



# LECTURE: Fungal Infections of Central Nervous System

## Editing File

- Important
- Doctor's notes
- Extra explanation
- Only F or only M

"لا حول ولا قوة إلا بالله العلي العظيم" وتقال هذه الجملة إذا  
داهم الإنسان أمر عظيم لا يستطيعه ، أو يصعب عليه القيام به .

# 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.**

Based on the doctor notes + foundation lectures راح تسهل عليكم المحاضرة :

FUNGI		
Yeast :	Moulds or filamentous:	Dimorphic:
<ul style="list-style-type: none"><li>• It's a normal flora present in our mouths, GIT...</li></ul> <p>(لكن في حالة ضعفت مناعتنا ممكن تسبب لنا انفكشن)</p>	<ul style="list-style-type: none"><li>• It present in the environment → inhalation لكن ماتسبب عدوى الا في حالة ضعف المناعة</li><li>• It's can be : septate or non-septate hypha</li></ul> <p>تنقسم حسب لونها الى قسمين</p> <p>1-Moniliaceous molds :colorless 2- dematiaceous molds : dark</p>	<p>Have two forms depending on change in the environmental factors</p> <ul style="list-style-type: none"><li>• Yeast : Parasitic form, Tissue form, Cultured at 37° C</li><li>• Filamentous : Saprophytic form, Cultured at 25 C</li></ul>

\*بنهاية  
المحاضرة فيه  
تشبيهات بسيطة  
ممكن تساعدكم

Types of fungal infections:	
<ul style="list-style-type: none"><li>• Superficial mycoses</li><li>• Cutaneous mycosis</li><li>• Subcutaneous mycoses</li></ul>	<ul style="list-style-type: none"><li>• Primary Systemic mycoses</li><li>• Opportunistic mycoses</li></ul>

- 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? **Because of the increase of the number of immunocompromised patients.**

- Risk factors:

<b>HIV/AIDS</b>	Hereditary immune defects
<b>Diabetes mellitus</b>	<b>Immunosuppressive medications</b>
Solid organs transplantation	<b>Hematopoietic stem cell transplant (HSCT)</b>
Malignancies	<b>Neutropenia</b>
<b>Surgery or trauma</b>	Indwelling catheters (e.g. candidemia → CNS seeding)

Normal flora = Opportunistic

Dimorphic = Primary

- 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 eg. Baby shunt
  - ✓ Head trauma
  - ✓ Injections
  - ✓ lumbar punctures we use it to get CSF

- Clinical syndromes

- These clinical syndromes can occur either **alone or in combination**:

1- Meningitis:	2- Brain abscess:
Sub acute <b>OR</b> Chronic	With or without vascular invasion

- Certain clinical syndromes **are specific for certain fungi** can give us a clue

Mold	<b>Brain abscess</b>
Yeast	<b>Meningitis</b>

- Etiology:

Several fungal agents can cause CNS infections:

Yeast:	Mould:	Dimorphic:
Candida spp	Aspergillus spp	Histoplasma spp
Cryptococcus spp	Zygomycetes	Blastomyces spp
	Exophiala spp	Coccidioides spp
	Cladophialophora bantiana	Paracoccidioides spp
	Rhinocladiella mackinziei	
	and Others	

- Cryptococcal meningitis:

AIDS is the leading predisposing factor *	
Etiology	<p><b>Cryptococcus neoformans</b> is the <b>most common</b> etiology</p> <ul style="list-style-type: none"> <li>✓ Capsulated <b>yeast cells</b> (capsulated)</li> <li>✓ Naturally in <b>Pigeon habitats</b> (soil rich with pigeon dropping)</li> </ul>
Acquired by:	Inhalation (not from human to human)
Clinical syndromes:	Mainly <b>chronic</b> meningitis

- Candidiasis: normal flora

Candida species are the fourth most common cause of hospital acquired blood stream infections	
Etiology:	<b>Candida albicans</b> , and other species including C. glabrata, C. tropicalis C. parapsilosis, and C. krusei.
can reach the CNS:	<ul style="list-style-type: none"> <li>• Hematogenously</li> <li>• Surgery, Catheters, <b>trauma</b></li> </ul>
Clinical syndromes:	<ul style="list-style-type: none"> <li>• Cerebral abscesses</li> <li>• Meningitis ( <b>premature babies</b>)</li> </ul>

Pigeon = حمامة

\*Cellular immunity is important to be infected by this organism if there is any defect

- CNS Aspergillosis:

<ul style="list-style-type: none"> <li>• Mortality rate is high</li> </ul>	
Etiology:	<b>Aspergillus fumigatus</b> most cause, but also A. flavus, and A. terreus
Clinical syndrome:	Usually brain abscesses (single or multiple) rarely as meningitis
can reach the CNS:	<ul style="list-style-type: none"> <li>• Spread Hematogenously</li> <li>• May also occur via direct spread from the anatomically adjacent sinuses,</li> </ul>
Common risk factors include :	<ul style="list-style-type: none"> <li>• <b>Malignancies</b></li> <li>• Transplantation</li> <li>• Chemotherapy</li> </ul>

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-it is inhaled through the respiratory system then goes to CNS through circulation or through paranasal sinuses then to CNS as local extension  
 -Mostly effect immunocompromised pt. as chemo therapy , transplant surgery , malignancy ( opportunistic infection ) \ -very rare for immune competent

- **CNS Zygomycosis (mucoromycosis) عفن الخبز :**

- The rhinocerebral (it is Mucorales) form is the most frequent presenting clinical syndrome in CNS zygomycosis.
- Mortality is high (80- 100%) Progression is rapid,

Etiology:

Zygomycetes e.g. Rhizopus, Absidia, Mucor Fast growing fungi ( all of them are Mucorales )

risk factors :

**Diabetics with ketoacidosis** because it can thrive in high acidic condition, 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 could be inhaled
- Facial edema, pain, necrosis, loss of vision, black discharge **Angiotropism** due to blood vessel invasion; As angio-invasion is very frequent

To improve the outcome:

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

-General term of opportunistic fungal infection caused by a class called : zygomycetes ( has two order 1-Mucorales 2-Entomophthorales.)

-like Aspergillosis in the mode of transmission , start in the respiratory system then through heamatogenous to CNS

-rhinocerebral has the tendency to invase blood vessel (important) usually the area involved has thrombosis , necrosis , infarction lastly will become plaque scar



- **Pheohyphomycosis:**

- Fungal infections caused by **dematiaceous** fungi darkly colored due to melanin pigment

- ✓ Neurotropic fungi

- CNS infections: Usually **brain abscess**, and chronic

- Reported in **immunocompetent** hosts not immunocompromised

- **Etiology:**

- ✓ **Rhinoctadiella mackenziei** ( Mainly reported from **Middle East**)

- ✓ Cladophialophora,

- ✓ Exophiala , many others

- **Other Infections:**

- Histoplasmosis / Blastomycosis / Coccidiomycosis / Paracoccidiomycosis →

- Caused by primary pathogens

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

- Following a primary infection, mainly respiratory mainly by inhalation then through blood goes to skin , bone , CNS

**Histoplasmosis** by *Histoplasma capsulatum*  
**Blastomycosis:** *Blastomyces dermatitidis*  
**Coccidiomycosis:** *Coccidioides immitis*  
**Paracoccidiomycosis:** *Paracoccidioides brasiliensis*

- **Diagnosis:**

• Clinical features (history, risk factors, etc):	Not Specific (Past surgery is important in history )
• Neuro-imaging: radiological finding	Good value in diagnosis and therapy monitoring
• Lab Investigations:	<ul style="list-style-type: none"> <li>✓ CSF examination (cell count, chemistry)</li> <li>✓ Histopathology                      ✓ Microbiology</li> </ul>

**Clinical Samples:** CSF - Biopsy- Pus, aspirate - Blood (for serology)

- **Lab Diagnosis:**

1. CSF abnormalities: Not specific for Fungal infections\*
  - ✓ Cell count
  - ✓ Glucose level (low) because it is consumed by the organism
  - ✓ Protein level (high) We check color too (bloody , turbid)
2. Direct Microscopy:
  - ✓ Fungal stains: Giemsa, GMS, PAS, **India ink** (mostly for Cryptococcus neoformans for the presence of polysaccharide capsule )
3. Culture:
  - ✓ Fungal media: SDA\*\*, BHI\*\*\*, other media if needed.

4. **PCR:** the most accurate test
5. **Serology:** for detection of antigen or antibody
  - ✓ Candida
  - ✓ Aspergillus
  - ✓ Cryptococcus
  - ✓ Histoplasma
  - ✓ Blastomyces
  - ✓ Coccidioides
  - ✓ Paracoccidioides

\*because pyogenic bacteria can be the same findings in CSF

\*\*SDA (Sabouraud dextrose agar)

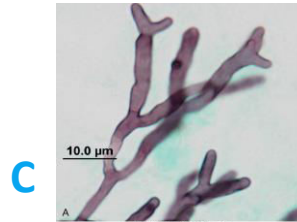
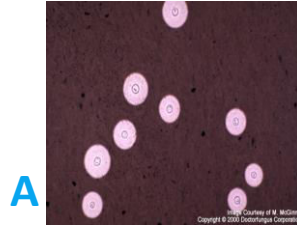
\*\*\*BHI (brain & heart infusion agar)

- Lab. Diagnosis:

CNS infection	Direct microscopy	Culture	Serology*
Cryptococcal meningitis	Yeast cells <b>A</b> Capsulated (india ink)	Yeast	Cryptococcal Ag (capsule) Latex agglutination
Candidiasis	Yeast cells and pseudohyphae <b>B</b>	Yeast	Manann Ag (cell wall)
Aspergillosis	Septate branching hyphae <b>C</b>	Hyaline mould	Galactomannan Ag
Zygomycosis	Broad non-septate hyphae <b>D</b>	Hyaline mould Fast growing	No serology available
Pheohyphomycosis	Brown septate hyphae	Dematiaceous mould	$\beta$ -D- Glucan

\*Serology:  $\beta$ -D- Glucan

For diagnosis of invasive fungal infections except **cryptococcosis and zygomycosis**



- **Management:**

1. Control of the underlying disease
2. Reduce immunosuppression, restore immunity if possible
3. Start antifungal therapy promptly: Polyenes/ Azoles/ Echinocandins
4. Consider surgery in certain situations
5. Key of treatment is early diagnose

- **Antifungal therapy:**

CNS fungal infection	Treatment
Cryptococcal meningitis	Amphotericin B (combination with Flucytosine)
CNS Candidiasis (some are resistance to azole )	Caspofungin, Fluconazole, Voriconazole, Amphotericin B
CNS Aspergillosis	Voriconazole
CNS Zygomycosis	Amphotericin B

# Mnemonics :

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## ANTIFUNGAL MNEMONICS:

1- in all the antifungal we use Amphotericin B **EXEPT** Aspergillosis we use Voriconazole SO:

**Aspergillosis** - **Voriconazole** = اصبري أجي لس أورييس

2- **Candidiasis** - **Caspofungin** = كسبوا كاندي

## LAB DIAGNOS MNEMONICS:

1- **Aspergillosis** - **Septate** branching hyphae = فيهم حروف متشابهة

## CNS ZYGOMYCOSIS (MUCOROMYCOSIS):

1-Etiology: Zygomycetes e.g. **Absidia**, **Rhizopus**, **Mucor** = عيسي ذا مكر علي وقال ابي رز بس ولما دخلنا البقالة ماخلى شىء

لو وصلتنا تشبيهات زيادة بنحطها بالاديتنق فايل ان شاء الله + شكرا لكل من أرسل لنا

# SUMMARY:

## Etiology

-Yeast: Candida spp, Cryptococcus spp.

-Mould: Aspergillus spp, Zygomycetes.

-Dimorphic :Histoplasma spp, Blastomyces spp, Coccidioides spp, Paracoccidioides spp.

### Cryptococcal meningitis

- AIDS (HIV) is the leading predisposing factor.
- Acquired by inhalation.
- Meningitis.
- Etiology: Cryptococcus neoformans → found naturally in pigeon habitats – capsulated yeast cells .
- Lab diagnosis: Microscope (india ink) → Capsulated . Serology → Cryptococcal Ag, Latex agglutination. culture → yeast.
- Treatment: Amphotericin B + Flucytosine.

### Candidiasis

- Reach CNS by: Hematogenous spread, surgery, catheters.
- Cerebral abscess and meningitis.
- Etiology is mainly C.albicans(normal flora).
- Lab diagnosis: Microscope → pseudohyphae. Serology: Manann Ag and β-D- Glucan (if invasive). Culture: yeast
- Treatment: Caspofungin, Fluconazole, Voriconazole, Amphotericin B.

### CNS Aspergillosis

- Brain abscesses.
- Risk factors: Malignancy, transplantation, chemotherapy.
- Spread Hematogenously, or direct spread from adjacent sinuses. -
- Mortality rate is high.
- Etiology: Aspergillus fumigatus, A.flavus and A.terrus
- Lab diagnosis: Microscope → Septate branching hyphae. Culture → Hyaline mould. Serology → Galactomannan Ag, β-D- Glucan (if invasive).
- Treatment: Voriconazole.

### CNS Zygomycosis (Mucoromycosis)

- The rhinocerebral form is the most frequent presenting clinical syndrome in CNS zygomycosis.
- Risk factor: Diabetic with ketoacidosis.
- Clinical manifestations: Start as Sinusitis → rapidly progress → involve the orbit → eye → optic nerve → brain.
- Symptoms: Facial edema, necrosis, loss of vision, black discharge, angiotropism.
- Mortality rate is high.
- etiology: Zygomycetes e.g. Rhizopus, Absidia.
- Lab diagnosis: Microscope → Broad non-septate hyphae. Culture → Hyaline mould, fast growing. No serology test is available.
- Treatment: Amphotericin B.

### Pheohyphomycosis

- Affects immunocompetent hosts.
- Caused by dematiaceous fungi (neurotropic fungi)
- Chronic brain abscess.
- Etiology: Rhinocladiella mackenziei → most common in middle east. -
- Lab diagnosis: Microscope → Brown septate hyphae. Culture → Dematiaceous mould. Serology → β-D- Glucan.

### Other infections

(Histoplasmosis, Blastomycosis, Coccidioidomycosis, Paracoccidioidomycosis)

- Etiology → primary pathogens
- Sub-acute or chronic meningitis(common) and brain abscess .
- following a primary respiratory infection.

# SUMMARY:

- **Fungal infections of CNS** are not common. Associated with Meningitis (sub-acute or chronic) or brain abscess.

- **Risk factors:**

HIV, hematopoietic stem cell transplant, DM, Indwelling catheters, Solid organs transplantation, Malignancies, Neutropenia, Hereditary immune defects, Immunosuppressive medications, Surgery or trauma.

- **Mechanisms to reach CNS :**

Hematogenous spread, Traumatic introduction (e.g. lumbar punctures), Local extension from the paranasal sinuses, the ear, or the orbits.

## Diagnosis: Clinical features (history, risk factors, etc), Neuro-imaging, Lab Investigations

### Lab Investigations

( CSF examination (cell count, chemistry), Histopathology, Microbiology)

CSF abnormalities	Direct microscopy	Culture	Serology	PCR
Not specific for fungal infection.	Fungal stains: Giemsa, GMS, PAS, India ink (Cryptococcus neoformans)	Fungal media: SDA, BHI	To detect the antigens	

# QUIZ:

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1/A 54-year-old man developed a slowly worsening headache followed by gradual, progressive weakness in his right arm. A brain scan revealed a cerebral lesion. At surgery an abscess surrounded by granulomatous material was found. Sections of the tissue and subsequent culture showed darkly pigmented septate hyphae indicating phaeohyphomycosis. This infection may be caused by which species below?

- (A) Aspergillus
- (B) Cladophialophora
- (C) Coccidioides
- (D) Malassezia

Answer: B

2/A patient was diagnosed with cerebral abscess. the serology test showed mannan AG. What are we going to see under the microscope?

- (A) pseudohyphae
- (B) non- septate hyphae
- (C) septate hyphae
- (D) brown septate hyphae

Answer: A

3/What is the best antifungal treatment for a patient with cryptococcal meningitis?

- (A) Amphotercin
- (B) combination of amphotercin and flucytocin
- (C) flucytocin
- (D) combination of amphotercin and voriconazole

Answer: B

4/A patient was diagnosed with chronic brain abscess. The culturing of the organism showed Dematiaceous mould. What is the most likely causing organism?

- (A) Rhinocladiella Mackenzie
- (B) Cryptococcus neoformans
- (C) C. albicans
- (D) Aspergillus fumigatus

Answer: A

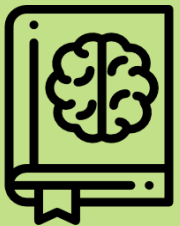
5/ A 52 years old male presented to the hospital with cryptococcal meningitis, history was taken and it showed that he had HIV. How did the fungus reach the CNS?

- (A) hematogenously
- (B) by inhalation
- (C) infection from the ear
- (D) infection from the paranasal sinuses

Answer: B



# THANK YOU FOR CHECKING OUR WORK, BEST OF LUCK!



Doctors slides



Hamad Alkhudhairy



Shrooq Alsomali  
Shoag Alahmari  
Alaa Alaqeel