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 marneffei

Mould

Aspergillus spp
Zygomycetes
Fusarium spp

Exophiala spp
Cladophialophora bantiana
Curvularia, Bipolaris
Rhinocladiella mackinziei
and Others

Cryptococcal meningitis

AIDS is the leading predisposing factor

Etiology:

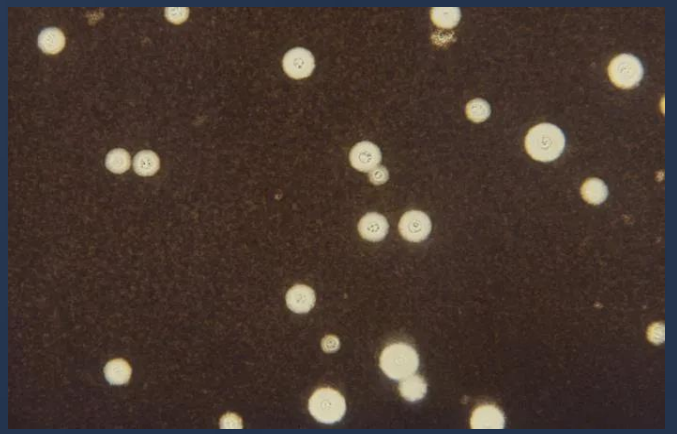
Cryptococcus neoformans is the most common etiology

Cryptococcus gattii

- Capsulated yeast cells
- Naturally in birds droppings (Pigeon), tree hollows, Soil

Acquired by inhalation

Mainly meningitis



INDIA INK PREPARATION

Candidiasis

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

Candida can reach the CNS

- Hematogenously,
- Surgery, Catheters
- Indwelling catheter and fever unresponsive to antibacterial agents

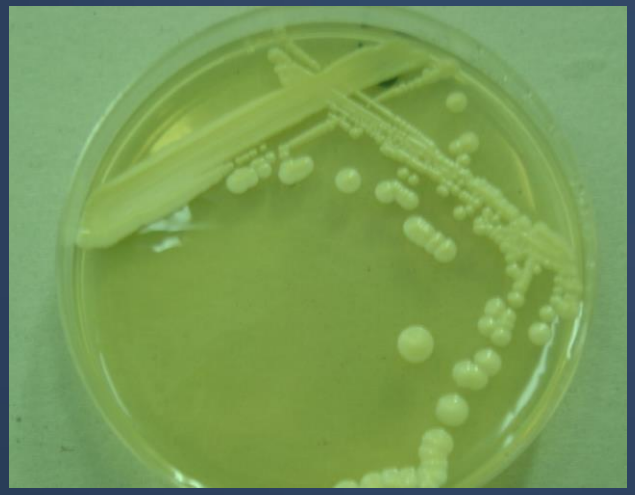
Clinical syndromes

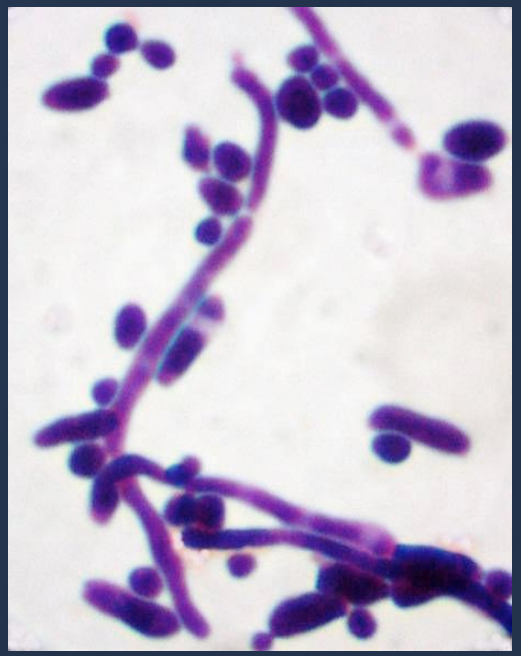
- Cerebral microabscesses
- Cerebral abscesses
- Meningitis
- Vascular complications (infarcts, hemorrhage)

Candidiasis

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,

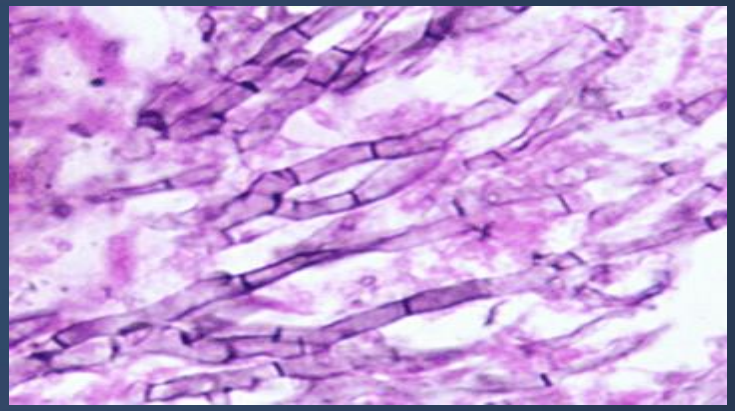
Angiotropism (infraction and hemorrhagic necrosis)

