

## Lecture ( 4 )

### Fungal infections of CNS



Color  
guide:

- Very important
- Additional information
- Male doctor's notes
- Female doctor's notes

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Lecture (4)  
Fungal infections of CNS

MICROBIOLOGY  
TEAM 432



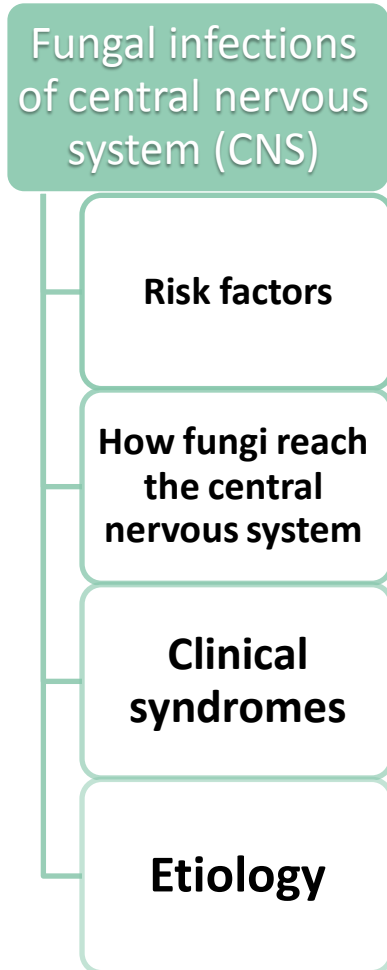
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**Objectives:**

**Not given**



# Mind map



Fungal infections of (CNS)	<ul style="list-style-type: none"> <li>➤ CNS infections are both diagnostic challenge and medical emergency</li> <li>➤ Delay in diagnosis and initiation of appropriate therapy will lead to high mortality rate or in permanent, severe neurological damage</li> <li>➤ Fungal infections of the CNS are not common</li> </ul>			
Risk factors	<ul style="list-style-type: none"> <li>-HIV/AIDS</li> <li>-Solid organs transplantation</li> <li>-Immunosuppressive medications</li> <li>-Indwelling catheters (e.g. candidemia → CNS seeding)</li> <li>-Hematopoietic stem cell transplant (HSCT)</li> <li>-Malignancies</li> <li>-Diabetes mellitus</li> <li>-Neutropenia</li> <li>-Surgery or trauma</li> <li>-Hereditary immune defects</li> </ul> <p>→ fungi will go to the blood circulation "septicemia"</p>			
How fungi reach the CNS	<p>Fungi reach the central nervous system by different mechanisms:</p> <ul style="list-style-type: none"> <li>➤ Hematogenous spread</li> <li>➤ Local extension from the paranasal sinuses, the ear, or the orbits.</li> <li>➤ Traumatic introduction ,Surgical procedures ,Head trauma ,Injections lumbar punctures</li> </ul>			
Clinical syndromes	<ul style="list-style-type: none"> <li>➤ Meningitis Sub acute ,Chronic most of the cases</li> <li>➤ Brain abscess With or without vascular invasion Cause thrombosis or hemorrhage</li> <li>❖ These clinical syndromes can occur either alone or in combination.</li> </ul> <p>Certain clinical syndromes are specific for certain fungi</p> <div data-bbox="1023 835 1584 949" style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>Mainly it causes respiratory disease but in immunocompromised patient it causes meningitis</p> </div>			
Etiology	<p>Several fungal agents can cause CNS infections.</p>			
	<p>Dimorphic</p> <ul style="list-style-type: none"> <li>-Histoplasma spp</li> <li>-Blastomyces spp</li> <li>-Coccidioides spp</li> <li>-Paracoccidioides spp</li> <li>-Penicillium marneffeii</li> </ul>	<p>Mould</p> <ul style="list-style-type: none"> <li>-Aspergillus spp</li> <li>-Zygomycetes</li> <li>"Dematiaceous" Black fungi"</li> <li>-Exophiala spp</li> <li>-Cladophialophora bantiana-Curvularia, Bipolaris</li> <li>-Rhinoctadiella mackinziei</li> <li>and Others</li> </ul> <p style="text-align: right;">microbiology team</p>	<p>Yeast</p> <ul style="list-style-type: none"> <li>-Candida spp <u>the most common</u></li> <li>-Cryptococcus spp</li> </ul>	

