CNS

MICROBIOLOGY

3

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Bacterial Meningitis Part 2

There are certain guidelines that are used in order to make diagnosis and treatment of acute bacterial meningitis. These guidelines are known as the ESCMID Guidelines.
(ESCMID= European Society for Clinical Microbiology and Infectious Diseases)

The format of those guidelines is found in the form of key questions followed by recommendations.

Please try to understand the following guidelines and focus on the important points only. The first 3 pages are mainly a recap for the previous lecture.

Key Question 1. What are the causative microorganisms of community-acquired bacterial meningitis in specific groups? (neonates, children, adults, and immunocompromised patients)?

The causative agent varies by the age of the patient. For example:

a) Most common causative pathogens in neonatal meningitis are Streptococcus Agalactiae (GBS) and Escherichia coli. Both of those pathogens can be found within the vaginal canal and are acquired by the neonate during birth. If the mother was known to bear either of those pathogens in her vaginal canal, antibiotic therapy before birth can be started.
b) Most common causative pathogens in children beyond the neonatal age and adults are Neisseria meningitidis and Streptococcus pneumoniae. Both can be found as colonizers of healthy individuals, from which they can spread to the blood and cross the BBB into the CSF and start an infection.
c) Another important causative microorganism in adults is Listeria monocytogenes as it can be found in immunocompromised patients and the elderly (above 60 YO)

Remember that Hemophilus Influenzae type B has been historically an important cause of meningitis. But with the advent of the vaccination programs, the incidence of Hemophilus influenzae type B meningitis has decreased.

Key Question 2. What are the clinical characteristics of community-acquired bacterial meningitis, and what is their diagnostic accuracy?

We can see the classical triad of fever, headache, and neck stiffness in both children and adults. Other meningeal signs such as Brudzinski's and Kernig's signs are expected to be positive (not always). However, there are no clinical signs of bacterial meningitis present in all patients.

Altered mental status and confusion indicate the involvement of the brain parenchyma (encephalitis).

Remember that in neonates, symptoms are nonspecific and not obvious. (continuous crying, inability to sleep, poor feeding)

Diagnostic accuracy of laboratory techniques in bacterial meningitis

One of the important laboratory techniques in diagnosing bacterial meningitis is lumbar puncture and examining the CSF. Classic characteristics of bacterial meningitis CSF sample include:

1) elevated protein levels
2) lowered glucose levels
3) CSF pleocytosis (mostly neutrophils)

However, in neonatal meningitis, the leukocyte count, glucose, and protein levels can be within normal range or slightly elevated.

Keep in mind that 60-90% of CSF cultures of bacterial meningitis are positive. Treatment reduces the yield of positive CSF cultures.

If a patient presents with a negative CSF culture and negative CSF gram stain, viral pathogens may be suspected and use PCR in order to identify the pathogen.

Blood cultures can also be used to isolate the causative organism since the pathogen enters the blood before traveling to the meninges.

Lumbar puncture can be delayed for suspected increase in intracranial pressure due to the risk of brain herniation. For example, if we find focal neurologic deficits, seizures, severe alteration in the mental status, or if the patient is severely immunocompromised, lumbar puncture is delayed. Otherwise, if none of these red flags are suspected, lumbar puncture can be performed, and antibiotic therapy should be started before the results of the lumbar puncture. (within a period that does not exceed 1 hour).

Empiric antibiotic treatment in neonates involves cefotaxime and ampicillin.
In older age groups, cefotaxime and ceftriaxone can be used. (refer to previous lecture)

Any delay in antibiotic treatment is associated with poor outcome.

Key question 3. Do corticosteroids (e.g. dexamethasone) have a beneficial effect on death or consequences following bacterial meningitis?

Corticosteroids significantly reduced hearing loss or other neurologic sequelae. However, no change in mortality has been observed.

(adjunctive dexamethasone treatment is recommended up to a few hours after the initiation of antibiotic treatment)

Key Question 4. Does the use of prophylactic treatment of household contacts decrease carriage or secondary cases?

