Bacterial meningitis

A. CHILDREN

[Image 54x1547 to 129x1566]

P.C.D.C

misnomer (term used just clinically)

REATMENT

PIDEMIOLOGY

TIOLOGY

HEMOPROPHYLAXIS

LINICAL

V

B

V

S

A

R

C

UBACUTE MENINGITIS

5.

4.

ACTERIAL MENINGITIS

ACTERIAL MENINGITIS

IRAL MENINGITIS

IRAL MENINGITIS

IMMUNOLOGIC

ECURRENT MENINGITIS

HRONIC MENINGITIS

CUTE MENINGITIS

CUTE MENINGITIS

IRAL MENINGITIS

IRAL MENINGITIS

ENINGISM

FEATURES

- almost any pathogenic bacteria (most cases are hematogenous)

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

In order of frequency:

NEONATES:
1. Group B streptococci (Streptococcus agalactiae) (20-50%)
2. Group B streptococci (Streptococcus agalactiae) (20-50%)
3. Listeria monocytogenes (2-10%)
4. Group D streptococci (enterococci)
5. Staphylococci (rare)

CHILREN (1 month ÷ 15 yrs):
1. Haemophilus influenzae (40-60%) – nearly all cases in children < 6 yrs.
2. N. meningitidis (25-40%)
3. St. pneumoniae (10-20%)

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

ADULTS:
1. N. meningitidis (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.
3. S. aureus and coagulase-negative staphylococci (5-15%) – predominant organisms in CSF shunts or subarachnoid Ommaya reservoirs.
4. Group B. cereus (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 (< 18%) - simultaneous recovery of two or more bacterial species.

PREdisposing host FACTORS

1) MECHANICAL disturbances (neurosurgical procedures, basilar skull fractures).
2) CONVCTUAL defects (dermoid sinus tracts, meningomyeloceles).
3) IMMUNOLOGIC deficiencies:
   a) self-mediated immunity (lymphoma, organ transplant recipients, corticosteroid therapy, AIDS) → intracranial bacterial infection (esp. the, 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

- nomenclature used just clinically - absence of bacteria on microscopic examination & culture:

A. Bacterial meningitis:
   a) partially treated

MENINGITIS

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

ETIOLOGY

BACTERIAL (PURULENT) MENINGITIS:

- NEONATE: L. monocytogenes
- CHILREN: H. influenzae and N. meningitidis
- ADULTS: S. pneumoniae, N. meningitidis, H. influenzae type b

Last updated: August 8, 2020
b) parameningeal infection (brain abscess, subdural empyema, epidural abscess, septic thrombosis of intracranial venous sinuses, osteomyelitis of spine or skull)

c) Listeria monocytogenes
d) Mucorales pneumoniae

e) Mycobacterium tuberculosis

f) chorioiditis, retinitis

spirochetes (Borrelia burgdorferi, Treponema pallidum)

B. Viral meningitis (precise definition of etiologic agent is often impossible)—in order of frequency:
- Enteroviruses (esp. echovirus, coxsackie virus B) - statistically encountered most commonly (up to 92% of aseptic meningitis cases!)
- Arboviruses (St. Louis encephalitis virus, California encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Colorado tick fever)
- HSV
- HIV
- Herpes simplex virus
- Epstein-Barr virus
- Influenza virus types A and B

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

C. Fungal meningitis (occurs only in immuno-suppressed hosts, esp. lymphoma & leukemia, AIDS):
- Cryptococcus neoformans*
- Coccioides immitis
- Histoplasma capsulatum
- Blastomyces dermatitidis
- Coccidioides immitis
- 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—infiltiration of subarachnoid space by carcinoma (MENINGEAL CARCINOMATOSES) or lymphoma (MENINGEAL LYMPHOMATOSES).
N.B. antileukemic drugs do not cross BBB!

