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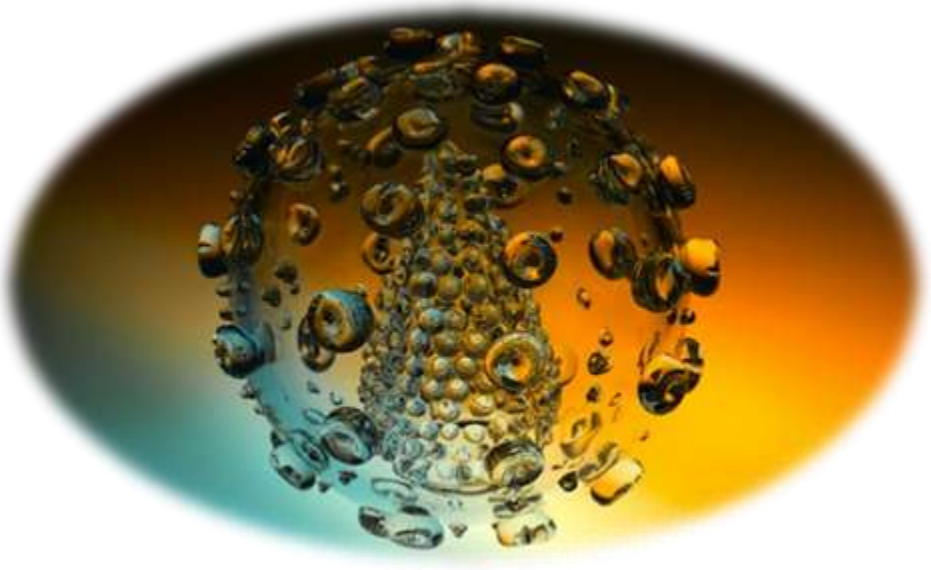
Microbiology Team

CNS BLOCK



Fungal Infections of Central Nervous System

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◆ Green: Doctor's notes

◆ Blue: team's notes

◆ Red: important

◆ Grey: not important

➢ 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

- "Increasing in number because of the rising population of immunocompromised patients (HIV, malignancies, transplantation)"

➢ Risk factors

- HIV/AIDS
- Hematopoietic stem cell transplant (HSCT)
- Solid organs transplantation
- Malignancies, Neutropenia
- Hereditary immune defects
- Immunosuppressive medications
- Diabetes mellitus
- Surgery or trauma
- Indwelling catheters "mainly the central lines as it goes directly to the blood and my cause candidemia "candida in the blood"→ CNS seeding)

➢ 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
  - Head trauma
  - Injections
  - 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 .\

➢ Etiology

- Several fungal agents can cause CNS infections.

Yeast:	**Mould:**
Candida spp	Aspergillus spp
Cryptococcus spp	Zygomycetes
Dimorphic:	*Fusarium spp*
Histoplasma spp	*Exophiala spp*
Blastomyces spp	*Cladophialophora bantiana*
Coccidioides spp	*Curvularia, Bipolaris*
Paracoccidioides spp	*Rhinocladiella mackinziei*
Penicillium marneffei	and Others

" (Cause respiratory diseases, but in immunocompromised may disseminate → meningitis, brain abscesses…)"

➢ Cryptococcal meningitis

AIDS is the leading predisposing factor

- Etiology:

Cryptococcus neoformans is the most common etiology

Capsulated yeast cells

Naturally in **Pigeon habitats** "**pigeon droppings**"

- Acquired by inhalation
- Mainly meningitis "no brain abscess"

➢ Candidiasis

- "Candida species are the most common fungal pathogens"
- Candida species are the fourth most common cause of hospital acquired blood stream infections
- Candida can reach the CNS Hematogenously,

* Candida is a normal flora of the oral cavity, skin and GIT*

Usually in patients with Surgery, Catheters

- Clinical syndromes
  - Cerebral microabscesses
  - Cerebral abscesses
  - Meningitis
  - Vascular complications (infarcts, hemorrhage)
- **Etiology**:

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

***** Indwelling catheter and fever unresponsive to antibacterial agents→ **Candidiasis***

➢ CNS Aspergillosis "Airborne fungi"

Usually brain abscesses (single or multiple) "no Meningitis"

- A severe complication of hematological malignancies and **cancer** chemotherapy, **transplantation**
- Spread Hematogenously "may be because of a lung invasive infection"
- may also occur via direct spread from the anatomically adjacent sinuses,
- Angiotropism (infraction and hemorrhagic necrosis)
- Mortality rate is high "difficult to treat , the mortality rate is 90%"
- **Etiology**: *Aspergillus fumigatus*, *A. flavus*, but also other *Aspergillus* species

➢ CNS Zygomycosis (mucoromycosis):

- The rhinocerebral form is the most frequent presenting clinical syndrome in CNS zygomycosis.
- **Diabetics with ketoacidosis**, in addition to other risk factors
- "Zygomycetes grow well in high Glucose levels and acidic PH levels"
- 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
- Presentations: Facial edema, pain, necrosis, **loss of vision**, black discharge, Angiotropism; As angio-invasion is very frequent
- **Mortality is high**, Progression is rapid "(very acute)"
- **To improve the outcome:**
  - Rapid diagnosis
  - Control the underlying disease
  - Early surgical debridement "of all infected tissues"
  - Appropriate antifungal therapy
- **Etiology:** Zygomycetes e.g. *Rhizopus, Absidia, Mucor* (Fast growing fungi)