	Cryptococcal meningitis	Candidiasis	CNS Aspergillosis	CNS Zygomycosis (mucoromycosis)	Pheohyphomycosis
Risk factors	AIDS is the leading predisposing factor	Candida species are the fourth most common cause of hospital acquired blood stream infections patient will develop candidemia then meningitis	A severe complication of hematological malignancies ,cancer chemotherapy, and transplantation “Septate hyphae “	<u>Diabetics with ketoacidosis</u> , in addition to other risk factors “Non-septate hyphae “	Reported in <u>immunocompetent hosts</u>
Acquired by	Inhalation Will cause asymptomatic pulmonary disease then meningitis	Candida can reach the CNS Hematogenously, Surgery, Catheters <u>Indwelling catheter and fever unresponsive to antibacterial agents</u>	via direct spread from the anatomically Adjacent sinuses <u>When they remove the nasal polyp And also through the blood</u>		Fungal infections caused by dematiaceous , Neurotropic fungi ( having an affinity to infect the nervous system)
Etiology.	<u>Cryptococcus neoformans</u> is the most common -Capsulated yeast cells -Naturally in Pigeon	<u>Candida albicans</u> ” the most common” , and other species including C. glabrata, C. tropicalis C.parapsilosis, and C. krusei	is the most common is <u>Aspergillus fumigatus</u> ,  A. flavus, but also other Aspergillus species	Zygomycetes e.g. Rhizopus, Absidia, Mucor Fast growing fungi	<u>Rhinoctadiella mackenziei</u> (Mainly reported from Middle East) Cladophialophora , Exophiala , Curvularia, Fonsecaea
	Mainly <u>meningitis</u>	<u>Cerebral microabscesses</u> <u>Cerebral abscesses</u> <u>Meningitis</u> Vascular complications ( infarcts, hemorrhage)	Usually <u>brain abscesses</u> (single or multiple)	The <u>rhinocerebral</u> form is the most frequent presenting clinical syndrome in CNS zygomycosis.	CNS infections: Usually chronic brain <u>abscess.Unlike Zygomycetes and aspergillus they cause acute brain abscesses.</u>
	It is the only Capsulated Yeast -Cryptococcus gatti can cause RTI	In pediatric patient with candidemia will develop meningitis that’s why we have to examine the eyes because they develop retinitis then meningitis	Angiotropism (infraction and hemorrhagic necrosis) Mortality rate is high microbiology team	Mortality is high ,Progression is rapid, Slide 6 is the most common presentation is rhinocerebral just like aspergillosis	- They’re usually inhaled. - Mortality rate is 100% despite treatment.



CNS Zygomycosis (mucoromycosis) Cont.	
<p>The clinical manifestations of the rhinocerebral form</p>	<p><b>start as sinusitis, rapidly progress and involve the orbit, eye and optic nerve and extend to the brain</b></p> <p><b>Facial edema, pain, necrosis, loss of vision, black discharge</b></p> <p><b>Angiotropism; As angio-invasion is very frequent</b></p>
<p>To improve the outcome</p>	<ul style="list-style-type: none"> <li>✓ <b>Rapid diagnosis</b></li> <li>✓ <b>control the underlying disease</b></li> <li>✓ <b>,Early surgical debridement</b></li> <li>✓ <b>Appropriate antifungal therapy</b></li> </ul>



