



FUNGAL INFECTION

FUNGAL INFECTIONS OF CNS



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.

Fungal Infection of Central Nervous System

- ❖ 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 Factor

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

How fungi reach the central nervous system?

Fungi reach the central nervous system by different mechanisms:

1. Hematogenous spread
2. Local extension from the paranasal sinuses, the ear, or the orbits.
3. Traumatic introduction:
 - Surgical procedures
 - Head trauma
 - Injections
 - lumbar punctures



Clinical Syndromes

These clinical syndromes can occur either alone or in combination:

1- Meningitis:	2- Brain abscess:
Sub acute or Chronic	With or without vascular invasion

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

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
	Rhinoctadiella mackinziei	Penicillium marneffeii
	and Others	

Cryptococcal Meningitis:

AIDS is the leading predisposing factor

Etiology	Cryptococcus neoformans is the most common etiology ❖ Capsulated yeast cells ❖ Naturally in Pigeon habitats
Acquired by:	Inhalation
Clinical syndromes:	Mainly meningitis



Candidiasis

Etiology	Candida albicans , and other species including C.glabrata, C. tropicalis C. parapsilosis, and C. krusei.
Can reach the CNS	<ul style="list-style-type: none"> ● Hematogenously(not inhalation it's normal flora) ● Surgery, Catheters ● Indwelling catheter and fever unresponsive to antibacterial agent
Clinical syndromes	<ul style="list-style-type: none"> ● Cerebral abscesses(sometimes) ● Meningitis(mostly)

CNS Aspergillosis

Etiology	Aspergillus fumigatus (common globally), but also A. flavus (common in our region), and A. terreus
Clinical syndrome	Usually brain abscesses (single or multiple)
Can reach the CNS	<ul style="list-style-type: none"> ● Spread Hematogenously ● May also occur via direct spread from the anatomically adjacent sinuses, ● Angiotropism(infarction and hemorrhagic necrosis)
Common risk factors include	<ul style="list-style-type: none"> ● Hematological Malignancies ● Transplantation ● Cancer Chemotherapy
Prognosis	Mortality rate is high



CNS Zygomycosis (mucormycosis) الخبز عفن

- 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: **Diabetes 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

Phaeohyphomycosis

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

CNS infections: • Usually brain abscess, and chronic

Risk factors: • Reported in immunocompetent hosts
not immunocompromised

Etiology:

- ➔ **Rhinoctadiella mackenziei** (Mainly reported from Middle East)
- ➔ Cladophialophora, Exophiala , Curvulara, Fonsecaea.



Other Infections:

- ★ Histoplasmosis /Blastomycosis /Coccidioidomycosis /Paracoccidioidomycosis
- ★ 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 CNS

Diagnosis:

Clinical features (history, risk factors, etc): (if HIV screen for cryptococcus coming from US think of dimorphic)	Not Specific (Past surgery is important in history)
Neuro-imaging: radiological finding	Good value in diagnosis and therapy monitoring
Lab Investigations:	CSF examination (cell count,chemistry) Histopathology (granuloma in TB) Microbiology

Lab Diagnosis:

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

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 (Sabouraud dextrose agar) BHI (brain & heart infusion) agar, other media if needed.

4.PCR:

 The most accurate test

5. Serology:

 for detection of antigen or antibody

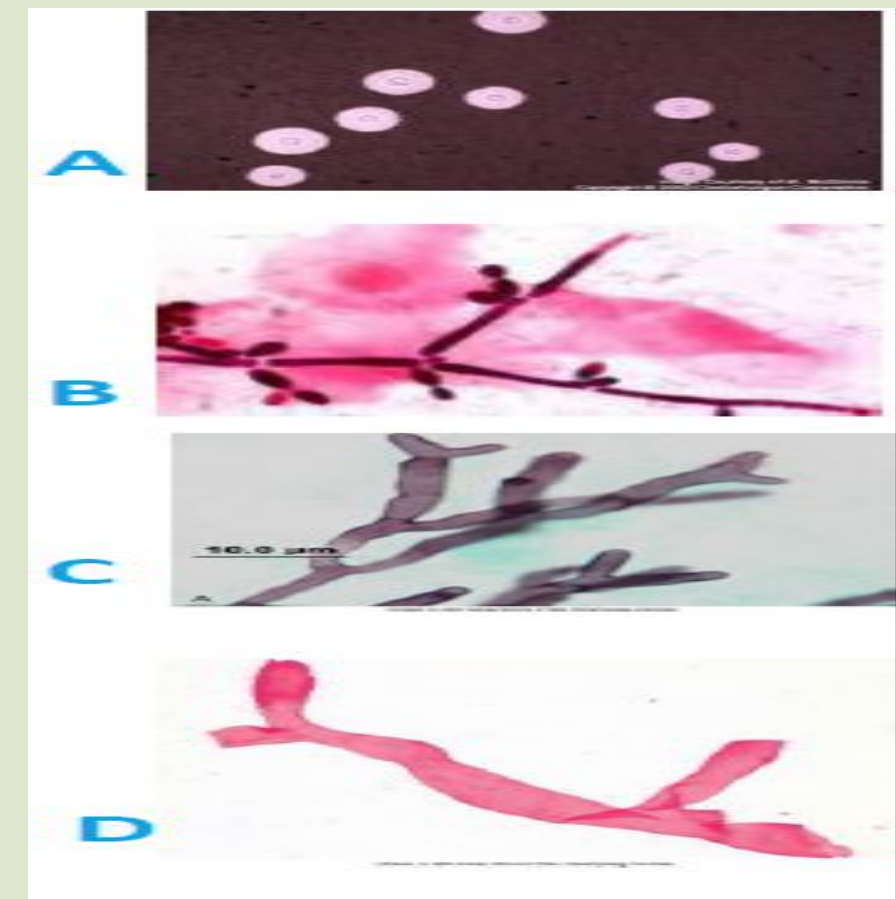
- ★ Candida
- ★ Aspergillus
- ★ Cryptococcus
- ★ Histoplasma
- ★ Blastomyces
- ★ Coccidioides
- ★ Paracoccidioides



CNS infection	Direct microscopic	Culture	Serology
Cryptococcal Meningitis	Yeast cells A Capsulated (india ink)	Yeast	Cryptococcal Ag (capsule) Latex agglutination
Candidiasis	Yeast cells and pseudohyphae B	Yeast	Manann Ag (cell wall)
Aspergillosis	Septate branching hyphae C	Hyaline mould	Galactomannan Ag
Zygomycosis	Broad non-septate hyphae D	Hyaline mould Fast growing	No serology available
Phaeohyphomycosis	Brown septate hyphae	Dematiaceous mould	β-D- Glucan*

*Glucan is found in the cell wall of the fungi So its non-specific test

Serology: β-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 (**abscesses**)
5. Key of treatment is early diagnose

Antifungal Therapy:

CNS fungal infection	Treatment
Cryptococcal meningitis	Amphotericin B (combination with Flucytosine)
CNS Candidiasis (depend on patient +some are resistance to azole)	Caspofungin, Fluconazole, Voriconazole, Amphotericin B
CNS Aspergillosis	Voriconazole (drug of choice), Amphotericin B (Combination of voriconazole and Caspofungin)
CNS Zygomycosis	Amphotericin B (in high dose followed by surgery)



Dr's Notes:

- CNS fungal infections are generally rare but they're very dangerous and has a very high mortality rate this why we have to diagnose them early.
 - They're mostly present in immunocompromised patients but could also present in normal ppl
- When a patient has sinusitis the risk of them developing a fungal CNS infection increases bc the fungi could reach the CNS through the paranasal sinus (if the patient is immunocompromised the risk will be higher)
- Mold fungi is mostly in north america
- the most common infection In uncontrolled HIV patient is cryptococcal meningitis.
- Cryptococcus neoformans has a polysaccharides capsule
- The most important risk factor for cns zygomycosis is **diabetic with ketoacidosis** and also iron overload or iron chelating agents
 - Rhinocerebral mucromycosis is the most frequent presenting clinical syndrome in CNS zygomycosis.
 - It start as a sinusitis, swelling and redness of the tissue around the eyes and nose, then reach the orbit and the optic nerve.
 - It has ability to invade and infect the blood vessels (**angiotropism**) where it will lead to infarction & necrosis and this will make the areas around the eyes and nose darker.
 - Zygomycosis is the most fatal infection 80-100%
- **Phaeohyphomycosis is caused by dematiaceous fungi (dark colored)**
 - Mostly in immunopment but when present in immunocompromised it will be more severe
- Yeast → mostly cryptococcus, meningitis and in HIV patients and caused by capsulated organism
- Candida → could cause meningitis or brain abscess
- Mould → aspergillus, mostly brain abscess
- Mucromycosis → starting from rhinocerebral, rapid progression, & **angiotropism**
- Phaeohyphomycosis → (dimorphic) caused by dematiaceous in immunocompetent & mostly acquired by inhalation



Dr's Notes:

- Risk factors : AID , diabetes or following trauma surgery ear or sinus infection
- How it reaches the CNS :hematogenous spread , local extension,trauma
- Some organisms only cause meningitis some cause abscess but others cause both
- Common etiologies : cryptococcus, candidas, aspergillus, zygomycetes
- Dimorphic is common in north america and rare in saudi
- Brain abscesses can be caused by a black pigmented fungi

Cryptococcus:AIDS is the main predisposing factor

Most commonly cryptococcus neoformans.

It's a encapsulated yeast (unlike candida),

its acquired by inhalation and causes mainly meningitis

Candidiasis :we don't acquire it from the environment the source is our own flora, it reaches the CNS most commonly by hematogenous spread

Or following neurosurgery

It causes meningitis and sometimes abscesses

The most common etiology is candida albicans

Aspergillosis: it usually causes brain abscesses it can reach the CNS by a hematogenous spread or local extension

it can invade the eye and extend to the brain in this case it's called :

Rhinocerebral aspergillosis

The most common etiology is aspergillus.fumigatus and A.flavus

zygomycosis(mucormycosis):mostly present as rhinocerebral mucormycosis

Starting as sinusitis and extending to the brain

Patient will have sinusitis then they will have facial edema then black discharge

it will causes necrosis,invade the eye and invade brain through optic nerve

So they will have facial edema and black discharge

High risk:uncontrolled diabetic patient with ketoacidosis

Once it involves the brain its very hard to treat (80-100% mortality)

They love acidic environment and glucose

Pheohyphomycosis:its a dark pigmented fungi Usually causes brain abscess

Rhinoctadiella mackenziei is endemic in middle east(100% mortality)



Dr's Notes

Case 1: 35 year old male AIDS patient

CD4 count less than 100 cells/mm³

Developed non-specific symptoms consisting of fever and headache

What investigations you will do ?

CSF (lumbar puncture)

MRI/CT

Investigations

What will you request for CSF ?

-Direct microscopy (gram staining and india ink)

→ It showed capsulated yeast cells

-biochemistry(glucose,protein,cell count with differentiation

-culture

-Serology → latex agglutination was positive (cryptococcus antigen)

Case 2: 55-year old female with poor compliance suffering from diabetes with ketoacidosis

3rd Jan 2011: visited the ophthalmology clinic

13 Jan 2011: the 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 to 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

So what sample will you prepare (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)