Anyone who encountered the salivary or respiratory droplet of a meningitis patient should be prophylactically treated in order to prevent secondary cases and eradicate meningococcal carriage.

Due to the risk of recurrence of meningitis, vaccination with pneumococcal vaccine after an episode of pneumococcal meningitis is beneficial to avoid the recurrence.

Key Question 5. What complications can happen following bacterial meningitis?

Usually, Neurologic and systemic complications can occur. MRI and CT scans are indicated in those patients. Repeated lumbar puncture and EEG may be indicated as well. Because bacterial meningitis complicated by hydrocephalus, subdural empyema, and brain abscess may require neurosurgical intervention.

Key Question 6. What follow-up of community-acquired bacterial meningitis patients should be provided?

Follow-up should involve testing for hearing loss. Because if it is detected early, cochlear implantation can be provided.

END OF RECAP

Chronic meningitis & Subacute meningitis

Acute meningitis, as we have previously defined it, is a neurological emergency that takes place within *hours.*

On the other hand, chronic meningitis is a neurologic syndrome that exists for more than 4 weeks and is associated with a persistent inflammatory response in the CSF.

Subacute meningitis develops over days to a few weeks.

The symptoms of chronic meningitis are quite similar to symptoms of acute meningitis.

Headache, neck stiffness, and a change if personality (due to brain parenchyma involvement).

Fever may be absent (in contrast to acute meningitis which has fever).

In contrast to acute meningitis, signs of increased intracranial pressure are common in chronic meningitis because the process has been going on for a longer period.

TABLE 37-1

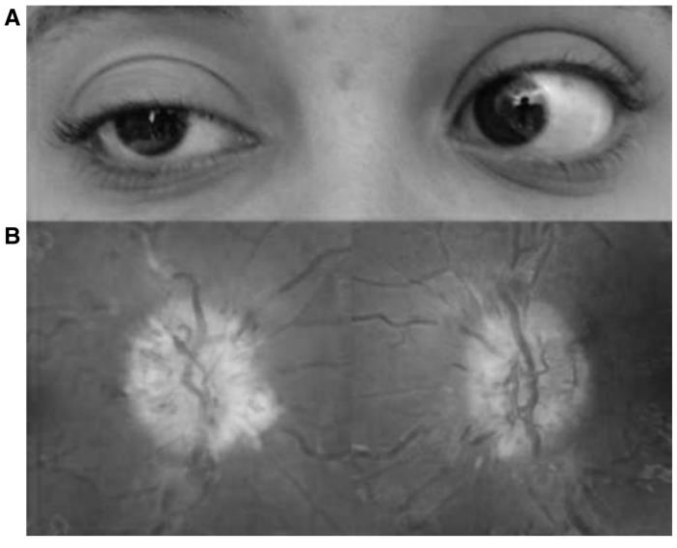
SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

SYMPTOM	SIGN
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/ incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

And, as shown in the adjacent table, some of the cranial nerves can be affected in the form of facial weakness, double vision, diminished vision, and hearing loss.