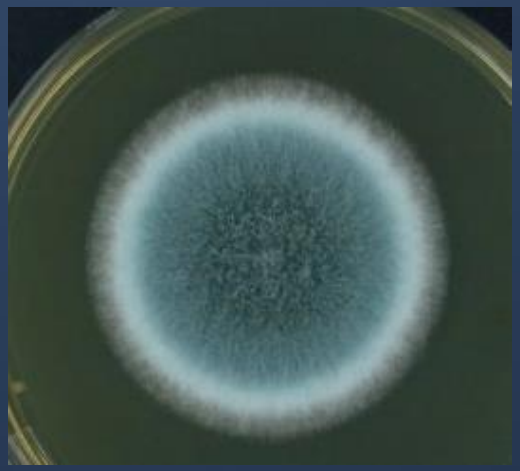
Mortality rate is high

CNS Aspergillosis

Etiology:

Aspergillus fumigatus, but also *A. flavus*, and *A. terrus*





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

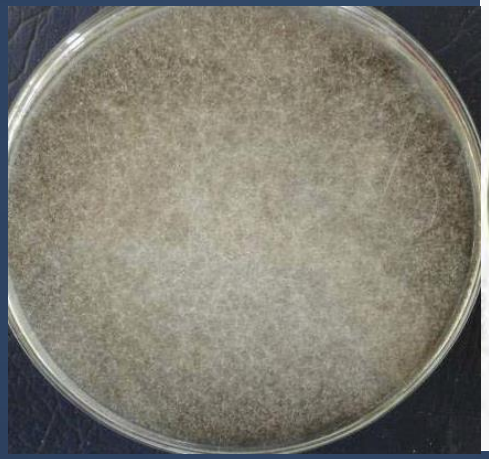
Mortality is high (80- 100%)
Progression is rapid,

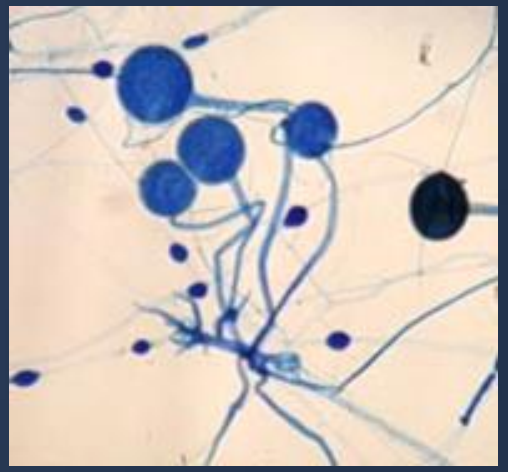
To improve the outcome:
- Rapid diagnosis
- Control the underlying disease
- Early surgical debridement
- Appropriate antifungal therapy

CNS Zygomycosis (mucoromycosis)

Etiology: Zygomycetes e.g. *Rhizopus, Absidia, Mucor*

Fast growing fungi





Pheohyphomycosis

Fungal infections caused by dematiaceous fungi

- Neurotropic fungi

CNS infections: Usually brain abscess, and chronic

Reported in immunocompetent hosts

Etiology:

Rhinocladiella mackenziei (Mainly reported from Middle East)

Cladophialophora, Exophiala , Curvularia, Fonsecaea ,

Other Infections

Histoplasmosis
Blastomycosis
Coccidiodomycosis
Paracoccidiodomycosis

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.

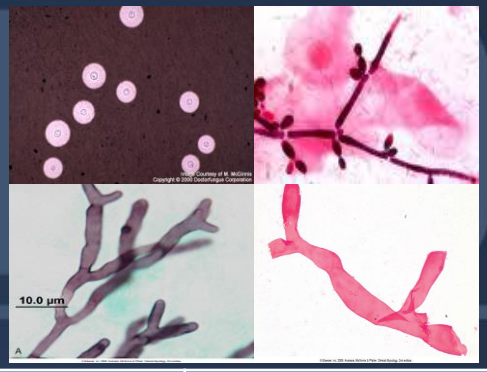
4. Serology

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	Manann 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

Management

1. Control of the underlying disease
2. Reduce immunosuppresion, restore immunity if possible
3. Start antifungal therapy promptly
    - Polyenes
    - Azoles
    - Echinocandins

Consider surgery in certain situations

Antifungal therapy

CNS fungal infection	Treatment
Cryptoccocal meningitis	Amphotericin B (combination with Flucytosine)
CNS Candidiasis	Amphotericin B, Caspofungin, Fluconazole, Voriconazole,
CNS Aspergillosis	Voriconazole, Amphotericin B (Combination of Voriconazole and Caspofungin)
CNS Zygomycosis	Amphotericin B

Thank You ☺

(CNS Block, Microbiology)

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