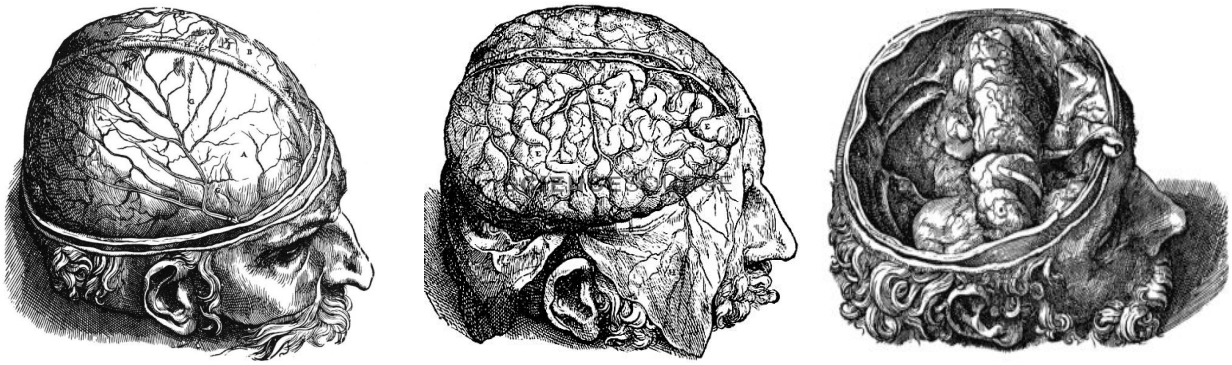
Microbiology

435's Teamwork
Neuropsychiatry Block



- Please contact the team leaders for any suggestion, question or correction.
- Pay attention to the statements highlighted in red.
- Extra explanations are added for your understanding in grey.
- **Footnotes color code:** General | Females | Male

Revised by

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Fungal Infections of the CNS

Resources: Sherris Medical Microbiology, LIR Microbiology, First Aid USMLE Step1, Prof. Maha's & Dr. Albarrag's 2017 lectures.

Learning Objectives:

By the end of this lecture, you should know the…

1. Etiology
2. Clinical Presentation
3. Diagnosis
4. Treatment

Of fungal CNS infections.

Fungi:

Fungi are nonphotosynthetic[1], generally saprophytic[2], eukaryotic organism. Some fungi are filamentous and called molds, whereas others (yeasts) are unicellular. Fungal reproduction may be Sexual, asexual or both. All fungi produce spores.

Introduction:

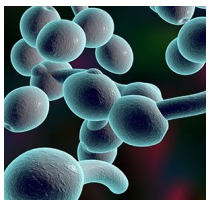
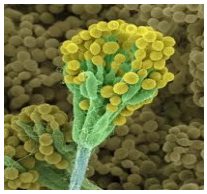
- CNS infections are both a diagnostic challenge[3] and a medical emergency[4].
- Any delay in diagnosing or appropriately treating these cases will lead to a high mortality rate or permanent, severe neurological damage.[5]
- Fungal CNS infections are not common[6], however, they are being increasingly diagnosed.[7]

Risk factors				
HIV/AIDS	Hematopoietic stem cell transplant (HSCT)[8]	Solid organs transplantation	Malignancy	Neutropenia[9]
Hereditary immune defects	Immunosuppressive medications	Diabetes mellitus	Surgery/Trauma[10]	Catheters[11]

[1] A term used for an organisms which does not obtain energy from a light (photo-) source.
[2] A term used for an organisms which obtain nutrients from dead organic matter. رمامي.
[3] Can be mistaken with TB or tumors and it has nonspecific symptoms (mimic bacterial infections).
[4] Rapidly progressive.
[5] You have to make an early diagnosis, in order to stop the prognosis.
[6] Bacterial are more common.
[7] Because of the growing population of immunocompromised individuals, resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs.
[8] Transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood.
[9] The presence of abnormally few neutrophils in the blood, leading to increased susceptibility to infection.
[10] Give fungi a chance to penetrate in the blood, CSF or meninges.
[11] Bacteria and fungi are common in catheters, it will be colonized by bacteria and yeast and then cause septicemia, infection of blood, from blood they can go to anywhere in the body (ex; brain). Catheters are used for kidney diseases or IV fluids, medications.

How do fungi reach the central nervous system?	
Hematogenous spread[12]	Most common
Local extension	From the paranasal sinuses, ear, or orbits to the brain[13].
Traumatic	Surgical procedures[14], head trauma[15], injections[16], lumbar punctures.

Clinical syndromes	
These clinical syndromes can occur either alone or in combination. Certain clinical syndromes are specific for certain fungi.[17]	
Meningitis[18] (Acute, Subacute or Chronic)	Brain abscess[19] (With or without vascular invasion)

Etiology		
Yeasts	Moulds	Dimorphic[20]
		
Unicellular organisms that grow as round oval	Grow as Hyphae multicellular filamentous structures	Have two forms depending on change in the environment
Candida species[23] *Cryptococcus species*[24]	*Aspergillus species* *Zygomycetes*[21] *Exophiala species* *Cladophialophora bantiana* *Rhinocladiella mackenziei*[22]	*Histoplasma species* *Blastomyces species* *Coccidioides species* *Paracoccidioides species*

[12] A primary systemic opportunistic pathogen starts in a specialized organ and travels to a distant organ via Hematogenous spread, caused mainly by mini-rods.
[13] Which means means those that are anatomically close to the brain
[14] Therapeutic procedures in hospitals like manipulation of the head
[15] Such as those caused in road traffic accidents
[16] Contaminated with fungi.
[17] The clinical presentation will differ from patient to another, and from fungi to another.
[18] Fungi can cause both meningitis and brain abscess, some cause either one of them.
[19] Is an abscess caused by inflammation and collection of infected material, coming from local (ear infection, dental abscess, infection of paranasal sinuses, infection of the mastoid air cells of the temporal bone, epidural abscess) or remote (lung, heart, kidney etc.) Infectious. It could be a single or multiple abscesses.
[20] Can be yeast or filamentous. Causes primary systemic fungal infection
[21] Along with Aspergillus, it is saprophytic in nature, and can be involved by inhalation of spores
[22] These last 3 kinds are called black fungi i.e. under the microscope as dark hyaline because of the presence of melanin in the cell wall.
[23] Most common especially in diabetics, found in the skin, oral cavity, and the GIT normal flora.
[24] Comes from the environment, inhaling and then going straight to the CNS. Also a saprophyte.

Yeasts		
	Cryptococcal meningitis	**Cerebral Abscesses/Meningitis**
Diseases	Fungal infection of the tissues covering the brain and spinal cord. These tissues are called meninges.	Fungal infection caused by yeasts that belong to the genus *Candida*. *Candida Species* are the fourth most common cause of hospital acquired (nosocomial) bloodstream infections.
Etiology	*Cryptococcus neoformans* (Most common)	*Candida albicans*[25] (Most common) *Candida Glabrata* *Candida Tropicalis* *Candida Parapsilosis* *Candida Krusei*
Risk factor	AIDS[28]	Neurosurgery[26] | Catheters[27]
Characteristics	Capsulated[29]. Abundant in soil containing bird (especially pigeon) droppings.[30]	Part of the normal flora of the mucous membranes of the respiratory, gastrointestinal and female vagina.
Transmission	Acquired by inhalation[31]	Hematogenous spread
Microbiological Notes	Polysaccharides capsule (india ink) surrounds the budding yeast cell.	-
Treatment	Amphotericin B + Flucytosine	Caspofungin, Fluconazole, Voriconazole, Amphotericin B

Dimorphic[32]	
By primary pathogen (Not opportunistic; does not require or come secondary to decreased immunity). Usually secondary to respiratory infection.	
Etiology	• *Histoplasmosis.* • *Blastomycosis.* • *Coccidioidomycosis.* • *Paracoccidioidomycosis.*
Notes	Cause Cerebral Abscesses or Meningitis.

[25] Considered as yeast at most time.
[26] Typical scenario: a 7 years-old child went to a new type of surgery, that will remove the tumor through the nose, and after a few weeks he develops meningitis caused by yeast or candida.
[27] Since there will be a break in the physical barrier (skin), the cut provides access for the fungi to enter
[28] Every AIDS patient in the hospital must be screened for Cryptococcus.
[29] While candida has no capsule, so it's a way you can differentiate between them.
[30] Everybody can inhale them, normally cause no harm, but in HIV patients it will cause meningitis.
[31] Inhalation of spores: so it starts out as pulmonary infection. Can be self limiting, but it can go to other sites via hematogenous spread and cause meningitis.
[32] They're common in South America but rare in our region.

Mould (filamentous)			
	Aspergillosis	**Zygomycosis [34](Mucormycosis)[35]**	**Phaeohyphomycosis[33]**
Diseases	The name is given to a wide variety of diseases caused by infection by fungi of the genus *Aspergillus*. Mortality rate is high	The broadest term referring to infections caused by bread mold fungi of the *Zygomycota Phylum*. Mortality rate is high (80-100%) Progression is rapid[36]	A heterogeneous group of mycotic infections, caused by dematiaceous fungi whose morphologic characteristics in tissue include hyphae, yeast-like cells, or a combination.
Etiology	*Aspergillus fumigatus* *(*Most common) *Aspergillus flavus*[39] *Aspergillus terrus*	*Zygomycetes* including: • *Rhizopus*[38] • *Absidia* • *Mucor*	Dematiaceous (Dark) Neurotropic[37] fungi: • *Rhinocladiella mackenziei* (Mainly in the Middle East) • *Cladophialophora* • *Exophiala*
Risk factor	• Malignancies. • Transplantations. • Chemotherapy. • Broad-spectrum antibiotics.	Diabetics[40] with ketoacidosis[41]	Immunosuppressed patients
Transmission	Hematogenously[43], may also occur via direct spread from the anatomically adjacent sinuses.[44]	Sinusitis → involve the orbit [42]→ eye → optic nerve → brain. Rhinocerebral form is the most common.	-
Result in	Single or multiple brain abscesses	Facial edema, pain, necrosis, loss of vision, black discharge Angiotropism[45]; angio-invasion is very frequent.	Chronic brain abscesses
Treatment	Voriconazole or Amphotericin B with surgical removal of fungal masses or infected tissue.	Amphotericin B with control the underlying disease and early surgical debridement to avoid progression.	-

[33] Spectrum of the disease ranging from superficial, to subcutaneous, and ending with the brain.
[34] Divided into Mucormycosis and entomophthoromycosis.
[35] Same case scenario as Aspergillosis.
[36] Urgent intervention to stop the progression by appropriate antifungal with surgical procedures to remove the necrotic tissue.
[37] Ability to affect neurons.
[38] Very high mortality.
[39] Most common in Saudi Arabia.
[40] Targets immunocompromised patients, especially diabetic with ketoacidosis.
[41] Because this organism favors low PH and sugar.
[42] It will starts with edema, cellulitis, swelling
[43] Commonly a pulmonary disease in the lung that goes to blood and CNS.
[44] Very common scenario: Patient develop chronic or invasive rhinosinusitis that is not treated, and then it'll spread to the eye, infect the optic nerve, then the CNS.
[45] Affinity to invade and infect the blood vessel. To explain, zygomycosis has black discharge due to infarction and necrotic tissue which then invades the blood vessel.

Diagnosis			
Clinical[47]	History [46](travel), risk factors, occupation, medical condition (HIV, transplant)… etc		
Neuroimaging	Used for diagnosis, prognosis and therapy monitoring → (MRI/CT)		
Lab Investigations	Microbiology	Microscopy	Stains: Giemsa, GMS[48], PAS[49], KOH[50], India ink (*Cryptococcus Neoformans*).
		Culture	Media: SDA[51], BHI[52].
	Samples	Pus biopsy, blood aspirate and CSF (Cell count - ↓ Glucose - ↑ Protein). Not specific for fungal infection.[53]	
	Serology[56]	*Candida, Aspergillus[54], Cryptococcus[55], Histoplasma, Blastomyces, Coccidioides, Paracoccidioides.*	
	PCR[57]	Polymerase Chain Reaction.	

Laboratory					
Infections	**Cryptococcal meningitis**	**Candidiasis**	**Aspergillosis**	**Zygomycosis**	**Phaeohyphomycosis**
Direct microscopy	Yeast cells Capsulated (india ink)	Yeast cells Budding yeast elongating[58] appear as pseudohyphae	Septate branching hyphae	Broad non-septate hyphae	Brown septate hyphae
Culture	Yeast	Yeast	Hyaline mould	Hyaline mould Fast growing	Dematiaceous mould
Serology	Cryptococcal antigen (capsule) Latex agglutination.	Mannan antigen (cell wall)	Galactomannan antigen	No serology Available	-
β-D- Glucan	X	✓	✓	X	✓

[46] History of any steroid therapy, immunosuppressive therapy, cancer, then followed by physical examination .
[47] Not specific i.e. it will not detect if it is a fungal infection, rather if the patient has meningitis or not
[48] Grocott-Gomori's (or Gömöri) methenamine silver stain.
[49] Periodic acid–Schiff stain.
[50] Potassium (K) hydroxide (OH) stain.
[51] Sabouraud Dextrose Agar.
[52] Brain-heart infusion medium.
[53] Because it's the same for bacterial infections.
[54] Candida and Aspergillus serology to detect galactomannan antigen. It turns out positive for invasive infections.
[55] latex agglutination to detect the antigen from the CSF and blood. More than 90% is specific and sensitive.
[56] Mainly for antigens
[57] Rapid, more sensitive, and more specific.
[58] Due to failure of budding detachment.

Management:

1. Control of the underlying disease.
2. Reduce immunosuppression, restore immunity if possible.
3. Start antifungal therapy [59]immediately, before the culture is ready with:
   - Polyenes[60]
   - Azoles
   - Echinocandins
4. Consider surgery in certain situations.

Antifungal therapy[61]	
CNS fungal infection	**Treatment**
Cryptococcal meningitis	Amphotericin B
Candidiasis	Caspofungin, Fluconazole, Voriconazole, Amphotericin B[62]
Aspergillosis	Voriconazole[63]
Zygomycosis	Amphotericin B

[59] Divided into groups based on its therapeutic target like the cell membrane, DNA synthesis
[60] For example: Amphotericin B, nystatin.
[61] Patient came with a fungal infection, but no lab tests are performed, which treatment would you chose? Amphotericin B.
[62] Depends upon the patient's and the organism's factors.
[63] Drug of choice.

Summary	
Fungal infection of CNS	**Rare**, usually affects **immunocompromised** pts. Associated with **Meningitis** (sub-acute or chronic) or **brain abscess**.
Risk factors	**HIV**, hematopoietic stem cell transplant, DM, Indwelling catheters
Mechanisms to reach CNS	- Hematogenous spread. - Traumatic introduction (e.g. lumbar punctures) - Local extension from the paranasal sinuses, ear, or orbits.

Etiology

Yeast: *Candida spp*, *Cryptococcus spp*. | **Mould**: *Aspergillus spp*, *Zygomycetes*, *Pheohyphomycosis*. | **Dimorphic** (1ry pathogen): *Histoplasma spp*, *Blastomyces spp*.

Candidiasis	- Opportunistic pathogen. - Reach CNS by: Hematogenous spread, **surgery**, catheters. - **Cerebral abscess** and **meningitis**. - Etiology is mainly ***C.albicans*** (normal flora). - **Dx**: Microscope → **psuedohyphae**. Serology: **Manann Ag** and β-D- Glucan (if invasive). - **Rx**: Caspofungin, Fluconazole, Voriconazole, Amphotericin B.
Cryptococcal meningitis	- Opportunistic pathogen. → **AIDS (HIV) is the leading predisposing factor**. - Acquired by inhalation. - **Meningitis**. - Etiology: ***Cryptococcus neoformans*** → found naturally in pigeon habitats. - **Dx**: india ink → **Capsulated** . Serology → Cryptococcal Ag, Latex agglutination. - **Rx**: Amphotericin B + Flucytosine.
CNS Aspergillosis	- Opportunistic pathogen. - **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*. - **Dx**: Microscope → **Septate branching** hyphae. Culture → Hyaline mould. Serology → **Galactomannan Ag**, β-D-Glucan (if invasive). - **Rx**: Voriconazole.
CNS Zygomycosis (**Mucoromycosis**)	- Opportunistic pathogen. - 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**. - **Dx**: Microscope → Broad **non-septate** hyphae. Culture → Hyaline mould, **fast growing**. No serology test is available. - **Rx**: Amphotericin B.
Pheohyphomycosis	- Affects **immunecompetent hosts**. - Caused by **dematiaceous (Dark) fungi** (neurotropic fungi) - Chronic **brain abscess**. - Etiology: ***Rhinocladiella mackenziei*** → most common in middle east. - **Dx**: Microscope → **Brown septate** hyphae. Culture → **Dematiaceoud** mould. Serology → **β-D- Glucan**.
Primary CNS infections	- Etiology → primary pathogens → causing: Histoplasmosis, Blastomycosis, Coccidiodomycosis, Paracoccidiodomycosis. - **Sub-acute or chronic meningitis**. - Usually following primary **respiratory** infection.

Diagnosis → Clinical features, Neuro-imaging or Lab investigation

Lab investigation → CSF, Biopsy, Pus, aspirate, Blood.

CSF abnormalities	Direct microscopy	Culture	Serology	PCR
Not specific for fungal infection.	Fungal stains: **Giemsa**, GMS, PAS, **India ink**.	Fungal media e.g. SDA, BHI.	To detect the Antigens.	The most sensitive one.

Multiple Choice and Short Answer Integrated Questions

-To open an answered sheet, please click here-

CASE - 1 A 54-Year male presented to the hospital with meningitis, history was taking and it shows that he had HIV.

Which of the following fungi is the most common cause based on his history?

A. Cladophialophora bantiana
B. Cryptococcal meningitis
C. Candida albicans
D. Aspergillus fumigatus

How does fungus reach the CNS?

What do you see under-microscope?

Which antifungal do we use to treat the patient?

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

What we will find in serology?

CASE - 2 A 45-Year male presented to the hospital with fungal infection in the brain.

Which of the following lab investigations is true about the CSF?

A. High glucose level
B. Low protein level
C. Low glucose level
D. None of the above

Which of the following is a risk factor for fungal infection in the CNS?

A. Organ transplantation
B. HIV
C. All of the above
D. None of the above

CONT… We cultured the organism and we find Hyaline mould.

Which organism is that?

Describe the picture:

CASE - 3

A 37-Year female with fungal infection the brain, in microscopy they found broad non-septate hyphae.

Which of the following is the cause?

A. Zygomycosis
B. Aspergillosis
C. Candidiasis
D. Phaeohyphomycosis

Which fungus is the most common?

What are the risk factors with that fungus?

Which antifungal do we use to treat the patient?

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

How does it reach CNS?

What other symptoms could be seen in the patient?

CASE - 4

A 67-Year patient presented to the hospital with fungal infection with abscesses in his brain, in history they found out that he had a kidney transplantation before 7 months.

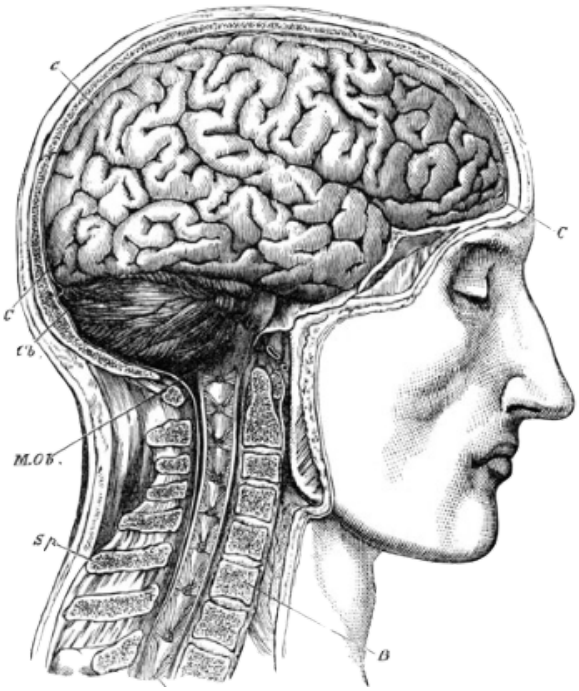
What is the most likely causing organism?

What can we see under the microscopy?

A. Brown septate hyphae
B. Broad non-septate hyphae
C. Yeast cells Budding yeast elongating appear as pseudohyphae
D. Septate branching hyphae

Mention three lab investigations we can use?

Mention one antifungal for the patient?



كَذَٰلِكَ يُبَيِّنُ ٱللَّهُ لَكُمْ ءَايَٰتِهِۦ لَعَلَّكُمْ تَعْقِلُونَ ﴿٢٤٢﴾

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