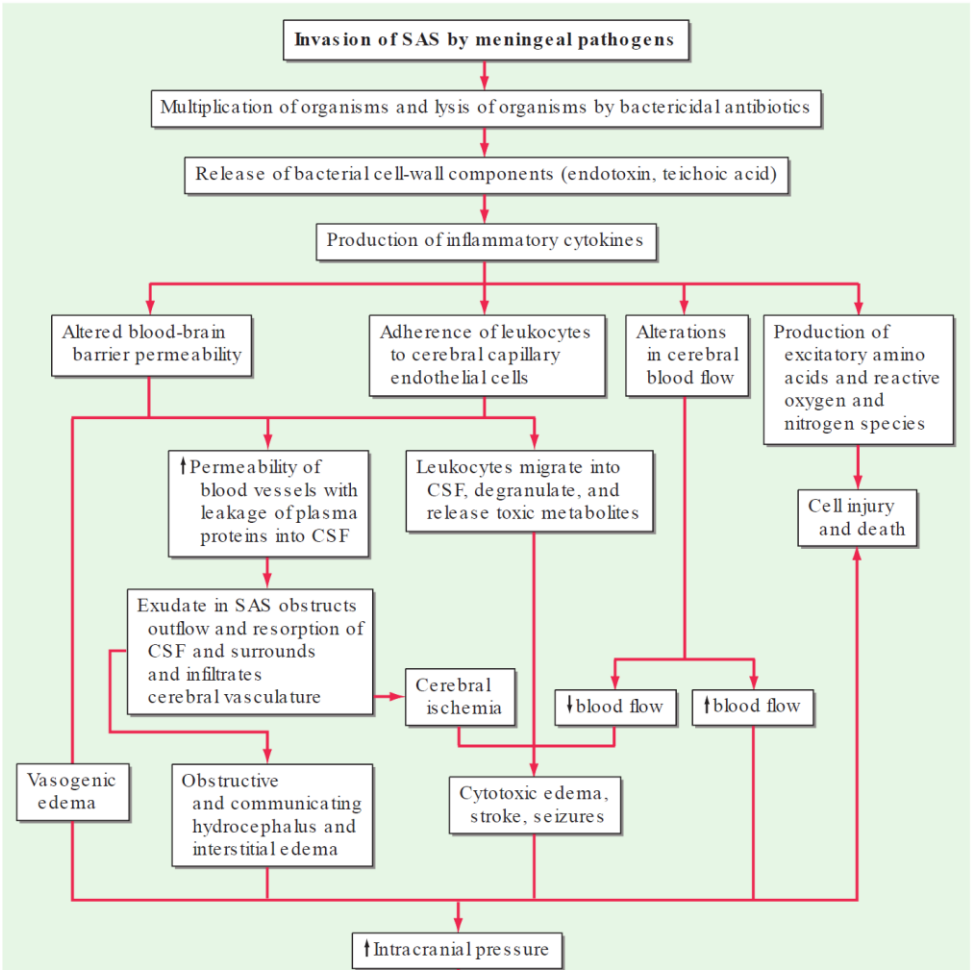
CSF flows in the subarachnoid space. Any disturbance to its flow can cause accumulation of the CSF which leads to an increase in intracranial pressure. And it can affect any of the cranial nerves. That can manifest as ptosis and an abduction deficit in the right eye of the patient or bilateral papilloedema.



(A) Ptosis and an abduction deficit in the right eye of the patient.

(B) Bilateral papilloedema

The following chart shows the reasons for the increase in intracranial pressure in meningitis.



The subarachnoid space (SAS) is invaded by a meningeal pathogen. The pathogen will multiply within the CSF (especially since the CSF is low in immunoglobulins, complement proteins, WBCs, etc.) And after a while the pathogen will be lysed by immune cells or antibiotics. This will cause the release of bacterial cell wall components (e.g. LPS, peptidoglycans).
These cell wall components will be detected by special pattern recognition receptors, and an inflammatory response will ensue. Production of inflammatory cytokines will increase the permeability of the BBB, increase adhesion of leukocytes to cerebral capillary endothelial cells, alternate the cerebral blood flow, and release reactive oxygen species and nitrogen species.

The result will be edema and obstruction of the subarachnoid space. As well as destruction of cells leading to cytotoxic edema. Which all eventually lead to an increase in intracranial pressure.

We can also have weakness and numbness in the arms and legs or urinary retention or incontinence due to radiculopathies, where the nerve roots are inflamed as they traverse the subarachnoid space (as they leave the spinal cord).

What are the common infectious causes of chronic meningitis?

As we said before, we have some infectious and non-infectious causes. As for the infectious causes, which we will discuss, we have some bacterial causes such as mycobacterium tuberculosis and spirochetes. We have some viruses such as Enteroviruses, herpes simplex virus, HIV, and we also have some fungi. And in the case of chronic meningitis. The history and the epidemiology are of great importance because they give us an important clue about the pathogen that we are dealing with.

