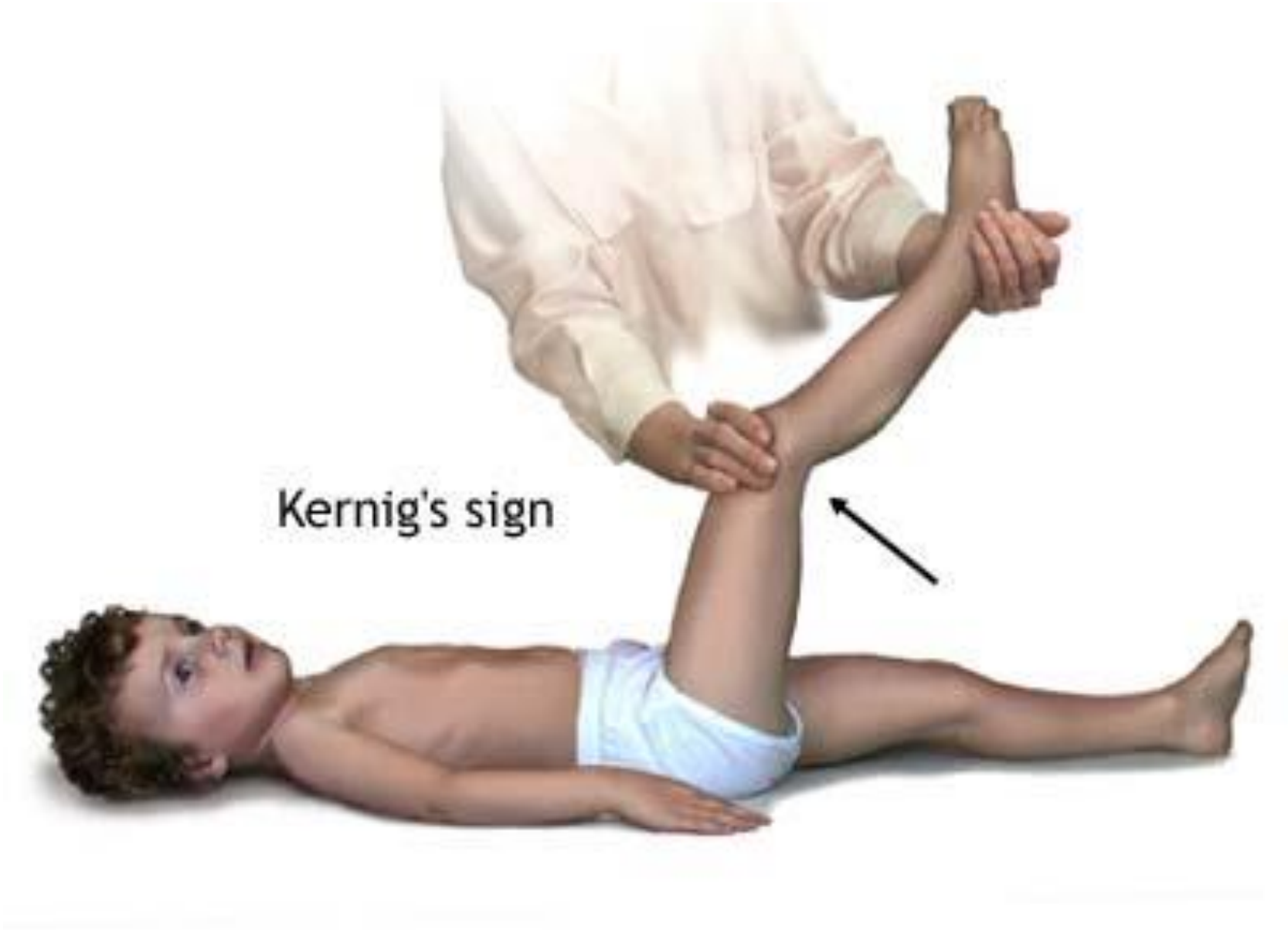


Cerebrospinal Fluid

- Produced by the choroid plexus in lateral, 3rd and 4th ventricles (20 ml/hr)
- Total volume = 125-150 ml (20% in ventricles with remainder in the subarachnoid space)
- CSF secretion & reabsorption in balance to maintain pressure < 150 mm H2O
- CSF pressure can be increased by infection, bleeding, or tumor

