Meningitis (s. Arachnoiditis, Leptomeningitis)

Last updated: December 22, 2020

MENINGITIS - inflammation of meninges (inflammatory response is generally confined to *arachnoid*, *subarachnoid space* and *pia* – i.e. **LEPTOMENINGITIS**).

ETIOLOGY

BACTERIAL (PURULENT) MENINGITIS

- almost any pathogenic bacteria (most cases are hematogenous!).

see INFECTION: p. 225 (12-14) (pneumococci) >>, p. 229 (2-5) (meningococci) >>

In order of frequency:

NEONATES:

1. Gr- enteric bacilli (predominantly *Escherichia coli* with K1 capsular antigen) (25-60%)
2. Group B streptococci (*Streptococcus agalactiae*) (20-50%)
3. *Listeria monocytogenes* (2-10%)
4. Group D streptococci (enterococci)
5. Staphylococci (rare)

CHILDREN (1 month ÷ 15 yrs):

1. *Haemophilus influenzae* (40-60%*) – nearly all cases in children < 6 yrs.
2. *N. meningitidis* (25-40%)
3. *Str. pneumoniae* (10-20%)

*now ↓↓↓ (widespread use of Hib conjugate vaccine)

ADULTS:

1. *Str. pneumoniae* (30-50%) (esp. in association with pneumonia, otitis media, skull base fracture with CSF leak); > 50% patients are *< 1 or > 50 years of age*.
2. *Neisseria meningitidis* (10-35%) - only major cause of ***EPIDEMICS* OF BACTERIAL MENINGITIS*** (in overcrowded conditions – military barracks, etc); most patients are *adolescents and young adults*. *epidemic cerebrospinal fever = meningococcal meningitis
3. *S. aureus* and coagulase-negative staphylococci (5-15%) - predominant organisms in *CSF shunts* or subcutaneous Ommaya reservoirs.
4. Gr- bacilli (1-10%) – most common in *elderly*.
5. *Listeria monocytogenes* (5%) – most common in *immunosuppressed patients*.
6. Streptococci (5%)
7. *Haemophilus influenzae* type b (0,5-3%)
8. Anaerobic bacteria (< 1%) - suggest intraventricular rupture of brain abscess.
9. Polymicrobial meningitis (< 1%) - simultaneous recovery of two or more bacterial species.

PREDISPOSING HOST FACTORS

1) MECHANICAL disturbances (neurosurgical procedures, basilar skull fractures).
2) CONGENITAL defects (dermoid sinus tracts, meningomyeloceles).
3) IMMUNOLOGIC deficiencies:
    a) **cell-mediated immunity** (lymphoma, organ transplant recipients, corticosteroid therapy, AIDS) → *intracellular bacteria* (esp. tbc, *L. monocytogenes*).
    b) **humoral immunity** (splenectomy, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's disease after radiotherapy or chemotherapy) → *encapsulated bacteria* (*S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*).
    c) **neutropenia** → *P. aeruginosa*, Enterobacteriaceae.

ASEPTIC (SEROUS) MENINGITIS

- misnomer (term used just clinically) - absence of bacteria on **microscopic examination & culture**:

A. **Bacterial meningitis**:
    a) partially treated

b) parameningeal infection (brain abscess, subdural empyema, epidural abscess, septic thrombosis of intracranial venous sinuses; osteomyelitis of spine or skull)
c) *Listeria monocytogenes*
d) *Mycoplasma pneumoniae*
e) *Mycobacterium tuberculosis*
f) ehrlichiosis, rickettsioses
g) spirochetes (*Borrelia burgdorferi*, *Treponema pallidum*)

B. **Viral meningitis** (precise definition of etiologic agent is often impossible) – in order of frequency:
1. *Enteroviruses* (esp. echovirus, coxsackie virus B) - statistically encountered most commonly (up to 92% aseptic meningitis cases!)
2. *Arboviruses* (St. Louis encephalitis virus, California encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Colorado tick fever)
3. *HIV*
4. *Herpes simplex virus* - 2 (MOLLARET'S MENINGITIS)
5. Mumps (most common viral meningitis before widespread MMR vaccine use!)
6. Lymphocytic choriomeningitis virus (during wintertime when mice migrate indoors)
7. Varicella-zoster virus
8. Epstein-Barr virus
9. Influenza virus types A and B

N.B. viral meningitis is disease of young (< 40 yrs)!

C. **Fungal meningitis** (occurs only in *immunosuppressed hosts*, esp. lymphoma & leukemia, AIDS):
1. *Cryptococcus neoformans** – may also occur in healthy individuals!
2. *Coccidioides immitis*
3. *Histoplasma capsulatum**
4. *Blastomyces dermatitidis*
5. *Candida albicans*

*common in AIDS patients

D. **Chemical meningitis** - response to **nonbacterial irritant** introduced into subarachnoid space (air, dyes, drugs, blood, etc)
- drug-induced meningitis (ibuprofen, trimethoprim, isoniazid, IVIG, OKT3, azathioprine).

E. **Malignant meningitis** - infiltration of subarachnoid space by **carcinoma** (**MENINGEAL CARCINOMATOSIS**) or **lymphoma** (**MENINGEAL LYMPHOMATOSIS**).
N.B. antileukemic drugs do not cross BBB!

F. **Meningitis in connective tissue disorders**:
1) serum sickness
2) vasculitis, periarteritis nodosa
3) SLE
4) Behçet's disease
5) sarcoidosis.

MENINGISM (PSEUDOMENINGITIS)

- syndrome of **headache** and signs of **meningeal irritation** in patients (child or young adult) with ***acute febrile illness*** (usually of viral nature) in whom CSF is under increased pressure but normal in other respects.
- condition is brief in duration.
- pressure reduction by removal of CSF results in disappearance of symptoms (rarely, more than one puncture is necessary).

CLASSIFICATION

ACUTE MENINGITIS

- patients with obvious meningitis who are evaluated in **less than 24 hours** after onset.
- most cases are bacterial.

SUBACUTE MENINGITIS

- symptoms and signs causing patient to seek care have developed during period of **1 to 7 days**.
- includes virtually all cases of viral meningitis, along with some of fungal etiologies.

CHRONIC MENINGITIS

- symptoms and signs persist **> 7-28 days**.
- causes are fungi, tuberculosis, syphilis, malignancy, systemic collagenoses, sarcoidosis, some viruses.

RECURRENT MENINGITIS

- bouts of acute meningitis with complete resolution between episodes.

RECURRENT BACTERIAL MENINGITIS signals host defect in:
A. **Immunologic defenses**
B. **Local anatomy** - usually after ***trauma.***

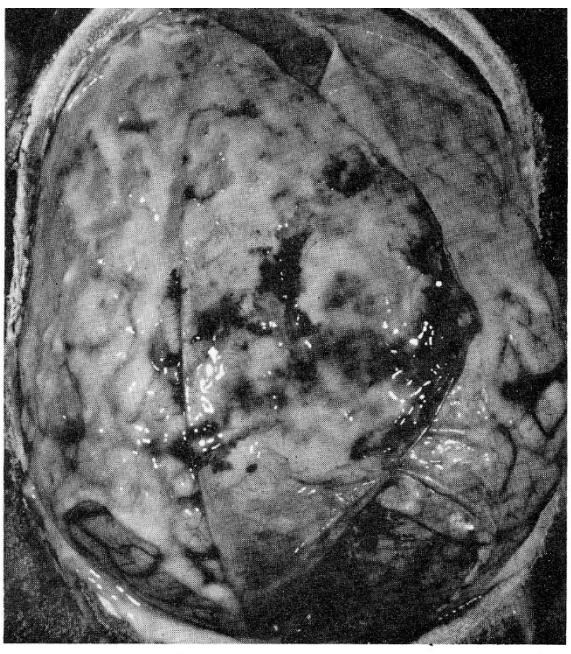
RECURRENT NON-BACTERIAL MENINGITIS:
1) herpes simplex virus type 2
2) chemical meningitis (leakage into CSF of contents from epidermoid tumor, craniopharyngioma, cholesteatoma)
3) primary inflammatory conditions (Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, Mollaret's meningitis, SLE)
4) drug hypersensitivity (with repeated administration).

PATHOLOGY, PATHOPHYSIOLOGY

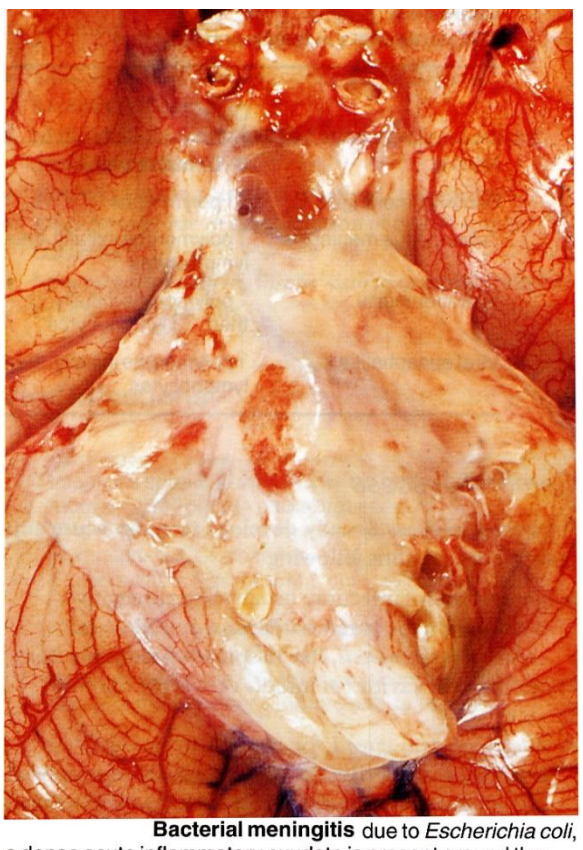
BACTERIAL MENINGITIS

- in CSF, humoral defense mechanisms (Ig and complement activity) are virtually absent; opsonic activity is often undetectable even in infected CSF (phagocytosis of encapsulated bacterial pathogens is inefficient) - bacteria commonly reach very high densities in CSF - use of ***bactericidal agents*** is mandatory part of therapy!
- inflammatory reaction may extend short distance along perivascular spaces into substance of brain and spinal cord, but rarely breaks into parenchyma.
- release of toxic factors form bacteria → activation of neutrophils → release of TNF-α, IL-1, 8, platelet activating factor:
  1) ***cytotoxic cerebral edema***.
  2) increase in BBB permeability → ***vasogenic edema***.

- large numbers of leukocytes in subarachnoid space contribute to purulent exudate and impair CSF absorption by arachnoid villi → *COMMUNICATING HYDROCEPHALUS*.
- pia-arachnoid becomes thickened → adhesions → interfere with CSF flow from 4th ventricle → *OBSTRUCTIVE HYDROCEPHALUS*.
- hydrocephalus causes transependymal movement of fluid from ventricular system into brain parenchyma (***interstitial edema***).
- cerebral edema causes ICP↑.