Extensive surgery, tissue debridement

Amphotericin B, Caspofungin, voriconazole were administered immediately

Patient died 14 days later



SUMMARY

Cryptococcal Meningitis.	Candidiasis	CNS Aspergillosis.	CNS Zygomycosis.	Pheohyphomycosis.
<p>-Etiology: cryptococcus Neoformans. -Capsulated Yeast cells. -AIDS is the leading predisposing factor. -Naturally in pigeon habitats -Acquired by inhalation. -Mainly meningitis.</p>	<p>-Etiology:Mainly Candida Albicans. -Candida reach CNS by: Hematogenously,surgery, catheters,Indwelling catheter and fever unresponsive to antibacterial agent. -Clinical Syndrome: 1-Cerebral microabscesses> 2-Cerebral abscesses> 3-Meningitis. 4-Vascular complications (infarctions.hemorrhage)</p>	<p>-Etiology:Aspergillus Fumigatus &A.Flavus. -Usually cause Brain abscesses (single or multi) -Complications of: Hematological malignancies, cancer chemotherapy, transplantation. -Reach CNS: Hematogenously-Spread from adjacent sinuses, Angiotropism. -HIGH mortality.</p>	<p>-Etiology: Zygomycetes. -Most frequent form of clinical syndrome in CNS Zygomycosis is: Rhinocerebral form. -High mortality. -Rapid Progression. -Risk factors: Diabetic Ketoacidosis. -Clinical Manifestations: Sinusitis-orbit,eye &Optic nerve involvement-extended to brain, face edema,necrosis,vision loss, <u>Angiotropism.</u></p>	<p>--Etiology: Rhinoctadiella Mackenziei. -Caused By Dematiaceous fungi (Neurotropic fungi) -CNS infection: brain abscesses, and chronic. -Immunocompetent hosts.</p>

Diagnosis	1-clinical features /2-Neuroimaging 3-Lab investigations
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Lab diagnosis;
samples(CSF-biopsy-pus-aspirate-blood)

1-CSF	2-Direct microscopy	3-Culture	4-Serology	5-PCR
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Cryptococcal meningitis therapy	CNS Candidiasis therapy.	CNS Aspergillosis therapy	CNS Zygomycosis therapy
Amph-B with Flucytosine	Amphotericin-B	Voriconazole then Amph-B	Amph-B



Quiz:

1. An AIDS patient with a CD4 count in the range 100 to 50 cells/mm³ complains of headache and neck stiffness and appears disoriented. The possibility of fungal meningitis is considered and tests for the common fungal etiology of meningitis are ordered. Tests included direct examination of spinal cord for the organism and serology. The purpose of serology test is detection of ...

- A. Antibody to capsular polysaccharide
- B. Antibody to cell wall mannoprotein
- C. Capsular polysaccharide
- D. Cell wall mannoprotein

2. In Q.1 which one of the following antifungal therapy is appropriate to this case?

- A. Amphotericin B
- B. Voriconazole
- C. Caspofungin
- D. Echinocandins

3. *Candida albicans* is isolated in blood culture from patient in a surgical intensive care unit. This most likely source of infection is ...

- A. A healthcare worker
- B. A visitor
- C. The patient
- D. The surgeon

4. Saad is 55 years old male gym coach poor compliance suffering from diabetes with ketoacidosis and he visited ophthalmology clinic because he complains from vision loss and we do microscopy stain that shows broad non-septate hyphae which of the following is causative organism?

