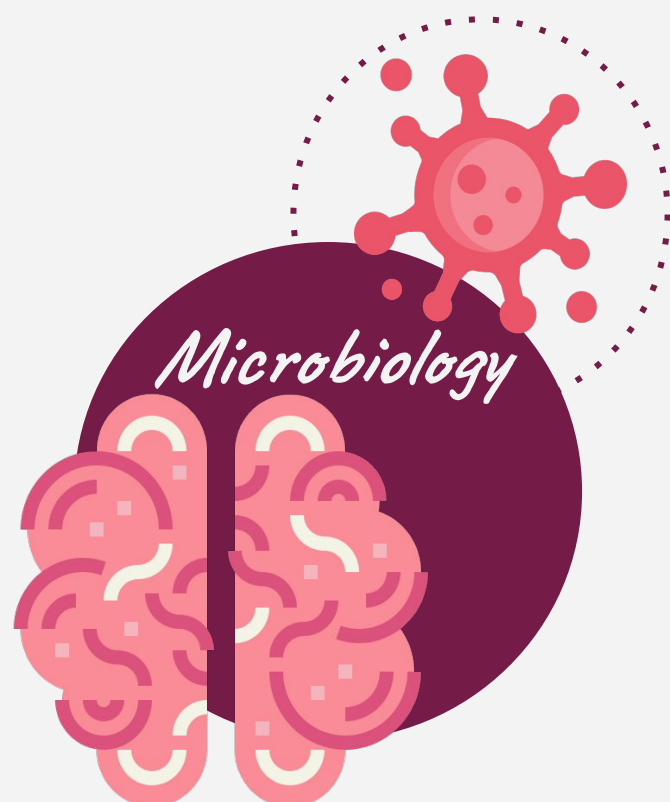


Chronic cerebral infections

Objectives:







- Identify the epidemiology and risk factors for chronic meningitis.
- Define chronic meningitis and the various causes of chronic meningitis.
- Determine microbiological etiology of chronic meningitis.
- Differentiate the clinical presentation of chronic meningitis from other clinical syndromes.
- Interpret the laboratory investigations used for the diagnosis of chronic Meningitis.
- Explain the management approach for a patients suspected to have chronic Meningitis.
- Define the prevention measures of these infection in the community.



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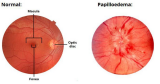



Chronic Meningitis		Meningeal inflammation that persists for more than 4 weeks
Causes	 1: Infectious <ul style="list-style-type: none"> ○ Bacterial including TB ○ Viral ○ Fungal ○ Parasitic 	
	 2: Neoplastic*	
	 3: Chemical*	
	 4: Parameningeal*	
	 5: Autoimmune*	
	 6: Idiopathic*	

Causes of Chronic Cerebral infection and Meningitis

Bacterial, Most important	<p>Common in Saudi Arabia: ○ Tuberculosis ○ Brucellosis</p> <p>Not common in Saudi Arabia : Lyme disease-caused by Borrelia burgdorferi .</p> <p>Others:</p> <ul style="list-style-type: none"> ○ Partially treated acute meningitis. ○ Syphilis-caused by Treponema Pallidum. ○ Lptosporosis- caused by L.Icterohaemorrhagiae. ○ Nocardiosis-caused by Nocardia species .g N. Asteroids. ○ Actinomycosis caused by actinomycetes. <p>These organisms can also cause Cerebral abscesses,, preferred as chronic infection</p>
Fungal Not important	<p>In Saudi Arabia :</p> <ul style="list-style-type: none"> ○ Candida species, mainly Candida albicans in immunocompromised patients <p>Others:</p> <ul style="list-style-type: none"> ○ Cryptococcus neoformans ○ Aspergillus species ○ Histoplasma capsulatum
Parasitic Not important	<ul style="list-style-type: none"> ○ Toxoplasma gondii (most common) ○ Trypanosomiasis: caused by T.gambiense ○ Rare causes Acanthamoeba spp
Virus Not important	<p>Some virus can some present as chronic meningitis these include:</p> <ul style="list-style-type: none"> ○ Mumps ○ Herpes simplex ○ HIV ○ VZV

Clinical Presentation of chronic cerebral & meningitic infection

Symptoms	Signs
Chronic headache	+/-Papilloedema ^[5] 
Neck or back pain	Brudzinski or Kerning 'positive sign of meningeal irritation' 
Change in personality ^[1]	Altered mental status, memory loss, etc
Facial weakness ^[2]	Seventh nerve palsy
Double vision+visual loss ^[3]	3,4,6th,Nerve palsy
Arm and leg weakness	Ataxia ^[6]
Clumsiness ^[4]	Hydrocephalus

