

Fungal infections of central nervous system (CNS)

CNS infections are both diagnostic challenges and medical emergencies

Delay in diagnosis and initiation of appropriate therapy will lead to high mortality rate or in permanent, severe neurological damage

Fungal infections of the CNS are not common
However, they are being increasingly diagnosed

Why?

- Hosts are more susceptible
[↓ immunity]

- ↑ exposure

- Antibiotic use



Fungal infections of central nervous system

Dr. Ahmed M. AL-Barrag



Risk factors

HIV/AIDS → Candidiasis
Hematopoietic stem cell transplant (HSCT)
Solid organs transplantation
Malignancies → aspergillosis
Neutropenia
Hereditary immune defects
Graft versus host disease (GvHD)
Chronic granulomatous disease (CGD)
Immunosuppressive medications
Diabetes mellitus
surgery or trauma
Indwelling catheters (e.g. candidemia → CNS seeding)

Objectives:

1. To know the main fungi that affect the central nervous system and the clinical settings of such infections
2. To acquire the basic knowledge about fungal meningitis and brain abscess: clinical features, etiology, diagnosis, and treatment

Etiology

Several fungal agents can cause CNS infections.

Yeast

Cryptococcus spp
Candida spp

Dimorphic

Histoplasma spp
Blastomyces spp
Coccidioides spp
Paracoccidioides spp
Penicillium marneffei

Mold

Aspergillus spp
Zygomycetes
Fusarium spp

Exophiala spp
Cladophialophora bantiana
Curvularia, Bipolaris
Ramichloridium mackenziei

Fungi reach the central nervous system by different mechanisms:

- Hematogenous spread (common)
- Local extension from the paranasal sinuses, the ear, or the orbits.
- Traumatic introduction
 - Surgical procedures
 - Head trauma
 - Injections
 - lumbar punctures



Cryptococcal Meningitis

AIDS is the leading predisposing factor

There are two varieties of *Cryptococcus neoformans*

Cryptococcus neoformans var. *neoformans* and var. *gatti*

Cryptococcus neoformans is the most cause of fungal meningitis

- Capsulated yeast cells
- Naturally y in Pigeon habitats

Mainly meningitis

Clinical syndroms

Meningitis

Subacute
Chronic

Brain abscess

With or without vascular invasion

(*aspergillus*) ← most common

These clinical syndromes can occur either alone or in combination.
Certain clinical syndromes are specific for certain fungi

CNS Zygomycosis (mucoromycosis)

Rhinocerebral syndrome

The rhinocerebral form is the most frequent presenting clinical syndrome in zygomycosis.

Diabetics with ketoacidosis, in addition to other risk factors

The clinical manifestations of the rhinocerebral form start as ^{sinusitis} rapidly progress and involve the orbit, eye and optic nerve and extend to the brain

Facial edema, pain, necrosis, loss of vision, black discharge
Angiotropism; As angio-invasion is very frequent

Mortality is high (80-100%)

Progression is rapid, to improve the outcome:

Rapid diagnosis
Control the underlying disease
Early surgical debridement
Appropriate antifungal therapy

Fast growing zygomycetes

Candidiasis

Candida species are the fourth most common cause of hospital acquired blood stream infections

Indwelling catheter and a fever unresponsive to antibacterial agents

Hematogenously, surgery, catheters

Clinical syndromes:

Cerebral microabscesses
Cerebral abscesses
Meningitis
Vascular complications (infarcts, hemorrhage)

most common

← *C. albicans*, and other species including *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*.

Phaeohyphomycosis

Fungal infections caused by dematiaceous fungi

Neurotropic fungi

Usually brain abscess, chronic

Reported in immunocompetent hosts

main one

← *Cladophiala bantiana*, *Exophiala*, *Curvularia*, *Fonsecaea*, *Ramichloridium* (Mainly reported from Middle East, i.e. restricted to ME)

mackenzii

CNS Aspergillosis

Usually brain abscesses (single or multiple)

A severe complication of hematological malignancies and cancer chemotherapy, transplantation

Hematogenously but may also occur via direct spread from the anatomically adjacent sinuses, Angiotropism (infarction and hemorrhagic necrosis)

Mortality rate is high

A. fumigatus, but also *A. niger*, *A. flavus*, and *A. terreus*

Imp. * *Ramichloridium mackenzii* restricted in the Middle East

Lab Diagnosis

Clinical Samples

CSF
Biopsy
Pus, aspirate
Blood

CSF abnormalities

Cell count
Glucose level (low)
Protein level (high)

↑ Not specific for fungal infections

Other infections :

Histoplasmosis
Blastomycosis
Coccidioidomycosis
Paracoccidioidomycosis

Caused by primary pathogens

Subacute or chronic Meningitis (common), and brain abscess

Following a primary infection, e.g. respiratory

Lab Diagnosis

Direct Microscopy :

Fungal stains: Giemsa, GMS, PAS, India ink (Cryptococcus neoformans)

Culture :

Fungal media: SDA, BHI, other media if needed.

Serology :

Candida → mannan antigen
Aspergillus → galactomannan antigen
Cryptococcus

Histoplasma
Blastomycetes
Coccidioides
Paracoccidioides

PCR

Diagnosis

Clinical features (history, risk factors, etc)

Not Specific

Neuro-imaging (CT scan, MRI)

Good value in diagnosis and therapy monitoring

Lab Investigations

Histopathology
CSF examination (cell count, chemistry)
Microbiology

* CNS fungal infections are hard to diagnose because sometimes serology, CSF examination... can be -ve [History & Risk factors are great indicators for fungal CNS infections]

Management

Control of the underlying disease
Reduce immunosuppression, restore immunity if possible
Start antifungal therapy promptly

- Polyenes
- Azoles
- Echinocandins

Consider surgery in certain situations

Antifungal therapy

Cryptococcal meningitis
Amphotericine B (combination with Flucytosine)

CNS Candidiasis :
Amphotericine B, Caspofungin, Voriconazole, Fluconazole

CNS Aspergillosis;
Voriconazole, Caspofungin, Posaconazole
(Combination of Vori conazole and Caspofungin)

CNS Zygomycosis :
Amphotericine B, Posaconazole (we can not use Caspofungin or voriconazole)

- CNS fungal infections are not treated only by antifungal drugs (surgery for example)