➢ Pheohyphomycosis

- Fungal infections caused by dematiaceous fungi "Black (dark pigmented) fungi"
  - Neurotropic fungi "love to grow in brain"
- CNS infections: Usually brain abscess, and chronic "NO lesions other than in the brain"
- Reported in **immunocompetent** hosts
- Chronic

Etiology:

Rhinocladiella mackenziei (Mainly reported from Middle East)

Cladophialophora, Exophiala , Curvularia, Fonsecaea ,

➢ Other Infections

- Histoplasmosis
- Blastomycosis
- Coccidiodomycosis
- Paracoccidiodomycosis

- Caused by primary pathogens
- Following a primary infection, mainly respiratory
  "disseminate to the brain in immunocompromised hosts"
- Sub acute or chronic Meningitis (common), and brain abscess

➢ Diagnosis

- Clinical features (history, risk factors, etc)
  - Not Specific
- Neuro-imaging
  - Good value in diagnosis and therapy monitoring
  - CT or MRI
- Lab Investigations
  - CSF examination (cell count, chemistry)
  - Histopathology
  - Microbiology

➢ Lab Diagnosis

Clinical Samples:

- CSF
- Biopsy
- Pus, aspirate
- Blood (for serology)

1. CSF abnormalities
   - Cell count
   - Glucose level (low)
   - Protein level (high)

   Not specific for Fungal infections
2. Direct Microscopy

   Fungal stains: Giemsa, GMS, PAS(Periodic acid-Schiff stain), India ink (*Cryptococcus neoformans*)
3. Culture

   Fungal media: SDA(Sabouraud dextrose agar), BHI(Brain Heart Infusion), other media if needed.
4. Serology to detect the antigens of the:

   Candida, Aspergillus, *Cryptococcus*

   Histoplasma, *Blastomyces*, *Coccidioides*, *Paracoccidioides*
5. PCR to detect the DNA of the fungi "not common"

CNS infection	Direct microscopy		Culture	Serology*
Cryptococcal meningitis	Yeast cells **Capsulated (India ink stain) *very important***		Yeast	Cryptococcal Ag (capsule) Latex agglutination method
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	No serology available

➢ Management

1. Control of the underlying disease
2. Reduce immunosuppresion, restore immunity if possible
3. Start antifungal therapy promptly
    - Polyenes
    - Azoles
    - Echinocandins

Consider surgery in certain situations

➢ Antifungal therapy

CNS fungal infection	Treatment
Cryptoccocal meningitis	Amphotericin B (sometimes combination with Flucytosine)
CNS Candidiasis	Amphotericin B, Caspofungin, Fluconazole, Voriconazole,
CNS Aspergillosis	**Voriconazole** "drug of choice" , Amphotericin B, Caspofungin, Posaconazole (Combination of Voriconazole and Caspofungin)
CNS Zygomycosis	Amphotericin B "drug of choice", Posaconazole

➢ Summary

- Cryptococcal Meningitis (Cryptococcus **Neoformans**): Usually by **capsulated yeast** cells, acquired by **Inhalation** mainly in **HIV** patients and mainly causes **meningitis**. Usually found in **pigeon droppings**.
- Candidiasis (Candida **Albicans**): **Yeast** cells. Acquired through **surgery** or **catheters** then goes to the brain **hemtogenously**. Causes **brain abscesses and meningitis**.
- Aspergillosis (Aspergillus **Fumigatus** + **Flavus**): **Septal hyphae**. Acquired **hematogenously** following an **invasive infection** or by **local extension** from **sinuses**. Has **high mortality**. Causes **brain abscesses**.
- Zygomycosis (**Rhizopus**): **Broad non-septate hyphae**. Mainly **Rhinocerebral** form (**Sinuses → Eye → Brain)**. **Very acute and very fatal**. In patients with **diabetic ketoacidosis**.
- Pheohyphomycosis: Caused by **black fungi (neurotropic)**. Cause **brain abscesses**. **Chronic**. **Rhinocladiella mackenziei** is common in the **Middle East**.
- Treatment (Drugs of choice):
    - Cryptococcal Meningitis, Candidiasis, Zygomycosis→ **Amphotericin B**
    - Aspergillosis → **Voriconazole**
- Serology:
    - Cryptococcal Meningitis → **Latex Agglutination**
    - Candidiasis → **Mannan Ag**
    - Aspergillosis → **Galactomannan Ag**

➢ Questions

1. A 60-year-old diabetic female with ketoacedosis presents to the emergency department with disturbance in vision and eye movement, she most probably has:
    a. Cryptococcal Meningitis
    b. Zygomycosis
    c. Pheohyphomycosis
    d. Aspergillosis

2. Which ONE of the following pathogens can be isolated from pigeon droppings:
    a. Aspergillus Fumigatus
    b. Rhinocladiella Mackenziei
    c. Candida albicans
    d. Cryptococcus Neoformans

3. The drug of choice for treatment of aspergillosis is:
    a. Amphotericin B
    b. Voriconazole
    c. Fluconazole
    d. Flucytosine

4. AIDS patient present with neurological abnormality and neck stiffness. The CSF sample show capsulated yest which one of the following is most likely to be the etiology:
    a. Candida albicans
    b. Rhinocladiella mackenziei
    c. Cryptococcus
    d. Rhizopus

5. Mannan antigen is specific for which of the following:
    a. Candida
    b. Cryptococcus
    c. Aspergillus
    d. Rhizopus

Answers: 1)b 2)d 3)b 4)c 5)a