Risk factors	<ul style="list-style-type: none"> ○ Age^[7] and Gender (listeria, brucella and SLE) ○ Regional preponderance. ○ Occupation and Recreational activities. ○ Immune status. ○ Sexual exposure ○ Animals or ticks contact.^[8]
Can produce	<ul style="list-style-type: none"> ○ Neurological disability ○ May be Fatal if not treated
They usually have	<ul style="list-style-type: none"> ○ Slow insidious onset ○ With progression of signs and symptoms over a period of weeks
They differ from those of acute infection which have	<ul style="list-style-type: none"> ○ Rapid onset of symptoms and signs
<ul style="list-style-type: none"> ○ They are usually diagnosed ,if the neurological syndrome exists for > 4 weeks , ○ Should differentiated from recurrent aseptic meningitis , aseptic meningitis symptoms are less than 4 weeks ○ Chronic meningitis affects about 10% of patients diagnosed with meningitis 	

^[1] Babies and young children are particularly at risk of developing learning and behavioral changes as a result of meningitis

^[2]Due to damage to the facial nerve

^[3]Poor coordination movement or action

^[4]Due to damage to the optic nerve

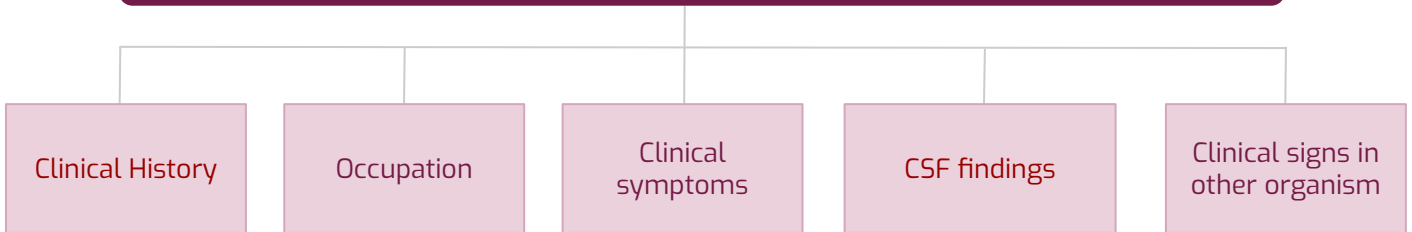
^[5]Is optic disc swelling that is caused by increased intracranial pressure

^[6]Ataxia means there is cerebellar involvement

^[7] Young children are particularly at risk because they have less developed immune system than older age group

^[8] Zoonotic bacterial meningitis is mainly associated with animal contact and Consumption of animal products

They should be differentiated on the basis of:



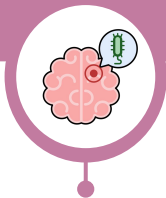
Tuberculosis

Etiology	Caused by <i>Mycobacterium tuberculosis</i> .
Epidemiology	<ul style="list-style-type: none"> ○ It is the most common cause of chronic meningitis ○ It infects one third of the human race.
Transmission	Airborne disease, the bacteria is very small and can stay in air for a long time and spread to a long distance.

Clinical Presentation



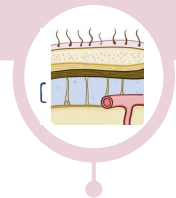
The patient usually presents with **fever of long duration**.



In some cases present as **meningitis and cerebral infection** presenting chronic neurological symptoms and signs. (**Headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies, and raised ICP**)



Symptoms of cough and coughing of blood (Haemoptysis) when the chest is affected.



It affects the base of the brain in the subarachnoid space where they cause arachnoid fibrosis which results in increased ICP and **hydrocephalus**

Tuberculosis	
Can cause (Only in girls slides)	Parenchymal CNS involvement can occur in the form of tuberculoma or more rarely abscess.
	Also can cause: <ul style="list-style-type: none"> ○ Spinal meningitis ○ Radiculomyelitis⁽¹⁾ ○ Spondylitis⁽²⁾ ○ Spinal cord infarction (Pott's spine, Pott's paraplegia).
Complications (Only in boys slides)	<ul style="list-style-type: none"> ○ Hydrocephalus due to obstruction of the foramina of Luschka and Magendie or the aqueduct of Sylvius ○ Vasculitis, sometimes causing arterial or venous occlusion and stroke ○ Cranial nerve deficits, particularly of the 2nd, 7th, and 8th cranial nerves
Prevention	Immunization with Bacille Calmette-Guerin (BCG) to newborns.

