NOTES
CEREBRAL CORTEX NERVOUS SYSTEM INFECTIONS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Infection, inflammatory disorders of central nervous system (CNS), surrounding tissues

CAUSES

- Bacteria (most common), viruses, fungi, parasites, prions, aberrant immune responses, reactions to medications

RISK FACTORS

- Immunocompromised individuals (e.g. HIV, diabetes, chemotherapy, corticosteroid use)

SIGNS & SYMPTOMS

- Fever
- Headache
- Focal neurological symptoms
- Altered level of consciousness

DIAGNOSIS

DIAGNOSTIC IMAGING

Brain CT scan/MRI

- *With contrast:* bright ring with dark center indicates brain abscess; underlying sinusitis, thickening of superior ophthalmic vein, irregular filling defects indicate cavernous sinus thrombosis; fluid collections in epidural space indicate epidural abscesses
- Focal/diffuse diffusion-restriction, cerebellar atrophy indicates Creutzfeldt–Jakob disease (CJD)

LAB RESULTS

- Lumbar puncture (if not contraindicated)
  - Culture, biochemical analysis of fluid
- Blood cultures

TREATMENT

MEDICATIONS

- Empiric antibiotic therapy followed by targeted therapy once cause identified
- Corticosteroids to manage inflammation/ cerebral edema

BRAIN ABSCESS

osms.it/brain-abscess

PATHOLOGY & CAUSES

- Localized focal necrosis of brain tissue with inflammation, usually caused by bacterial infection
- Rare (*de novo* within brain; primary infection typically arises elsewhere, spreads to brain)

Sources of infection

- Direct implantation
  - Traumatic inoculation (e.g. head trauma → skull fracture with broken skin → bacterial contamination)
  - *Iatrogenic:* contamination through invasive procedures
- Local extension from adjacent foci of infection
  - Ear infection, dental abscess, paranasal sinusitis, mastoiditis, epidural abscess
- Hematogenous spread
  - Distant sources of infection (e.g. organ infection)
  - Congenital heart disease with right-to-left shunt → loss of pulmonary filtration of microorganisms → abscesses in distribution of middle cerebral artery
- Common causative bacterial organisms (abscesses often polymicrobial)
  - *Staphylococcus aureus*, *Streptococcus*, *Bacteroides*, *Enterobacteriaceae*, *Pseudomonas*
- Immunocompromised hosts may develop viral/fungal abscesses, commonly caused by poliovirus, *Toxoplasma gondii*, *Cryptococcus neoformans*

RISK FACTORS

- Right-to-left cardiac shunts, bronchiectasis, immunosuppression

COMPLICATIONS

- Ischemia/necrosis of pituitary → pituitary insufficiency → Addisonian crisis

SIGNS & SYMPTOMS

- Classic triad (20% of cases)
  - Fever, progressively worsening focal neurology, headache
  - Increased intracranial pressure (ICP) while supine → worse headache early morning, at night/increased ICP stimulates medullary center, area postrema → morning vomiting
- Mental status change, seizures, nausea, vomiting, papilledema

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI/CT scan with contrast

- *Initial immature lesions without capsule:* difficult to distinguish from space-occupying lesions/infarcts
- *4–5 days after initial infection:* formation of capsule around necrotic focus → ring-enhancing appearance
  - Intravenous contrast material cannot pass through capsule → accumulation around lesion → bright ring with dark center

LAB RESULTS

- Lumbar puncture
  - If intracranial pressure not significantly raised
  - ↑ white cell count, ↑ protein concentration, normal glucose content
- Abscess aspirate
  - Sample obtained via imaging-guided aspirate/during surgical drainage; culture of causative organism → specific treatment

TREATMENT

MEDICATIONS

- Targeted antibiotic therapy
  - Penetration through abscess wall poor, typically accompanies surgical management
- Hyperbaric oxygen therapy
  - Reduces intracranial pressure, bacteriostatic, enhances oxidative immune function
- Corticosteroids in complicated cases with pituitary insufficiency