F. Meningitis in connective tissue disorders
1) serum sickness
2) vasculitis, priaptriitis nodosa
3) SLE
4) Behcet’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) other chemical meningitis (leakage into CSF of contents from epidemoid tumor, craniopharyngioma, cholesteatoma)
3) primary inflammatory conditions (Vogt-Koyanagi-Harada syndrome, Behcot’s syndrome, Mollaret’s meningitis, SLE)
4) drug hypersensitivity (with repeated administration).

PATHOLOGY, PATHOPHYSIOLOGY

BACTERIAL MENINGITIS
- in CSF, humoral defense mechanisms (lg 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 agent 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 from 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.

*common in AIDS patients
Meningitis

- 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 transpendymal movement of fluid from ventricular system into brain parenchyma (interstitial edema)
- cerebral edema causes ICP↑
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).

- meningal 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).
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).
4. Brain abscess, subdural empyema
5. Cerebral thrombophlebitis
6. Stroke:
   a) vasospasm caused by subarachnoid infection
   b) loss of cerebral autoregulation + hypertension
   c) inflammatory infiltration of arterial wall (vasculitis).
7. Cranial nerve palsy (esp. sensorineural hearing loss; ocular motor paresis)
8. Consequences of ICP* (incl. brain herniation)
9. Chronic adhesive arachnoiditis, hydrocephalus

DIAGNOSIS

1. All meningitis suspects may be fatal if not successfully treated.

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

- 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 meningitis 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/mm³ PMNs in bacterial meningitis;
     - 5-1,000/mm³ mononuclears (may be PMNs at onset*) in viral meningitis (also in bact. meningitis; normal in viral meningitis).

- *esp. in enteroviral infections

- glucose - most specific (esp. in bacterial, tuberculous, cryptococcal meningitis, normal in viral meningitis*).

- protein* (bacterial meningitis > 100 mg/dl; viral meningitis < 100 mg/dl).

- LDH↑ (in bacterial, fungal meningitis).

- 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), Zielh-Neelsen acid-fast stain (bce).

2) antigen tests (PCR, latex particle agglutination, counterimmunoelectrophoresis, limulus lysate test*, immunofluorescence, etc).

*highly sensitive at detecting LPS (Gr. organisms).
Meningitis

APERT FORMULA - 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 neutrophile:

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.

EEG is usually normal or slightly slow.

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

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

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!

Etiologic diagnosis in chronic meningitis may require meningeval 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 - sarcoïd (31%), metastatic adenocarcinoma (25%).

India ink stain (black shadow organisms - Cryptococcus):

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

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 ventriculitis (MRI contrast medium): A) T2-weighted spin-echo; B) T1-weighted spin-echo. Necrotic right-sidated periventricular lesion shows central low signal on T1 and high on T2 with peripheral enhancement. Enhancement of periventricular tissues (thus 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-limited - 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. ANTIMICROBIAL THERAPY (must be bactericidal in CSF* – i.e. maximum tolerated doses!)
   intravenously (intrathecal / intraventricular therapy is not effective).
   *titer 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 PENCILLIN G before transporting to hospital!

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

*CEFEPIME* 2 g q8h + VANCOMYCIN 15mg/kg q12h (goal trough 15 – 20 mg/L)
2. *Gram positive bacteria* → *AMICILLIN or PENICILLIN G or OXACILLIN* 
   *Neisseria meningitidis → AMICILLIN or PENICILLIN G or OXACILLIN* 
   *Streptococcus pneumoniae → VANCOMYCIN + CEFOTAXIME or CEFTRIAXONE* 
   *Enterococcus faecalis (except Pe. aeruginosa) → CEFOTAXIME or CEFTRIAXONE or AMICILLIN or GENTAMICIN* 
   *Pseudomonas aeruginosa → CEFTRIAXONE or CIPROFLOXACIN or TICARCILLIN or GENTAMICIN* 
   *Zytozoon meningitidis → AMICILLIN or AMARICIN or GENTAMICIN* 
   *Haemophilus influenzae type b → CEFOTAXIME or CEFTRIAXONE or CHLORAMPHENICOL (with AMICILLIN)* 
   *Staphylococcus aureus (methillin-sensitive) → METHICILLIN or OXACILLIN* 
   *Staphylococcus aureus (methillin-resistant) → VANCOMYCIN* 
   *Streptococcus pyogenes → VANCOMYCIN = RIFAMPICIN* 

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**Neonatal meningitis:**

- **Neonatal meningitis** occurs in infants aged 0-60 days and is due to *Streptococcus pneumoniae* or *Neisseria meningitidis*.