Classification of CNS TB (Only in girls slides)

Not important

Intracranial

- Tuberculous meningitis (TBM).
- TBM with miliary tuberculosis.
- Tuberculous encephalopathy.
- Tuberculous vasculopathy.
- Space-occupying lesions: tuberculoma.
- (single or multiple); multiple small.
- Tuberculoma with miliary tuberculosis.
- Tuberculous abscess.

Spinal

- Pott's spine and Pott's paraplegia.
- Tuberculous arachnoiditis (myeloradiculopathy).
- Non-osseous spinal tuberculoma.
- Spinal meningitis.

Diagnosis of chronic cerebral & meningeal infections

1 History for brucellosis & TB

2 Clinical examination

3 Laboratory findings

4 Imaging
X-ray, MRI or Ultrasound

⁽¹⁾Inflammation that can affect the spinal cord and nerve roots, causing symptoms of pain, sensory disturbances, weakness, and dysfunction of bowel and bladder

⁽²⁾Inflammation in the spinal bones, or vertebrae

Diagnostic Features of Tuberculous Meningitis (Only in girls' slides)

Clinical	CSF	Imaging
<ul style="list-style-type: none"> - Fever and headache (for more than 14 days). - Vomiting. - Altered sensorium or focal. - Neurological deficit. 	<ul style="list-style-type: none"> - Pleocytosis (more than 20 cells, more than 60% lymphocytes) - Increased protein (more than 100 mg/dl) - Low sugar (less than 60% of corresponding blood sugar) - India ink studies and microscopy for cryptococcus Neoformans - Malignant cells should be negative 	<ul style="list-style-type: none"> - Exudates in basal cisterns or in sylvian fissure - Hydrocephalus - Infarcts (basal ganglionic) - Gyral enhancement - Tuberculoma formation

Disease	Brucellosis
Etiology	In KSA caused by Br.melitensis. ^[1]
Epidemiology	<ul style="list-style-type: none"> o It is common disease in Saudi Arabia.
Transmission	<p>It affect people who:</p> <ul style="list-style-type: none"> o Are in contact with domestic animals. ^[2] o Consume raw milk and milk products. o And through inhalation.
Clinical presentation	<ul style="list-style-type: none"> o It usually presents with Pyrexia (fever) of unknown organism of intermittent nature (rising and falling) o The fever is accompanied by night sweating, in between the attacks of fever the patient is not very ill. o Influenza-like symptoms.
Can cause	<ul style="list-style-type: none"> o It can cause chronic cerebral infections & meningitis.
Prevention	<ul style="list-style-type: none"> o Prevention in animal: Vaccination. o Eradication: can only be achieved by test-and slaughter combined with effective prevention measures and control of animal movements o Cook the meat ,avoid contact with animals when they are giving birth and drink pasteurized milk

^[1] You don't have to remember it

^[2] Particularly sheep. Not always the case, sometimes it could be dust particles or aerosol.

Diagnosis

★ CSF and Laboratory Findings

Tuberculosis & Brucellosis

Collect of **2-5 ml of CSF** and check for the pressure → ↑ CSF pressure indicating increased intracranial pressure **common with TB**.

Biochemical investigation for:

- Total protein → ↑ **protein** level due to presence of inflammatory substance, dead organism, protein and WBC.
- Glucose level in comparison to the serum glucose level → ↓ **glucose** level (Normally is 2/3 of serum glucose level).

Microscopy:

- Presence of organism.
- Total white cell count → ↑ local white cell count but in chronic infection the differential shows **lymphocytosis** while in acute infections there is ↑ of polymorph.
- Gram stain can same time rarely shows causative organism.
- Differential count mainly for:
 - Polymorphic
 - Lymphocytes → **Neutrophil**

Culture for CSF:

- For Brucella, T.B Mycobacterium tuberculosis, Leptospira other Bacteria.
- TB:
 - Media :CSF culture a solid medium L.J or fluid medium.
 - Stain: **Z-N Stain** can show **AFB** of T.B

PCR :

- Or other molecular biopsy test for presence of bacterial element

Serology :

- For Brucella.

Other:

- Mantoux test, Tuberculin skin test (TST).
- Chest x-ray for primary focus.
- Combination of these finding with clinical history and examination finding

Other Organisms

Not important

- India ink for Cryptococcus neoforman.
- Modified Z-N stain can show Nocardia.
- **VDRL** and other serological causes for syphilis.
- Wet preparation of CSF for fungal and parasite.

