NOTES
CENTRAL NERVOUS SYSTEM INFECTIONS

MICROBE OVERVIEW

PATHOLOGY & CAUSES

- Rare infections of central nervous system (CNS) by ameba, parasites

RISK FACTORS

- Immunosuppression (*Acanthamoeba*, *Toxoplasmosis gondii*), immersion in infested water (*Naegleria fowleri*)

SIGNS & SYMPTOMS

- Fever, headache, seizures, focal neurological signs, mental status change

DIAGNOSIS

LAB RESULTS

- Presence of infectious agent via microscopy, culture, polymerase chain reaction (PCR), presence of specific antibodies

Granulomatous amebic encephalitis

- *Brain biopsy*: trophozoites in perivascular space and thick walled cysts, PCR/DNA probes may show *Acanthamoeba*

Primary amoebic meningoencephalitis

- Lumbar puncture
  - *CSF microscopy*: motile amebae/ fluorescent antibody staining
  - *CSF PCR*: *Naegleria fowleri* DNA
  - *CSF culture*: *Naegleria fowleri* can be grown on nonnutrient agar coated with *Escherichia coli*

Toxoplasmosis

- PCR (blood, CSF): *Toxoplasma gondii* DNA (inactive cysts may evade detection)
- Antibody titres
  - *IgG*: evidence of current/previous infection
  - *IgM*: occur in weeks after initial infection
  - *Antibody avidity testing*: affinity for antigen increases with duration of infection
- *Sabin–Feldman dye test*: high titers → acute infection
- *Tissue biopsy*: tachyzoites in tissues/ smears

TREATMENT

MEDICATIONS

- Antifungal, antiparasitic agents

ACANTHAMOEBA

osmosis.org/learn/acanthamoeba

PATHOLOGY & CAUSES

Genus of amebae

- Single-celled eukaryotes
- Environmentally ubiquitous organisms
  - *Acanthamoeba* spp. isolated from soil, air, fresh water, sewage, seawater, chlorinated swimming pools, domestic tap water, bottled water, hospitals, air-conditioning units, contact lens cases
- Life stages
  - Metabolically active trophozoite
  - Dormant stress resistant cyst
- Generally free living bacterivores, can cause human infection (acanthamebiasis)

Granulomatous amoebic encephalitis

- Infection associated with immunosuppression (e.g. diabetes, HIV/AIDS, hematological malignancy, malnutrition, hepatic cirrhosis, chronic renal failure, systemic lupus, chemotherapy)
- Parasite enters body through cuts in skin/inhalation → hematogenous spread to CNS → invasion of connective tissue → inflammatory response → neuronal damage

Endosymbiosis, secondary infection

- Several human pathogens infect, replicate within Acanthamoeba
  - *Legionella pneumophila*, *Pseudomonas aeruginosa*, some strains of *E. coli*, *Staphylococcus aureus*
- Replication inside *Acanthamoeba* → enhanced growth in human macrophages, increased antibiotic resistance → more virulent, fulminant infections

SIGNS & SYMPTOMS

- Fever, headache, seizures, focal neurological signs (e.g. cranial nerve palsies), mental status change (e.g. confusion), sepsis → progressive worsening over weeks/months → death

DIAGNOSIS

DIAGNOSTIC IMAGING

Brain CT/MRI

- Meningeal exudate, pseudotumoral lesions, multiple space-occupying lesions with ring enhancement

LAB RESULTS

Lumbar puncture

- Often contraindicated due to risk of herniation associated with mass lesions
- Analytical findings generally nonspecific
  - Intermediate elevations in white blood cell count, elevated protein, decreased glucose levels
- Giemsa staining, microscopy
  - Trophozoites

Tissue biopsy

- Brain biopsy
  - Trophozoites in perivascular space, thick-walled cysts on light microscopy; PCR/DNA probes may reveal *Acanthamoeba*
  - *Immunocompetent host*: granulomatous lesions
  - *Severely immunosuppressed host*: insufficient CD+ve T-cells to mount granulomatous response → perivascular cuffing with amoebae in necrotic tissue
- If other organs involved (e.g. skin, conjunctiva, lungs)
  - Trophozoites

TREATMENT

MEDICATIONS

- Current treatment regimes uncertain (based on in vitro studies, case reports)
  - Antifungal, antiparasitic agents in combination
  - *Empiric antifungal regime*: miltefosine, fluconazole, pentamidine isethionate +/- trimethoprim-sulfamethoxazole, metronidazole, macrolide antibiotic

