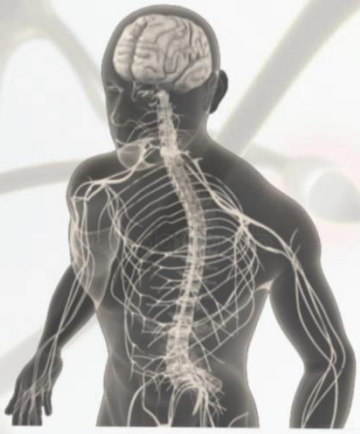
Central Nervous System

Sheet 2



Subject | Microbiology

Done by | Ali A.

Correction | ...

Doctor | Anas

Acute Meningitis:

We will start with a small review of the bacterial and viral meningitis we took the previous lecture:

1.) **Causative microorganisms in community bacterial meningitis**: S. agalctiae & E. Coli (neonates), N. meningitidis & S. pneumoniae (children > 1 mo. and adults), L. monocytogenes (adult)

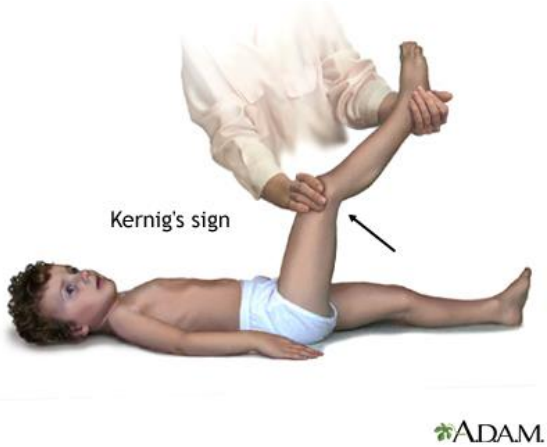
S. agalctiae and E. coli are both found in the vaginal canal and can be passed from the mother to her child at birth. In cases where the mother is known to be colonized/infected with these, prophylactic antibiotics are given as treatment. L. monocytogenes is a common infection of transplant patients and the elderly. Historically, H. influenza B was a common pathogen that caused meningitis but has decreased in prevalence due to vaccines.

2.) **Clinical characteristics of bacterial meningitis and diagnostic accuracy**: neonates have unspecific symptoms (poor feeding, crying, inability to sleep), children and adults have a classical triad of fever, headache, and neck stiffness

There are no clinical signs that are present in all patients (nothing is 100% specific), but some patients may present with vomiting, altered mental status & confusion (most likely brain parenchyma involvement), and 2 signs the doc mentioned, Brudzinkski's Sign and Kernig's Sign. These 2 signs are expected to be found in meningitis, but they are not always present.

Brudzinkski's sign is due to sever stiffness of the neck, when the patient is supine flexion of the neck will cause flexion of the hips and knees.

Kernig's sign is due to stiffness of the hamstrings, when the patient's hip and knee are flexed at 90° angles, extension of the knee will cause pain.



3.) **Laboratory techniques and diagnostic accuracy:** one of the most important techniques is <u>lumbar puncture and analysis of CSF.</u> Other techniques include CSF & blood cultures, gram staining, and PCR.

Common findings in the CSF of bacterial meningitis patients are: increased protein levels, lowered glucose levels, and pleocytosis (increased WBC; PMNs in bacterial and lymphocytes in viral). In neonates, all these values can be within the normal range or slightly elevated. CSF cultures are positive in 60-90% of patients, but if antibiotic treatment has already been started it is possible to have a negative CSF culture and gram stain. Gram staining has good specificity but varying sensitivity based on treatment with antibiotics. Patients with negative cultures and gram stains may use PCR in order to identify the causative organism.

In some cases (high intracranial pressure) lumbar puncture should be delayed and cranial imaging should be performed before the puncture in order to prevent risk of brain herniation. Patients with the following conditions should have a cranial CT done before their lumbar puncture: focal neurological deficits, seizures, severely altered mental status, severely immunocompromised state (note: despite the delay in lumbar puncture, empricic treatment with antibiotics should be started within 1 hour based on clinical suspicion).

4.) **Treatment:** empiric antibiotic treatment should be started as soon as possible in suspected cases of acute bacterial meningitis, delay of treatment is associated with poor outcome. Corticosterroids (methadoxasone) can be used in children and adults with meningitis to prevent functional damage to the CNS.

Neonates: cefotaxime and ampicillin

Children and adults: cefotaxime and ceftriaxone

The drugs above are for empiric treatment, more specific drugs should be used after susceptibility testing comes back from cultures of the CSF or blood.