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Children &amp; Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Vancomycin</em> + CEFOTAXIME or CEFTRIAXONE</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td><em>Penicillin G</em> or AMICILLIN or CEFOTAXIME or CEFTRIAXONE</td>
</tr>
</tbody>
</table>

*Some pneumococci are resistant to penicillins, cephalosporins, chloramphenicol!*

**Neonatal meningitis** in infants aged 0-60 days is caused by *Streptococcus pneumoniae* or *Neisseria meningitidis*.

- **Neonatal meningitis** due to *Streptococcus pneumoniae* is caused by the bacteria type *Streptococcus pneumoniae*.

- **Neonatal meningitis** due to *Neisseria meningitidis* is caused by the bacteria type *Neisseria meningitidis*.

**Treatment:**

- **Neonatal meningitis** due to *Streptococcus pneumoniae* is treated with *Vancomycin* + CEFOTAXIME or CEFTRIAXONE.

- **Neonatal meningitis** due to *Neisseria meningitidis* is treated with *Penicillin G* or AMICILLIN or CEFOTAXIME or CEFTRIAXONE.

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**Prevention:**

- **Primary focus of infection** should be eradicated by surgery if necessary; e.g. persistent CSF fistulas must be closed by suturing of dura.

- **Drug dosages** should be reduced when clinical improvement occurs (drug generation decreases as meningitis become less inflamed).

- **Duration of therapy** should be individualized and based on clinical response: 3-4 weeks for *Neisseria meningitidis*; 2-3 weeks for *Streptococcus pneumoniae*; 8-10 days for meningitis due to *Streptococcus pyogenes*.

- **Post-treatment CSF examination** is not meaningful for recovery (i.e. CSF should not be re-examined if patient is clinically well).

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**2. PSEUDOMONAS AERUGINOSA**

- **Treatment:** In adults with community-acquired bacterial meningitis, a broad-spectrum antibiotic should be administered 20 min before first antimicrobial dose.

- **Prevention:** In adults with community-acquired bacterial meningitis, a broad-spectrum antibiotic should be administered 20 min before first antimicrobial dose.

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**3. OTHER MEASURES**

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**7. OTHER MEASURES**

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- **Post-treatment CSF examination** is not meaningful for recovery (i.e. CSF should not be re-examined if patient is clinically well).
time-honored treatment of SIAIDH 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 ½-½ normal saline and 20 to 40 mL/kg 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 mL/kg, fluids can be gradually increased.

Purulent ventriculitis - in severe ventriculitis, EVD/limbar drain is not efficient enough, especially when the CSF contains pus/flakes (mildus of infection adherent to the choroidal 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 unseats purulent material
- after the ipsilateral ventricle is cleansed, a generous neostigmine 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) antimyocobacterial 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 ≤ 5 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) q24h 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, pneumothorax, 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 anesthesia for weeks to months).
- infants / neonates - prognosis is less ominous (intellectual impairment, learning disabilities, hearing loss have been reported).

SPECIFIC FEATURES

Mycobacterium tuberculosis

Epidemiology:

- INCIDENCE is slowly increasing (30% of着 was tuberculosis in all developing countries)
- most common in childhood (in 3rd countries) and early adult life (in Western countries).