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common Bacterial Causes			
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBCs/μL); low CSF glucose, high protein	Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR	Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome): Borrelia burgdorferi	Mononuclear cells; elevated protein	Serum Lyme antibody titer; western blot confirmation (patients with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary): Treponema pallidum	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody–absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain	History consistent with acute bacterial meningitis and incomplete treatment

The table above: **some common bacterial causes**, we have **Mycobacterium tuberculosis, Borrelia burgdorferi which causes Lyme disease and Treponema Palladium which causes syphilis**. Now, if we examine the CSF for this patient who came with the meningitis symptoms, along with some focal neurological symptoms, if we look at the CSF, **unlike** what we see in acute bacterial meningitis (Polymorphonuclear cells), **we will see mononuclear cells except early up in the infection where we can see polymorphonuclear cells like neutrophils**, while in most cases we will encounter mononuclear cells because as the infection progresses, **adaptive immunity** will be handling the problem and that's why in the CSF, we will find mononuclear cells like **lymphocytes**.

Now, other than the CSF, which can give us some very important clues on the pathogen we're dealing with, ***risk factors and epidemiology*** give some important clues. So, for example, if we have an immunosuppressed or AIDS

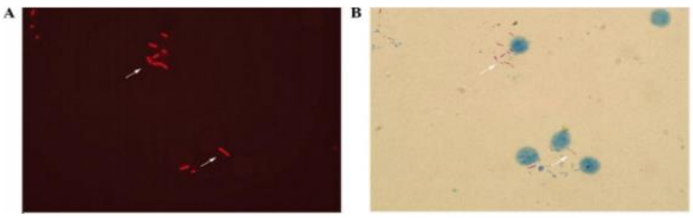
patients or if there is an exposure history to someone with tuberculosis, then we should suspect mycobacterium tuberculosis. On the other hand, if we have a history of going on **hikes**, for example, or a history of a **tick bite**, or if the common rash called **erythema migrans** which happens with Lyme disease is present or if there's **arthritis**, we should suspect **Lyme disease** that caused by Borrelia burgdorferi.

If we have a history of untreated **STDs**, then we should suspect syphilis.

According to the pathogen that we suspect, we can order the tests we have, so, we can ask for a tuberculin skin test and for an acid-fast bacilli culture if we suspect Mycobacterium tuberculosis.

We can look at **antibody titers** in the case of **Lyme disease**, we look for antibodies against Borrelia in the CSF. And in the case of **syphilis**, we can do the **Venereal Disease Laboratory Test**. Or we can do some more, which are a bit unspecific like looking for **anti-cardiolipin antibodies** within the CSF, or we can go for more specific tests that look for antigens of Treponema pallidum in order to confirm the infection with **Treponema pallidum**.

YOU should remember that partially treated bacterial meningitis can present as chronic meningitis. So, if there is a history that is consistent with acute bacterial meningitis and the patient has been given some antibiotics, but those antibiotics did not manage to clear the infection, or if the patient himself has been self-medicating, then we can expect **partially treated suppurative meningitis,** and that can be the cause of the chronic meningitis that we are dealing with, and of course, we will do CSF culture and other tests.



Micrographs of acid-fast bacilli obtained with fluorescence microscopy and transmitted light microscopy (modified Z-N staining)

Because tuberculous meningitis has a rapid and destructive course and because diagnostic tests are limited, this infection should be **treated based on clinical suspicion**. Currently, the WHO recommends treatment with the **anti-TB drugs** isoniazid, rifampin, pyrazinamide, and ethambutol for 2 mo followed by isoniazid and rifampin for 6 to 7 mo. **Corticosteroids** (prednisone or dexamethasone) may be added if patients present with stupor, coma, or neurologic deficits.

