Central nervous system infections

ROUTES FOR CNS INFECTIONS:

1) **hematogenous spread** – most common
2) **direct implantation** (traumatic, iatrogenic e.g. lumbar puncture)
3) **local extensions** of pathogens e.g. located at the site of mastoiditis or sinusitis, infected roots of tooth.
4) **intraneural pathways** (the least common route to the CNS, exceptions are: rabies virus; HSV, VZV, polio)

Mechanism of microbial traversal of the blood-brain barrier: a. **transcellular traversal** (e.g. encapsulated bacteria like Str. pneumoniae, H. influenzae, N. meningitidis, E. coli K1), b. **paracellular traversal** (spiral bacteria, some viruses), c. the "Trojan horse" mechanism (within white blood cells e.g. M. tuberculosis, some viruses e.g. EBV, CMV, Listeria monocytogenes).

MENINGITIS:

a) **ACUTE PYOGENIC/PURULENT** – usually caused by bacteria (neonates: **E. coli K1; Str. agalactiae, Listeria monocytogenes**; children and adults: **Str. pneumoniae, N. meningitidis, H. influenzae type B**). Characterized by headache, photophobia, fever, irritability, neck stiffness, nausea, vomiting and various degrees of neurological dysfunction. Most bacteria reach CNS via bloodstream, some through Trojan mechanism (Listeria monocytogenes).

**CSF indicators:** increased pressure, increased neutrophils (PMNs pleocytosis), increased proteins concentration, markedly decreased glucose concentration.

b) **ASEPTIC** – usually acute, most often attributed to **viral infection.** Usually self-limiting. No clinical involvement of neural tissue. Characterized by fever, headache, stiff neck and back, nausea, and vomiting. Viral meningitis is generally less severe: usually resolves without treatment (self-limiting). Viral meningitis rarely fatal if there is a competent immune system. Patient usually recovers completely. Caused by several types of virus: **90% of cases by enteroviruses** (polio-, echo-, coxackie-), other involved: **herpesvirus and mumps virus**. Most viruses reach CNS via bloodstream, some through Trojan mechanism (within white blood cells) or by travelling along nerves (rabies, polio, HSV, VZV).

Some spiral bacteria can produce aseptic meningitis: Leptospira interrogans, Borrelia burgdorferi, Treponema pallidum.

**CSF indicators:** glucose near normal, proteins only moderately elevated, lymphocytic pleocytosis (MN, mononuclear)

c) **CHRONIC MENINGOEENCEPHALITIS** – more insidious onset than purulent meningitis. Signs and symptoms develop over weeks. Usually caused by **Mycobacterium tuberculosis, fungi, or protozoan parasites.**

**Mycobacterial infection** characterizes by headache, malaise, vomiting, confusion. **CSF indicators:** moderate pleocytosis (PMNs and MNs), proteins markedly increase, glucose slightly decreased or normal.

**Neurosyphilis** – tertiary stage (ca. 10% of untreated patients) – meningeovascular neurosyphilis that characterizes progressive loss of mental and physical functions with mood alterations.
Boresiosis: aseptic meningitis, facial nerve palsies, mild encephalopathy, polyneuropathy.

ENCEPHALITIS
Describes signs of CNS dysfunction with no symptoms of aseptic meningitis. Involves seizures, paralysis, or defective mental faculties. Problem is not with the meninges, but the actual nervous tissue. Infections range in severity from subclinical symptoms to rapid death.

VIRAL ENCEPHALITIS
Infections are all characterized by chills, headache, and fever. Can lead to mental confusion and coma. Survivors can subsequently develop permanent neurological disease. Generally caused by viruses. Brain involvement is also observed in neurosyphilis, neuroborreliosis and fungal infections.