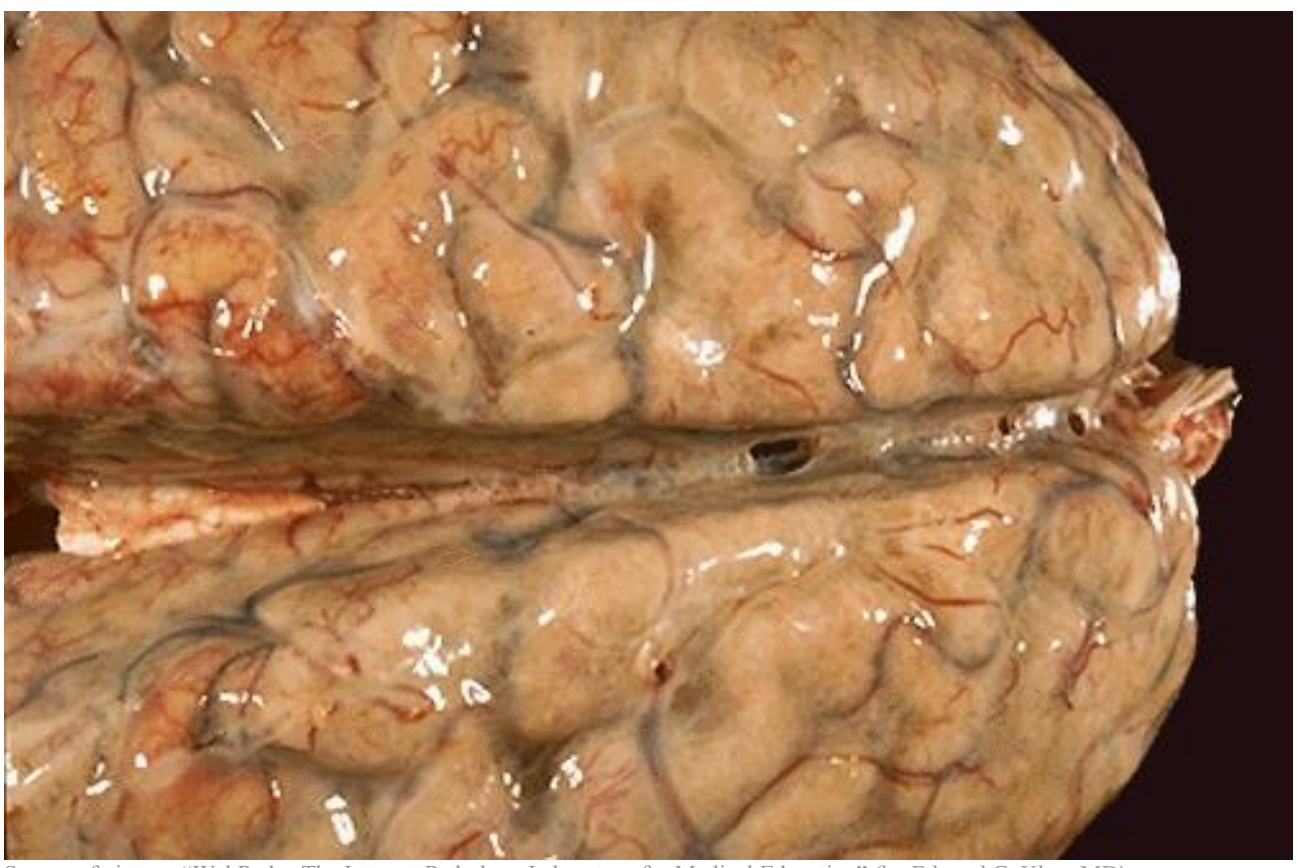


Pyogenic meningitis. A heavy layer of suppurative exudate is disclosed by folding back the dural covering.

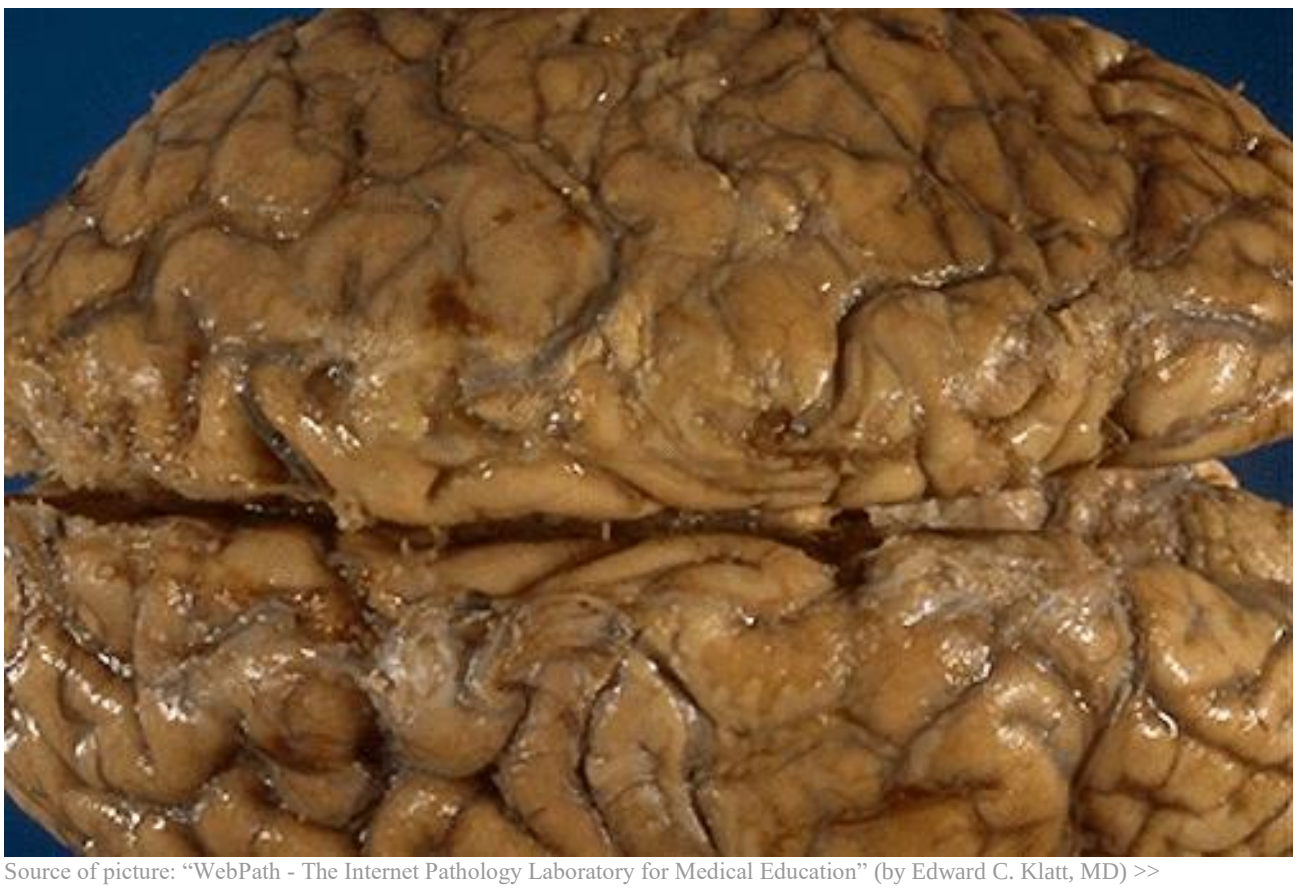


Bacterial meningitis due to *Escherichia coli*, a dense acute inflammatory exudate is present around the brainstem, cerebellum and adjacent structures at the base of the brain. Obstruction of the fourth ventricle exit foramina resulted in acute hydrocephalus in this case.

Source of picture: James C.E. Underwood "General and Systematic Pathology" (1992); Churchill Livingstone; ISBN-13: 978-0443037122 >>



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



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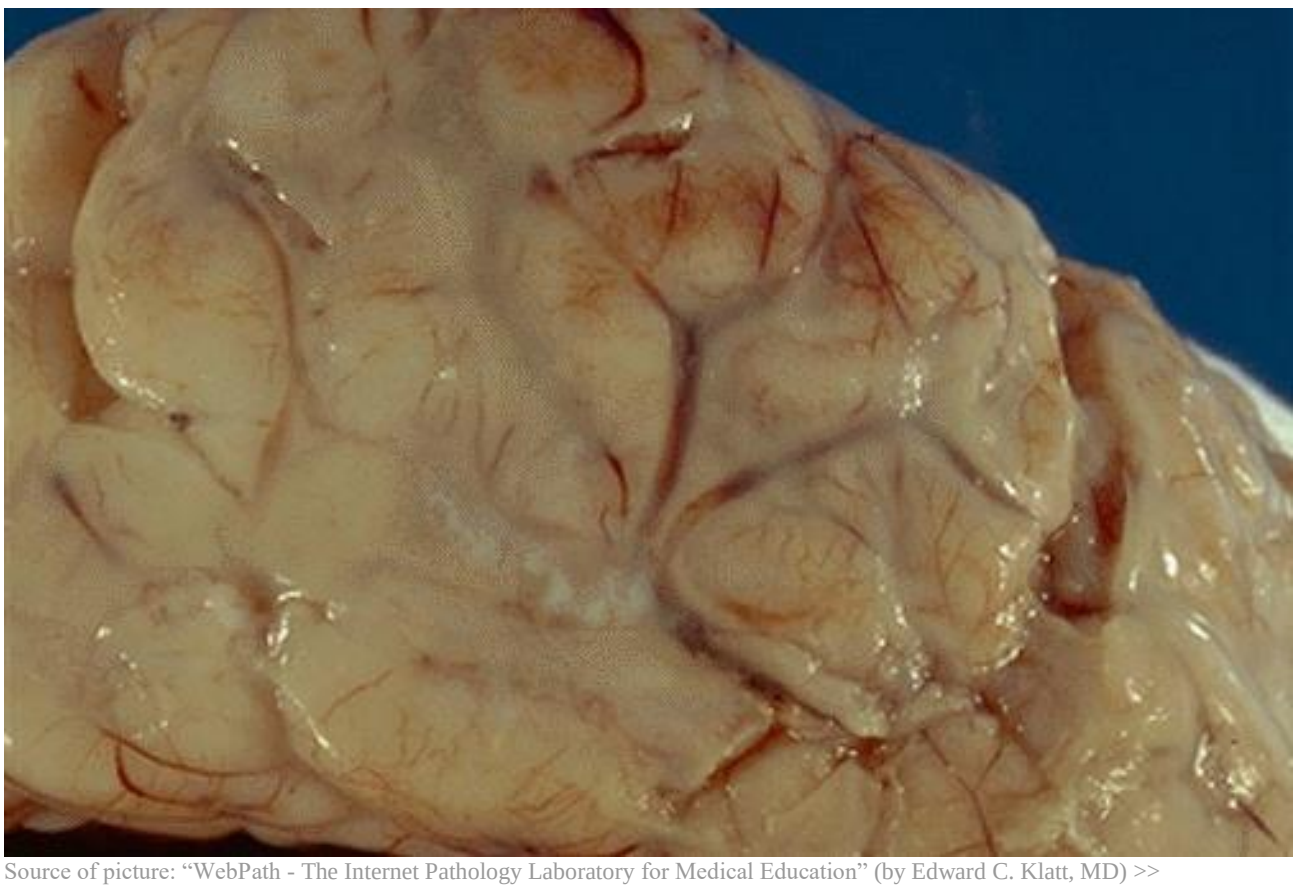

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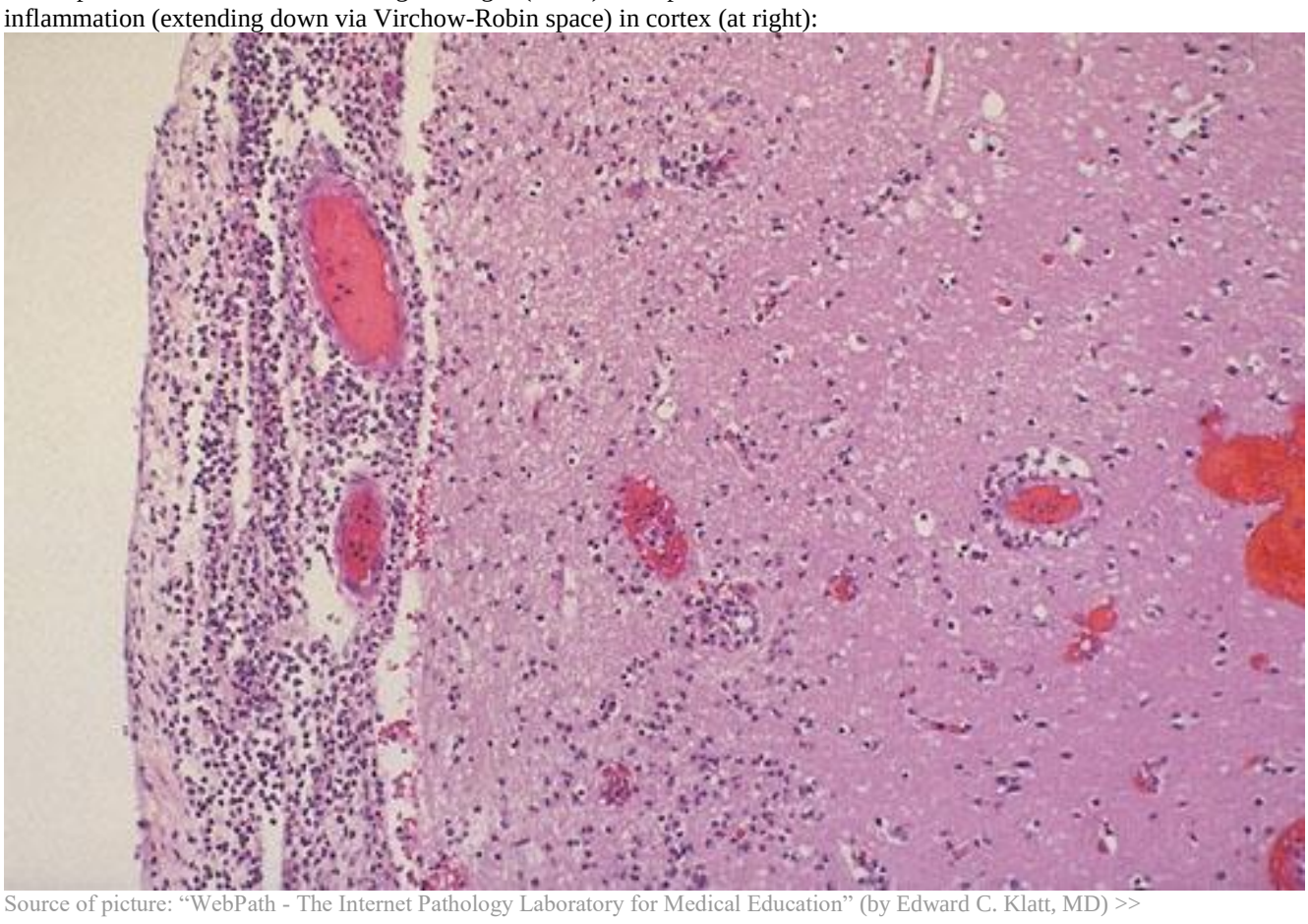
Neutrophilic exudate is seen involving meninges (at left), with prominent dilated vessels; there is edema and focal inflammation (extending down via Virchow-Robin space) in cortex (at right):



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- meningeal and superficial cortical vessels are engorged and stand out prominently.
- since subarachnoid space is continuous over brain, spinal cord, and optic nerves, infection in this space *extends throughout cerebrospinal axis* unless there is obstruction of subarachnoid space.
- ventriculitis is nearly uniformly present.
- brain parenchyma (cerebritis → abscess), dura (pachymeningitis), subdural and epidural spaces may be secondarily involved.
- when patient recovers, phagocytes completely clear subarachnoid space; if low-grade infection persists, adhesions and leptomeningeal fibrosis develops (see *COMPLICATIONS* >>).

