



Lecture - 4

Fungal infections of the central nervous system



*Microbiology team 430*

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## Fungal infections of central nerves system:

- CNS infections are both difficult to diagnose and a medical emergency.
- Delay in diagnosis and initiation of appropriate therapy will lead to high mortality rate or in permanent and severe neurological damage.
- Fungal infections of the CNS are not common

### Why fungal infections are being increasingly diagnosed?

Because we have a large population of immunocompromised patients (AIDs patients or patients under the chemotherapy)

## Risk factors:

- **HIV/AIDS**
- Hematopoietic stem cell transplant (HSCT)
- **Solid organs transplantation**
- **Malignancies**
- Neutropenia (Decrease level of neutrophil in the blood )
- Hereditary immune defects
- Immunosuppressive medications (such as chemotherapy )
- **Diabetes mellitus**
- Surgery or trauma
- **Indwelling catheters** (e.g. Candidemia (candida in the blood)  $\Rightarrow$  CNS seeding)

## How fungi reach the central nervous system?

### Fungi reach the central nervous system by different mechanisms:

- **Hematogenous spread “by blood”** (very common)
- Local extension from the paranasal sinuses (common), the ear, or the orbits.
- Traumatic introduction such as (surgical procedures, head trauma, injections and 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 such as: *Cryptococcus* only causes meningitis, doesn't cause brain abscess.**

## Etiology:

## Several fungal agents can cause CNS infections:

**Yeast:**

- *Candida* spp
- *Cryptococcus* spp

**Dimorphic:** one that lives as a yeast or mold, depending on environmental conditions

- *Histoplasma* spp
- *Blastomyces* spp
- *Coccidioides* spp
- *Paracoccidioides* spp
- *Penicillium marneffei*

**Mould**

- *Aspergillus* spp
- *Zygomycetes*
- *Fusarium* spp
- **Dematiaceae:**
  - ✓ *Exophiala* spp
  - ✓ *Cladophiala* spp
  - ✓ *Curvularia*, *Bipolaris*
  - ✓ *Rhinochlamydomonas*

And Others

- **Cryptococcal meningitis:**

**Organisms:**

- ✓ *Cryptococcus neoformans* (is the most common one)
- ✓ *Cryptococcus gattii*

**Clinical syndrome:**

- **mainly cause meningitis**

**Features:**

- ✓ capsulated yeast cells
- ✓ naturally in pigeon habitats
- ✓ **acquired by inhalation**
- ✓ **usually affected immunocompromised patients [ mainly AIDS patients ]**

## • Candidiasis :

### Organisms:

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

### Candida can reach the CNS by:

- Hematogenously
- Surgery
- Catheters

When the patient has catheter and fever with unresponsiveness to antibacterial agent → we should think about Candida

### Clinical syndromes

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

### Features:

- Candida species are the fourth most common cause of hospital acquired blood stream infections (septicemia)
- Usually affect immunocompromised patients.

## • CNS Aspergillosis :

### Organisms:

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

### Clinical syndrome:

- Usually brain abscesses (single or multiple)

### CNS Aspergillosis can reach the CNS by:

- Hematogenously
- May also occur via direct spread from the anatomically adjacent sinuses (sinusitis).

### Risk factors:

- A severe complication of hematological malignancies and cancer Chemotherapy.
- Transplantation.

### Features:

- Mortality rate is high
- Angiotropism is one of the symptoms.

## CNS Zygomycosis (Mucoromycosis):

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

### Organisms:

Zygomycetes e.g. *Rhizopus*, *Absidia*, *Mucor* → fast growing fungi

### Rhinocerebral Zygomycosis can reach the CNS by:

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.

### Clinical Presentation:

- Facial edema
- pain
- necrosis
- loss of vision
- black discharge
- **Angiotropism**; As angio-invasion is very frequent (invasion of blood vessels)

### Risk Factors:

- **Diabetics with ketoacidosis** [ Diabetic ketoacidosis is a problem that occurs in people with diabetes. It occurs when the body cannot use sugar (glucose) as a fuel source because there is no insulin or not enough insulin. Fat is used for fuel instead. Byproducts of fat breakdown, called ketones, build up in the body ]

### Features:

- Mortality is high (80- 100%)
- Progression is rapid. ( from 3-4 weeks)

### To improve the outcome:

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

## Pheohyphomycosis:

### Organisms:

- Dematiaceous fungi (neurotropic fungi) :
  - ✓ Exophiala spp
  - ✓ Cladophiala phorantiana
  - ✓ Curvularia, Bipolaris
  - ✓ Rhinocladiella mackenziei

Reported in immunocompetent hosts  
(Healthy individual)

### Clinical syndrome:

- Usually brain abscesses
- Chronic meningitis

## Other infections

### Organisms:

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis

### Features:

- Caused by primary pathogens
- Following a primary infection, mainly respiratory

### Clinical syndrome:

- Subacute and chronic meningitis
- Brain abscesses

## Diagnosis:

Clinical features	Neuro-imaging	Lab Investigations
<ul style="list-style-type: none"> <li>• History</li> <li>• risk factors</li> <li>• others</li> </ul> <p>not specific</p>	<ul style="list-style-type: none"> <li>• MRI</li> <li>• X- Ray</li> <li>• CT scan</li> </ul> <p>Good value in diagnosis and therapy monitoring</p>	<ul style="list-style-type: none"> <li>• CSF examination (cell count, chemistry)</li> <li>• Histopathology</li> <li>• Microbiology</li> </ul>

## Lab diagnosis:

### Clinical Samples

- CSF
- Biopsy (in case of brain abscesses)
- Pus, aspirate
- Blood (for serology)

CSF abnormalities	Direct Microscopy	Culture	Serology	PCR
<ul style="list-style-type: none"> <li>• Cell count</li> <li>• Glucose level (low)</li> <li>• Protein level (high)</li> </ul> <p>Not specific for fungal infection</p>	<p>Fungal stains:</p> <ul style="list-style-type: none"> <li>• Giemsa</li> <li>• GMS</li> <li>• PAS</li> <li>• India ink (<i>Cryptococcus neoformans</i>)</li> </ul>	<p>Fungal media:</p> <ul style="list-style-type: none"> <li>• SDA (Saboraud Dextrose Agar)</li> <li>• BHI (Brain Heart Infusion Agar)</li> </ul>	<p>Def. look for Antibody and Ag in the serum</p> <p>Of The following organisms:</p> <ul style="list-style-type: none"> <li>• Candida</li> <li>• Aspergillus</li> <li>• Cryptococcus</li> <li>• Histoplasma</li> <li>• Blastomyces</li> <li>• Coccidioides</li> <li>• Paracoccidioides</li> </ul>	<p>Look for DNA</p>

Cont. Lab diagnosis: **(important)**

CNS infection	Direct microscopy	Culture	Serology*
Cryptococcal meningitis	Yeast cells Capsulated (india ink)	Yeast	<b>cryptococcal Ag</b> (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:  $\beta$ -D- Glucan:**

For diagnosis of invasive fungal infections except for cryptococcosis and zygomycosis.

## 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:

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

## Summary

- Fungi can reach CNS by: **Hematogenous spread** or Local extension (paranasal sinuses, ear, orbits). And sometimes by Traumatic introduction (surgery, head trauma, lumbar puncture)
- Several fungal agents can cause CNS infections it could be: Yeast (Candida, Cryptococcus), Mould (Aspergillus, Zygomycetes, Rhinocladiella mackenziei) or Dimorphic (Histoplasma)
- Cryptococcal Meningitis "Cryptococcus neoformans": it's capsulated yeast that **found mainly in AIDs patients**, it reaches the CNS by **inhalation** & then cause **meningitis only**.
- Candidiasis "Candida albicans": it usually diagnosed if the patient has catheter and fever with unresponsive to antibacterial agents, it **reaches** the CNS mainly **by Catheters & Surgery**, and it also **cause both cerebral abscesses & meningitis**.
- Aspergillosis "Aspergillus fumigatus": found mainly in patients with hematological malignancies or had cancer **chemotherapy or any transplantation**, it **reaches the CNS hematogenously or by adjacent sinuses**. It cause single or multiple **brain abscesses only**.
- Zygomycosis "Rhizopus": it grow in acidic PH that's why being **Diabetics with ketoacidosis is a risk factor**, the **Rhinocerebral Zygomycosis can reach the CNS by starting as sinusitis**. It usually present with Facial edema & Angiotropism
- Pheohyphomycosis: it caused by dematiaceous fungi (such as: Rhinocladiella mackenziei). **It cause both brain abscesses & chronic meningitis**
- Lap Investigation:

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- To treat Cryptococcal meningitis, Candidiasis, Zygomycosis we mainly use **Amphotericin B**.
- The drug of choice to treat **Aspergillosis** is **Voriconazole**