## Other infections

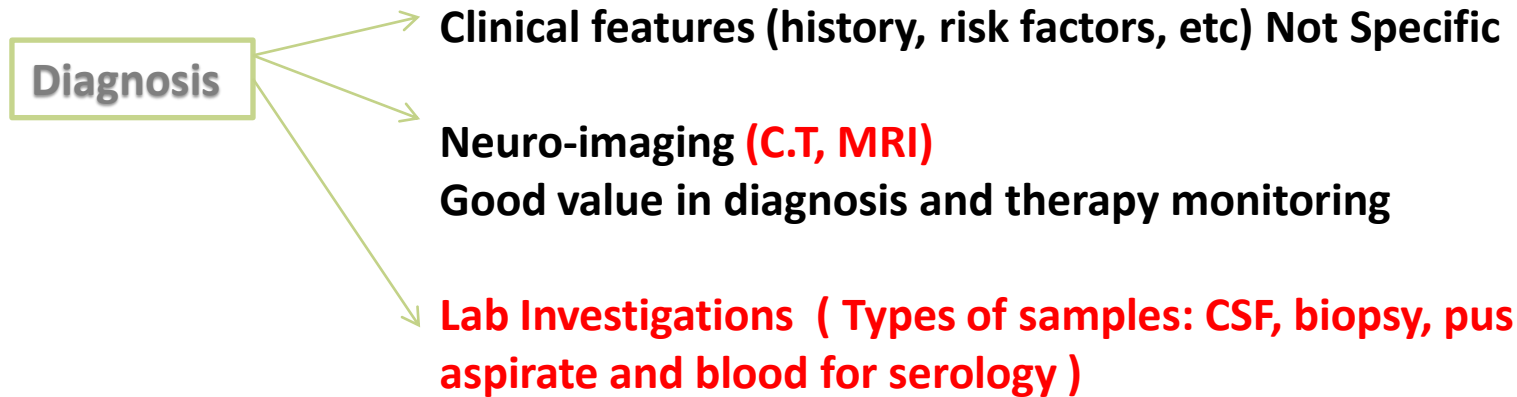
Histoplasmosis

Blastomycosis

Coccidioidomycosis

Paracoccidioidomycosis

- **Caused by : primary pathogens .**
- **Causes : Both sub acute and chronic meningitis which is very common as well as brain abscess.**
- **Usually patients are affected by a primary infection mainly respiratory mild in immunocompetent and severe in immunocompromised then it will disseminate causing meningitis and brain abscess. Very rare in our region.**



### Lab investigations

- 1. CSF abnormalities:** Cell count (mainly WBCs) , Glucose level (low), Protein level (high)( Not specific for Fungal infections).
- 2. Direct microscopy:** Fungal stains: Giemsa, GMS(Grocott's methenamine silver stain), PAS(Periodic acid –Schiff stain) , **India ink** (*Cryptococcus neoformans*) **Stains every thing except the capsule.**
- 3. Culture :** Fungal media: SDA (Sabouraud agar), BHI ( Brain heart infusion agar), other media if needed.
- 4. Serology ( looking for antigens) :** Candida, Aspergillus, Cryptococcus , Histoplasma, Blastomyces, Coccidioides and Paracoccidioides.
- 5. PCR ( Polymerase chain reaction) :** **looking for the DNA of a certain fungus in blood and csf.**



CNS infection	Direct microscopy	Culture	Serology*
Cryptococcal meningitis	Yeast cells Capsulated ( <b>India ink</b> )	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	

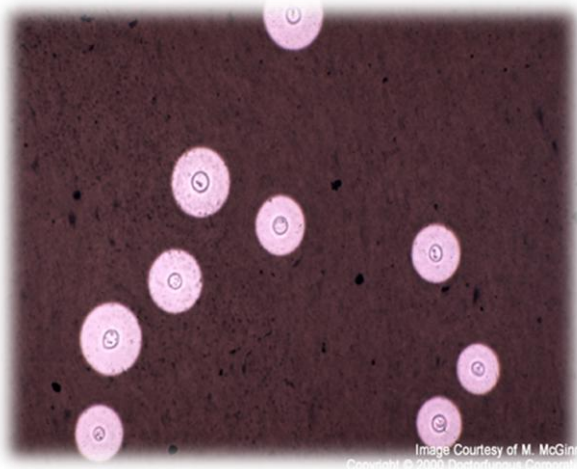
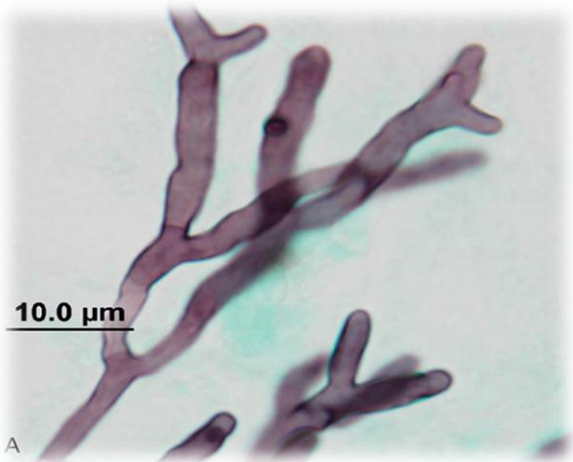