- A. Zygomycosis
- B. Candidiasis
- C. aspergillosis
- D. Phaeohyphomycosis

5. In Q.4 which one of the following antifungal therapy is appropriate to this case?

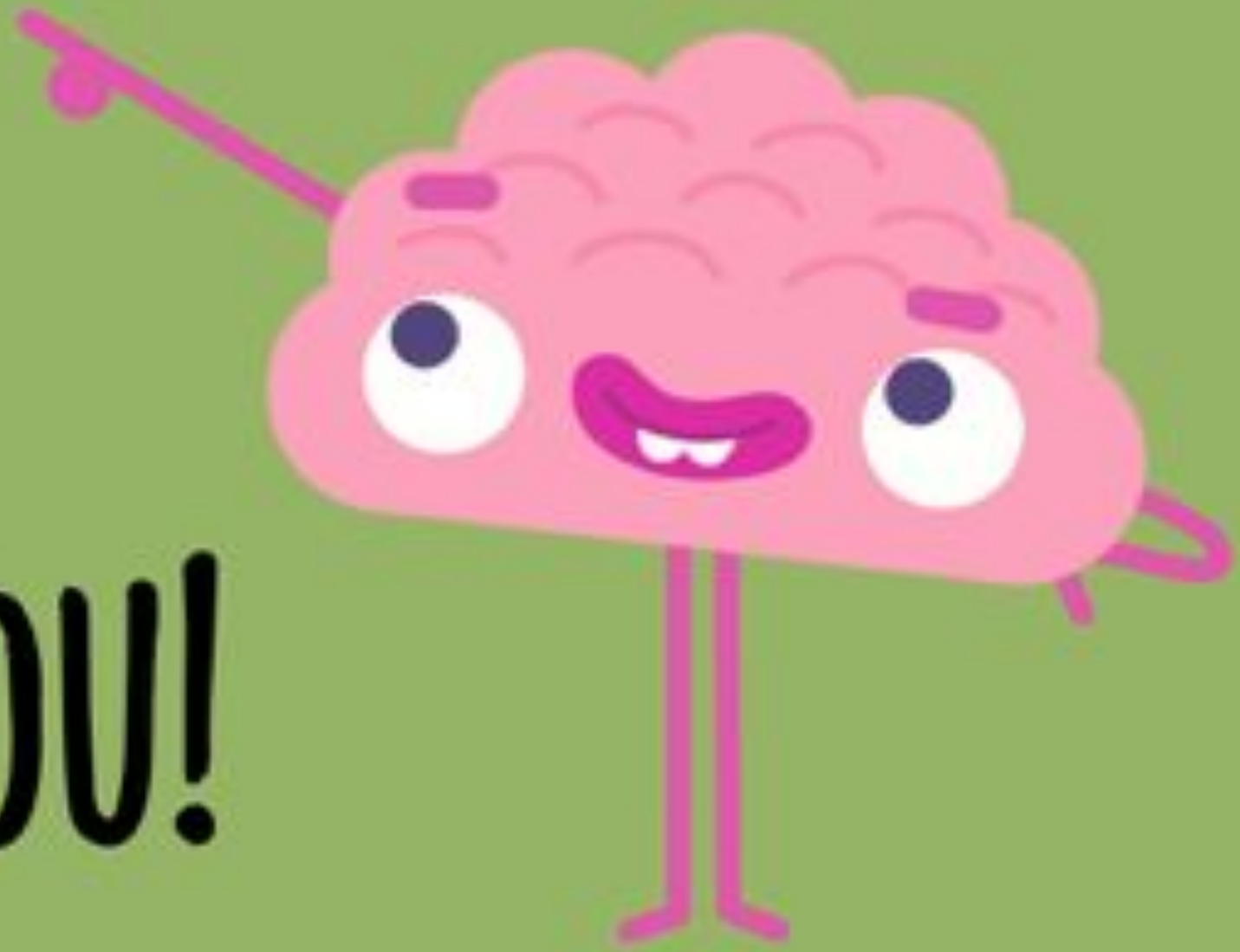
- A. Amphotericin B
- B. Flucytosine
- C. Caspofungin
- D. Voriconazole

6. Which one of the following is **more** correct?

- A. phaeohyphomycosis causes brain abscess in an immunocompetent host
- B. phaeohyphomycosis is a hyaline septate hyphae
- C. *aspergillus.flavus* and *rhinocladiella mackenziei* are more prevalent in our region compared to the united state
- D. .A&C

Answers:
1-C 2-A 3-C 4-A 5-A 6-D





THANK YOU!



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