SURGERY

- Single cerebral lesions
  - Surgical resection

NAEGLERIA FOWLERI (PRIMARY AMEBIC MENINGOENCEPHALITIS)

osmosis.org/learn/naegleria_fowleri

PATHOLOGY & CAUSES

- Thermophilic, free-living ameba, found in bodies of warm (stagnant), freshwater

TYPES

- Life cycle, three forms

1. Cyst
   - Immotile, dormant, survival phase
   - Smooth, single-layered cell wall with single nucleus, naturally resistant to environmental factors
   - Formation of cysts induced by unfavorable conditions such as food shortage, overcrowding, desiccation, accumulation of waste products, cold temperatures (< 10° celsius)
2. Trophozoite (ameboid)
   - Feeding, reproductive, infective phase
   - Transformation into trophozoites occurs around 25° celsius
   - Reproduction occurs via binary fission (single cell divides into two offspring), optimal temperature 42° celsius
3. Biflagellate (two flagella)
   - Mobile, infective phase
   - Pear-shaped body with two flagella
   - Flagellate phase occurs when ameba encounters change in fluid ionic concentration → allows movement to suitable environment

- In human tissues *Naegleria fowleri* exists as ameboid trophozoite; flagellate form may be found in CSF/during initial nasal insufflation

Primary amoebic meningoencephalitis

- AKA naegleriasis
- Rare infection, fatality rate > 95%
- Mechanism of entry
  - Insufflated into sinuses during water-based activities → attaches to olfactory epithelium → follows olfactory axon through cribiform plate → migration to olfactory bulbs → spread throughout brain → diffuse meningoencephalitis
- In tissues, Naegleria fowleri feeds via two mechanisms; feeding on neurological tissue → necrosis, bleeding
  - Phagocytosis of red, white blood cells
  - Piecemeal consumption of astrocytes, neurons via amoebostome (actin-rich sucking apparatus extended from cell surface)

SIGNS & SYMPTOMS

- Symptoms appear 1–9 days after nasal exposure → death likely follows within two weeks
- Change in sensation of taste, smell; headache, fever, nausea, stiff neck, seizures, coma

DIAGNOSIS

DIAGNOSTIC IMAGING

Brain imaging

- Initially unchanged
  - Reveals associated complications Leptomeningeal enhancement, diffuse subarachnoid hemorrhage, oedema, hydrocephalus, multiple cerebral infarcts

LAB RESULTS

- Lumbar puncture
  - *CSF microscopy*: motile amebae/ fluorescent antibody staining
  - *CSF PCR*: *Naegleria fowleri* DNA
  - *CSF culture*: *Naegleria fowleri* can be grown on nonnutrient agar coated with *E. coli* → drop of CSF of infected individual added, incubated at 37° celsius; clearing of *E. coli* in thin tracks indicative of trophozoite feeding → likely infection

TREATMENT

MEDICATIONS:

- Amphotericin B +/- fluconazole
- Miltefosine

TOXOPLASMA GONDII (TOXOPLASMOSIS)

osmosis.org/learn/toxoplasma_gondii

PATHOLOGY & CAUSES

- Obligate intracellular parasite capable of infecting nearly all warm-blooded animals
  - *Only definitive hosts*: biological family *Felidae* (e.g. house cats)
- 30–50% of global population exposed, may be chronically infected

Life cycle

- Sexual reproduction
  - Consumes infected animal meal (e.g. mouse) → parasite survives transit through stomach → infects small intestinal epithelial cells → parasites undergo sexual development, reproduction → millions of thick-walled, zygote-containing, oocytes produced
- Felid shedding
  - Infected epithelial cells rupture → release oocytes into intestinal lumen → shedding in feces → spread via soil, water, food
  - Oocysts highly resilient; can survive, remain infective for months in cold, dry climates
- Infection of intermediate host
  - Ingestion of oocysts by warm blooded animals (e.g. humans) → oocyst wall dissolved by proteolytic enzymes in stomach, small intestine → frees sporozoites from within oocyst → parasites invade intestinal epithelium, surrounding cells → differentiation into tachyzoites (motile, quickly-multiplying phase)
- Asexual reproduction in intermediate host
  - Tachyzoites replicated inside specialized vacuoles until host cell dies, ruptures → release, hematogenous spread of tachyzoites to all tissues

- Formation of tissue cysts
  - Host immune response → tachyzoite conversion → bradyzoites (semi-dormant, slowly dividing stage) → inside host cells known as tissue cysts → can form in any organ; predominantly brain, eyes, striated muscle (including cardiac muscle)
  - Consumption of tissue cysts in meat from infected animal
  - Primary means of infection (e.g. pork, lamb)
  - Tissue cysts maintained in host tissue for remainder of life via periodic cyst rupture, re-encysting