VIRAL MENINGITIS

- brain swelling, mild to moderate infiltration of leptomeninges with lymphocytes.

EPIDEMIOLOGY

BACTERIAL MENINGITIS

- overall INCIDENCE (in USA*) - **3-10 cases** (per 100,000 persons per year).
  *bacterial meningitis is much more prevalent in developing countries
- incidence is highest in first month of life.
- incidence increases in ***late winter ÷ early spring***.
- men > women.

VIRAL MENINGITIS

- actual incidence is unknown (most cases are unreported); ≈ **11-27 cases** (per 100,000 persons per year).
- prominent increase in ***summer*** (seasonal predominance of enteroviruses & arboviruses).

CLINICAL FEATURES

ACUTE MENINGITIS

Patients rapidly deteriorate:
- course is most dramatic in **pyogenic** meningitis;
- course is much less acute in **viral** meningitis - patients may be in great discomfort but are not critically ill.

1. Patient looks unusually ill with **altered consciousness** (up to coma with shock); in viral meningitis – only mild lethargy or drowsiness.

2. **Fever**
   - temperature is higher in bacterial than viral CNS infection.
   - temperature may be below normal (tuberculosis).

3. Diffuse **headache** due to displacement & traction of blood vessels traversing through meninges.
   - typically frontal or retroorbital with pain on moving eyes in ***viral meningitis***.
   - pain often causes infant to emit peculiarly shrill cry (*meningeal cry*).

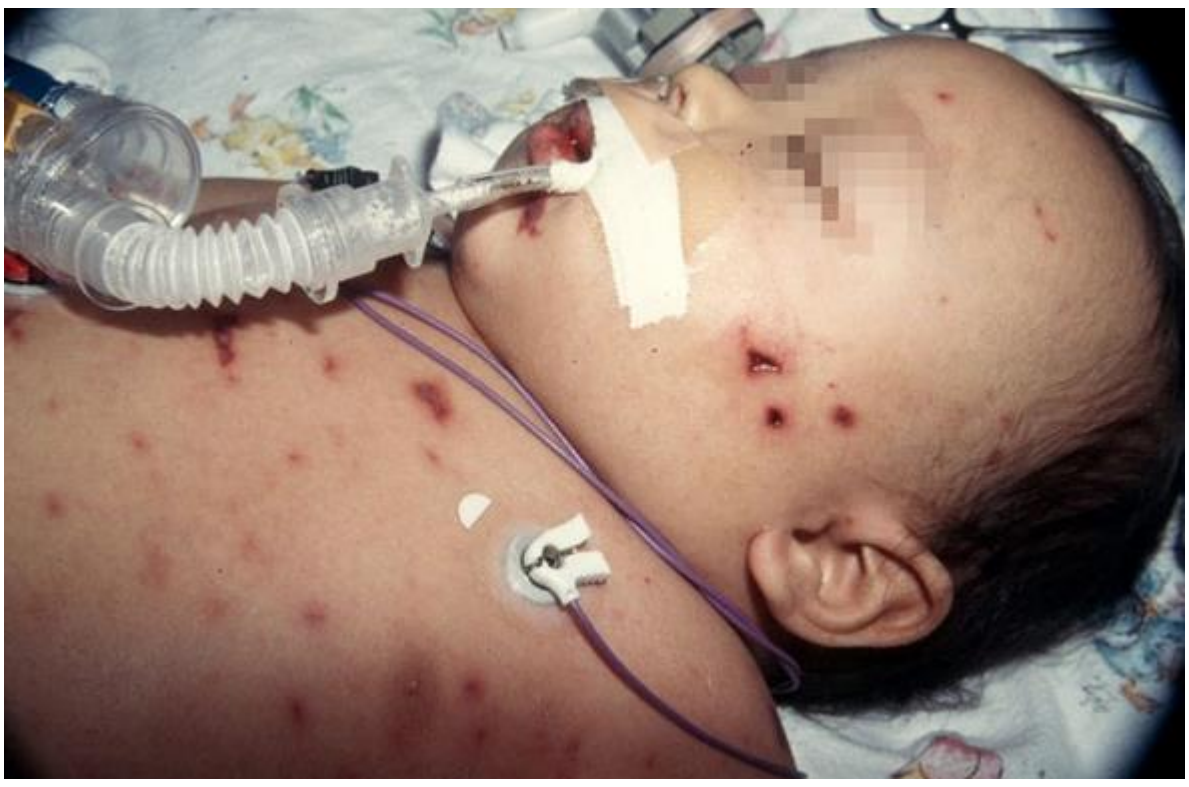
   N.B. TRIPTANS can relieve any neurovascular headache (incl. SAH and meningitis) - *TRIPTANS should never be used as diagnostic tool*.

4. **Meningeal irritation signs** – nuchal rigidity, Kernig's sign, Brudzinski's sign, tense bulging fontanel.
   - meningeal signs are milder in ***viral meningitis***.
   - meningeal signs may be *falsely absent* in:
     1) elderly, infants
     2) debilitated, immunosuppressed
     3) receiving anti-inflammatory drugs or antibiotics.

5. **Vomiting, photophobia, irritability**

6. **Seizures** (30-40% ***bacterial meningitis*** cases, typically during 1st week of illness; focal signs are not typical for uncomplicated *viral meningitis*); etiology:
   1) fever
   2) focal ischemia, cortical venous thrombosis with hemorrhage
   3) hyponatremia
   4) subdural effusion / empyema (mass effect)
   5) antimicrobial agents (e.g. imipenem, penicillin).

- look for typical *petechial-purpuric rash* of meningococcemia (esp. in extremities):



similar rash may be seen in other forms of meningitis (e.g. enteroviruses*, *S. aureus*, *Acinetobacter* sp., and, rarely, *S. pneumoniae* or *H. influenzae*).

*rash resembling rubella

SUBACUTE / CHRONIC MENINGITIS

- manifestations are similar to acute meningitis but evolve more slowly:
  1. Low-grade fever
  2. Chronic headaches
  3. Neck stiffness
  4. Subtle personality / mental status change (may be the only sign in elderly!)
  5. Cranial neuropathies, radiculopathies, hydrocephalus.
- may be fatal if not successfully treated.

COMPLICATIONS

BACTERIAL MENINGITIS

1. **Seizures**
2. **DIC, shock**
3. **Subdural effusions** - usually in infants as self-limited process (as inflammatory process subsides, subdural fluid is reabsorbed);
   Treatment – *repeated daily* ***needle aspirations*** through coronal sutures;
   – *indications*: infected fluid (prolonged fever), increased ICP, rapidly enlarging head circumference in child, focal neurological findings (seizures).
   – *no more than 20 mL/d of CSF should be removed from one side* (to prevent sudden shifts in intracranial contents).
   – if effusion persists after 3-4 wk of taps → surgical exploration for possible excision of subdural membrane is indicated.
4. **Brain abscess, subdural empyema**
5. **Cerebral thrombophlebitis**
6. **Stroke**:
   a) vasospasm caused by subarachnoid infection
   b) loss of cerebral autoregulation + hypotension
   c) inflammatory infiltration of arterial wall (vasculitis).
7. **Cranial nerve palsies** (esp. sensorineural hearing loss; oculomotor paresis)
8. **Consequences of ICP↑** (incl. brain herniation)
9. **Chronic adhesive arachnoiditis, hydrocephalus**

DIAGNOSIS

1. All meningitis suspects must have **LUMBAR PUNCTURE** ASAP - gold standard for diagnosis!

> If ***mass lesion is consideration*** (focal neurologic deficit, papilledema, seizures, evidence of head trauma) - obtain contrast-enhanced CT or MRI first.

– nevertheless, two ***blood samples are drawn*** for culturing → ***empirical antimicrobial therapy*** is started.

- if ICP↑ is present – administer IV bolus of **MANNITOL** 1 g/kg (ideally 20 min before LP), use small (but minimum 22G) needle, obtain minimum required sample; in addition, patient can be intubated and hyperventilated.

- parameters of meningitic CSF: for more detailed explanations → see p. D40 >>
  1) **opening pressure** moderately↑ (bacterial meningitis > viral meningitis).
  2) **cloudy & straw-colored** (bacterial meningitis) or **clear-cloudy & colorless** (viral meningitis).
  3) **cell count**↑ (esp. in untreated meningitis):
     500-20,000/mm^3 PMNs in bacterial meningitis;
     5-1,000/mm^3 mononuclears (may be PMNs at onset*) in viral meningitis (also in tbc, fungal**, Lyme, syphilitic, toxoplasma, or chronic meningitis).
     *esp. in enteroviral infections
     **PMNs with Blastomyces infection
  4) **glucose**↓ - most specific (esp. in bacterial, tuberculous, cryptococcal meningitis; normal in viral meningitis*).
     *but ↓ in mumps, lymphocytic choriomeningitis virus
  5) **protein**↑ (bacterial meningitis > 100 mg/dl; viral meningitis < 100 mg/dl).
  6) **LDH**↑ (in bacterial, fungal meningitis).
  7) **lactate**↑ (>4 mmol/L considered diagnostic; due to PMNs presence, i.e. only in bacterial meningitis).

- organism detection: for more detailed explanations → see p. D40 >>
  1) **stains** - *Gram stain* (for all cases with PMNs), *India ink stain* (in cryptococcal meningitis), *Ziehl-Neelsen acid-fast stain* (tbc).
  2) **antigen tests** (PCR, latex particle agglutination, counterimmunoelectrophoresis, limulus lysate test*, immunofluorescence, etc).
     *highly sensitive at detecting LPS (Gr- organisms).

XPERT EV TEST® - FDA approved fully automated *reverse transcription-PCR* test for Enterovirus detection; result in 2.5 hours!

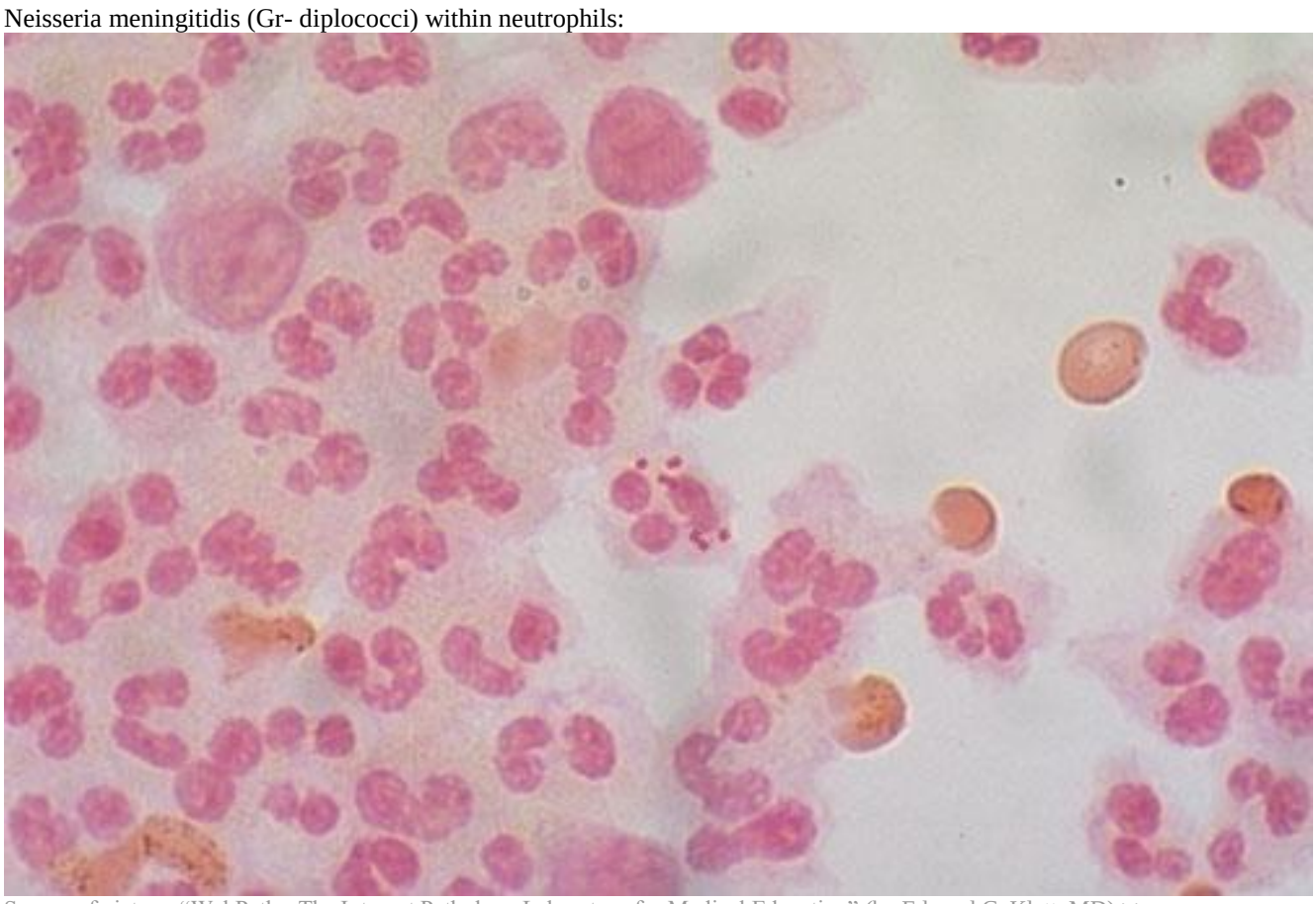
3) **cultures**
   - positive in 70-85% bacterial meningitis cases;
   - gold standard for diagnosis of enteroviral CNS infection, but negative in 25-33% patients; also in mumps.
4) **CSF antibody titers**↑ → CSF/serum antibody index (for viruses, syphilis, Lyme disease); unfortunately, antibodies appear in CSF too late to aid in any therapeutic decisions (used only for retrospective diagnosis).

In 2-3% CSF culture-proven bacterial meningitis cases, CSF profile is normal (incl. Gram stain)! CSF may be normal early in course – do not hesitate to repeat LP if clinical signs persist!

Antimicrobial therapy:
- will not significantly alter CSF profile (WBC count, glucose & lactate concentration, antigen test results) for at least 2-3 days.
- will decrease sensitivity of Gram's stain & culture (window of *2-3 hours after giving parenteral antibiotics* when CSF cultures are not adversely affected).

Gram's stain and culture ***should be negative*** in CSF obtained 24 hours after initiation of IV antimicrobial therapy, if organism is sensitive to that antibiotic.

Neisseria meningitidis (Gr- diplococci) within neutrophils:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

India ink stain (budding organisms - cryptococci):

2. **CT** - findings are highly variable (usually normal in uncomplicated meningitis) - vast majority of patients do not require neuroimaging.

CT should not unnecessarily delay LP or antimicrobial therapy!

a) **severe acute meningitis**:
   1) striking *pial and ependymal enhancement* (superficially looks like SAH, but seen only in contrast-enhanced CT; vs. SAH)

      contrast enhancement of meninges is always abnormal except after recent neurosurgical procedure.
   2) abnormal signal or density in CSF (high protein content or frank pus)
   3) secondary brain edema.
   4) complications of meningitis (subdural collections, hydrocephalus, cerebral infarction).

b) **chronic meningitis** – may be *no imaging findings* or merely minimal ventricular enlargement.

3. **EEG** is usually normal or slightly slow.

4. **WBC count** is markedly elevated in bacterial meningitis (mildly in viral meningitis).

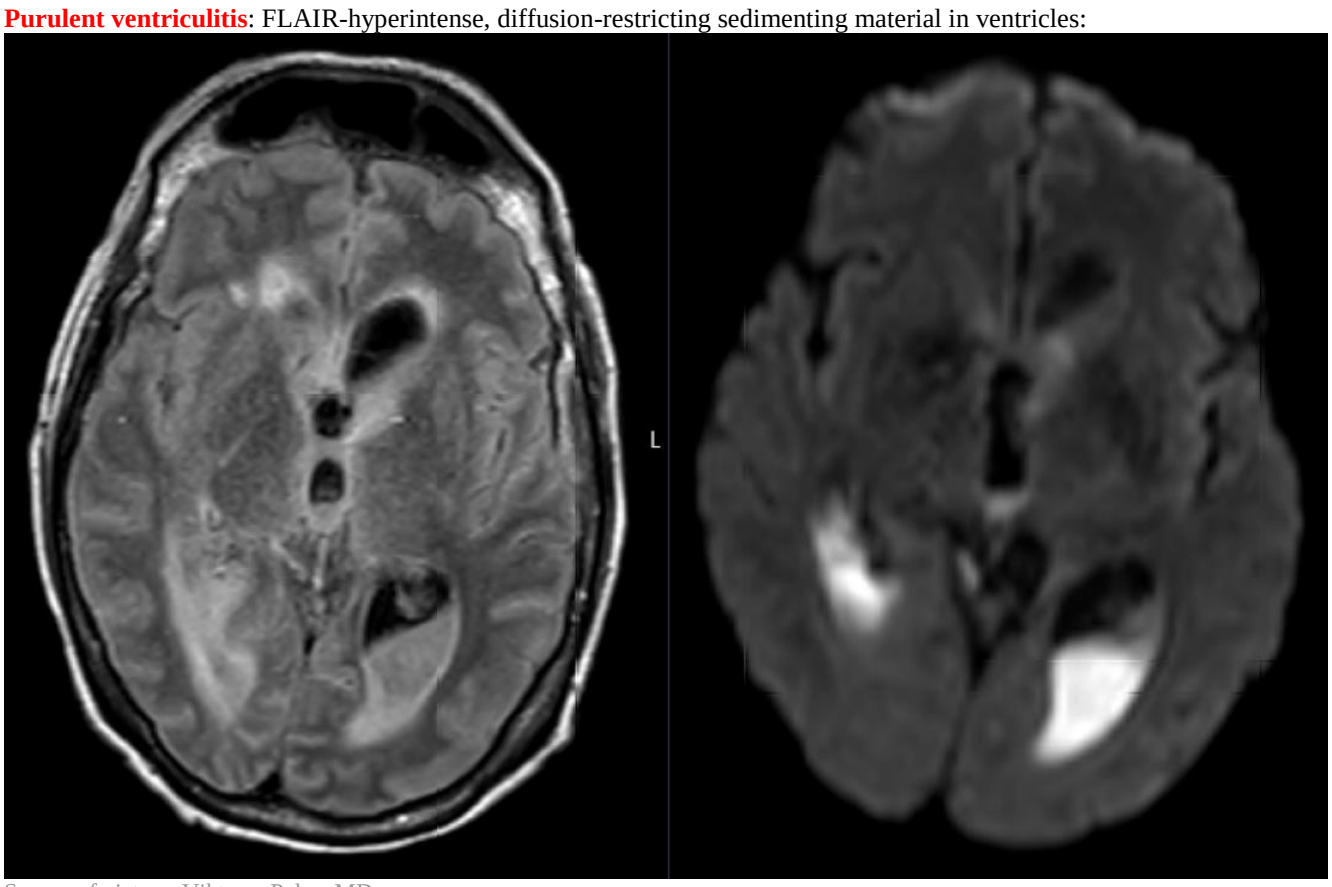
5. Serum **antibody titers**↑ - ≥ fourfold rise in paired sera (for viruses).

6. Organism detection in other fluids:
   1) ***blood cultures*** (positive in 80-90% patients with bacterial meningitis!; some viruses).
   2) ***stool specimen*** may be better source of viral isolate (enteroviruses), but is not diagnostic of meningitis.
   3) mumps virus may be isolated from ***saliva***, ***throat washing***.
   4) meningococci may be found in ***skin lesions***, ***nasopharyngeal secretions***.

      In general, cultures of body surfaces and orifices are not helpful in identifying causative pathogen!

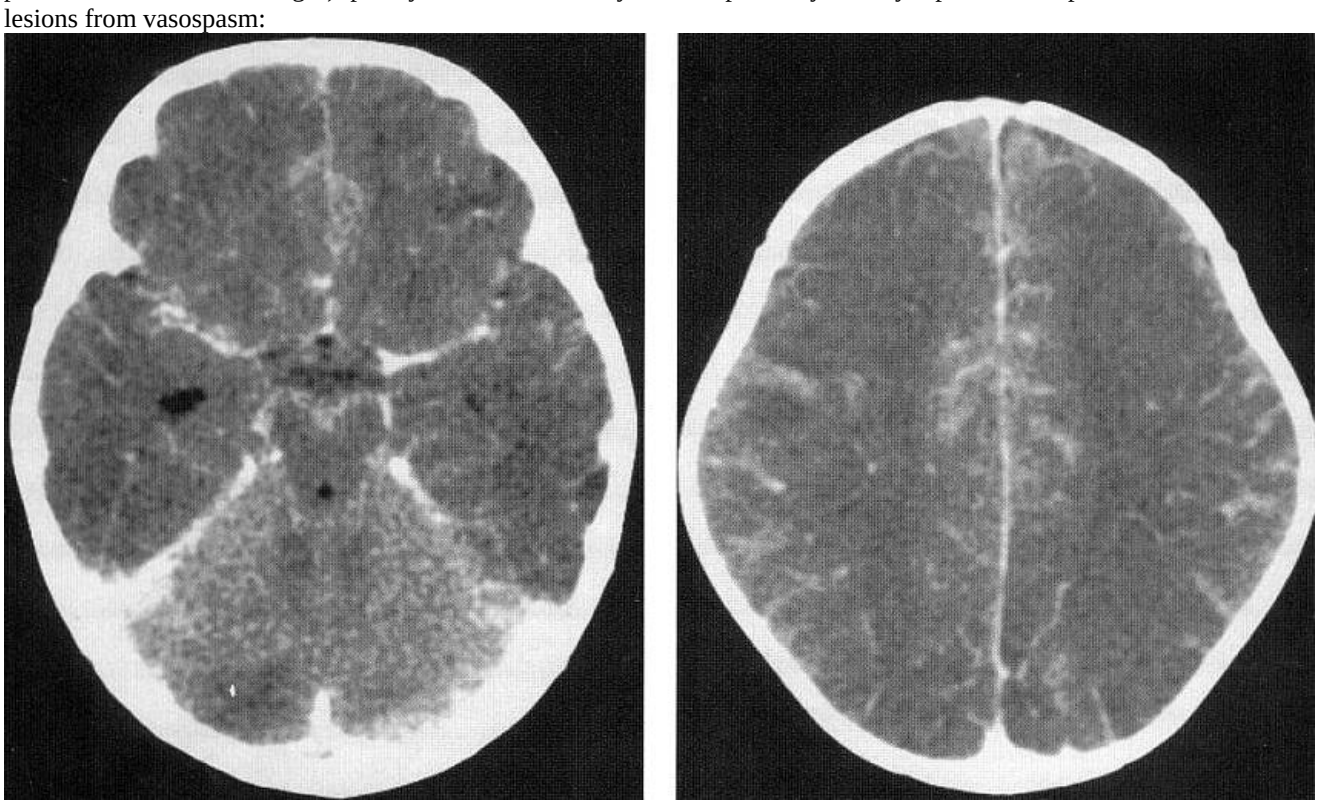
7. Etiologic diagnosis in ***chronic meningitis*** may require meningeal biopsy (→ histology, electron microscopy, PCR, cultures).
- target regions that enhance with contrast on MRI or CT.
- with current microsurgical techniques, most areas of basal meninges can be accessed via limited craniotomy.
- most common conditions identified - sarcoid (31%), metastatic adenocarcinoma (25%).