SURGERY

- Drainage
- Removal of any foreign material

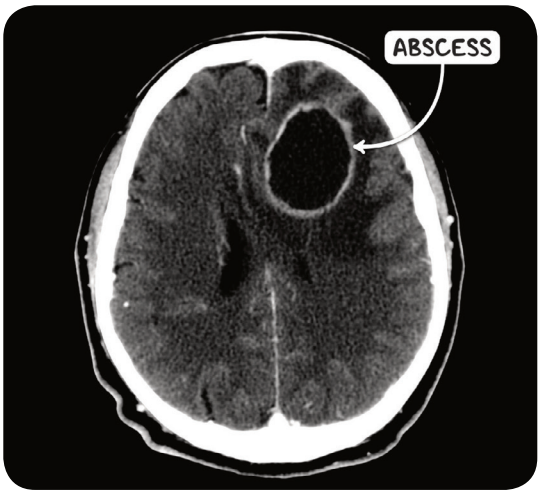

Figure 65.1 A CT scan of the head in the axial plane demonstrating a abscess in the left frontal lobe. This example developed five weeks following a repair of a depressed skull fracture.

CAVERNOUS SINUS THROMBOSIS

osms.it/cavernous-sinus-thrombosis

PATHOLOGY & CAUSES

Cavernous sinuses

- Irregularly shaped, trabeculated, blood filled cavities, acts as venous channel between endosteum, dura mater at base of skull
- Numerous important structures pass through cavernous sinuses
  - Internal carotid artery
  - Cranial nerves III, IV, V (branches V1, V2), VI
- Drain into internal jugular vein

Infection

- Infection → formation of blood clot within cavernous sinus
- Infection often arises via contiguous spread from nearby infection (e.g. nasal furuncle, sphenoidal/ethmoidal sinusitis/dental infection)
  - *Commonly associated organisms: Staphylococcus aureus, Streptococcus*

RISK FACTORS

- Immunosuppression (e.g. uncontrolled diabetes, corticosteroid use, cancer, chemotherapy)
- Thrombophilia
- Obesity
- Severe dehydration

COMPLICATIONS

- Dural venous, cavernous system valveless → communication with dural sinuses, cerebral, emissary veins → meningitis, dural empyema, brain abscess
- Spread via jugular vein to pulmonary vasculature → septic emboli, pulmonary abscesses, pneumonia
- Carotid artery narrowing → stroke
- Ischemia/direct infectious spread → hypopituitarism

SIGNS & SYMPTOMS

- Local compression, inflammation of cranial nerves (III–VI) → several partial/complete cranial neuropathies
  - Diplopia, limited eye abduction, non-reactive pupil, numbness/paresthesia around eyes, nose, forehead, facial pain
- Decreased drainage from facial vein, superior, inferior ophthalmic veins → periorbital edema, chemosis (conjunctival swelling), proptosis, headache

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- *Non-contrast:* high-density thrombus in cavernous sinus
- *With contrast:* underlying sinusitis, thickening of superior ophthalmic vein, irregular filling defects in cavernous sinus

MRI

- *T1, T2:* absent flow void, abnormal signal characteristics of affect cavernous sinus
- *Contrast venogram:* deformity of internal carotid artery in cavernous sinus, signal hyperintensity in thrombosed vascular sinuses

TREATMENT

MEDICATIONS

- Broad spectrum empiric antibiotic therapy until primary agent, source identified

SURGERY

- Sinus drainage (e.g. drainage, sphenoidotomy if primary infection arises from sphenoidal sinuses)

CREUTZFELDT–JAKOB DISEASE

osms.it/creutzfeldt-Jakob-disease

PATHOLOGY & CAUSES

- Universally fatal prionopathy; spongiform encephalopathy → rapidly progressive dementia
- Native prions play role in long-term memory, neuronal repair
- Infectious prions composed entirely of protein, folded in structurally abstract conformations; able to pass on "misfolded" conformation
  - Infectious prions propagate by inducing misfolding of native host prion proteins → formation of new infectious prions
  - Malformed prion proteins extremely stable (resistant to denaturation by enzymes) → accumulation in infected neuronal tissue → formation of amyloid sheets → eventual tissue damage, death → holes form where nerves died → sponge-like appearance on microscopy