CAUSES OF VIRAL ENCEPHALITIS
1. Arbovirus infections (Western equine encephalitis, Estern equine encephalitis, Venezuelan equine encephalitis, St. Louis encephalitis, Japanese B. encephalitis, Yellow fever, Dengue)
2. Arthropod tick–borne encephalitis (Russian tick–borne complex, Colorado tick fever)
3. Picornavirus (enterovirus) infections (Poliomyelitis, Coxackievirus infections, Echovirus meningoencephalitis)
4. Myxovirus infections (Influenza, Mumps, Measles, Rabies, Rubella, Newcastle disease)
5. Herpesvirus infections (Herpes simplex, Herpes zoster and chicken pox, Virus B (herpesvirus simiae) Cytomegalic inclusion disease)
6. Poxvirus infections (Smallpox encephalitis)
7. Others

Rabies is an acute and fatal viral CNS infection. Can affect all mammals. Transmitted by infected secretions (usually through a bite). Rabies involves severe neurological symptoms. CNS abnormalities include: relentless progression of excess motor activity, agitation, hallucinations, overproduction of saliva - can be an inability to swallow.
First event of rabies infection is introduction of the virus. Usually through the epidermis via an animal bite. Also through inhalation of heavily contaminated material such as bat droppings. Virus replicates at the site of infection. Immunization immediately after infection keeps virus from migrating into the nervous tissue. Without intervention, virus moves into peripheral nervous system. Spreads into the CNS. Replicates exclusively in gray matter. After replication, virus moves into other tissues. Adrenal medulla, kidneys, lungs, and salivary glands. Lymphocytes and plasma cells infiltrate into the CNS - destroy nerve cells. Primary lesion is the Negri body.
Rabies presents as acute fatal encephalitis. Once symptoms appear the infection is irreversibly fatal. Illness begins with nonspecific fever, headache, malaise, nausea, and vomiting. Involvement of respiratory centers causes respiratory paralysis. Major cause of death.
Median survival after the onset of symptoms is 20 days. Prevention is the best cure. Treatment consists of a course of injections. Only beneficial if administered before the onset of symptoms. Mortality for rabies is 90%.

Polio
Infection which destroys cells associated with the anterior horn of the spinal cord, and brain stem. Causes weakness or paralysis of muscle groups. Can cause respiratory difficulties. Characterized by asymmetrical paralysis. Risk of paralysis actually increases with age. Essentially nonexistent in most modern countries. There is an effective vaccine. Still a major problem in undeveloped countries.
Virus is an enterovirus with an affinity for the CNS. Normally crosses the blood-brain barrier. Can also use axons or the perineurial sheath of the peripheral nervous system. Motor neurons are particularly vulnerable. Various levels of neuronal destruction cause: necrosis of neural tissue and infiltration by mononuclear cells, primarily lymphocytes.
90% of poliomyelitis infections are very mild and subclinical. Incubation time varies from 4 to 35 days. Average is about 10 days.
Three types of polio infection:
Abortive poliomyelitis: Nonspecific febrile illness. Lasts two to three days. No signs or symptoms
Nonparalytic poliomyelitis (aseptic meningitis): Characterized by meningeal irritation, stiff neck, back pain, and back stiffness. Rapid and complete recovery
Paralytic poliomyelitis: Occurs in 2% of persons infected. Characterized by asymmetric flaccid paralysis. Extent varies from case to case. Temporarily damaged neurons can regain function. Recovery can take six months. Paralysis persisting after this period is permanent.
Polio vaccine essentially wiped out this infection. Two types of vaccine:
Inactive form –developed by Jonas Salk
Live attenuated form –developed by Albert Sabin

Fungal Meningoencephalitis – encountered primarily in immunosuppressed patients; blood – borne; brain involved late in the disease; Examples of fungi causing: Cryptococcus neoformans, Candida sp., Mucor sp., Aspergillus sp. and dimorphic fungi
Three major patterns of fungal CNS infections:
  a) chronic meningitis
  b) vasculitis (thrombosis and infracts) – Mucor and Aspergillus
  c) brain parenchyma invasion (granulomas and abscesses) – Candida and Cryptococcus

Infection begins with inhalation of the yeast cells. After inhalation, yeast cells multiply outside the lungs and move into the nervous system. Initial symptoms can continue for weeks or months. Intermittent headache, dizziness, and difficulty with complex cerebral function. Later stages of the infection show:

- Seizures, cranial nerve damage, and papilledema (edema of the optic nerve)
- Dementia and decreased levels of consciousness
- Progression of disease is accelerated in patients with AIDS.