Purulent ventriculitis: FLAIR-hyperintense, diffusion-restricting sedimenting material in ventricles:

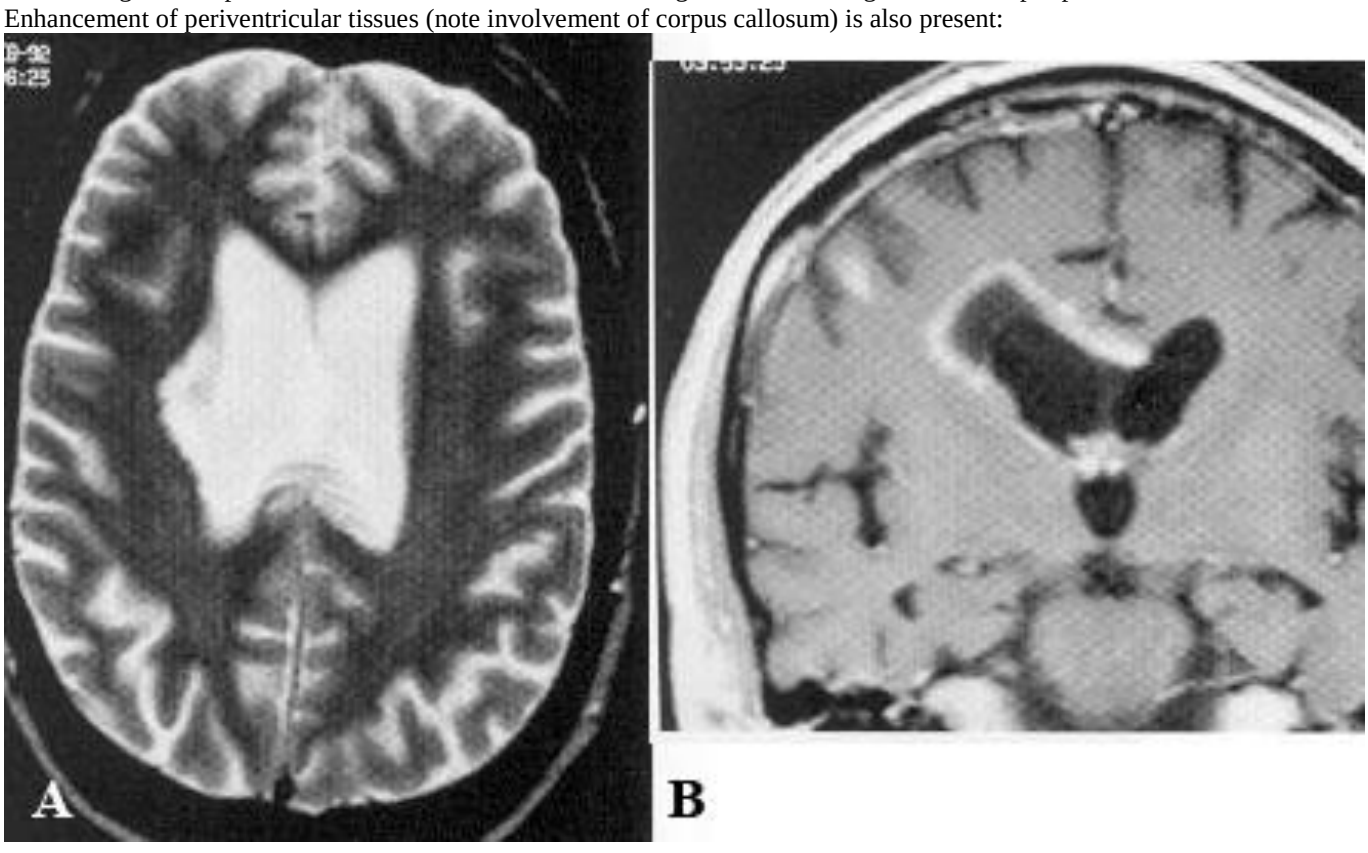


Source of picture: Viktoras Palys, MD

Pyogenic meningitis (postcontrast axial CT) - high-attenuation of pial surfaces and filling subarachnoid spaces (it was not present on noncontrast images); patchy diminished density in brain parenchyma may represent encephalitis or ischemic lesions from vasospasm:



Herpes simplex ventricilitis (MRI contrast medium): A) T2-weighted spin-echo; B) T1-weighted spin-echo.
Necrotic right-sided periventricular lesion shows central low signal on T1 and high on T2 with peripheral enhancement. Enhancement of periventricular tissues (note involvement of corpus callosum) is also present:



TREATMENT

- patients prefer **quiet, darkened room**.
- ANALGESICS - to relieve headache (often reduced by initial diagnostic lumbar puncture).
- ANTIPYRETICS - to reduce fever.

VIRAL MENINGITIS

- self-limiting - **treated symptomatically** OUTPATIENTS (with close follow-up within 24 hours).

- indications for hospitalization:
  1) severe cases
  2) deficient humoral immunity (→ trial of **IVIG**)
  3) herpes meningitis (→ intravenous **ACYCLOVIR**)
  4) potential nonviral causes.
- **PLECONARIL** is active against *enteroviruses*, but FDA has rejected its approval.

BACTERIAL MENINGITIS

1. DEXAMETHASONE

- if **BACTERIAL MENINGITIS** is strongly suspected - *prevents neurological disability and death* by decreasing meningeal inflammation (due to released bacterial components by bactericidal antibiotics)

> In a 2015 Cochrane meta-analysis of 25 randomized controlled trials including 4121 participants, corticosteroids were found to significantly decrease rates of severe hearing loss, any hearing loss, and neurological complications. Corticosteroids did not significantly impact mortality, although a subgroup analysis demonstrated a reduction in mortality due to meningitis caused by S. pneumoniae

- for adults and children ≥ 2 months of age.
- dose - 0.15 mg/kg q6h (i.e. **10q6**) IV.
- use **H_2 antagonist** to avoid GI bleeding.

N.B. **VANCOMYCIN** effect may be adversely affected (since meningeal inflammation improves VANCOMYCIN penetration into CSF); H: use **higher doses** of VANCOMYCIN (15 mg/kg q6h) or **intrathecal** VANCOMYCIN.

- course - first 4 days of antimicrobial therapy

  First dose of DEXAMETHASONE should be administered 20 min before first antimicrobial dose.
  - if no bacteria grows in culture or is otherwise identified after 24-48 h, corticosteroids should be stopped, and antibiotic coverage reassessed (corticosteroids for 1 day should not be detrimental even if cause is virus, fungus, or TB).

2. ANTIMICROBIAL THERAPY (must be bactericidal in CSF* – i.e. maximum tolerated doses!) intravenously (intrathecal / intraventricular therapy is not effective).

*titers of 10 times minimum bactericidal concentration are required to achieve CSF sterilization

Crucial step is to initiate ANTIMICROBIAL THERAPY immediately!!!!!!!!!!

If you suspect meningococcus, give PENICILLIN G before transporting to hospital!

Empiric therapy (all patients must be isolated for first 24 h of therapy): dosages → see p. Inf1 >>

CEFEPIME* 2 g q8h + VANCOMYCIN 15mg/kg q12h (goal trough: 15 – 20 mg/L)
*for type I penicillin hypersensitivity (i.e. anaphylaxis) substitute with AZTREONAM 2 g q6h or CIPROFLOXACIN 400 mg q8h

NEONATE (most likely group B streptococci, *E. coli*, *L. monocytogenes*) – combination:
1) **AMPICILLIN**
2) **GENTAMICIN** or **CEFOTAXIME** or **AMIKACIN** or **TOBRAMYCIN**

INFANT 4-12 WEEKS (*H. influenzae* and *Str. pneumoniae* join neonatal pathogens) – combination:
1) **AMPICILLIN**
2) **CEFOTAXIME** or **CEFTRIAXONE** or **CHLORAMPHENICOL**

OLDER INFANT ÷ CHILD (*N. meningitidis* joins pathogens) – combination:
1) **VANCOMYCIN**
2) **CEFOTAXIME** or **CEFTRIAXONE**

ADULT (*S. pneumoniae*, *N. meningitidis*) – combination:
1) **VANCOMYCIN**
2) **CEFTRIAXONE*** or **CEFOTAXIME***
   * for **neurosurgical / immunocompromised patient** use **CEFTAZIDIME** (*Pseudomonas aeruginosa* may be etiological agent).
3) for **adult > 50 yrs / immunocompromised / pregnant** - add **AMPICILLIN** (Gr- aerobic bacilli; *L. monocytogenes* – resistant to cephalosporins); if severe penicillin allergy – **TMP/SMX**

Therapy according to Gram stain:

Gr+ organisms → CEFOTAXIME or CEFTRIAXONE + VANCOMYCIN.
- if organisms are pleomorphic (*Listeria* sp.) - add AMPICILLIN.

Gr- bacilli → TICARCILLIN or CEFTAZIDIME + *aminoglycoside*.

Once causative organism has been identified:

Microbe	Infants (> 2000 g)	Children & Adults
Group B streptococcus	**PENICILLIN G** or **AMPICILLIN** + **AMIKACIN** or **GENTAMICIN**	
Neisseria meningitidis		**PENICILLIN G** or **AMPICILLIN** or **CEFOTAXIME** or **CEFTRIAXONE** or **CHLORAMPHENICOL** + (at end of therapy) oral **RIFAMPIN** for 2 d.*
Streptococcus pneumoniae		**VANCOMYCIN**** + **CEFOTAXIME** or **CEFTRIAXONE**
Enteric Gr- bacilli (except *Ps. aeruginosa*)	**CEFOTAXIME** + **AMIKACIN** or **GENTAMICIN**	**CEFOTAXIME** or **CEFTRIAXONE** + **AMIKACIN** or **GENTAMICIN**
Pseudomonas aeruginosa	**CEFTAZIDIME** or **CIPROFLOXACIN** or **TICARCILLIN** ± **GENTAMICIN**	
Listeria monocytogenes	**AMPICILLIN** + **AMIKACIN** or **GENTAMICIN**	**AMPICILLIN** or **TMP-SMX**
Haemophilus influenzae type b	**CEFOTAXIME**	**CEFOTAXIME** or **CEFTRIAXONE** or **CHLORAMPHENICOL** (with **AMPICILLIN**)
Staphylococcus aureus (methicillin-sensitive)	**METHICILLIN**	**OXACILLIN**
Staphylococcus aureus (methicillin-resistant)	**VANCOMYCIN**	
Staphylococcus epidermidis	**VANCOMYCIN** ± **RIFAMPIN**	

*to eradicate nasopharyngeal carriage
**some pneumococci are resistant to penicillins, cephalosporins, chloramphenicol!

- ***PRIMARY FOCUS OF INFECTION*** should be eradicated (by surgery if necessary; e.g. persistent CSF fistulas must be closed by suturing of dura - otherwise meningitis will almost certainly recur).
- unless dramatic response to therapy occurs, ***CSF should be re-examined 24-48 hours after initiation of treatment*** (to assess effectiveness of medication – CSF sterility + conversion to lymphocytic predominance).
- drug dosages should not be reduced when clinical improvement occurs (drug penetration decreases as meninges become less inflamed).
- duration of therapy (based largely on tradition; should be individualized and based on clinical response): neonates – 3 weeks; *H. influenzae*, *S. pneumoniae* – 10-14 days; *N. meningitidis* – 7 days; Gr- aerobic bacilli - 3 weeks.
- post-treatment CSF examination is not meaningful criterion of recovery (i.e. CSF need not be re-examined if patient is clinically well!).

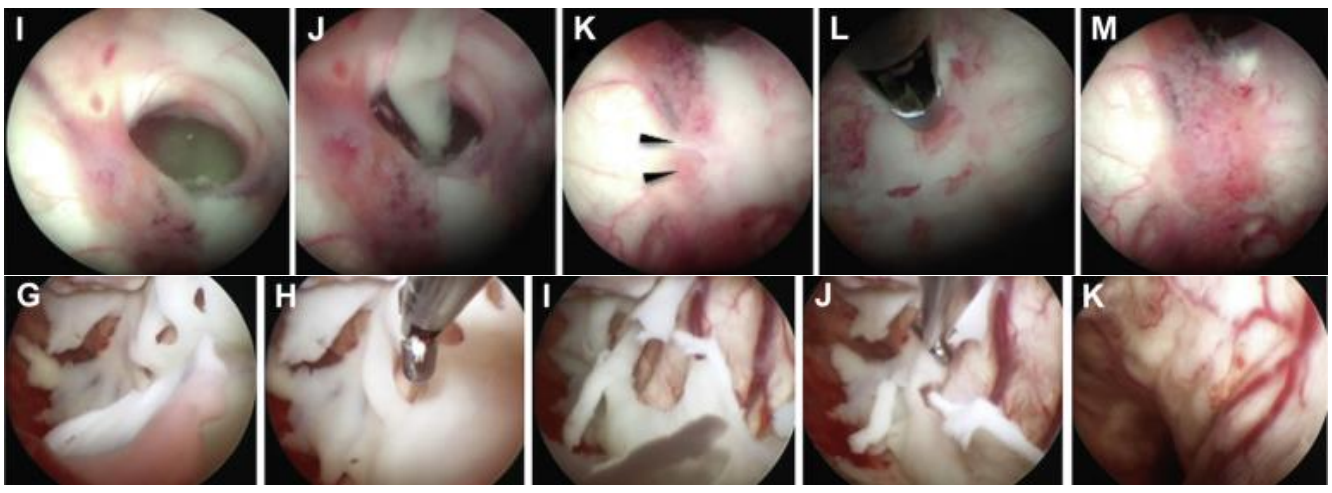
3. OTHER MEASURES (treatment of dehydration, coagulopathy, seizures, raised ICP & cerebral edema)

Hyponatremia

- majority of children are hyponatremic (serum [Na^+] < 135 mEq/L) – due to **syndrome of inappropriate antidiuretic hormone secretion (SIADH)**.
- *time-honored* treatment of SIADH was ***fluid restriction*** (but autoregulation of cerebral blood flow is lost - decrease in mean systemic arterial pressure → decrease in cerebral blood flow).
- *present recommendations* - limit initial IVI rate to 3/4 of normal maintenance requirements; IV fluid should be multielectrolyte solution containing ¼-½ normal saline and 20 to 40 mEq/L potassium in 5% dextrose.
  - if child has seizures as result of low serum sodium, infuse ***3% NaCl*** (5 ml/kg over 1 hour).
  - once serum [Na^+] increases > 135-140 mEq/L, fluids can be gradually increased.