Image above: If we do an acid-fast stain, and then we find this acid-fast bacillus as well with antibodies against it and we see some fluorescence then we should suspect Mycobacterium tuberculosis. And because mycobacterium tuberculosis has a ***destructive course*** and sometimes the diagnostic tests can take a long time, then we can start treating based on clinical suspicion. And as the case with all the other pathogens that we will discuss today with chronic meningitis, you usually go back to the guidelines on how you treat that pathogen, and you follow them. So, in the case of TB, they recommend four drugs at the start for two months which are **Rifampin**, **Isoniazid**, **pyrazinamide** and **ethambutol** (RIPE). Then you follow with **isoniazid** and **rifampin** for around six to seven months and sometimes similarly to what you do in acute meningitis there is a place for dexamethasone.

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Fungal Causes			
Cryptococcus neoformans	Mononuclear cells; count not elevated in some patients with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum	Exposure history—southwestern U.S.; increased virulence in dark-skinned races
Candida spp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; post surgery; prolonged IV therapy; disseminated candidiasis
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern U.S.; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus spp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression

We also have Some **fungal causes** of chronic meningitis, and we will mention only two of them, Cryptococcus neoformans and Coccidioides Immitis.

You should remember that in chronic meningitis, we would always face those mononuclear cells, but with fungal infections, we should always suspect some sort of **immunosuppression**.

So, in certain cases, we might not find an elevated count of mononuclear cells in the CSF, Why? Because the patient is already **immunosuppressed**, for example, in the case of AIDS lymphocyte count is low. So, we do not see many lymphocytes within the CSF.

And to diagnose this, if we have suspicion of those kinds of fungi, we should always do a wet mount of the CSF and look for **budding yeast**. And again, as we said always, the risk factors are of great importance, AIDS and

immune suppression, **pigeon exposure** (for example, those Cryptococcus neoformans are found in the excretions of pigeons).

We also have some helminthic and protozoal causes and even viral causes, especially if we have a recurrent type of chronic meningitis so the symptoms can disappear for a while and then come back and then disappear, then we should suspect that it is herpes simplex virus and most commonly it is dealt with herpes simplex virus type two. Again, mumps can cause acute or chronic viral meningitis.

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Helminthic Causes			
Cysticercosis (infection with cysts of Taenia solium)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive patients
Viral Causes			
Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Herpes simplex (HSV)	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Toxoplasma gondii, which is a common pathogen in HIV patients, is also a common protozoan cause of chronic meningitis.

Cysticercosis which is an infection with cysts of **Taenia Solium** which can be found within the uncooked meat or pork. The cysts are found within the feces of infected patients and will not be contracted from the undercooked meats, and in the case of helminths we can expect to find **some polymorphonuclear cells** such as **eosinophils** because they are very important against Helminths.

How do we approach the patients with chronic meningitis?

we know that we have a patient with some meningeal symptoms of chronic headache, maybe some increase in intracranial pressure -some cranial neuropathies (cranial nerves will be compressed)- Or we can have some parenchymal symptoms, such as cognitive decline. All of this, along with some clues from the history, should always prompt us to think of chronic meningitis. And when we think of meningitis, then we should consider

lumbar puncture to examine the CSF and look for meningeal inflammation. But we should note that if there is a chance of raised intracranial pressure, which we said is quite common in chronic meningitis, then a CT scan or an MRI or brain imaging study in general should be performed before the lumbar puncture, because if the increased intracranial pressure is due to a mass lesion, then our lumbar puncture will **risk in herniation of the brain**.

Once we confirm chronic meningitis by examining the CSF, and presence of those symptoms for more than four months, we look at the CSF, we see there is an increase in mononuclear cells. Then this is time to identify the cause. **History** that we take from the patient is quite important to know what sort of tests we should order, so, for example, if there is a history of tick bites then we should consider looking for antibodies to Borrelia within the CSF, and we can do some serological testing, and PCR to find DNA sequences of Borrelia.