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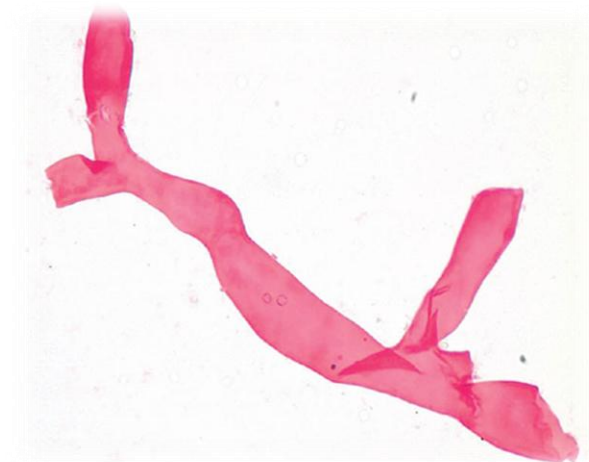
**Capsulated yeast  
(Cryptococcus)**



**Pseudohyphae and budding yeast  
cells (Candida)**



**Septate hyphae (Aspergillus)**



**Non-septate hyphae (Zygomycetes)**



## Management plan:

1. Control of the underlying disease.
2. Reduce immunosuppression, restore immunity if possible.
3. Start antifungal therapy promptly ( Polyenes, Azoles and Echinocandins).
4. Consider surgery in certain situations.

CNS fungal infection	Treatment
<b>Cryptococcal meningitis</b>	Amphotericin B (combination with Flucytosine)
<b>CNS Candidiasis</b>	Amphotericin B, Caspofungin, Fluconazole, Voriconazole,
<b>CNS Aspergillosis</b>	<b><u>Voriconazole</u></b> ( Drug of choice) Amphotericin B, (Combination of Voriconazole and Caspofungin)
<b>CNS Zygomycosis</b>	Amphotericin B ( Low penetration rate through BBB)



## summary

- **AIDS** is the most important risk factor for **Cryptococcal meningitis**.
- **Transplantation** is the most important risk factor for **Aspergillosis**.
- **Diabetes with ketoacidosis** is the most important risk factor for **Zygomycosis**.
- **Zygomycosis and Aspergillosis** patients usually have the same clinical presentation including the eyes involvement.
- Meningitis can be caused by : **Cryptococcus (Neoformans or gatii)** in immunocompromised patients.
- While brain abscesses can be caused by : **Aspergillus , Zygomycetes and Rhinocladiella mackenziei**.

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

- **Zygomycosis and Aspergillosis** cause acute brain abscesses in immunocompromised hosts rarely seen in immunocompetent. On the other hand, **Pheohyphomycosis** causes chronic brain abscess usually in immunocompetent hosts.
- **Pheohyphomycosis** is a slowly progressive disease with high mortality rate cause patients don't respond to treatment in most cases.



## Questions

1) A 55 year old diabetic male with ketoacidosis recently removed a nasal polyp with sinusitis. After 2 \*days from surgery he came back to the emergency department with left periorbital swelling and pain. A biopsy was taken from the patient and lab diagnosis was done. Direct microscopy showed broad non-septate hyphae. The patient is most likely infected by ?

- A. **Coccidioides spp**
- B. **Aspergillus spp**
- C. **Zygomycetes**

\* **notice the fast progression of the infection.**

2) The drug of choice for treatment of aspergillosis is ?

- A. **Amphotericin B**
- B. **Voriconazole**
- C. **Caspofungin**



## Questions

3) A 33-year-old HIV positive man complains of headache , fever, neck stiffness , inability to tolerate light . Which one of the following microorganisms is most likely responsible for his illness ?

- A. **Candida albicans**
- B. **Cryptococcus neoformans**
- C. **Cryptococcus gatti**
- D. **Aspergillus fumigatus**

4) which of the followed is a widely accepted way to stain a CSF sample for Cryptococcus neoformans?

- A. **India ink**
- B. **Modified Gram stain**
- c. **Giemsa**

Q	Answer
1	C
2	B
3	B
4	A



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*Thank you*