Purulent ventriculitis - in severe ventriculitis, EVD/lumbar drain is not efficient enough, especially when the CSF contains pus/flakes (niduses of infection adherent to the choroid plexus and ependymal lining) - act as continuous source of infection and are thus difficult to eliminate – consider **endoscopic lavage**:

- clamp EVD ~12 hours before surgery, if ventricles are not dilated.
- insert ***rigid endoscope*** ~4–5 cm lateral to the midline and ~1–2 cm anterior to the coronal suture.
- poor visibility because of turbidity is improved with copious ***irrigation with Ringer lactate***.
- ***pus is aspirated*** with a 5-mL syringe attached to one of the ports of the endoscope sheath after taking the endoscope close to the site of pus;
  - if aspiration is not successful, fluid is pushed with a 10-mL syringe after taking the endoscope close to where the pus was settled - this maneuver unsettles purulent material
- after the ipsilateral ventricle is cleansed, a generous ***septostomy*** is performed, the opposite ventricle entered, and all the purulent material is removed in a similar fashion.
- ventricular surfaces are thoroughly inspected and any flakes attached to the ventricular wall or choroid plexus are removed gently with an endoscopic forceps.



EMPIRICAL THERAPY for CHRONIC MENINGITIS

- when all attempts at diagnosis fail:

1) **antimycobacterial** agents
2) AMPHOTERICIN B
3) **glucocorticoids** (for noninfectious inflammatory causes).

CHEMOPROPHYLAXIS

- for family members and other intimate contacts of child with meningococcal or *H. influenzae** infection.

*only if there are children < 4 years between contacts (then administer chemoprophylaxis to all contacts [except pregnant women], independent to their Hib vaccination status, because vaccination does not prevent nasopharyngeal colonization)

- not routinely warranted for *medical personnel* (except those who have had direct mucosal contact with patient's secretions - mouth-to-mouth resuscitation, intubation, suctioning, etc).

RIFAMPIN (started within 24 hours of diagnosis of contact case)

meningococci - 10 mg/kg (5 mg/kg for newborns; 600 mg for adults) q12h for 2 d.
H. influenzae type B - 20 mg/kg (10 mg/kg for newborns; 600 mg for adults) × 1/d for 4 d.

N.B. RIFAMPIN prophylaxis eradicates organisms only from nasopharynx!

PROGNOSIS

BACTERIAL MENINGITIS

- MORTALITY ≤ 10-20% (many deaths occur during *first 48 hours of hospitalization*); 50-90%* in untreated cases.

*almost 100% in pneumococcal meningitis!

Austrian syndrome (triad of pneumococcal meningitis, pneumonia, and endocarditis) has particularly high fatality rate.

- PERMANENT NEUROLOGIC SEQUELAE occur in 20-50% survivors: permanent hearing loss (10%), mental retardation*, cerebral palsy, permanent seizure disorders, behavioral problems.

*bacterial meningitis is one of most preventable causes of mental retardation!

VIRAL MENINGITIS

Death is exceptional!

- **adults** - prognosis for full recovery is excellent (rarely - persisting headache, mild mental impairment, incoordination, generalized asthenia for weeks to months).
- **infants / neonates** – prognosis is less certain (intellectual impairment, learning disabilities, hearing loss have been reported).

SPECIFIC FEATURES

MYCOBACTERIUM TUBERCULOSIS

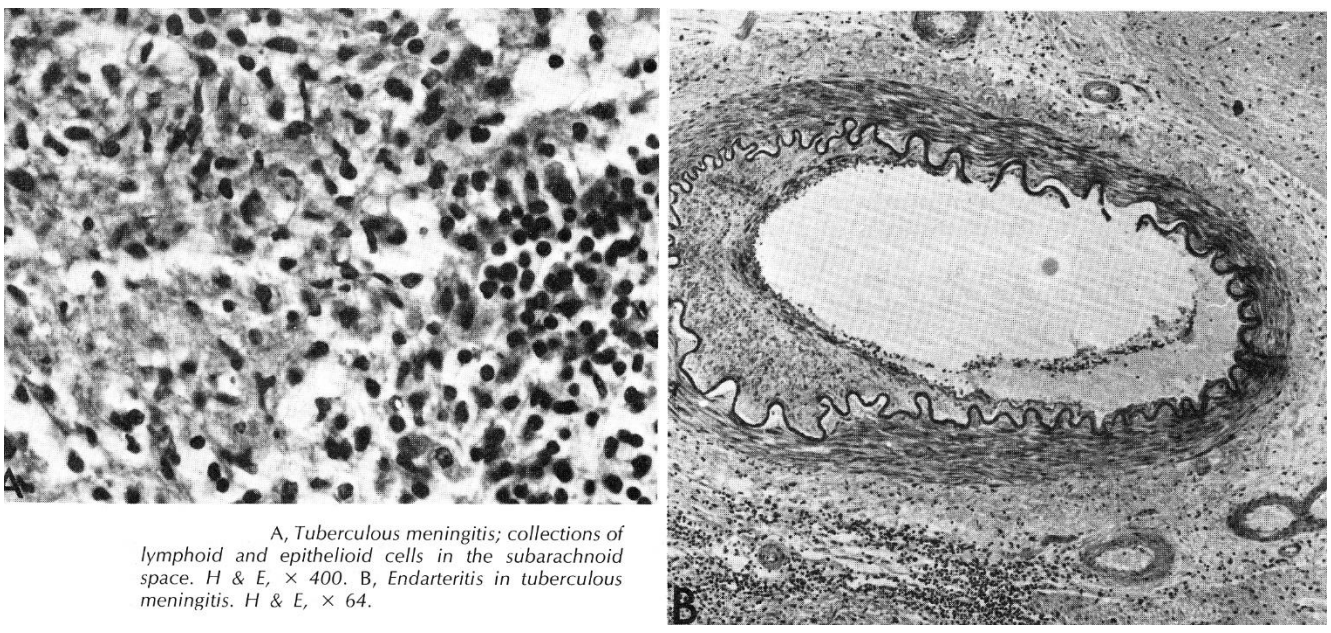
Epidemiology

- INCIDENCE is slowly increasing (HIV-infected individuals + immigration from Asian, Latin American, and African countries).
- most common in childhood (in 3rd countries) and early adult life (in Western countries).

Etiopathophysiology

- tuberculous meningitis is always **secondary to tuberculosis elsewhere in body** (usually in lungs, but may be in any organ).
- progression of primary infection (children) / reactivation (adults) → bacteremia & miliary dissemination → CNS entrance → miliary tubercles (sharply outlined round white nodules) in brain parenchyma and/or meningeal tissue.

- caseous foci (subependymal or near subarachnoid space) may rupture and discharge (esp. in presence of impaired host immunity) bacilli and tuberculous antigens into subarachnoid space → *subacute / chronic granulomatous meningitis* (most common form of tbc infection in nervous system).
- gelatinous gray-white exudate tends to pool in ***basilar cisterns*** - surrounds cranial nerves (CN lesions), major blood vessels (vasculitis & ischemia); obstructive hydrocephalus may develop.
  - ependymal lining is covered with exudate or appears roughened (GRANULAR EPENDYMITIS).
  - thick collar of fibrosis (FIBROUS ADHESIVE ARACHNOIDITIS) may form around optic nerves, cerebral peduncles, and basilar surface of pons and midbrain.
- complications are initiated by ***hypersensitivity reaction*** (to tuberculoproteins) in subarachnoid space.
- proliferative changes in inflamed vessels of meninges (OBLITERATIVE ENDARTERITIS) → thrombosis → infarcts (most frequently in basal ganglia).



A, *Tuberculous meningitis; collections of lymphoid and epithelioid cells in the subarachnoid space. H & E, × 400.* B, *Endarteritis in tuberculous meningitis. H & E, × 64.*

Clinical Features

- insidious onset, *vague nonspecific protracted progressive course**: moderate constitutional symptoms (low-grade fever, anorexia, weight loss, night sweats, malaise), unrelenting headache, ± meningismus.

  *some patients present with *acute meningoencephalitis* (coma, ICP↑, seizures, focal neurological deficits)
- later – CN palsies (esp. CN6, CN3), seizures, plegias, alteration of mental status.
  - frequently, *hydrocephalus* develops.

Diagnosis – CSF examination:

1) pressure↑, CSF clear or cloudy (straw-colored) with fibrin web formation on standing, 10-500 **lymphocytes** (in early stages may be > 80% **PMN**), protein ↑↑ 100÷500, **glucose** ↓↓ < 45.
2) **Ziehl-Neelsen acid-fast stain** - usually negative (small numbers of organisms in CSF)
3) **CSF cultures** onto ***Lowenstein-Jensen medium*** (wait at least for 8 weeks – will be positive in 45-90% cases); large CSF volume (10 mL) is required for adequate culture!
4) **PCR tests** (likely will replace many of current tests for mycobacteria!).

N.B. CSF chloride↓ as diagnostic aid for tbc meningitis is no longer clinically relevant!

- MRI after gadolinium enhancement - florid contrast enhancement within basal cisterns; hydrocephalus, areas of infarction, tuberculomas.
- additional diagnostic data:
  1) positive tuberculin skin test (30-80% patients).
  2) chest X-ray evidence of tuberculous lesion (most children, 50% adults).
  3) evidence of active infection elsewhere (20-70% patients).
  4) history of contact with case of tuberculosis.

If suspicion is high, treatment should begin before bacteriologic proof: see p. 237 >>

1. 4 agents for first 2 months (**ISONIAZID** + **RIFAMPIN** + **PYRAZINAMIDE** + **ETHAMBUTOL**) → **ISONIAZID** + **RIFAMPIN** for at least 7-10 months (i.e. 9-12 months*; up to 24 months)

   *longer than for pulmonary tbc
2. **Corticosteroids** indicated for all patients (esp. with ICP↑, cerebral edema, mental status↓, focal signs, spinal block, hydrocephalus) – for first 3 weeks (then gradually decreased during next 3 weeks).
3. Shunting for hydrocephalus.

Untreated patient is unlikely to survive beyond 4-8 weeks.

Drug	*Children*	*Adults*
ISONIAZID†	10 mg/kg/d* once daily	300 mg/d + 50 mg/d PYRIDOXINE
RIFAMPIN	10 mg/kg/d*	600 mg/d
PYRAZINAMIDE†	30 mg/kg/d	
ETHAMBUTOL	15-25 mg/kg/d	
STREPTOMYCIN	20-40 mg/kg/d	
RIFABUTIN		300 mg/d

*up to 15 mg/kg/d in HIV-infected patients
†penetrate CSF with or without meningeal inflammation

Prognosis - treatment is less effective - mortality is higher (than in bacterial meningitis).

- SEQUELAE occur in ≈ 25% patients who recover (facial weakness, intellectual disorganization, deafness, seizures, blindness, plegias).
- *intracranial calcifications* may appear after 2-3 years.

Intracerebral **TUBERCULOMA** - rounded *tumorlike intraparenchymal mass* (localized tuberculosis infection); always secondary to tuberculosis elsewhere in body (e.g. frequent finding in tuberculous meningitis, usually asymptomatic);

- tend to ***lie superficially*** in brain (most characteristically *adjacent to Sylvian fissure*; brain stem and cerebellum are other favoured sites).
- central core of caseous necrosis surrounded by typically tuberculous granulomatous reaction.
- up to several centimeters in diameter → mass effect (mimics tumor).
- CT density as brain (or slightly denser) + little or no surrounding edema ← tuberculoma is one of few supratentorial mass lesions which might be overlooked on CT without IV contrast.
- on CT with IV contrast, tuberculomas *enhance strongly* (solid or thick-walled mass).
- calcification may occur in inactive lesions.
- treatment is based on **chemotherapy**; large accessible lesion → **surgical excision**.

Tuberculous **ENCEPHALOPATHY** - purely **allergic phenomenon** - *cerebral edema* (occasionally with perivascular demyelination) or *hemorrhagic leukoencephalopathy* deep in white matter at distance from vascular abnormalities and purulent exudate.

Potts disease - vertebral tuberculosis (compression fractures, etc).

MYCOBACTERIUM AVIUM, MYCOBACTERIUM INTRACELLULARE

- clinically identical.

- CNS disease is result of hematogenous dissemination from respiratory or GI source of infection.
- occurs primarily in patients with advanced HIV disease (< 50 $CD4^+$ cells/µl).
- meningitis, meningoencephalitis, rhombencephalitis, brain abscess, or cranial neuropathies.

Treatment at least four-drug regimen:

CLARITHROMYCIN and **AZITHROMYCIN** have excellent activity!

1) **CLARITHROMYCIN** (500 mg ×2/d)
2) **RIFAMPIN** (600 mg/d)
3) **ETHAMBUTOL** (25 mg/kg/d for 2 months then 15 mg/kg/d)
4) **STREPTOMYCIN** (0.75-1.0 g at least three times per week).

- alternative regimen: **AZITHROMYCIN** (250 mg/d), **RIFABUTIN** (300 mg/d), **ETHAMBUTOL**, **STREPTOMYCIN**.
- treatment is continued until cultures are negative for at least 12 months (will likely need to be continued for life of patient).

FUNGAL MENINGITIS (GENERAL), CRYPTOCOCCAL MENINGITIS

Etiology – see *above >>*

Pathogenesis: inhalation* → hematogenous spread to CNS.

*history of exposure to agent is important

Clinical presentation – **subacute / chronic meningitis** (resembles tbc meningitis) can be obscure even in healthy adult population (headache, low-grade fever, lassitude, weight loss).

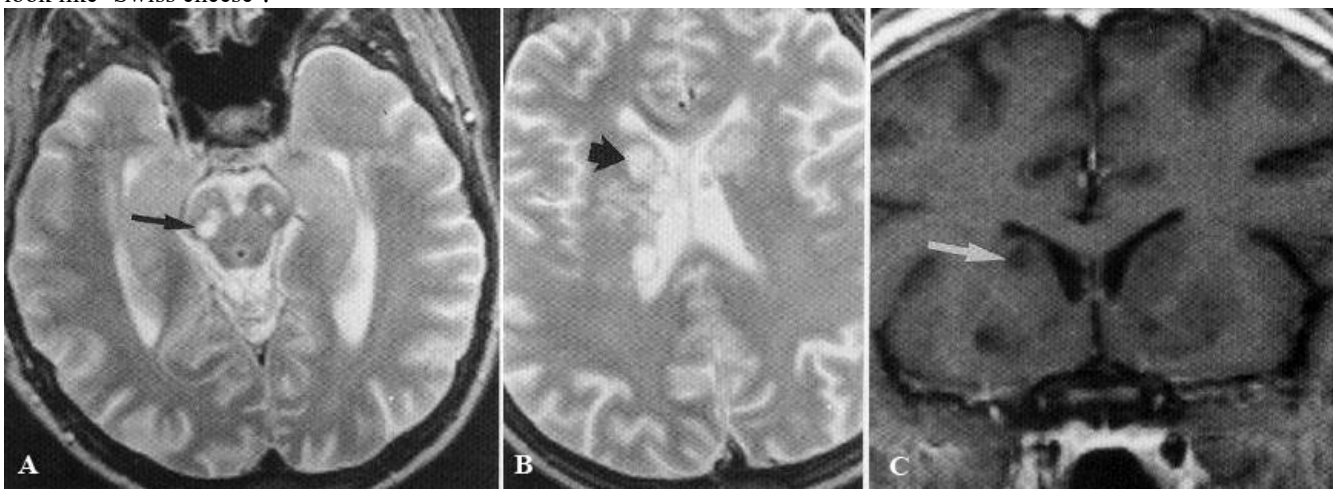
- reflects *immune status of host* (more severe immunological compromise - more rapid clinical onset).
- frequent hydrocephalus.

May be no enhancement in neuroimaging.

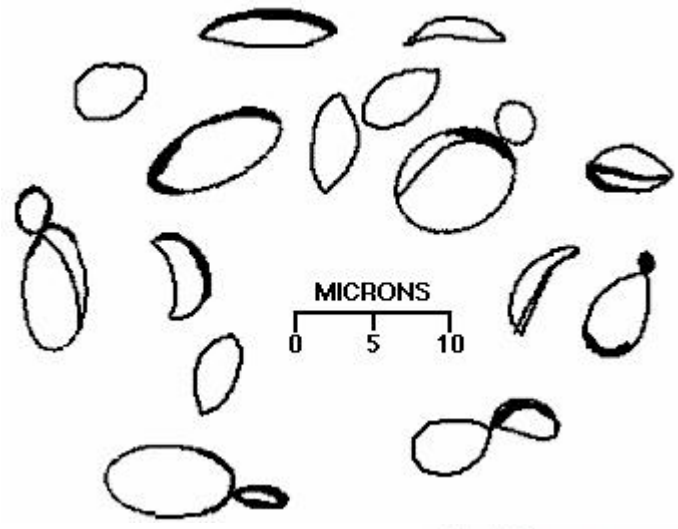
- 10% *CRYPTOCOCCAL* meningitis cases develop **CRYPTOCOCCOMAS** – dilated Virchow–Robin spaces filled with cryptococcus organisms – rounded* lesions (low intensity on T1-MRI and high intensity on T2-MRI); most commonly in basal ganglia (in distribution of lenticulostriate arteries) but may occur elsewhere (e.g. brain stem); minimal or absent inflammation (non-enhancing, no edema).

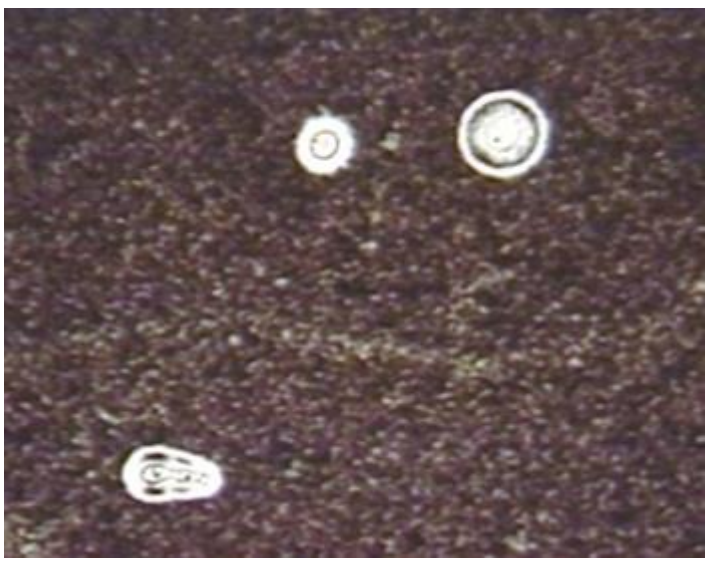
*tubular on coronal or sagittal imaging.

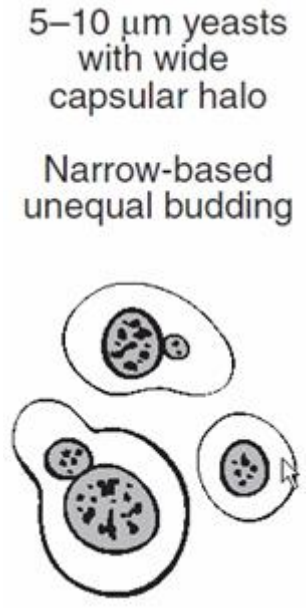
Cryptococcomas (*arrows*) in brain stem and basal ganglia - transverse T2-MRI (A, B) and coronal T1-MRI (C); ganglia look like 'Swiss cheese':

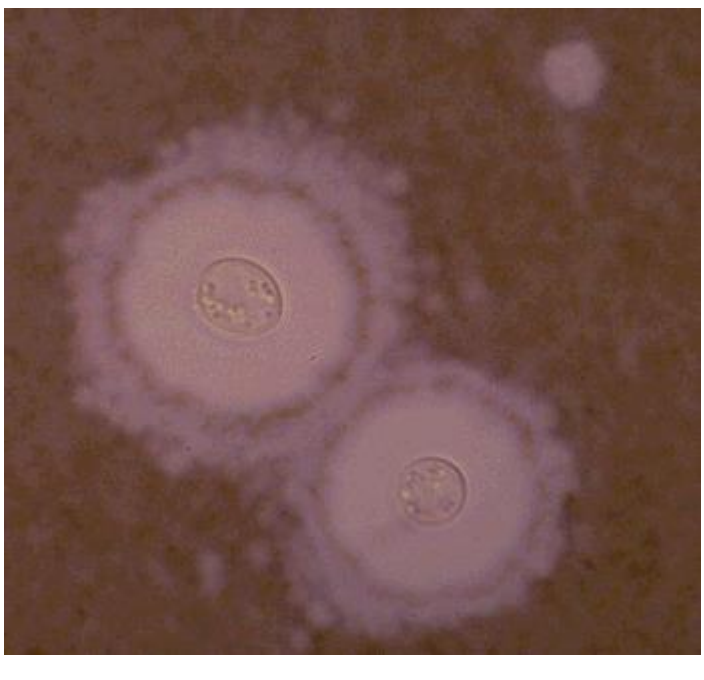


Cryptococcus neoformans – polysaccharide capsule visible by India ink preparation in CSF:



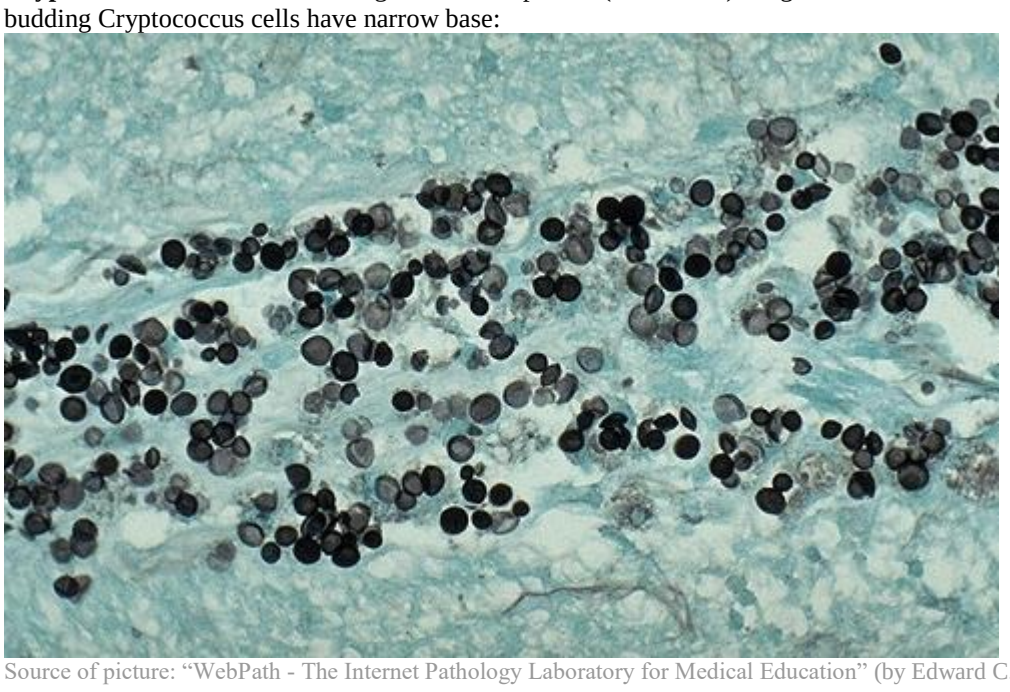






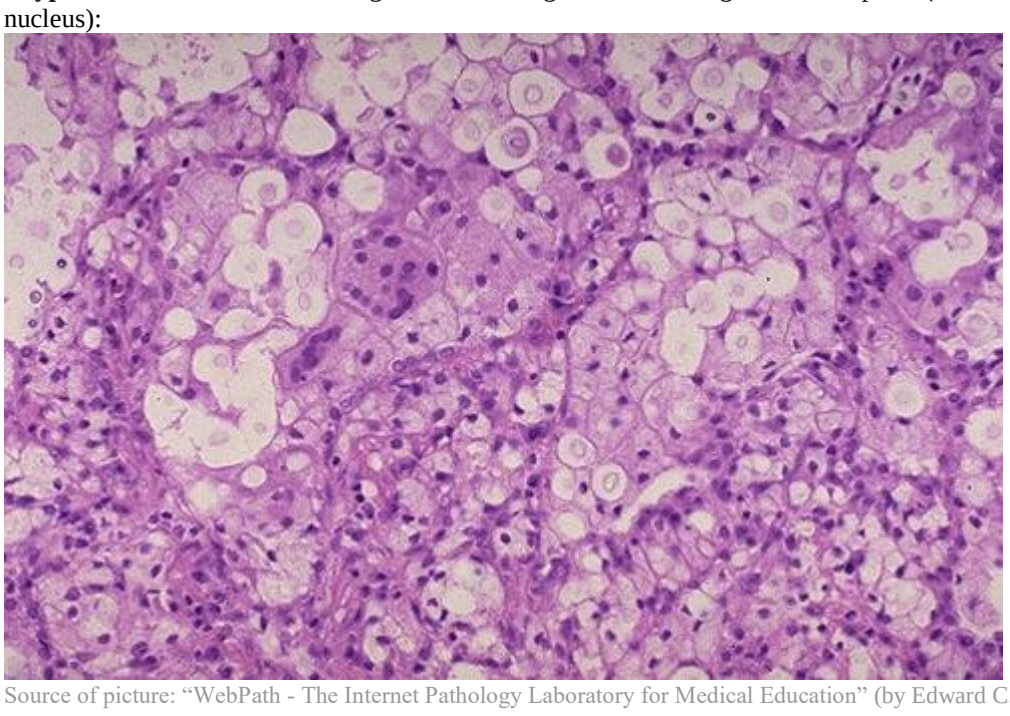
Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