TYPES

- Sporadic (sCJD)
  - Majority (> 85%) of cases occur spontaneously
- Familial (fCJD)
  - Minority (< 10%) transferred via autosomal dominant inheritance
- Variant (vCJD)
  - Bovine-to-human transmission of bovine spongiform encephalopathy
- Iatrogenic (iCJD)
  - Exposure to brain/spinal tissue from infected individual (e.g. cadaveric human pituitary hormone)

RISK FACTORS

- Exposure to harvested human brain products (e.g. corneal grafts, dural grafts, human growth hormone), ingestion of infected bovine products, cannibalism

COMPLICATIONS

- Progressive neurodegeneration → dysphagia → aspiration pneumonia common

SIGNS & SYMPTOMS

- *Rapidly progressive dementia:* memory loss, personality change, hallucinations
- *Movement disorders:* myoclonus, ataxia, rigid posture
- *Psychiatric:* anxiety, depression, psychosis

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Diffusion-weighted MRI
  - Focal/diffuse diffusion-restriction involving cerebral cortex/basal ganglia
- Fluid-attenuated inversion recovery (FLAIR)/T2-weighted
  - Hyperintense signal changes in basal ganglia, thalamus, cortex
- Cerebellar atrophy

LAB RESULTS

- Cerebrospinal fluid (CSF)
  - Elevated concentration of 14-3-3 protein
- Tissue biopsy
  - Prion deposits in brain (definitive diagnosis) skeletal muscle, tonsils, spleen; classical histological appearance → spongiform change in gray matter

OTHER DIAGNOSTICS

- Electroencephalography (EEG)
  - Generalized periodic sharp wave pattern

TREATMENT

MEDICATIONS

- Sedatives/antidepressants/antipsychotics
  - Palliative, relief of psychiatric symptoms
- Benzodiazepines/antiepileptics
  - Palliative, relief of movement disorders (e.g. myoclonic jerks)

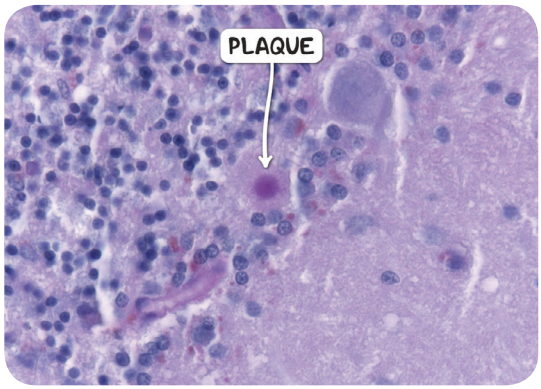

Figure 65.2 A section of the brain demonstrating a prion plaque. This individual displayed the symptoms of variant CJD.

ENCEPHALITIS

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PATHOLOGY & CAUSES

- Acute inflammatory brain disease due to direct invasion/pathogen-initiated immune response → inflammation of brain parenchyma (often with meningitis)
  - Peripheral nerves conduits to brain parenchyma for viral infection—rabies, herpes simplex virus (HSV)
  - Hematogenous spread → transfer of infections from distant sites

CAUSES

- *Viral (most common):* HSV-1 (most common), arbovirus (e.g. West Nile virus), enterovirus (e.g. Polio), varicella zoster virus (VSV), Epstein Barr virus (EBV), HIV, influenza
- *Bacterial:* Listeria monocytogenes, mycobacteria, spirochetes (e.g. syphilis)
- Parasites: protozoa (e.g. Toxoplasma), malaria
- *Fungi:* cryptococcus
- *Non-infectious, autoimmune:* acute disseminated encephalomyelitis, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, T-cell lymphoma

RISK FACTORS

- Immunosuppression
- Travel to low-income nations
- Exposure to disease vectors in endemic areas

COMPLICATIONS

- Seizures, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), increased ICP, coma