RISK FACTORS

- Consumption of raw/undercooked meat; ingestion of contaminated water, soil/vegetables; previous blood transfusion/organ transplant; transplacental transmission

COMPLICATIONS

- Toxoplasmic chorioretinitis
  - AKA ocular toxoplasmosis
  - Common cause of posterior segment infection
  - Majority of cases acquired; also strongly associated with congenital infection

Figure 8.1 A histological section of the cerebrum demonstrating cerebral toxoplasmosis. There are bradyzoites present and a mixed inflammatory infiltrate which includes eosinophils.

SIGNS & SYMPTOMS

- Initial infection (immunocompetent host)
  - Mild flu-like symptoms (e.g. swollen lymph nodes, headache, fever, fatigue, muscle aches, pains)
- Congenital infection
  - Chorioretinitis (unilateral decrease in visual acuity), hydrocephalus, seizures, lymphadenopathy, hepatosplenomegaly
- Chronic/latent infection
  - Asymptomatic in healthy hosts
- Immunocompromised host
  - Active infection (toxoplasmosis)
  - Headache, confusion, poor coordination, seizures, cough, dyspnea
  - *Reactivation of latent infection*: worsening of immunosuppression due to progression of underlying disease (e.g. HIV/AIDS, iatrogenic immunosuppression) → loss of immune balance → progression to active infection

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan with contrast

- Multiple 1–3 cm hypodense regions with nodular/ring enhancement predominantly in basal ganglia, corticomedullary junction

T2 weighted MRI

- Iso/hyper-intense lesions surrounded by perilesional edema

Fundoscopy

- Toxoplasmic chorioretinitis
  - Unifocal area of acute-onset inflammation adjacent to old chorioretinal scar

LAB RESULTS

PCR (blood, CSF)

- *Toxoplasma gondii* DNA (inactive cysts may evade detection)

Antibody titres

- IgG (persist for life)

- Evidence of current/previous infection
- IgM (acute infection)
  - Occur in weeks after initial infection, remain detectable for months
  - Antibody avidity testing may clarify nature of infection; early toxoplasma-specific IgG has low affinity for toxoplasma antigen; affinity increases with duration of infection
- Sabin–Feldman dye test
  - Requires specialised laboratories (live Toxoplasma gondii required); high titers → acute infection
  - Patient serum treated with Toxoplasma trophozoites + complement, incubated → methylene blue added (membrane stain) → if anti-toxoplasma antibodies present, complement facilitates lysis of parasite membrane → no staining of lysed membrane
  - No antibodies in serum → intact membranes → membrane stained blue under microscopy
- Tissue (brain/lymph node/muscle) biopsy
  - Tachyzoites (acute infection) may be demonstrated in tissues/smears

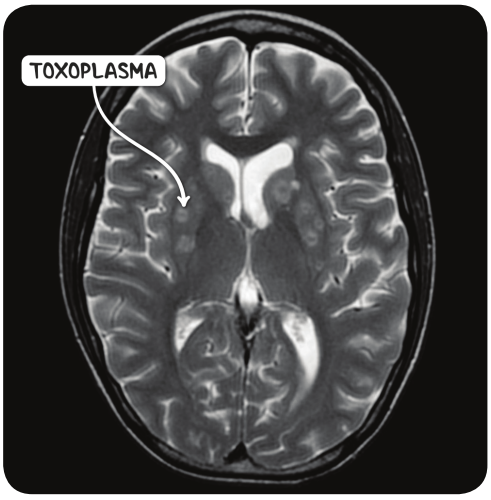

Figure 8.2 An MRI scan of the head in the axial plane demonstrating cerebral toxoplasmosis. There are numerous peripherally enhancing nodules in the basal ganglia.

TREATMENT

MEDICATIONS

- Prevention
  - Trimethoprim/sulfamethoxazole
- Acute infection
  - *Antimalarials*: pyrimethamine
  - *Antibiotics*: sulfadiazine with pyrimethamine, clindamycin, spiramycin
- Latent infection
  - Cysts not sufficiently penetrated by traditional therapy
  - Atovaquone (antimalarial) +/- clindamycin (lincomycin antibiotic)
- Toxoplasmic chorioretinitis
  - Sight-threatening lesions
  - *Triple therapy*: pyrimethamine, sulfadiazine, folinic acid
  - *Mono-antibiotic therapy*: trimethoprim-sulfamethoxazole, clindamycin, spiramycin