Cryptococcus neoformans meningitis in AIDS patient (GMS stain) - organisms didn't even bother to make capsule; budding Cryptococcus cells have narrow base:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

Cryptococcus neoformans in lung – numerous organisms with large mucoid capsule (clear zone around faint round nucleus):



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

Treatment is complex (prolonged, often with multiple agents);
AMPHOTERICIN B (drug of choice for all fungi and yeasts):

adults – 1-mg test dose (by slow IV infusion) → gradually increase as tolerated to *maximum 1 mg/kg/d*; total of 2-6 g is usually given.
children – test dose 0.25 mg/kg IV in 6-h infusion → daily dosage is increased by 0.25 mg/kg to *no more than 1 mg/kg/d*.

- AMPHOTERICIN B need not be continued for > 10 wk if its blood level can be maintained at concentration at least twice that needed to inhibit fungal growth in culture.
- ***intraventricular*** (via Ommaya reservoir) AMPHOTERICIN B is sometimes necessary to eradicate infection (e.g. coccidioidal meningitis).

Treatment of *CRYPTOCOCCAL* meningitis – dual-agent induction: **AMPHOTERICIN B** deoxycholate (Fungizone) or liposomal (AmBisome) + **FLUCYTOSINE** 25-35 mg/kg q6h for 2 weeks → consolidation: **FLUCONAZOLE*** 400 mg/d for 8 weeks or until CSF is sterilized; in HIV-positive patients → lifelong suppressive therapy 200 mg/d. see p. 269 >>

*the only "azole" that crosses BBB;
less effective alternatives - **ITRACONAZOLE**, **VORICONAZOLE**

- often develop ***symptomatic intracranial hypertension***.
  - ventriculomegaly (hydrocephalus) is not always present
  - most patients do well with serial lumbar punctures combined with antifungal therapy.
  - in one case series (50 patients), only 26% patients needed permanent shunting.
    Jacob Cherian et al. Shunting in cryptococcal meningitis. DOI: https://doi.org/10.3171/2015.4.JNS15255
    - ACETAZOLAMIDE and MANNITOL are not helpful.
    - corticosteroids, primarily PREDNISONE, are used in the setting of IRIS (immune reconstitution syndrome).
    - indications for shunting: insufficient response to antifungal therapy and serial LPs (e.g. unrelenting headaches), unable to tolerate LPs.
    - when required, shunting provides sustained relief from intracranial hypertension symptoms.
    - authors favor shunt placement over trials of external lumbar or ventricular drains (external drains require immobilization and demand a higher level of nursing care, high rate of eventual progression to shunting).
    - ventriculoperitoneal shunts are the favored method of CSF diversion (fixed medium-pressure valve).
    - no cases of shunt infection.
    - no cases of cryptococcal peritonitis after shunting.
  - shunting during active fungal infection is not an issue if antifungal therapy has been started prior to implantation.

CANDIDA MENINGITIS

- see p. Inf1 >>

NEONATAL MENINGITIS

- etiology – see *above* >>
- risk factors: maternal infections (esp. urinary tract and uterus), obstetrical risk factors (prolonged rupture of membranes, birth trauma, prematurity, low birth weight, congenital anomalies, perinatal hypoxia / asphyxia, cardiopulmonary resuscitation).
- meningitis occurs in *25-30% neonatal sepsis* cases!
- symptoms and signs are often *subtle and nonspecific* (≈ as in sepsis) - lethargy, seizures, irritability, poor feeding, vomiting, high-pitched crying, respiratory alterations; most appear toxic or moribund.
  - handling is painful and child cannot be comforted.
  - **temperature instability** (may be normal or even subnormal, esp. in preterms).
  - 25-75% will not have **nuchal rigidity***; tense bulging fontanel is more reliable sign (but may be absent in dehydration). see p. D5 >5
    *Kernig's and Brudzinski's signs appear at or shortly after 1st year of life.
    N.B. in GI vomiting fontanel is sunken!
- treatment – see *above* >>

GERIATRIC MENINGITIS

- only presenting sign may be alteration of mental status.
- elderly patient is at high risk for meningitis - identification of infection outside CNS (in patient with ***mental status change***) is clear indication for LP (because of risk of bacteremic seeding).

POSTTRAUMATIC MENINGITIS

Trauma (basilar fractures with CSF leak, penetrating head injuries, linear fractures through nasal sinuses or middle ear) → host defect in local anatomy → RECURRENT BACTERIAL MENINGITIS

- meningitis develops 2-8 days after injury but several years may pass between trauma and first bout of meningitis (esp. with fractures through mastoid or nasal sinuses).
- etiology:
  a) early meningitis (within 3 days of injury) - usually *Str. pneumoniae* → **PENICILLIN G** or **CEFOTAXIME**.
  b) meningitis more than 3 days after trauma - often Gr- organisms → **CEFOTAXIME** or **CEFTRIAXONE** + **NAFCILLIN** (coverage of *S. aureus*).
  c) in children, posttraumatic meningitis may be due to *Haemophilus influenzae*.
- CSF rhinorrhea / otorrhea (detected by significant concentration of glucose in nasal or aural secretions) may be transient (H: monitoring course of radioiodine-labeled albumin instilled intrathecally or CT after intrathecal injection of metrizamide).
- prophylaxis: pneumococcal vaccine + long-term prophylactic penicillin (?*) + surgical closure of CSF fistulas. see p. S64 >>

*prophylactic antibiotics are not recommended in acute setting in CSF leaks caused by basilar skull fractures

HEMOGENIC MENINGITIS

- ***temperature*** may be elevated for first few days after most craniotomies.
  – if fever continues > 72 hours (in setting of good pulmonary toilet), aseptic or bacterial meningitis should be suspected.
- diagnosis - sterile xanthochromic CSF under pressure with several hundred ÷ several thousand leukocytes / mm^3.
- treatment - **antipyretics** and **DEXAMETHASONE**.

BASAL MENINGITIS

- around brainstem and cranial nerves, along undersurface of frontal and temporal lobes.
  - **multiple cranial neuropathies** (CNI-XII).

SPINAL MENINGITIS (ARACHNOIDITIS)

- *injury to roots* (as they traverse subarachnoid space and penetrate meninges; permanent intradural adhesions) → **multiple radiculopathies**: radicular pain, sensory loss, motor weakness, sphincter dysfunction.
  - usually begins as intracranial meningitis.
  - etiology:
    a) most commonly - iatrogenic (myelography performed with **iophendylate (Myodil)** - involves caudal sac (rarely ascending above L3/4 disc); lumbar disc surgery itself is rarely cause.
    b) trauma
    c) intradural infections - tuberculosis, fungal and parasitic (esp. cysticercosis)
    d) spinal SAH
    e) intraspinal tumors (rarely)
    f) spinal sarcoidosis.
  - inflammation can encircle cord → myelopathy.
    – ***myelomalacia*** and ***syringomyelia*** often develop in extensive cases.
  - on rare occasions, organized exudates become calcified and even ossified (ARACHNOIDITIS OSSIFICANS).
  - MRI with IV gadolinium (modality of choice):

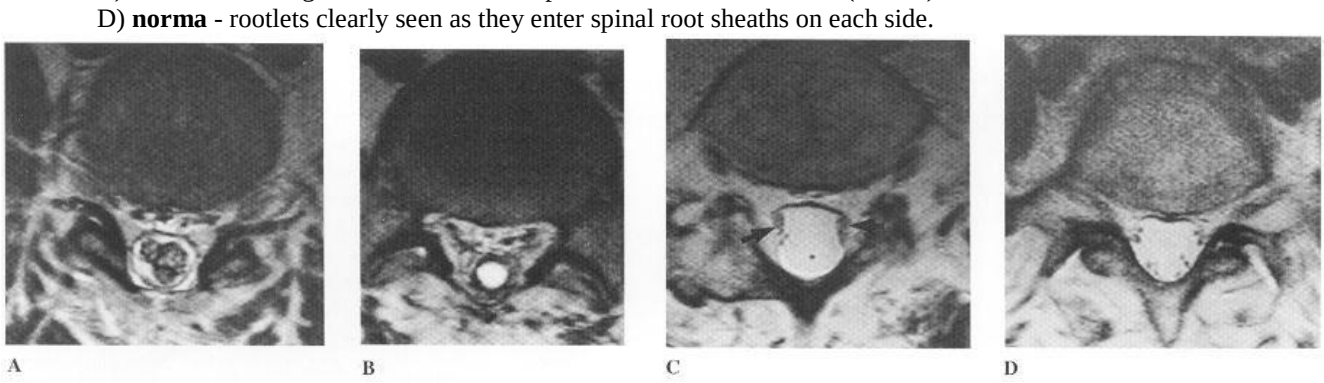
N.B. myelography should be avoided when arachnoiditis is suspected!

acute meningitis - variable patterns of surface enhancement of nerve roots and meninges (linear, nodular, plaque-like, etc).

chronic meningitis - loculation & deformity of subarachnoid spaces, tapering / obstruction of lower end of subarachnoid space, central clumping / peripheral adhesion of roots of cauda equina (empty thecal sac with thickened sac walls), irregular deformity of spinal cord (with central signal change in severe cases).

Patients with slowly progressive involvement of multiple *cranial nerves* and/or *spinal roots* are likely to have chronic meningitis.

Spinal adhesive arachnoiditis (high resolution T2- MRIs of lumbar spine) - three main diagnostic features:
A) central clumping of nerve roots (CSF is white).
B) peripheral adhesion of roots leaving clear central subarachnoid space.
C) adhesion of margins of thecal sac near point of exit of root sheaths (arrows).
D) **norma** - rootlets clearly seen as they enter spinal root sheaths on each side.



Spinal meningitis due to Lyme disease (T1-MRI of lumbar spine after IV gadolinium) - diffuse enhancement of outer surface of cord and spinal roots:

MOLLARET MENINGITIS (s. benign recurrent lymphocytic meningitis)

- recurrent spontaneous, short-lived, benign aseptic meningitis.

- proposed etiology - **herpes simplex type 2**: primary infection / reactivation in sacral dorsal root ganglion → seeding of subarachnoid space.
- first attack may appear at any age (childhood ÷ late adult years).
- **mild meningitis** without associated neurologic abnormalities: temperature, signs of meningeal irritation.
- there may also be symptoms of **sacral radiculitis**.
- meningitis episodes last 2-5 days.
- **CSF**: pleocytosis (200 to several thousand mononuclears /mm^3), slight protein elevation, normal sugar, *large fragile endothelial cells* (in early phases of disease; their presence is variable and is not considered essential for diagnosis); positive **PCR** for HSV-2 DNA.
- rapid spontaneous recovery without specific therapy (no effective therapy for shortening attack or preventing fresh attacks; may benefit from prophylactic **ACYCLOVIR**?).
- between attacks, patient enjoys good health.
- episodes last for 3-5 years.

BIBLIOGRAPHY for ch. "Infections of Nervous System" → follow this LINK >>