SIGNS & SYMPTOMS

- Fever, chills, malaise
- Meningeal involvement → meningism
  - Nuchal rigidity (inability to flex neck forward passively due to increased muscle tone, stiffness), headache, photosensitivity
- Parenchymal involvement → focal neurological signs, seizures, altered mental state

DIAGNOSIS

DIAGNOSTIC IMAGING

Brain CT scan (with/without contrast)

- Complete prior to lumbar puncture to exclude significantly increased ICP, obstructive hydrocephalus, mass effect

Brain MRI

- Increased T2 signal intensity in frontotemporal region → viral (HSV) encephalitis

LAB RESULTS

Blood tests

- Blood, CSF cultures
  - Bacterial pathogens
- Blood glucose
  - Comparison with CSF glucose; exclude confusion due to hypoglycemia
- Toxoplasma serology

CSF

- CSF chemistry
  - Lymphocytosis (> 5WBC/mL) with normal glucose → viral encephalitis
- CSF polymerase chain reaction (PCR)
  - Diagnosis of specific viral cause
- Specific antibody testing for EBV, arbovirus

Tissue analysis

- Tzanck smear (from base) of suspicious skin lesions → identify presence of VZV/HSV
- Brain biopsy (definitive diagnosis)
  - Cowdry type A inclusions (HSV, VZV, CMV)
  - Hemorrhagic necrosis in temporal, orbitofrontal lobes (HSV)

OTHER DIAGNOSTICS

- EEG
  - Temporal lobe discharges → viral (HSV) encephalitis

TREATMENT

MEDICATIONS

- Viral encephalitis
  - *HSV encephalitis:* acyclovir
  - *CMV encephalitis:* ganciclovir/foscarnet
  - Most viral infections lack specific antiviral agent
- Bacterial encephalitis
  - Targeted antibiotics

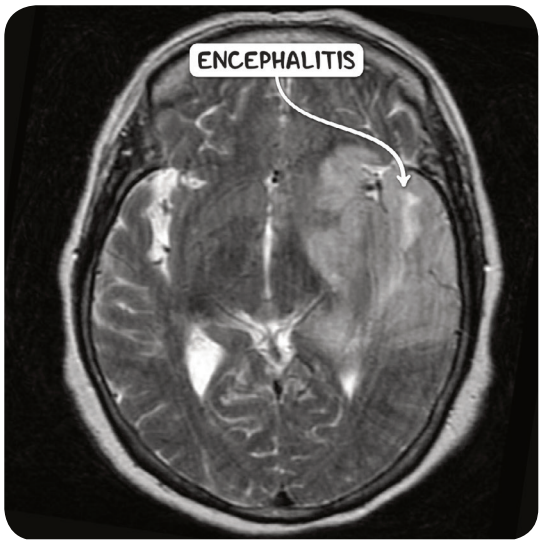

Figure 65.3 An MRI scan of the head demonstrating increased signal in the left temporal lobe. HSV encephalitis was later confirmed by PCR of the cerebrospinal fluid.

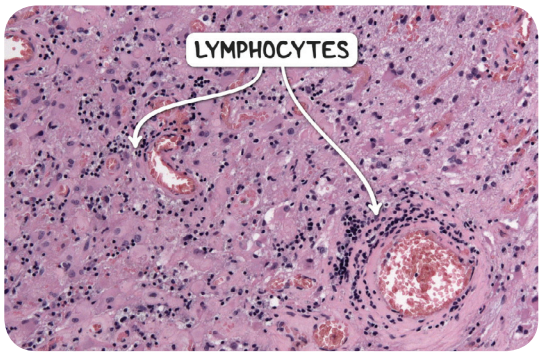

Figure 65.4 A histological section of the brain demonstrating a lymphocytic infiltrate in an individual with encephalitis.

EPIDURAL ABSCESS

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PATHOLOGY & CAUSES

- Collection of pus, infectious material in epidural space of CNS

TYPES

Intracranial epidural abscess

- Dura mater (tough outermost layer of meninges) directly in contact with skull
- Puss, granulation tissue accumulate between dura mater, cranial bone
- Dura adheres tightly to skull → limits expansion → dangerously increases ICP
- Typically caused by *Staphylococci*/*Streptococci* reaching dural space
  - Direct extension from local infection (e.g. ear/paranasal sinuses) → osteomyelitis → abscess formation
  - Hematogenous seeding from distant infection
  - Iatrogenic spread due to invasive procedures
- *Risk factors:* prior craniotomy, head injury, sinusitis, otitis media, mastoiditis
- *Complications:* seizures, increased ICP → uncal/tonsillar herniation, hemorrhage into abscess, septic shock

Spinal epidural abscess

- Spinal epidural space
  - Outermost space within spinal canal (formed by vertebrae, lying outside dura mater)
  - Contains lymphatics, spinal nerve roots, connective tissue, fat, vasculature
- Collection of pus/inflammatory granulation tissue between dura mater, vertebral column → spinal epidural abscess → physical compression, inflammation of surrounding tissues, spinal cord → local ischemia
- Loose association between dura, vertebral bodies → extension of spinal epidural abscess to multiple spinal levels → extensive neurological findings
- Typically caused by *Staphylococcus aureus*, enteric gram-negative bacilli (e.g. *E. coli*), coagulase-negative *Staphylococci* reaching dural space
  - Direct extension of local infection; vertebral osteomyelitis, psoas abscess, soft-tissue infection
  - Hematogenous seeding from distant infection
  - Iatrogenic spread due to invasive procedures
- *Risk factors:* old age, invasive spinal procedures, immunocompromised states, intravenous drug use, most common in thoracolumbar area (epidural space larger, contains more fat tissue)
- *Complications:* recurrent sepsis, spinal cord injury → bladder dysfunction

SIGNS & SYMPTOMS

- Fever, malaise
- Cranial epidural abscess
  - Pain/tenderness over abscess site, pus draining from ear/sinuses, neck stiffness, headache, nausea, vomiting
- Spinal epidural abscess (staging follows clinical progression)
  - Back pain, tenderness, fever
  - Radicular pain, reflex abnormalities
  - Sensory abnormalities, motor weakness, loss of bowel/bladder control
  - Paralysis (progresses to irreversible paralysis without rapid surgical intervention)

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan with contrast

- Fluid collections in epidural space

MRI with contrast

- Homogeneous enhancement of abnormal area, liquid abscess surrounded by inflammatory tissue showing varying degrees of peripheral enhancement

X-ray

- Osteomyelitis, vertebral collapse

LAB RESULTS

- Blood cultures
  - May culture causative organism
- Lumbar puncture contraindicated
  - Risk of spreading infection to subarachnoid space
- CT-guided aspirates/surgically-obtained fluid
  - Culture causative organism

TREATMENT

MEDICATIONS

- Initial empirical antibiotic therapy, broad-spectrum coverage for gram-positive, gram-negative organisms
  - Vancomycin (Gram-positive coverage), third-generation cephalosporins (Gram-positive, Gram-negative)
- Targeted antibiotics specific to isolated organisms

SURGERY

- Intracranial
  - Craniotomy → removal of infected bone, surgical decompression
- Spinal
  - Decompressive laminectomy (CT-guided drainage)

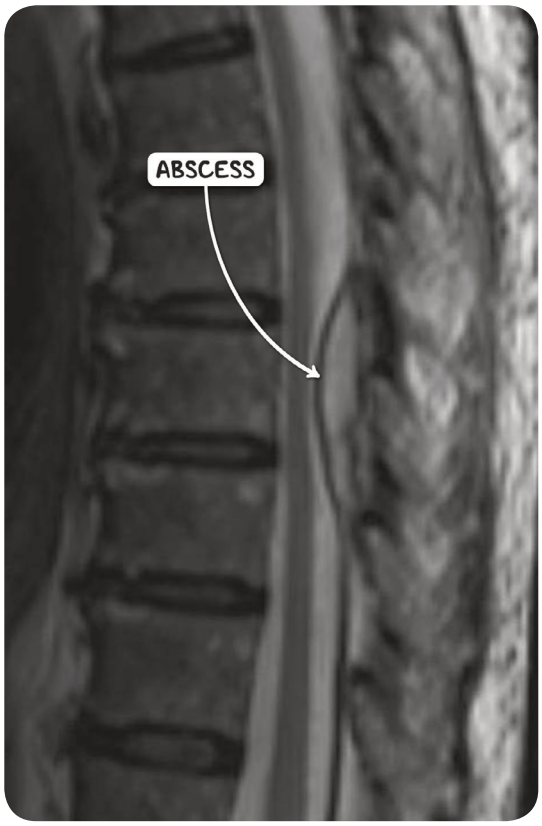

Figure 65.5 A histological section of the brain demonstrating a lymphocytic infiltrate in an individual with encephalitis.

MENINGITIS

osms.it/meningitis

PATHOLOGY & CAUSES

- Inflammation of meninges surrounding brain, spinal cord

CAUSES

Bacteria, viruses, fungi, parasites, non-infectious causes

- *Non-infectious:* e.g. medications, autoimmune disease, malignancy
- "Aseptic meningitis"
  - Don't culture on typical bacterial media (e.g. viruses, fungi, parasites, non-infectious causes)
- Acute illness
  - *Onset:* hours, days
  - Likely viral/bacterial causes
- Chronic meningitis
  - *Onset:* weeks, months
  - Likely mycobacteria, fungi, Lyme disease, parasitic causes
- Pyogenic meningitis
  - Most likely bug by age group
  - Mnemonic: **E**xplaining **B**ig **H**ot **N**eck **S**tiffness (in order from birth to death)

MNEMONIC: Explaining Big Hot Neck Stiffness

Causative microorganisms in meningitis by age group

***E**. coli*, *Group **B** streptococcus* (infants)

***H**aemophilus influenzae* (older infants, kids)

***N**eisseria meningitidis* (young adults)

***S**treptococcus pneumoniae* (elderly)

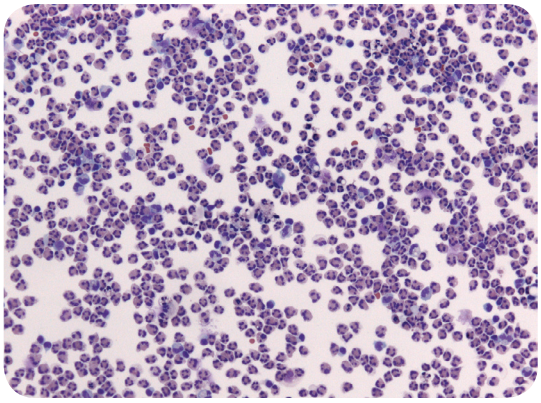

Figure 65.6 A sample of cerebrospinal fluid taken from an individual with bacterial meningitis.

Microbial spread to CNS

- Hematogenous spread (from distant site of infection)
- Retrograde transport along cranial/peripheral nerves (viral illness)
- Contiguous spread from local infections of sinuses, ears, overlying bone
  - Infectious agents colonize nasopharynx/respiratory tract
  - Preceding viral infection → breakdown of normal nasal mucosal barrier → colonizing bacteria enter bloodstream → seeding of subarachnoid space in areas where blood-brain barrier vulnerable (e.g. choroid plexus)
- Traumatic inoculation

Other sources of inflammation

- Significant inflammation not directly due to bacterial action
- Presence of bacterial antigens (e.g. cell wall products) in CNS → recognition by astrocytes, microglia → cytokine release → inflammation
- Inflammation → increased blood-brain barrier permeability → vasogenic cerebral edema

MENINGITIS: COMMON CAUSATIVE ORGANISMS

	AGE	MICROORGANISM
BACTERIAL	0 - 4 weeks	Group B streptococcus, *E. coli*, *L. monocytogenes*, *Klebsiella*
	1 - 23 months	Group B streptococcus, *E. coli*, *S. pneumoniae*, *N. meningitidis*, *H. influenza*
	Children, adults	*S. pneumoniae*, *N. meningitidis*, *H. influenzae*
	Elderly >50	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*
VIRAL		HSV-1, -2, VZV, Enteroviruses, Parechoviruses, West Nile virus
FUNGAL		*Cryptococcus*, *Coccidioides*
OTHER		Lyme disease, Neurosyphilis, TB