Amphotericin B and fluconazole are effective. 75% patients with cryptococcal meningitis initially respond to treatment. Significant portion relapse when therapy is stopped. Patients with chronic infection require repeated courses. Residual neurological damage occurs in more than half of cured patients.

**Cryptococcal meningitis** Cryptococcus neoformans often produces an indolent infection; its symptoms occasionally may extend back months or even years before the diagnosis is made. A debilitated state, immune incompetence or suppression, and diabetes mellitus are frequently associated conditions. Headache is the most common symptom, and mental deterioration may occur. Cranial nerve palsies and focal brain stem dysfunction secondary to arteritis can be prominent. The CSF is similar to that seen in persons with tuberculous meningitis. The fungus may be seen on India ink preparations and may grow in culture. Cryptococcal antigen can often be detected in the CSF, providing a valuable aid to the diagnosis. Treatment is with systemic and intrathecal (drug administration via an injection into the spinal canal or into the subarachnoid space) amphotericin B and 5-fluorocytosine. Rarely, other fungal infections (such as Coccioidioides, Mucor, Candida, Actinomyces, Histoplasm, or Aspergillus) can present with chronic meningitis (usually in an immunocompromised host).

**ACUTE POLYNEURITIS (Gullain-Barre syndrome)**

Inflammatory infection of the peripheral nervous system. Characterized by symmetrical paralysis. Can be caused by e.g. diphtheria toxin, enteric pathogens (Campylobacter), Lyme disease, Mycoplasma pneumoniae RTI, cytomegalovirus, and Epstein-Barr virus and other.

**BRAIN ABSCESSES**

Brain abscesses are relatively rare. Cerebral abscesses are destructive lesions. Commonly formed by bacteria (Staphylococci and streptococci are the most common; other; GN rods, anaerobes) or fungi from a distant site – may arise from a variety of routes. Complications: spreading of microorganismsm to the subdural space causing subdural empyema, rupture of an abscess causing venous sinus thrombosis, meningitis etc.

**CSF indicators**: CSF under increased pressure, WBC and protein increased, glucose normal.

**TETANUS AND BOTULISM** - affect the CNS in different ways. Produce exotoxins with an affinity for CNS tissue. Antibiotic therapy is ineffective once the exotoxin has been produced.

**CEREBROSPINAL FLUID:**

CSF from the lumbar region contains **15 to 45 mg/dl protein** (lower in children) and **50-80 mg/dl glucose** (two-thirds of blood glucose). Protein concentration in cisternal and ventricular CSF is lower. Normal CSF contains **0-5 mononuclear cells**. The CSF pressure, measured at lumbar puncture (LP), is 100-180 mm of H2O (8-15 mm Hg) with the patient lying on the side and 200-300 mm with the patient sitting up.

Increased inflammatory cells (pleocytosis) may be caused by infectious and noninfectious processes. Polymorphonuclear pleocytosis indicates acute suppurative meningitis. Mononuclear cells are seen in viral infections (meningoencephalitis, aseptic meningitis), syphilis, neuroborreliosis, tuberculous meningitis, multiple sclerosis, brain abscess and brain tumors.

**Increased protein:** In bacterial meningitis, CSF protein may rise to 500 mg/dl. A more moderate increase (150-200 mg/dl) occurs in inflammatory diseases of meninges (meningitis, encephalitis), intracranial tumors, subarachnoid hemorrhage, and cerebral infarction.

**Low glucose in CSF** is seen in suppurrative, tuberculous and fungal infections and meningeal dissemination of tumors. Glucose is consumed by leukocytes and tumor cells.
CSF FINDINGS IN MAJOR CNS INFECTIONS

<table>
<thead>
<tr>
<th>Purulent Meningitis (Acute bacterial)</th>
<th>Viral Meningo-encephalitis (Less than 500/cu mm; first PMNs then lymphs)</th>
<th>Granulomatous Meningitis (tuberculosis, fungal meningitis, syphilis, Listeria, Brucella, etc.)</th>
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<tbody>
<tr>
<td>WBC's</td>
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<tr>
<td>More than 1,000/cu mm; mostly PMNs</td>
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<td></td>
</tr>
<tr>
<td>Less than 500/cu mm; first PMNs then lymphs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 200/cu mm; mostly lymphs</td>
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<td>Protein</td>
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<td>High</td>
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<td>Glucose</td>
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<tr>
<td>Low (often less than 20 mg%)</td>
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<td>Low (rarely as low as in bacterial meningitis)</td>
</tr>
</tbody>
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Neonatal meningitis
Group B beta-hemolytic streptococci
Enteric bacilli (Escherichia coli, Proteus, Klebsiella)
Listeria (also in elderly)
Unknown

Meningitis in children and adults
H. influenzae
Meningococcal
Streptococcal pneumonia
Unknown

Meningitis under unusual circumstances
Staphylococcal (penicillinase-positive)
Gram-negative meningitis
Pseudomonas
Tuberculous meningitis
Neurosyphilis

COMPLICATIONS OF PURULENT MENINGITIS
1. Cerebral edema (may lead to herniation)
2. Vasculitis
   - Arteritis (stroke)
   - Cortical venous thrombosis (stroke, seizures)
   - Venous sinus thrombosis (increased intracranial pressure)
3. Hydrocephalus
4. Cranial nerve palsies
5. Subdural effusion or empyema
6. Disseminated intravascular clotting
7. Lactic acidosis
8. Residual findings
   - Cranial nerve palsies
   - Mental retardation
   - Seizures

ANTIMICROBIALS USED TO TREAT CNS INFECTIONS:
1) β-lactams: penicillin, ampicillin (Listeria monocytogenes), cephalosporins, monobactams, carbapenems
2) aminoglycosides (e.g. gentamycin, amikacin, netilmicin) – intrathecal application
3) fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin): suitable therapy for GN aerobic rods, Listeria monocytogenes
4) tetracyclines – neuroboreliosis, brucellosis, syphilis
5) Linezolid – St. aureus, enterococcal CNS infections (reserve atb)
6) rifamycins (rifampin) – tuberculous meningitis, St. aureus, Str. pneumoniae CNS infections
7) TMP-SMX – reserve antimicrobial for Listeria monocytogenes and T. gondii CNS infections
8) glycopeptides (high doses of vancomycin) – standard therapy for CNS infections by MRSA, multiresistant Str. pneumoniae  
9) acyclovir, gancyclovir – HSV CNS infections  
10) fluconazole, flucytosine, voriconazole (Aspergillus), amphotericin B – Cryptococcus, Candida CNS infections.

Antibiotic doses are higher in CNS infections. Commonly combined therapy is used to treat CNS infections.

**Examples of empiric therapy for meningitis**

<table>
<thead>
<tr>
<th>Pathogens suspected</th>
<th>Antimicrobials used commonly</th>
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<tbody>
<tr>
<td>pneumococci, meningococci, H. influenzae</td>
<td>vancomycin+ceftriaxone or moxifloxacin + vancomycin</td>
</tr>
<tr>
<td>pneumococci, meningococci, H. influenzae, Listeria monocytogenes, group B streptococci</td>
<td>vanco+ampicillin or moxifloxacin+vancomycin+TMP-SMX</td>
</tr>
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**BACTERIOLOGIC DIAGNOSIS OF CNS**

*Patient’s samples: CSF in Meningomedium (mainstay in diagnosis) + blood in Hemomedium + some CSF (0.5 ml–1.5) in sterile tube for slide (stained with Gram, acid–fast for mycobacteria, ink–negative staining for Cryptococcus) and rapid tests.*

In all cases of suspected meningococcal CNS infections (seasonality, outbreaks) pharyngeal swabs from a patient and from all persons having contact with the infected individual can be useful.

**Rapid tests: detection of antigens:**

a) bacterial – polysaccharide capsular antigens of N. meningitidis, Str., pneumoniae, H. influenzae, E. coli K1

b) fungal (less specific) – Candida, Cryptococcus, Aspergillus

c) endotoxin (LPS) from GN bacteria