Epidemiology:

- tuberculosis is always secondary to tuberculosis elsewhere in body (usually in lungs, but may be in any organ).
- progression of primary infection (children) / reactivation (adults) → bacterial & miliary dissemination → CSN 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 →
Corticosteroids

Potts disease

from vascular abnormality (perivascular demyelination) or tuberculous meningitis, usually asymptomatic; intracerebral

Prognosis

If suspicion is high, additional diagnostic data: MRI after gadolinium enhancement (esp. CN6, CN3), seizures, plegias, alteration of mental status. Frequency; hydrocephalus develops.

Diagnosis

1. pressure; CSF clear or cloudy (straw-colored) with fibtin 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 on blood + protein-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! PCR tests (likely will replace many of current tests for mycobacteria). N.B. CSF-chloride as diagnostic aid for the 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 + ETAMBUTOL) → ISONIAZID + RIFAMPIN (for at least 7-10 months (i.e. 9-12 months*; up to 24 months) *longer than for pulmonary tuberculosis.
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.
4. Untreated patient is unlikely to survive beyond 4-8 weeks.

Drug
ISONIAZID* 10 mg/kg/d* since daily 300 mg/d + 50 mg/d pyrazinamide
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

Penicillin - treatment is less effective - mortality is higher (than in bacterial meningitis). Treatment 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 tuberculous infection); always secondary to tuberculosis elsewhere in body (e.g. frequent finding in tuberculous meningitis, usually asymptomatic):
- located 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
- central core of caseous necrosis surrounded by typically tuberculous granulomatous reaction.
- CT density as brain (or slightly denser) + little or no surrounding edema ← tuberculoma
- tuberculoma color varies (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 homolateral leuкоencephalopathy deep in white matter at distance from vascular abnormalities and parenchyma edema.

Potis disease - vertebral tuberculosis (compression fractures, etc).
**MENINGITIS**

- 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, thombocerephalitis, brain abscess, or cranial neuropathies.

**Treatment**

- at least four-drug regimen:
  1. **CLARITHROMYCIN** and **AZITHROMYCIN** have excellent activity!
  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), **RIFAPHTIN** (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 tb 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% of cases develop CRYPTOCOCOMAS – 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.

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, building Cryptococcus cells here narrow base.

Sources of picture: "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 reaction).

Sources of picture: "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 Omaya reservoir) AMPHOTERICIN B is sometimes necessary to eradicate infection (e.g. coccidioidal meningitis).

[Image 54x1547 to 129x1566]

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/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.

[Image 71x51]

Jacob Cherian et al. Shunting in cryptococcal meningitis. DOI: https://doi.org/10.1177/1043819415581255

- ACETAZOLAMIDE and MANITOL 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 shunt placement.
- when required, shunting provides sustained relief from intracranial hypertension symptoms.
- 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.

**CRYPTOCOCCAL PERITONITIS**

- 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 asphyxia / asphyxia, cardiopulmonary resuscitation).
- meningitis occurs in 25–30% neonatal sepsis cases!
- symptoms and signs are often subtle and nonspecific (*i.e.* 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. 355

*Keruing’s and Braudzukis’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.

- see Inf1

**INFECTIOUS DISEASES**

- see Inf2

**INFECTIOUS DISEASES**

- see Inf3

**INFECTIOUS DISEASES**

- see Inf4

**INFECTIOUS DISEASES**

- see Inf5

**INFECTIOUS DISEASES**

- see Inf6

**INFECTIOUS DISEASES**

- see Inf7

**INFECTIOUS DISEASES**

- see Inf8

**INFECTIOUS DISEASES**

- see Inf9

**INFECTIOUS DISEASES**

- see Inf10

**INFECTIOUS DISEASES**

- see Inf11

**INFECTIOUS DISEASES**

- see Inf12
Spinal adhesive arachnoiditis

and/or

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

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 meningeval irritation.
- there may also be symptoms of sacral radiculitis.
- meningitis episodes last 2-5 days.
- CSF: pleocytosis (200 to several thousand mononuclears/mm³), slight protein elevation, normal sugar, large fragile endothelial cells (in early phases of disease; their presence is variable and is not considered especially essential for diagnostics); 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] >>

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