- Extravasation of white blood cells, plasma into CSF → interstitial edema
- Immune cell activity (e.g. further cytokine release, oxidative burst) → inflammation of walls of blood vessels → cerebral vasculitis → decreased blood flow → cytotoxic edema
- Collectively edema subtypes → raised intracranial pressure
- Administration of antibiotics → greater amounts of bacterial antigens (from dead bacteria) enter CSF → worsening inflammation (initially)

RISK FACTORS

- Immunocompromised individuals, unvaccinated individuals (*S. pneumoniae*, *H. influenzae* Type B)
- Penetrating head trauma
- Anatomical meningeal defects (CSF leaks)
- Contact with colonized/infected individuals

COMPLICATIONS

- Cerebral edema, cerebral herniation, deafness, epilepsy, hydrocephalus, cognitive deficits

SIGNS & SYMPTOMS

- Neonates, children
  - Fever, lethargy, irritability, vomiting, poor feeding
- Adults
  - *Classic triad (< 50% of cases):* sudden onset headache, fever, nuchal rigidity
  - Photophobia, phonophobia (discomfort with loud sounds), confusion, vomiting, papilledema
  - *Brudziński's sign:* passive neck flexion → pain, involuntary flexion of hips, knees
  - *Kernig's sign:* resistance to knee extension when hip flexed to 90°

- *Jolt accentuation of headache:* headache worsens if individual asked to "jolt" head from side to side in horizontal plane

- Meningococcal meningitis
  - Petechial rash; non-blanching when pressure applied; trunk, lower extremities

DIAGNOSIS

LAB RESULTS

- Lumbar puncture
  - Gram stain; bacterial culture, susceptibility; WBC count, differential; RBC count; glucose, protein concentration
  - Acid-fast bacilli stain in TB endemic areas/if suspected exposure
  - HSV/enterovirus PCR

CHANGES IN CSF PARAMETERS

CSF CHARACTERISTICS (NORMALS)	BACTERIAL	VIRAL	FUNGAL	TB	CRYPTOCOCCAL
APPEARANCE (CLEAR)	Cloudy	Clear	Clear/cloudy	Opaque	Clear
PRESSURE (5–15 CM WATER)	↑	Normal	Normal	↑	↑
WBC (<5/μL)	500-10,000 (Neutrophils)	10-100 (Lymphocytes)	10-500 (Mononuclear)	50-500 (Neutrophils, monocytes)	100-200 (Lymphocytes)
GLUCOSE (50–75 MMOL/DL)	↓	Normal	↓	↓	↓
PROTEIN (< 60 MG/DL)	> 150	↑	> 1000	> 100	50-200
MICROBIOLOGY	Gram stain, culture	PCR assay	India ink stain	Acid-fast bacillus stain, PCR	India ink stain

TREATMENT

MEDICATIONS

Prevention

- Immunization with meningococcal, mumps, pneumococcal, Hib vaccines

- Preemptive treatment to any close contacts of individuals with meningococcal meningitis is a single dose of ceftriaxone/rifampin

Acute bacterial meningitis

- Empiric antibiotic therapy based on age
  - If immediate lumbar puncture performed, obtain sample prior to antibiotics

- *< one week:* penicillin (e.g. ampicillin) + third-generation cephalosporin (e.g. cefotaxime)/aminoglycoside
- *1 week–3 months:* third-generation cephalosporin + vancomycin
- *> three months:* vancomycin
- Targeted antibiotic therapy
- *Corticosteroids:* inflammation, cerebral edema (dexamethasone)

Aseptic meningitis

- *HSV, VZV meningitis:* acyclovir
- *Fungal meningitis (cryptococcal meningitis):* amphotericin B, flucytosine