If there is a history in an AIDS patient who got in contact with pigeon excretions, then we should suspect the Fungai **cryptococcus neoformans,** and accordingly, we can do **wet mount** and look for the Fungai. If there is a history of sexually transmitted disease or syphilis, we can do **VDRL test**. So, depending on the history, this will guide us in what sort of tests we will further ask to identify that pathogen. Now, other than CSF tests, we can ask for other tests that give us an idea about the underlying illness. So, for example. Tuberculin skin test, and chest radiograph Might Guide us in the way of tuberculosis or tuberculous meningitis.

After we identify the causative agent with a proper history and a proper test, we can start therapy against the specific causative agent. But in certain places, because of the destructive nature of chronic meningitis on the central nervous system, sometimes they can start empiric therapy and that is most geared toward Mycobacterium tuberculosis. So, even without confirming Mycobacterium tuberculosis, you can directly start with empiric therapy with anti-Mycobacterium agents. As well as in some cases of fungal infections, you can start also empirically with amphotericin, and in non-infectious inflammatory meningitis you can give dexamethasone to lessen the inflammation and thereby lessen the damage to the CNS.

What is chronic meningitis?

- Most common etiologies of chronic meningitis:

(1) meningeal infections,
(2) malignancy,
(3) autoimmune inflammatory disorders,
(4) Para-meningeal infections.

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SYMPTOM	SIGN
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/ incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Good Luck

Common causes of infectious chronic meningitis?

- Possible causes include fungi, Mycobacterium tuberculosis, spirochetes, Toxoplasma gondii, HIV, enteroviruses
- History is important in identifying risk factors. (e.g. Exposure to TB cases, tick bites, Syphilis)

Table 19.5 Causes of chronic meningitis/meningoencephalitis

	Syndrome	Causes
Infectious	Meningitis	*Acanthamoeba* spp., *A. cantonensis*, brucellosis, candidiasis, coccidioidomycosis, cryptococcosis, *Ehrlichia chaffeensis*, *F. tularensis*, histoplasmosis, *Leptospira* spp., *Listeria* spp., Lyme disease, sporotrichosis, syphilis, TB, Whipple's disease
	Focal lesions	Actinomycosis, blastomycosis, cysticercosis, aspergillosis, nocardiosis, schistosomiasis, toxoplasmosis, TB
	Encephalitis	African trypanosomiasis, CMV, enterovirus (hypogammaglobulinaemia), EBV, HIV, HTLV, HSV, measles, SSPE, rabies, VZV
Non-infectious	Meningitis	Drugs (NSAIDs, IVIG, intrathecal agents), Behçet's disease, benign lymphocytic meningitis, CNS vasculitis, Fabry's disease, granulomatous angiitis, malignancy, sarcoidosis, SLE, Wegener's granulomatosis, Vogt–Koyanagi–Harada disease

How to approach a patient with chronic meningitis?

- The occurrence of **chronic headache**, **hydrocephalus**, **cranial neuropathy**, and/or **cognitive decline** in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation.
- If the possibility of **raised ICP** exists, a **brain imaging study (CT scan, MRI) should be performed before lumbar puncture**. If ICP is elevated because o a mass lesion, lumbar puncture carries the potential **risk of brain herniation**.
- Once chronic meningitis is confirmed by CSF examination, effort is focused on **identifying the cause**.
- The **epidemiologic history** is of considerable importance and may provide hints to the causative agent as well as selection of laboratory studies.
- **CSF samples** sent or bacterial, fungal, and tuberculous **culture**; Venereal Disease Research Laboratories (**VDRL**) test; **cell count and differential**; **Gram's stain**; and measurement of **glucose** and **protein**. **Wet mount** for fungus and parasites, Rapid diagnosis may be facilitated by **serologic tests** and polymerase chain reaction (**PCR**) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen.
- In addition to the CSF examination, an attempt should be made to uncover pertinent **underlying illnesses**. (e.g. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential).