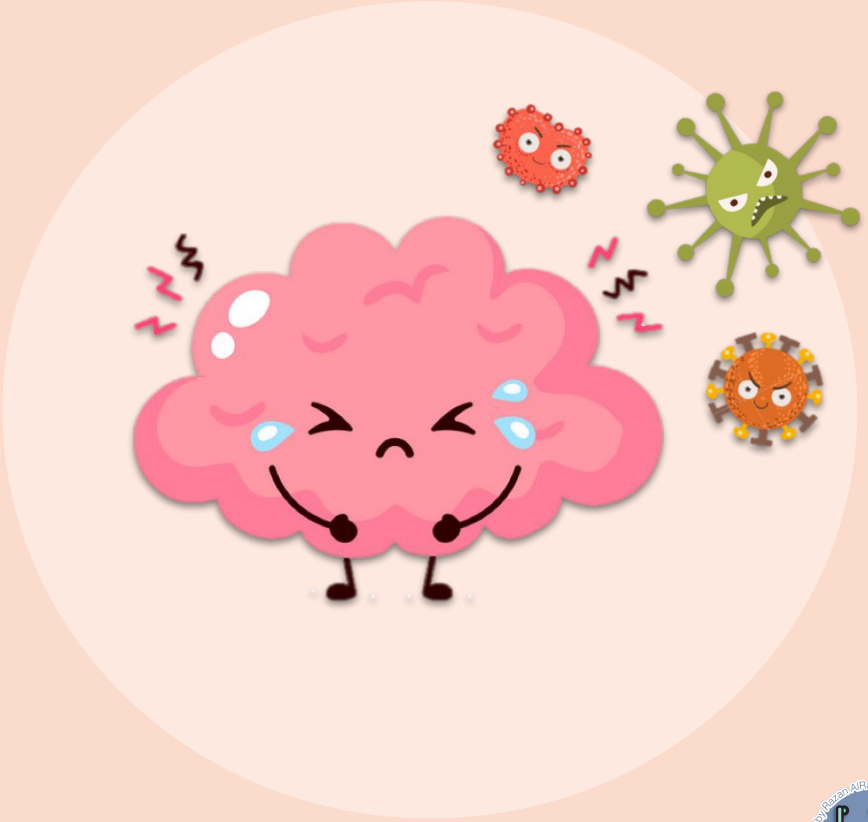
MICROBIOLOGY
TEAM 438

MED438

Fungal Infections



Reviewed by Yazan AlRabah & Ibrahim AlBakri

Objectives

- ★ To know the main fungi that affect the central nervous system and the clinical settings of such infections.
- ★ To acquire the basic knowledge about fungal meningitis and brain abscess:
  - clinical features
  - etiology
  - diagnosis
  - and treatment

Color index:
- Important
- Doctors note
- Extra

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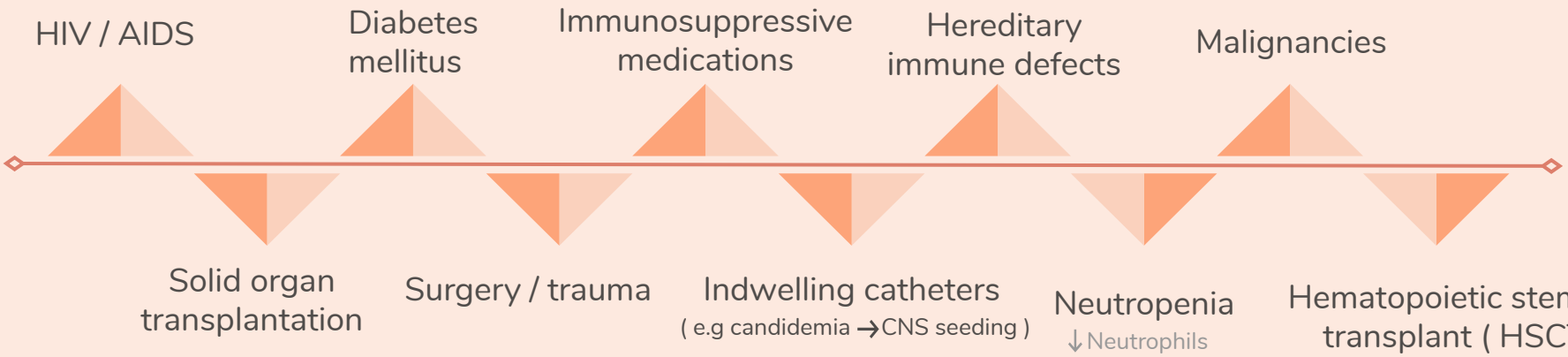
Fungal Infection of Central Nervous System:

- CNS infections are both diagnostic challenge & medical emergency.
- Delay in diagnosis & 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 in the number of immunocompromised patients (due to transplant , cancer... etc)

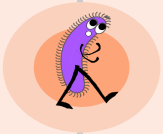
Risk factors:

immunocompromised patients



How fungi reach CNS ?

Hematogenous spread



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

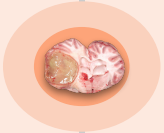
Traumatic introduction:

1. Surgical procedures (neurosurgery , major abdominal surgery)
2. Head trauma
3. Contaminated Injections
4. lumbar punctures

Clinical syndromes:

Meningitis : Mostly caused by yeast

A. Sub acute
B. Chronic usually



Brain abscess : Mostly cause by filamentous

A. With vascular invasion
B. Without vascular invasion

- These clinical syndromes can occur either alone or in combination
- Certain clinical syndromes are specific for certain fungi can give us a clue.

Etiology:

Note:
1. hyaline (translucent) filamentous, the rest are dematiaceous (pigmented) filamentous

Several fungal agents can cause CNS infections:

You don't have to memorize all the names in this table , but the names of the organisms in each disease are important

Yeast	Mould / Filamentous	Dimorphic rare in our region
Candida spp	Aspergillus spp[1]	Histoplasma spp
	Zygomycetes[1]	Blastomyces spp
	Fusarium spp[1]	Coccidioides spp
	Exophiala spp	Paracoccidioides spp
Cryptococcus spp **Encapsulated** yeast	Cladophialophora bantiana	Penicillium marneffei
	Rhinocladiella mackenziei	
	Curvularia, Bipolaris	
	& others	

Cryptococcal Meningitis	predisposing factor	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 and soil

	Acquired by	Inhalation , but they mainly infect the brain more than the lungs **especially in AIDS** (some of the organisms can infect both the lung and the brain e.g: cryptococcus gattii)
	Clinical syndrome	Mainly meningitis

Candidiasis

Candida species are the **4th most common cause** of hospital acquired **bloodstream infections.**

Etiology	• Candida albicans (normal flora) & other species including : ○ C.glabrata, C. tropicalis C. parapsilosis, & C. krusei.
Reach CNS by	• Hematogenously • Surgery, Catheters • Indwelling catheter & fever unresponsive to broad antibacterial agent → Septicemia caused by candida
Clinical syndrome	• Meningitis (mostly) • Cerebral abscesses (sometimes) • Cerebral microabscesses • vascular complications (infarcts , hemorrhage)

CNS Aspergillosis		
	Etiology	• Aspergillus fumigatus (common globally) • A. flavus (common in our region) • A. terrus
	Reach CNS by :	• Spread Hematogenously, from the lung after inhalation of the spores • May also occur via direct spread from the anatomically adjacent sinuses "rhinocerebral aspergillosis" • Angiotropism (infarction and hemorrhagic necrosis)
	Common risk factors	• Hematological **Malignancies** . • **Transplantation.** • Cancer Chemotherapy .
	Clinical syndrome	Usually brain abscesses (single or multiple)
	Prognosis	Mortality rate is High , because it takes time to diagnose .

CNS Zygomycosis (mucormycosis)

Etiology	• Zygomycetes e.g: Rhizopus, Absidia, Mucor Fast growing fungi (all of them are Mucorales)
Common risk factors	Diabetes with ketoacidosis because it can thrive in high acidic condition, in addition to other risk factors. Malignancy, transplantation, trauma.
Clinical syndrome	• The **rhinocerebral form** is the most frequent presenting clinical syndrome in CNS zygomycosis • The clinical manifestations of the rhinocerebral form start as sinusitis, rapidly progress & involve the orbit, eye & optic nerve & extend to the brain . • Facial edema, pain, necrosis, eye infection, loss of vision, black discharge Angiotropism due to blood vessel invasion; As angio-invasion is very frequent • Usually brain abscesses
Prognosis	Mortality rate is High (80- 100%) - Progression is rapid -
To improve outcome	• Rapid diagnosis • Control the underlying disease • **Early surgical debridement** • Appropriate antifungal therapy

Phaeohypho-mycosis	• Fungal infections caused by dematiaceous fungi darkly colored , due to melanin pigment. • Neurotropic fungi, they love to grow in the brain.	
	Etiology	• Rhinocladiella mackenziei (Mainly reported from Middle East) • Cladophialophora, Exophiala , Curvulara, Fonsecaea.
	Common risk factors	Reported in immunocompetent hosts
	Clinical syndrome	Usually brain abscesses & chronic
	Prognosis	Mortality is high almost 100%

Other Infections: Caused by dimorphic fungi

1. Histoplasmosis
2. Blastomycosis
3. Coccidioidomycosis
4. Paracoccidioidomycosis

1. Cause by primary pathogens
2. Subacute or chronic Meningitis (common), & brain abscess
3. Following a primary infection, mainly respiratory by inhalation then through blood goes to CNS

diagnosis

Clinical features
(history, risk factors... ect) :
Not specific for fungal infection

Neuro-imaging:
Good value in diagnosis & therapy monitoring

Lab investigations:
CSF examination
(cell count,chemistry)
Histopathology
Microbiology

Clinical samples :
1. CSF [1]
2. biopsy [2]
3. pus [2]
4. aspirate [2]
5. blood
(for serology)

1. in meningitis
2. in cerebral abscesses

CSF Abnormalities:
1. Cell count
2. Glucose level (low)
because it is consumed by the organism.
3. Protein level (high):
Not specific for Fungal infections , it can be seen in bacterial infections too.

Direct microscopy :
Fungal stains:
Giemsa,
GMS,
PAS,
India ink :
(mostly for Cryptococcus neoformans for the presence of polysaccharide capsule)

Serology:
for detection of antigen or antibody
1. Candida
2. Aspergillus
3. Cryptococcus
4. Histoplasma
5. Blastomyces
6. Coccidioides
7.Paracoccidioides

PCR:
makes many copies of small sections of DNA

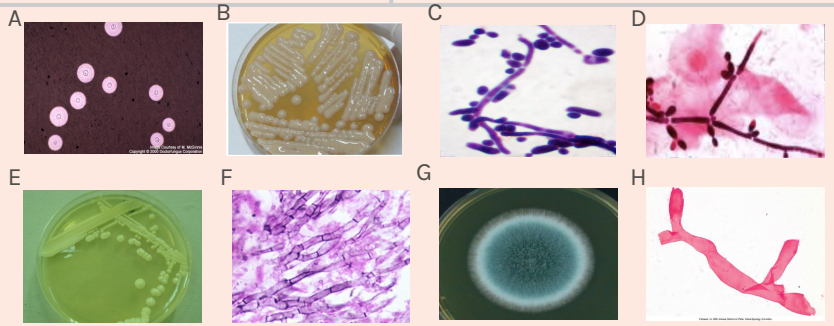
Culture:
Fungal media:
1. SDA agar
(Sabouraud dextrose agar)
(silver agar)
2. BHI agar
(brain & heart infusion)
3. other media if needed.

CNS infection	Direct microscopic	Culture	Serology
Cryptococcal Meningitis	Yeast cells Capsulated [A] (india ink)[1]	Yeast Capsule will appear as **Mucoid** [B] colonies	- Cryptococcal Ag (capsule) - Latex agglutination[1] (name of the method)
Candidiasis	Pudding yeast [C] cells and pseudohyphae [D]	Yeast Not mucoid [E], because it has no capsule	Manann Ag (cell wall)
Aspergillosis	Septate branching hyphae [F]	Hyaline mould [G]	Galactomannan Ag
Zygomycosis	Broad non-septate hyphae [H]	Hyaline mould Fast growing	No serology available
Phaeohyphomycosis	Brown septate hyphae	Dematiaceous (Black) mould	No serology available

Serology:
β-D- Glucan, for diagnosis of invasive fungal infections except cryptococcosis and zygomycosis

Notes:

1. Detect capsule , used only in cryptococcus because it's the only yeast with capsule
2. Serology of cryptococcus is very specific (detect small amounts of Ag) , if positive then its cryptococcal infection regardless of other findings



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 (abscesses)
5. Key of treatment is early diagnose

	CNS fungal infection	Treatment
Antifungal therapy	Cryptococcal meningitis	Amphotericin B (combination with Flucytosine)
	CNS Candidiasis	Caspofungin, Fluconazole, Voriconazole, Amphotericin B
	CNS Aspergillosis	Voriconazole (drug of choice) ,Amphotericin B (Alternative) (Combination of voriconazole and Caspofungin)
	CNS Zygomycosis	Amphotericin B (in high dose followed by surgery)

Dr Cases:

Case 1	
35 year old male AIDS patient CD4 count less than 100 cells/mm^3 developed non-specific symptoms consisting of fever and headache then he develop more neurologic specific manifestations including altered mental status, nick deafness and cranial abnormalities.	
Investigations	1. undergo lumbar puncture CSF 2. brain CT
CSF	glucose , protein , cell count with differential
direct microscopy	capsulated yeast (Wet mount, gram staining and India ink)
Serology	cryptococcal antigen latex agglutination was positive
Antifungal therapy	amphotericin B

Case 2

55 y/o female with poor compliance suffering from diabetes with ketoacidosis
3rd Jan 2011: visited ophthalmology clinic
13 Jan 2011: patient was admitted to KKUH in the MICU.
In severe condition with unilateral periorbital erythematous edema.
Imaging of the face showed signs of subcutaneous tissue invasion associated with cutaneous thickening
Invasion and extension of the homolateral nasal cavity was observed, also observed in the meninges and adjacent to the right temporal lobe, suggesting extension of the lesion to the CNS
Extensive secretion drainage was performed, very extensive surgery.

investigations	1- CSF 2- biopsy tissue 3- aspirate
Microscopic examination:	• GMS (silver stain), PAS (periodic-acid-schiff) • Broad irregular non-septate hyphae (zygomycetes) • Septate hyphae were also observed (aspergillus)
Management	• Extensive surgery, tissue debridement • Amphotericin B, caspofungin, voriconazole were administered immediately • Patient died 14 days later

Quiz :

Q1/ Fungal infections are more common in immunocompromised patients , which one of these organisms is a risk factor in immunocompetent hosts?

A. Cryptococcus neoformans
B. Rhizopus
C. dematiaceous fungi
D. Aspergillus fumigatus

Q2/ What is the most common risk factor in Zygomycosis?

A. Diabetes with ketoacidosis
B. AIDS
C. Hematological Malignancies
D. Transplantation

Q3/ A 56 year old cancer patient came to the hospital complaining of sinusitis and neurological symptoms , what is the drug of choice to treat the neurological symptoms?

A. Amphotericin B
B. Voriconazole
C. Fluconazole
D. Caspofungin

Q4/ which of these fungi is more likely to cause septicemia ?

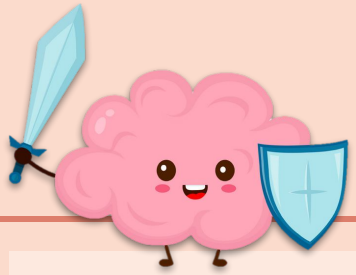
A. Aspergillus fumigatus
B. Cryptococcus neoformans
C. Rhizopus
D. Candida albicans

SAQ/ A 44 years old AIDS patient came to the hospital complaining of neurological symptoms
investigations:
culture : yeast with a mucoid appearance
microscope: showed an encapsulated yeast .

A. what is the most likely organism ?
B. what is the clinical syndrome associated with this organism?
C. what serology method would you use?
D. what is the best treatment in this case?

MCQ:
Q1/C
Q2/A
Q3/B
Q4/D

SAQ:
A. Cryptococcus neoformans
B. meningitis
C.Latex agglutination
D.Amphotericin B



THANK YOU

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Editing file

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