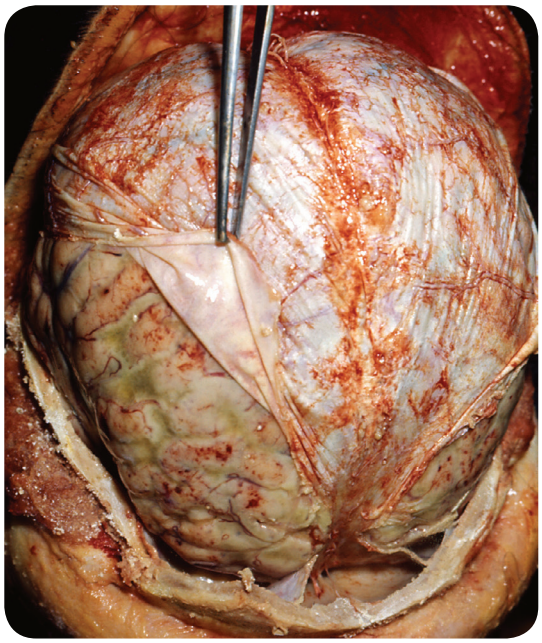

Figure 65.7 The brain of an individual at post mortem following death from meningitis. Removal of the dura mater reveals pus surrounding the brain.

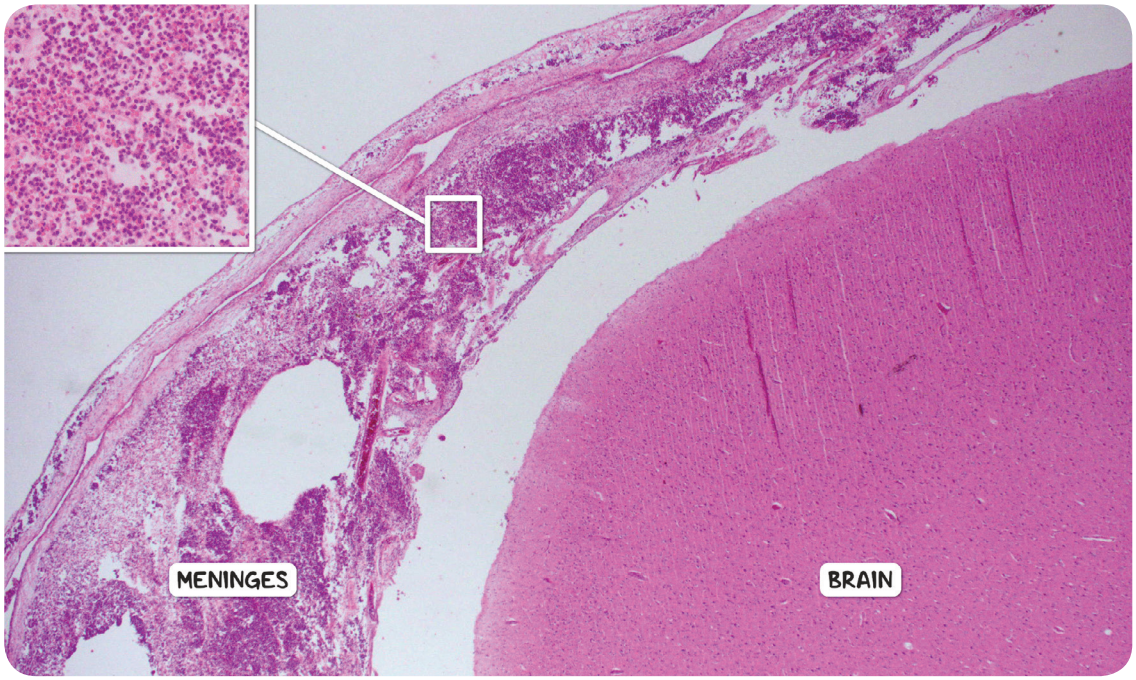

Figure 65.8 Post mortem histology of the brain and meninges of an individual who died from acute bacterial meningitis. The zoomed in area demonstrates numerous neutrophils infiltrating the meninges.