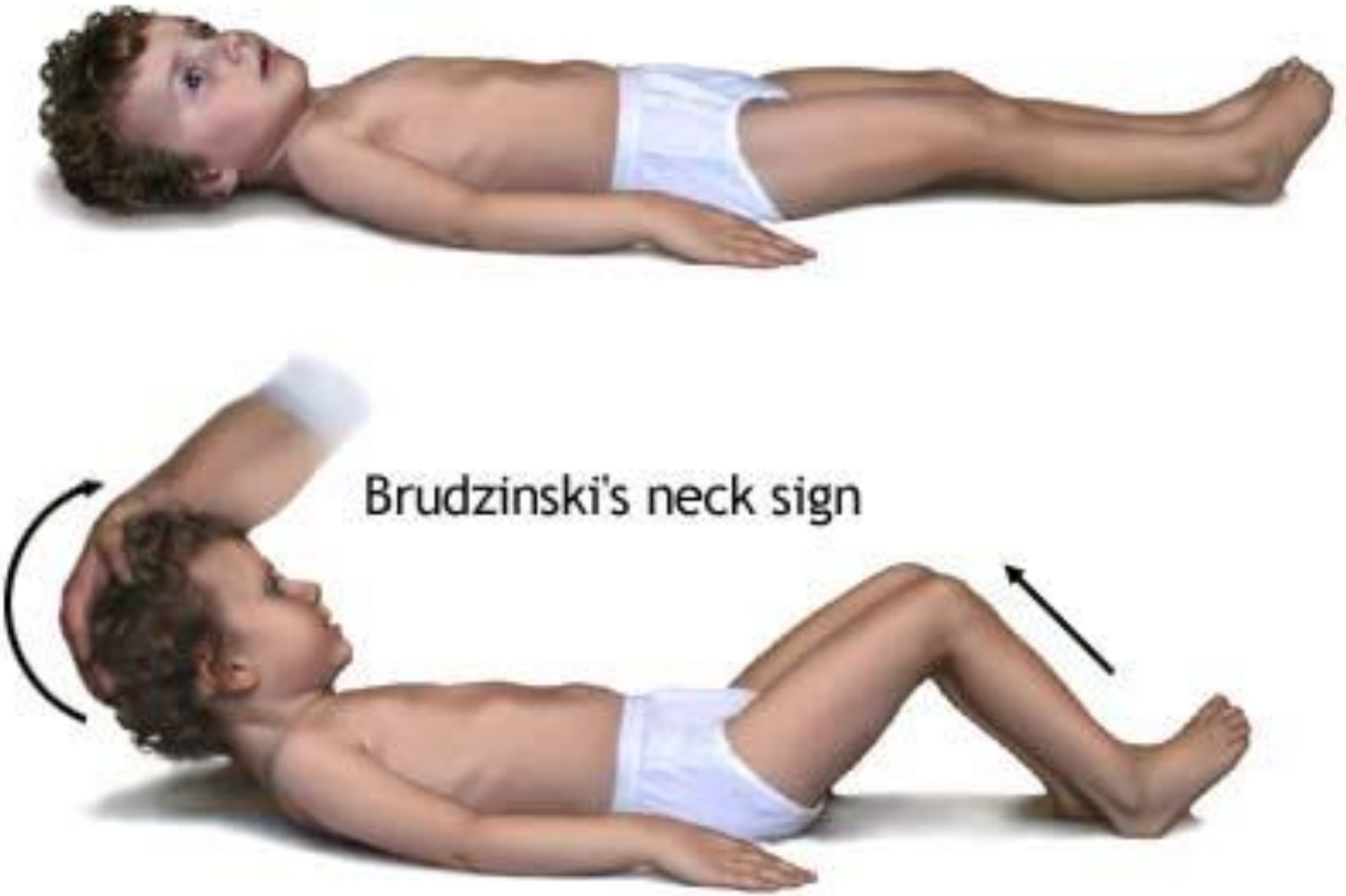
Kernig's Sign

- Patient placed supine with hips flexed 90 degrees. Examiner attempts to extend the leg at the knee
- Positive test elicited when there is resistance to knee extension, or pain in the lower back or thigh with knee extension



Brudzinski's Sign

- Patient placed in supine position and neck is passively flexed towards the chest
- Positive test is elicited when flexion of neck causes flexion at knees and/or hips of the patient


Brudzinski's neck sign
A.D.A.M.

Blood - Brain/CSF Barriers

- Prevent diffusion of fluid, electrolytes, and other substances from blood into CSF/brain
- Blood-Brain Barrier: formed by capillary endothelium & astrocytes; controls content of brain interstitial fluid
- Blood-CSF Barrier: formed by choroid plexus capillary endothelium & arachnoid membrane; controls composition of CSF
- Microbes attach to endothelial cells, traverse the BBB inside monocytes and cause cytokine release resulting in an inflammatory response

CSF Evaluation

- Cell counts
- Protein
- Glucose
- Stains/cultures
- Serologies
- PCRs

CSF Cell Counts

- Normal RBC & WBC counts=0-5/cmm
- WBC subtypes must be correlated with clinical findings
  - EV meningitis: 67% have PMN predominance early with shift to lymphs in 12-24 hrs
  - Bacterial meningitis: may have lymphs early
- Should be done within 60 min to avoid false decrease due to settling/adherence to tubes
- Traumatic tap:
  - Rough estimate of 1 WBC/1000 RBCs=traumatic tap
  - Calculate ratio of WBC/RBC in blood & apply to CSF

CSF Protein

- Normal=23-38 mg/dl
- Largely excluded by the BBB
  - Normal blood/CSF Ig ratio<500:1
- Gains access by transport within pinocytotic vesicles traversing capillary endothelial cells
- Protein>500 mg/dl seen in:
  - Meningitis (bacterial, mycobacterial, syphilitic)
  - Block secondary to tumor, abscess, hemorrhage
  - Arachnoiditis
  - Subarachnoid hemorrhage (>100,000 RBCs/cmm required
    to produce CSF protein>150 mg/dl)

LP

- Tube #1 – glucose and protein
- Tube #2 – cell count and differential
- Tube #3 – gram stain and rountine culture, cyrptococcal antigen, AFB stain and culture
- Tube #4 – viral studies (PCR)

Classification of CSF

- Aseptic/Viral
- Bacterial
- Granulomatous

Aseptic Meningitis

- Clinical and laboratory evidence of meningeal inflammation with negative bacterial cultures
- Usually has self-limited course and resolves without specific therapy
- Viral is the most common etiology

Viral Meningitis

- Enteroviruses
- Mumps virus
- Arboviruses
- Herpesviruses
- Lymphocytic Choriomeningitis
- HIV
- Adenovirus
- Parainfluenza viruses 1&2
- Measles virus

Clinical Manifestations of Viral Meningitis

NONSPECIFIC

- Headache
- Fever
- Nausea/Vomiting
- Photophobia
- Stiff neck

SPECIFIC

- MP rash-Echovirus 9
- Herpangina-Coxsackie A
- Pericarditis/Pleuritis-Coxsackie B
- Paralysis/Peripheral neuropathy-WN Virus
- Bizarre behavior/Olfactory hallucinations-HSV
- Mono Syndrome-EBV, CMV, HIV, Toxo

Seasonality of Viral Meningitis

- Summer and Fall:
  - Enteroviruses
  - Arboviruses
- Winter and Spring:
  - Mumps
  - Lymphocytic Choriomeningitis

CSF Findings of Viral Meningitis

- Increased WBC count
  - Usually<250 cells/cmm
  - Lymphocytic predominance (2/3 have PMNs early)
- Elevated protein concentration
  - Usually<150 mg/dl
- Normal glucose concentration
  - Exceptions: HSV, mumps, LCM, some EV
- Normal RBC count
  - Exception: HSV

Diagnosis of Viral Meningitis

- Viral cultures (pharyngeal, stool, CSF)
- Viral antigens/antibodies in CSF
- CSF viral antibody index
- PCR

Primary HSV Meningitis

- In 13% of men and 36% of women with primary genital herpes
- Genital lesions present in 85% of pts with HSV-2 meningitis
- Most common clinical findings:
  - Headache
  - Photophobia
  - Meningeal signs
- Minority of pts have more severe symptoms:
  - Urinary retention
  - Paresthesias/weakness of lower extremities
  - Ascending myelitis

Treatment of HSV Meningitis

- No controlled trials demonstrate efficacy of antiviral agents in HSV meningitis
- Unknown if treatment shortens duration of symptoms or decreases incidence of more severe symptoms
- Antiviral therapy appropriate for the following:
  - Patients with primary HSV infection
  - Patients with severe neurologic symptoms
- Inpatients: ACV 10 mg/kg IV q 8 hrs
- Outpatients: ACV 800 mg po 5 X/day, Famciclovir 500 mg po TID, or Valacyclovir 1000 mg po TID

Approach to Patients with Viral Meningitis

- Consider clinical syndrome & season
- Elicit detailed travel & exposure history
- Look for PE findings associated with specific viruses
- Obtain viral cultures (CSF, throat, stool)
- Consider CSF PCR for EV, HSV, VZV, CMV, EBV
- Consider serum/plasma PCR for above and HIV
- Consider serologies for the above
- Consider nonviral causes for patient's illness
- If encephalitis present, start empiric ACV

Nosocomial Meningitis

- Risk Factors
  - Neurosurgery or head trauma within last month
  - Neurosurgical device
  - CSF leak

Mechanisms for Developing Bacterial Meningitis

- Colonization of nasopharynx with subsequent BSI and CNS invasion
- Bacteremia (SBE) with CNS invasion
- Direct entry into CNS from contiguous source (sinusitis, otitis, mastoiditis)

Pathogenesis

- Nasopharyngeal colonization by pathogen
- Mucosal invasion
- Bacteremia
- Bacterial invasion of CSF via choroid plexus
- Bacterial replication
- Release of LPS or endotoxin in subarachnoid space
- Cytokine production
  - SAS inflammation → cerebral vasculitis/infarction, increased CSF outflow resistance and cytotoxic edema
  - Increased BBB permeability → vasogenic edema
- Increased ICP

Predisposing Factors to Bacterial Meningitis

- Absence of opsonizing antibody
- Asplenia
- Complement deficiency
- Corticosteroid excess
- HIV infection
- Bacteremia/Endocarditis
- Fracture of cribiform plate

Important Historical Information

- Drug allergies
- Recent travel
- Recent exposure to patient with meningitis
- Recent infection (respiratory/otic)
- Recent use of antibiotics
- History of IVDU
- Presence of petechial/ecchymotic rash

Clinical Features of Bacterial Meningitis

- Headache
- Fever
- Photophobia
- Clouding of sensorium
- Seizures
- Focal neurologic signs
- Petechiae/Purpura
- Nuchal rigidity
  - Kernig's Sign
  - Brudzinski's Sign
- Rapidly progressive course

Laboratory Features of Bacterial Meningitis

- Leukocytosis with left shift
- Thrombocytopenia (DIC)
- Bacteremia-seen in 50% of patients
- CSF findings:
  - Increased WBC
  - Increased Protein
  - Decreased Glucose
  - Positive Gram Stain in 60-90%
  - Positive Culture in 70-85%

Diagnostic CSF Findings of Bacterial Meningitis

- Greater than 99% PPV of bacterial meningitis with the following:
  - CSF Glucose/Serum Glucose<0.23
  - CSF Protein>220 ng/dl
  - CSF WBC>2000 cells/cmm

Treatment of Bacterial Meningitis

- Initiate antibiotic therapy immediately after L.P.
- Empiric therapy should consist of bactericidal agents that achieve significant levels in the CSF
- Determine if steroid therapy indicated
- Change to more specific antimicrobial therapy when the etiologic agent is identified
- Repeat CSF analysis when indicated

Empiric Treatment

- 3rd Generation Cephalosporins
  - Ceftriaxone
  - Activity against major pathogens (except Listeria and resistant PNC and GNRs)
- Vancomycin
  - Resistant gram positive organisms
- Ampicillin
  - Listeria

CSF Characteristics

	Bacterial	Viral	Fungal	TB
Opening Pressure	Elevated	Slightly elevated	Normal or High	Ususally high
Glc	Low	Normal	Low	Low
Pro	Very high	Normal	High	High
Rbcs	Few	None	None	None
Wbcs (c/mm3)	>200	<200	<50	20-30
Diff	PMNs	Mono	Mono	Mono

Neurologic Complications

Seen in 28 % of adults with community-acquired bacterial meningitis:

- Cerebrovascular abnormalities
- Brain edema/increased ICP
- Seizures
- Intellectual impairment
- Hearing loss/cranial neuropathy
- Subdural effusion/empyema

Cerebrovascular Abnormalities

- Thrombosis
- Vasculitis
- Acute cerebral hemorrhage
- Aneurysm formation of cerebral vessels

Increased Intracranial Pressure

- Causes In Meningitis:
  - Vasogenic cerebral edema due to increased permeability of BBB
  - Cytotoxic factors released from PMNs & bacteria
  - Normal interstitial flow of CSF from subarachnoid space impeded by infection-induced inflammation
  - Loss of cerebral autoregulatory mechanisms
  - Venous sinus thrombosis

Clinical Manifestations of Increased ICP

- Headache
- Altered Mental Status (confusion→coma)
- Bradycardia with hypertension (Cushing's reflex)
- Papilledema +/- visual loss
- Herniation

Seizures Associated with Bacterial Meningitis

- Pathogenesis:
  - Bacterial toxins:
  - Secondary neurochemical changes

Intellectual Impairment

Most common abnormalities related to:

- **Visuospatial reasoning**
- **Performing attention & executive functioning tests**
- **Reaction speed**

Sensorineural Hearing Loss

- May be transient or permanent
- More common in children
- Risk factors include:
  - Delayed sterilization of CSF
  - Young age
  - More severe clinical illness

Cranial Neuropathies

- Occurrence rate in meningitis depends on:
  - Duration of illness before treatment
  - Age of patient
- CN VI most common
- CNs III, IV, VII can also be involved
- Pathogenesis:
  - Compression of nerve from cerebral edema
  - Perineuritis from adjacent inflammatory reaction

Mortality Rate of Bacterial Meningitis

- Determining Factors:
  - Age of patient
  - Underlying disease processes
  - Causative organism (Pnc=21%, List.=15%, Mening.=3%)
- Prognostic Factors:
  - Hypotension
  - Altered Mental Status
  - Seizures
- Overall Mortality=27%
- Persistent Neurologic Deficits=9%

Bacterial Meningitis-Summary

- Initiate antibiotic therapy immediately after LP
- If cranial imaging deemed necessary, perform blood cultures, then administer antibiotics empirically
- Empiric therapy should consist of appropriate bactericidal agents that achieve significant levels in the CSF:
- Determine if steroid therapy indicated
- Change to more specific therapy when etiologic agent identified
- Repeat CSF analysis when indicated

TBM

- Serious manifestation of TB
- Hematogenous spread from lungs
- Rich focus
- Fibrinous exudate
- Histiocyte infiltration
- Endarteritis obliterans
- Complications
  - ICP
  - Hydrocephalus
  - Cranial nerve involvement

TBM

- Diagnosis
  - Slow onset
  - ICP
  - 75% has lung involvement
  - 3 Stages:
    - Symptoms without signs
    - Level of consciousness affected but no focal signs
    - Coma, very ill, focal neurological signs
    - CSF
- Treatment
  - 4 drugs

Encephalitis

- Definition
  - Acute infection of brain parenchyma characterized clinically by fever, headache and altered level of consciousness, may associated with focal or multifocal neurological deficits and focal or generalized seizure activity

Major etiology

- Major cause of encephalitis
  - Herpes simplex virus type 1 (HSV-1)
  - Herpes simplex virus type 2 (HSV-2) in neonate
  - Mumps
  - Arthropodborne virus: St Louis encephalitis virus, Japanese B encephalitis
  - Tickborne rickettsial infection: Rocky Mountain spotted fever

Immunocompromised patient

- Causal agent of encephalitis in the immunocompromised patient
  - HIV
  - HSV
  - Varicella zoster virus (VZV)
  - Epstein Barr virus (EBV)
  - Cytomegalovirus (CMV)
  - Human herpes virus-6 (HHV-6)
  - Enterovirus

Postinfectious encephalomyelitis

- Definition: acute inflammatory demyelinating disease of brain, optic nerves and spinal cord that typically occurs a few days or weeks after a respiratory tract infection or after a vaccination
- Postulated to be an autoimmune disease of the CNS
- Encephalitis and postinfectious encephalitis can not be distinguished by clinical presentation

Sporadic and epidemic encephalitis

- Sporadic encephalitis:
  - 3 major virus: HSV, mumps and EBV
  - Most common is HSV
- Epidemic encephalitis:
  - Arbovirus such as JCV
  - Von Economo's encephalitis lethargica
  - Fever, consciousness change than movement disorder
  - Triad: oculogyric crisis, psychiatric/personality change and involuntary movement

Chronic encephalitis

- Subacute/chronic virus encephalitis syndrome: cause by slow virus
  - Slow virus: long latency, typical disease progression course, single spaces transmission
  - Conventional virus: measle (SSPE), rubella (PRP), retrovirus (AIDS dementia), papova virus (PML)
  - Unconventional virus: prion disease—Creutzfeldt-Jakob disease, Gerstmann-Straussler disease, Bovine spongiform encephalitis

Herpes simplex encephalitis

- Acute sporadic encephalitis
- Age distribution: biphasic model, 5-30y/o and over 50y/o; 95% is type 1
- Primary infection is asymptomatic, occurs in the oropharyngeal mucosa;
- Symptomatic disease is characterized by fever, throat pain and lesion in buccal mucosa, duration is 2-3 weeks

Herpes simplex encephalitis

- Infection route: from mucosa transport by retrograde transneuronal spread to trigeminal nerve
- Reactivation of virus than→trigeminal root and come to temporal/frontal lobe
- Immunosuppression increase the risk of reactivation of virus

Clinical presentation

- Acute/subacute sporadic encephalitis
- Prodromal: fever, hemicranial or general headache, → (few days) behavioral change, seizure and amnesia, consciousness disturbance (2-3 week to maximum)
- Fever (89%); headache (78%); consciousness change (96%); seizure (38%); focal sign (35-50%)

Diagnosis

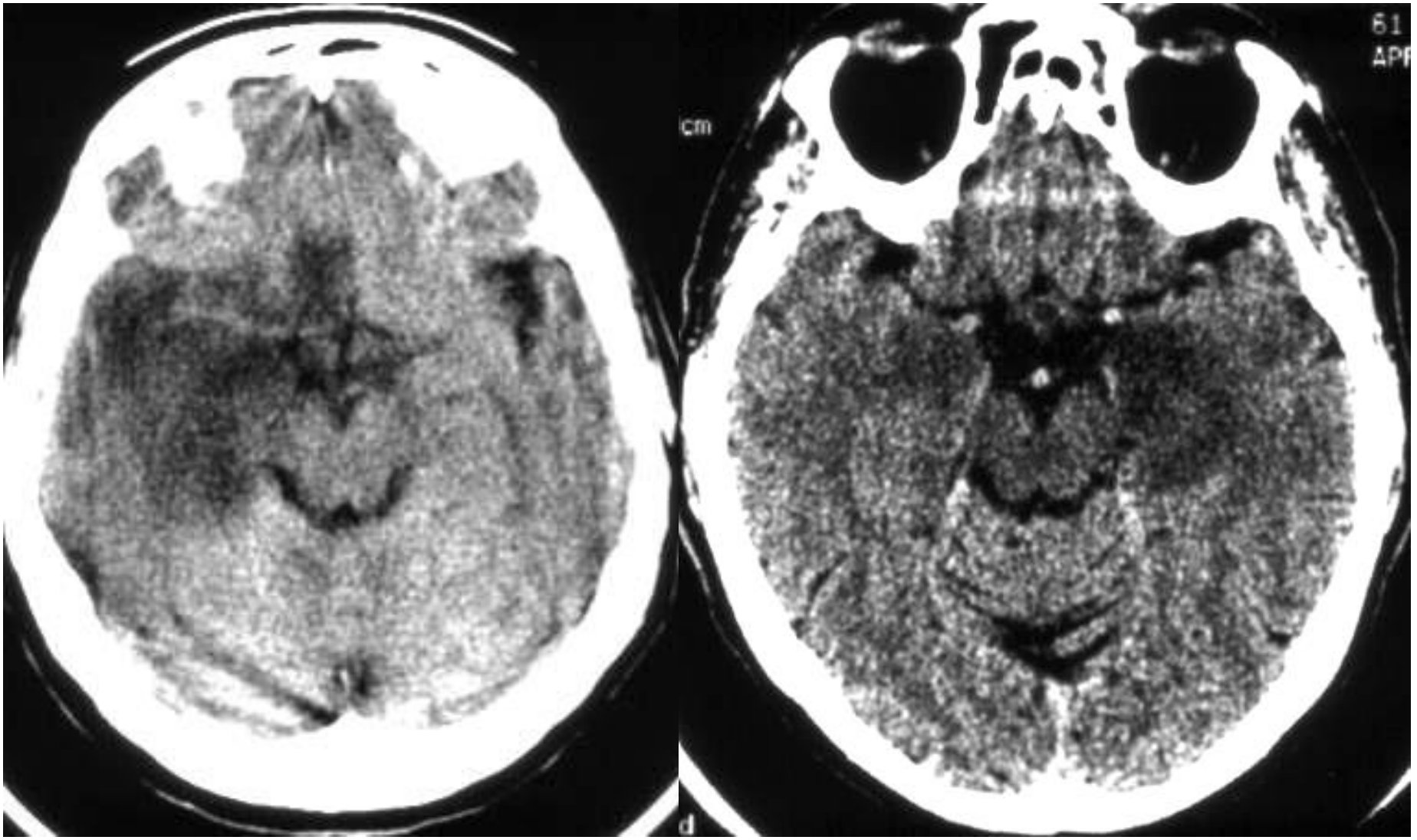
CSF	HSV-1	Bacterial meningitis
Opening pressure	> 180	> 180
WBC	5-500, lymphocyte	10-10000, neutrophil
RBC	present	absent
glucose	Normal or decrease	< 40
protein	> 50	> 50
culture	Negative	70-80% positive

Diagnosis

- CSF: HSV DNA appear by days, 8-12 days HSV-Ab appear and gradually increase to 2-4 weeks
- CSF virus culture: always negative
- PCR: collection of CSF should within 10days after onset of symptoms
- Negative PCR: no virus or inhibitory activity is present

Image/ EEG character

- MRI is the neuroimaging procedure of choice
- T1WI: low density and T2WI: high signal in medial and inferior temporal lobe, extending to insula or frontal lobe
- EEG: periodic lateralized epileptiform discharge with 2-3 Hz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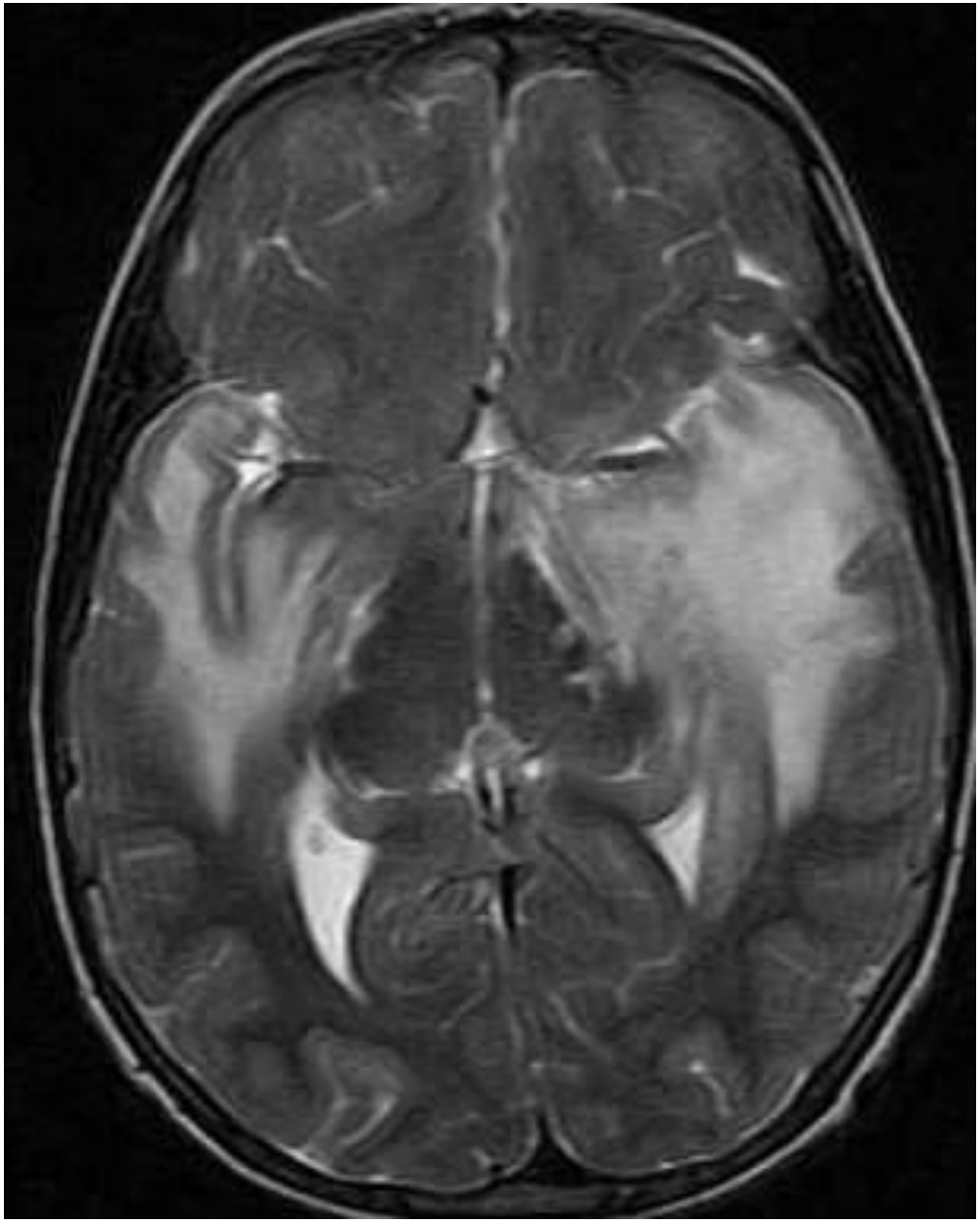

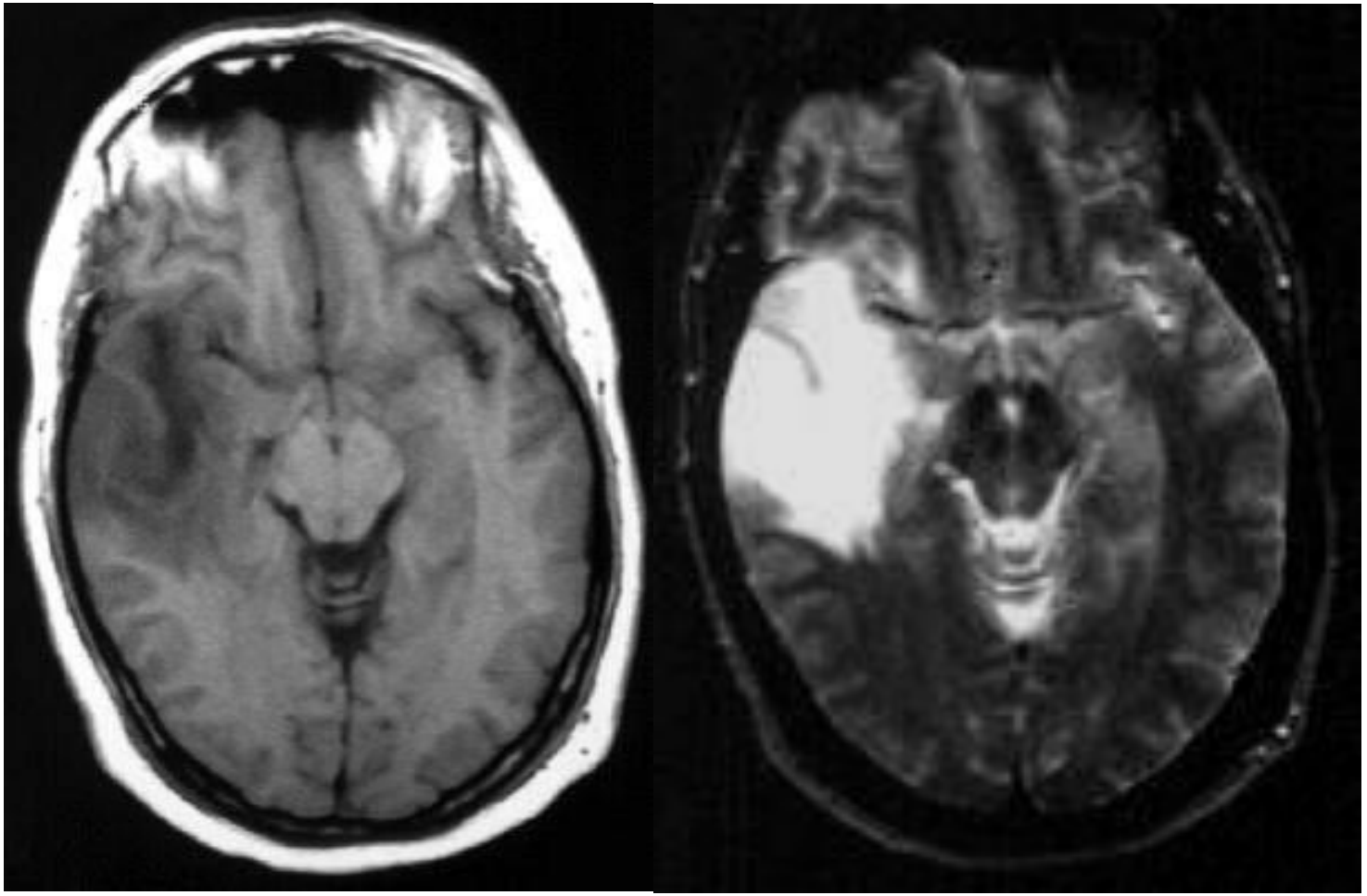

Treatment

- Iv acyclovir 10mg/kg q8h for 2-3 weeks
- Side effect is renal impairment
- Without treatment mortality: 80%; with treatment mortality: 30%

Epstein Barr virus, cytomegalovirus and Human Herpesvirus-6

- EBV, CMV and HHV-6 common in the immunosuppressed patients
- EBV: patient(90%) have antibody, may due to reactivation of virus
- CMV encephalitis may associated with HIV infection
- Diagnosis: PCR for virus
- Treatment: ganciclovir