

Lecture Title:

Fungal Infections of Central Nervous System

(CNS Block, Microbiology)

Lecturer name:

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Lecture 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.

Fungal infections of central nervous system (CNS)

- CNS infections are both diagnostic challenge and medical emergency
- 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?

Risk factors

HIV/AIDS

Hematopoietic stem cell transplant (HSCT)

Solid organs transplantation

Malignancies

Neutropenia

Hereditary immune defects

Immunosuppressive medications

Diabetes mellitus

Surgery or trauma

Indwelling catheters (e.g. candidemia  CNS seeding)

How fungi reach the central nervous system?

Fungi reach the central nervous system by different mechanisms:

➤ Hematogenous spread

➤ Local extension from the paranasal sinuses, the ear, or the orbits.

➤ Traumatic introduction

Surgical procedures

Head trauma

Injections

lumbar punctures

Clinical syndromes

➤ Meningitis

Sub acute

Chronic

➤ Brain abscess

With or without vascular invasion

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

Etiology

- Several fungal agents can cause CNS infections.

Yeast:

Candida spp

Cryptococcus spp

Dimorphic

Histoplasma spp

Blastomyces spp

Coccidioides spp

Paracoccidioides spp

Penicillium marneffe

Mould

Aspergillus spp

Zygomycetes

Fusarium spp

Exophiala spp

Cladophialophora bantiana

Curvularia, Bipolaris

Rhinocladiella mackenziei

and Others

Cryptococcal meningitis

AIDS is the leading predisposing factor

Etiology:

Cryptococcus neoformans

Cryptococcus gattii

Cryptococcus neoformans is the most common etiology

Capsulated yeast cells

Naturally in Pigeon habitats

Mainly meningitis

Acquired by inhalation

Candidiasis

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

Candida can reach the CNS

Hematogenously,
Surgery, Catheters

Clinical syndroms

Cerebral microabscesses

Cerebral abscesses

Meningitis

Vascular complications (infarcts, hemorrhage)

Etiology:

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

CNS Aspergillosis

Usually brain abscesses (single or multiple)

A severe complication of hematological malignancies and cancer chemotherapy, transplantation

Spread Hematogenously

may also occur via direct spread from the anatomically adjacent sinuses,

Angiotropism (infraction and hemorrhagic necrosis)

Mortality rate is high

Etiology:

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

CNS Zygomycosis (mucoromycosis)

The rhinocerebral form is the most frequent presenting clinical syndrome in CNS 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

Etiology: Zygomycetes e.g. *Rhizopus*, *Absidia*, *Mucor*
Fast growing fungi

Mortality is high (80- 100%)
Progression is rapid,

To improve the outcome:

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

Pheohyphomycosis

Fungal infections caused by dematiaceous fungi

Neurotropic fungi

CNS infections: Usually brain abscess, and chronic

Reported in immunocompetent hosts

Etiology:

Cladophialophora, *Exophiala* , *Curvularia*, *Fonsecaea* ,
Rhinoctadiella mackenziei (Mainly reported from Middle East)

Other Infections

Histoplasmosis

Blastomycosis

Coccidioidomycosis

Paracoccidioidomycosis

➤ Caused by primary pathogens

➤ Sub acute or chronic Meningitis (common), and brain abscess

➤ Following a primary infection, mainly respiratory

Diagnosis

Clinical features (history, risk factors, etc)

Not Specific

Neuro-imaging

Good value in diagnosis and therapy monitoring

Lab Investigations

CSF examination (cell count, chemistry)

Histopathology

Microbiology

Lab Diagnosis

Clinical Samples

CSF

Biopsy

Pus, aspirate

Blood (for serology)

1. CSF abnormalities

Cell count

Glucose level (low)

Protein level (high)

Not specific for Fungal infections

Lab Diagnosis

2. Direct Microscopy

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

3. Culture

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

4. Serology

Candida

Aspergillus

Cryptococcus

Histoplasma

Blastomyces

Coccidioides

Paracoccidioides

5. PCR

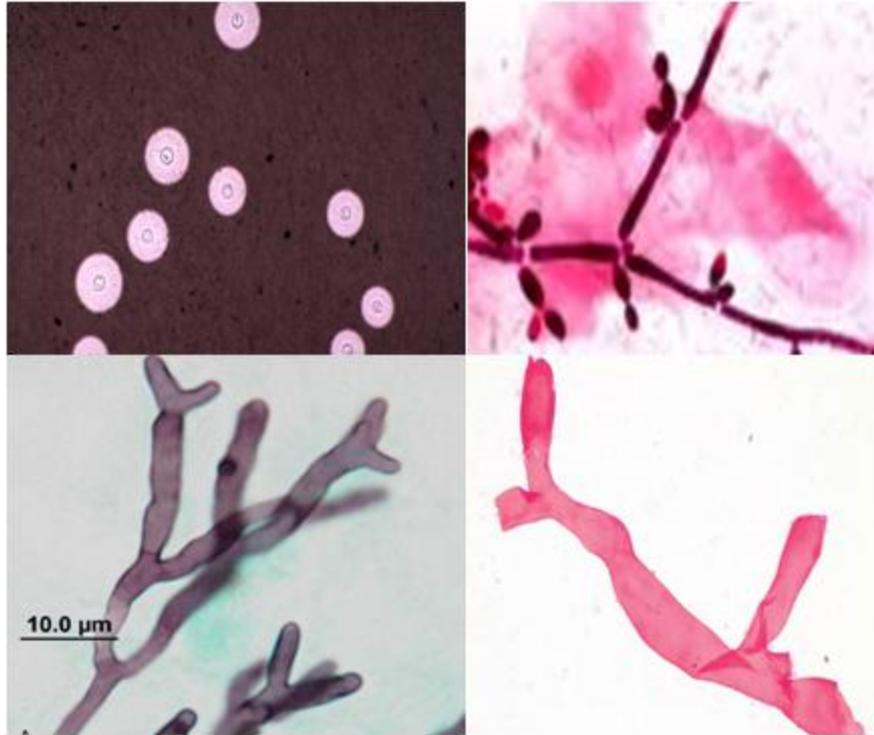
Lab. Diagnosis

CNS infection	Direct microscopy	Culture	Serology*
Cryptococcal meningitis	Yeast cells Capsulated (india ink)	Yeast	Cryptococcal Ag (capsule) Latex agglutination
Candidiasis	Yeast cells and pseudohyphae	Yeast	Mannan Ag (cell wall)
Aspergillosis	Septate branching hyphae	Hyaline mould	Galactomannan Ag
Zygomycosis	Broad non-septate hyphae	Hyaline mould Fast growing	No serology available
Pheohyphomycosis	Brown septate hyphae	Dematiaceous mould	

***Serology: β -D- Glucan :**

For diagnosis of invasive fungal infections except cryptococcosis and zygomycosis

Lab. Diagnosis



Management

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

Polyenes

Azoles

Echinocandins

Consider surgery in certain situations

Antifungal therapy

CNS fungal infection	Treatment
Cryptococcal meningitis	Amphotericin B (combination with Flucytosine)
CNS Candidiasis	Amphotericin B, Caspofungin, Fluconazole, Voriconazole,
CNS Aspergillosis	Voriconazole, Amphotericin B, Caspofungin, Posaconazole (Combination of Voriconazole and Caspofungin)
CNS Zygomycosis	Amphotericin B, Posaconazole (other azoles are not effective)