Treatment

Tuberculosis

total 9-12 months

For the first **2** months:

- **Rifampicin**
- ★ **Isoniazid (INH)**
- **Ethambutol**
- **Pyrazinamide**

For the next (**4-6**), (**7-10**) months:

- **Rifampicin**
- **INH**

Brucellosis

Two of the following **3** drugs:

- Tetracycline⁽¹⁾
- **Rifampicin**
- **Cotrimoxazole**

Usually Rifampicin and Cotrimoxazole are preferred as they have good penetration power in the Blood-Brain-Barrier

⁽¹⁾ Tetracycline is contraindicated for pregnancy AND children <8

CSF findings in different cases

Topic	Viral meningitis	TB meningitis	Fungal meningitis	Bacterial meningitis
Cell count 0-5	< 2000 cell/ mL predominantly lymphocytes	100-2000 cells/mL predominantly lymphocytes	100-500 cells/mL predominantly lymphocytes	>1000-20000 cell/mL predominantly Neutrophil
Protein 15-50	30-150 mg/dl	High (100-500 mg/dl)	40-150 mg/dl	High (>250 mg/dl)
Glucose 45-100	30-70 mg/dl	Decreased <40 mg/dl	30-70 mg/dl	<40 mg/dl (<40% of serum Glucose)

Others rare causes of chronic meningitis Not important

Disease	Etiology	RF	Presentation	Diagnosis	Treatment	Prognosis
Syphilis (Neurosyphilis)	Treponema pallidum	Only from Human Secondary Syphilis HIV/AIDS	headache and confusion cranial nerves VII and VIII	lymphocytosis ↑ protein normal glucose -serum & CSF-VDRL	IV Penicillin G 10-14 days	Depend on the stage of the disease
Lyme Disease (neuroborreliosis)	Borrelia burgdorferi	Exposure to an ixodes scapularis or tick. Endemic area	Peripheral and cranial neuropathies	lymphocytosis ↑ protein normal glucose -Serology	IV ceftriaxone, Penicillin G or Doxycycline	resolve slowly over weeks to months
Leptospirosis	Leptospira interrogans	Exposure to Rat urine	Intense throbbing Headache and delirium Anicteric second stage 50%	lymphocytosis ↑ protein normal glucose -Serology -PCR	Ceftriaxone, Penicillin G or Doxycycline	Meningoence phalitis /hemiplegia

Prof. Ali

- Cerebral infections are not very common, but they are very serious. The most important ones that I need you to concentrate on are TB and Brucella since we live in an endemic area for these pathogens (with TB being the most common)
- When we say chronic, we mean that the infection has been present for more than 1 month. Anything less is called acute (less than a week) or subacute (more than a week).
- Taking a detailed history is important because there are a variety of differential diagnoses, and because some agents are more common among a specific gender, age, and geographic location. Taking a detailed history is also important because it will help you differentiate between TB and Brucella by considering epidemiology and the patient's exposure to certain animals.
- Brucellosis is common in people who are in contact with domestic animals- mainly goats, cows, and sheep. A typical presentation of brucellosis is **night sweats, fever, and body aches**. Otherwise not severe. (The majority of brucellosis cases are just fever, but they can develop into chronic meningitis if left untreated).
- **TB is very important for the exam.** You have to know it because it is very fatal, can be missed easily, and **our region is endemic for TB**. Patients with TB usually present with **fever for a long duration in a gradual onset** (nothing severe). Patients also might come with respiratory symptoms caused by the reactivation of pulmonary tuberculosis which will lead to the dissemination of the infection into the blood and finally seed into meninges. However, when TB finally presents as a CNS infection, it can cause severe neurological damage.
- A major complication of TB is **basal meningitis** (meninges covering the base of the skull). This is a very sensitive area because of the high number of structures that are located there, especially those that relate to CSF flow. The infected meninges will become edematous and cause obstruction, leading to **hydrocephalus**. Other complications of TB include **vasculitis** and **cranial nerve deficits**.
- ★ **In TB investigation, funduscopy must be done before taking the CSF sample** because if there was an increase in intracranial pressure, you might not be able to take CSF from the patient. Other modalities are indicated in this case.

Important to remember all TB investigations that should be done with the CSF sample:

- (1) Cell count → **lymphocytosis** (2) Protein → **slight elevation** (3) Glucose → **slight reduction**
 (4) Gram & Z-N stains, (5) TB/blood Culture, and you might need to do (6) PCR as well.

★ Possible SAQ

TB is a very waxy organism. Sometimes, it sticks to the meninges, making sample aspiration very difficult; therefore, a negative CSF sample does not rule out TB (in this case, you need to take meningeal tissue for pathology findings). **The best sample is meningeal tissue** because you will be looking at the pathology itself, not the fluid around it. However, it is not that reasonable/easy procedure.

Mantoux test is very sensitive test for TB, but it is not specific. (It shows that the patient has the infection, but it does not necessarily mean that TB is reactivated).

