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

Objectives:
Not given
Mind map

Fungal infections of central nervous system (CNS)

- Risk factors
- How fungi reach the central nervous system
- Clinical syndromes
- Etiology

microbiology team
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

- HIV/AIDS
- Solid organs transplantation
- Haematopoietic stem cell transplant (HSCT)
- Immunosuppressive medications
- Malignancies
- Neutropenia
- Diabetes mellitus
- Hereditary immune defects
- Surgery or trauma
- Indwelling catheters (e.g. candidemia → CNS seeding) -> fungi will go to the blood circulation "septicemia"

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

Meningitis
Sub acute, Chronic most of the cases
Brain abscess With or without vascular invasion Cause thrombosis or hemorrhage
These clinical syndromes can occur either alone or in combination.
Certain clinical syndromes are specific for certain fungi

Several fungal agents can cause CNS infections.

**Dimorphic**
- Histoplasma spp
- Blastomyces spp
- Coccidioides spp
- Paracoccidioides spp
- Penicillium marneffi

**Mould**
- Aspergillus spp
- Zygomycetes

**Yeast**
- Fusarium spp
- Candida spp
- Cryptococcus spp

"**Dematiaceous**" Black fungi"
- Exophiala spp
- Cladophialophora bantiana-Curvularia, Bipolaris
- Rhinocladiella mackinziei
and Others

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

<table>
<thead>
<tr>
<th>The clinical manifestations of the rhinocerebral form</th>
</tr>
</thead>
<tbody>
<tr>
<td>start as sinusitis, rapidly progress and involve the orbit, eye and optic nerve and extend to the brain</td>
</tr>
<tr>
<td>Facial edema, pain, necrosis, loss of vision, black discharge</td>
</tr>
<tr>
<td>Angiotropism; As angio-invasion is very frequent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>To improve the outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔ Rapid diagnosis</td>
</tr>
<tr>
<td>✔ control the underlying disease</td>
</tr>
<tr>
<td>✔ Early surgical debridement</td>
</tr>
<tr>
<td>✔ Appropriate antifungal therapy</td>
</tr>
</tbody>
</table>
Other infections

- Histoplasmosis
- Blastomycosis
- Coccidiodomycosis
- Paracoccidiodomycosis

- 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.
## Clinical features (history, risk factors, etc) Not Specific

- Neuro-imaging (C.T, MRI)
  - Good value in diagnosis and therapy monitoring

## Lab Investigations (Types of samples: CSF, biopsy, pus aspirate and blood for serology)

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 everything 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.
<table>
<thead>
<tr>
<th>CNS infection</th>
<th>Direct microscopy</th>
<th>Culture</th>
<th>Serology*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal meningitis</td>
<td>Yeast cells, Capsulated (India ink)</td>
<td>Yeast</td>
<td>Cryptococcal Ag (capsule) Latex agglutination</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Yeast cells and pseudohyphae</td>
<td>Yeast</td>
<td>Manann Ag (cell wall)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>Septate branching hyphae</td>
<td>Hyaline mould</td>
<td>Galactomannan Ag</td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>Broad non-septate hyphae</td>
<td>Hyaline mould Fast growing</td>
<td>No serology available</td>
</tr>
<tr>
<td>Pheohyphomycosis</td>
<td>Brown septate hyphae</td>
<td>Dematiaceous mould</td>
<td></td>
</tr>
</tbody>
</table>
Capsulated yeast (C. neoformans)

Pseudohyphae and budding yeast cells (Candida)

Septate hyphae (A. fumigatus)

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).

<table>
<thead>
<tr>
<th>CNS fungal infection</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal meningitis</td>
<td>Amphotericin B (combination with Fluycytosine)</td>
</tr>
<tr>
<td>CNS Candidiasis</td>
<td>Amphotericin B, Caspofungin, Fluconazole, Voriconazole,</td>
</tr>
<tr>
<td>CNS Aspergillosis</td>
<td><strong>Voriconazole</strong> (Drug of choice) Amphotericin B, (Combination of Voriconazole and Caspofungin)</td>
</tr>
<tr>
<td>CNS Zygomycosis</td>
<td>Amphotericin B (Low penetration rate through BBB)</td>
</tr>
</tbody>
</table>
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 gattii) 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.
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
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 neoformes?

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

<table>
<thead>
<tr>
<th>Q</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
</tr>
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</table>
For any problems and suggestions please contact:

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Thank you