- ★ **In Brucellosis investigation, we do the same tests indicated for TB. In addition, we must do (1) serology & (2) culture.** Note that the patient being in close contact with animals does not necessarily mean that it is brucella. It can be TB as well.
- When a patient is suspected to have a chronic CNS infection, we do all test for both TB and Brucella.
- Chronic infections can be easily differentiated from acute CNS infections just by asking the patient simple questions like "how long have you been sick?". If it was an acute infection, the answer will be 2-3 days.
- Symptoms of cerebral/meningeal chronic infections include **meningeal irritation and cranial nerve palsy**. Their progression is slow but can be fatal if left untreated.
- The duration of drug therapy depends on the patient and his condition.
- We need to be sure of our diagnosis because (1) less drugs and a shorter course of antimicrobials are followed in the case of brucellosis and (2) a misdiagnosed case (i.e. we thought it was brucellosis but it is actually TB) results in an increased risk of rifampicin resistance by mycobacterium tuberculosis.

Dr. Fawzia

- If a patient is diagnosed with chronic TB meningitis, you must do an HIV test. "للي ما يطلبه ما يفهم طب ولا ذاكر زين"
- Spinal involvement of TB is called **potts disease**.
- Imaging is more helpful in cases of abscesses than it is in cases of meningitis.
- Unfortunately, detection rate of PCR is only 60%; however, it is very diagnostic.
- Resistance rate to Rifampicin among HIV patients is very high, so their prognosis is very poor.

Quiz

Click on the icon to check out the team's summary
Finally we reached the last micro's theoretical lecture, see you in GI 🤗

MCQ

Q1: Which of the following is a diagnostic method that detect Br.melitensis:

- A- Z-N stain
- B- Serology
- C- India Ink
- D- Mantoux test

Q2: A 28 years old man was admitted to the hospital. He suffered from headache and neck pain, his temperature was high the last 20 days. Recently he started to cough blood.

2.1- what is the most likely causative agent?

- A- Br.melitensis
- B- Candida albicans
- C- Mycobacterium tuberculosis
- D- Nocardia speciese

2.2: What do we expect to see in the CSF?

- A- Pleocytosis(especially macrophages)
- B- Decreased proteins level
- C- High glucose level.
- D- Pleocytosis (especially lymphocytes)

Q3: CNS tuberculosis can affect the spinal cord and cause?

- A- Tuberculoma
- B- Tuberculous abscess
- C- Pott's
- D- Tuberculous vasculopathy.

Q4: A farmer came to the hospital complaining of fever, headache and night sweating. Which one of the following is the most likely causative organism?

- A- Borrelia burgdorferi
- B- Br.melitensis
- C- Mycobacterium tuberculosis.
- D- Toxoplasma gonodii

Q5: which of the following drugs are preferred in treatment of brucellosis?

- A- Rifampicin + Pyrazinamide
- B- Rifampicin + Ethambutol
- C- Rifampicin + Cotrimoxazole
- D- Rifampicin + Isoniazid

Answers: Q1:B | Q2.1:C | Q2.2:D | Q3:C | Q4:B | Q5:C

SAQ

CASE: A 22-year-old college student brought to our hospital with complaint of on and off fever, loss of appetite of 1-month duration. Patient recently became irritable and was in altered sensorium since 4 days. There was no history suggestive of respiratory, cardiac, or urinary abnormalities. Evaluation for sexually transmitted disease was negative. On examination patient was pale, febrile with toxic look, disoriented with Glasgow coma scale of 12/15. Patient had signs of meningeal irritation along with right sixth nerve palsy, resting tremors in both hands, generalized rigidity of extra pyramidal type (lead pipe and cogwheel) but he did not had any weakness. Patient had cognitive defects like apathy, psychomotor retardation, and impaired memory.

Q1: What is the most likely diagnosis?

A: Chronic Meningitis

★ Q2: What investigations must be done to confirm the causative organism (include the expected results)?

- A: (1) Cell count → it will show lymphocytosis
(2) Protein → it will show slight elevation
(3) Glucose → it will show slight reduction
(4) Gram stain & Z-N stains.
(5) Culture: LJ culture (for TB) & culture (for brucella)
(6) PCR
(7) Serology (for brucella)

Q3: If TB was detected, what is the appropriate treatment for this patient?

A: **For the first 2 months:** Rifampicin + Isoniazid (INH) + Ethambutol + Pyrazinamide
For the next 4-6 months: Rifampicin + INH

Q4: If Brucella was detected, what is the appropriate treatment for this patient?

A: Rifampicin + Cotrimoxazole

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