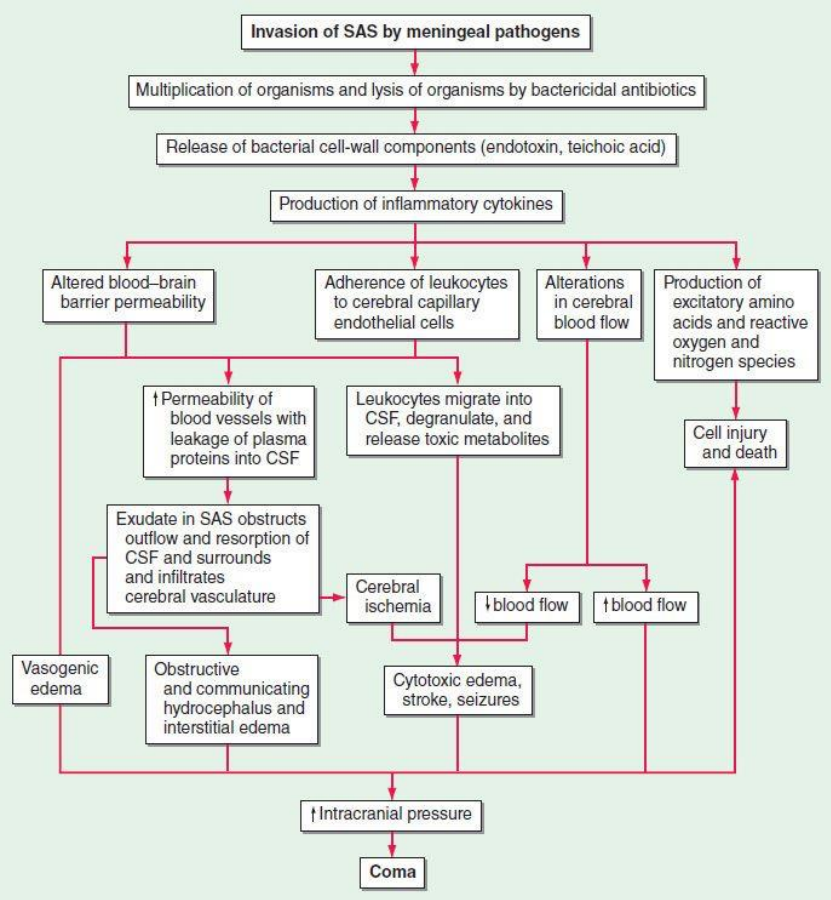
Corticosteroids can be used in children and adults, not neonates, in order to prevent hearing loss and other consequences of CNS damage due to meningitis. It is recommended to start adjunct therapy with corticosteroids within 4 hours of antibiotic treatment (note: corticosteroid use was found to have **no** effect on mortality).

5.) **Prophylaxis:** a committee found that prophylactic use of antibiotics for household contacts of patients decreases recurrence and carriage of meningiococcal microorganisms. In the case of S. pneuominae, vaccination was found to have profound benefits for household contact as well as patients with CSF leakage.
6.) **Complications, further investigations and treatment:** complications that occur due to meningitis can be neurological or systemic, and they occur often. Neurological complications include hydrocephalus, subdural empyema, and brain abscess. All of these can lead to neurological detoriation where further investigations are warranted. MRI, CT, repeated lumbar punctures, and EEGs may be indicated, and neurosurgery may be required for treatment.
7.) **Follow up:** many patients end up having some lasting damage due to meningitis, and even after the active infection is cleared some tests should be done. Common sequelae occur include, hearing loss, focal neurologic defecits, and neuropsychologic defects. Detection of these defects early can help in treatment and in the case of hearing loss, facilitate cochlear implants.

Now on to the subject of today's lecture:

Chronic Meningitis:

Chronic meningitis is diagnosed when a patient has a **characteristic neurologic symptom** (headache, neck stiffness, altered mental status) persisit for **more than 4 weeks,** and is associated with an **elevated WBC in the CSF** (>5 / µL). Other symptoms commonly found in chronic meningitis are increased intracranial pressure, ptosis & abduction defecit in right eye, and papilloedema (swelling of optic discs). The reasons for increased ICP are due to the production of cytokines in the CSF, which eventually leads to edema. Below is a chart showing the exact pathogenesis, but the doc didn't mention everything in it (I would just stick to infection → cytokine production → edema).



We can also have weakness and numbness in the arms and legs due to radiculopathies, which is caused by the spinal roots becoming inflamed when leaving the CNS and passing through the meninges.

The causes of chronic meningitis can be infectious or non-infectious, so make sure you take a good history before starting treatment with antimicrobials. Some causes of infectious chronic meningitis are: fungi, M. tuberculae, spirochetes, T. gondii, HIV, and enteroviruses (Coxsakie, polio, rota, and adenoviruses). Going back to the history, this is done to rule out non-infectious causes, and to point us in the right direction (Mtb exposure, tick bites, syphilis).

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

On the previous page are some common bacterial causes of chronic meningitis. Notice in the CSF, **we tend to find mononuclear cells (lymphocytes and monocytes) instead of PMNs**, like in acute meningitis (note: we will find PMNs in the early stages, but the adaptive immune system will take over). Another thing that differentiates between the causative organisms is the epidemiology; Mtb patients have exposure history or are immunosurpressed, Borrelia patients have a history of tick bites, erythema migrans, or arthritis, while Treponema patients have a history of STIs. Accordingly, we can order tests based on the suspected microorganism (acid fast for Mtb, antibody titers for borrelia, and antibodies against treponema).

Lets speak about Mtb specifically. Due to its rapid and destructive course, as well as the diagnostics specific for Mtb taking several weeks, if you suspect Mtb you should **start treatment based on clinical suspicion.** Therapy for Mtb is 2 months of isoniazid, rifampiun, pyrazinamide, and ethambutol for 2 months, then isoniazid and rifampin for 6-7 months. Corticosteroids/dexamethasone can be added (like in acute meningitis) in order to assist neurological symptoms (coma, stupor, and sequalae).

Before moving on, as with all chronic bacterial infections, chronic meningitis can be due to partially treated acute bacterial meningitis. These patients present classically, but with a history of acute bacterial meningitis that was partially treated by a physician (or the patient may have been self-medicating).

Fungal:

Now we will be talking about fungal causes for chronic meningitis. We will only be talking about 2 fungi, Cryptococcus neoformans and Coccidioides immitis.

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

Same as bacterial when it comes to the CSF, we will mainly see mononuclear cells. The difference is, with fungal infections we should suspect immune surpression (AIDS), and this will cause some cases to **not** have elevated mononuclear cell count. When we want to specify the causative organism we should do a wet mount of the CSF in order to see budding yeast. Risk factors and epidemiology are important as well (immunosurpression/AIDS & pigeon exposure for C. neoformans).

Others:

The doctor didn't say a lot about these and just read off the slide mostly:

Viral: HSV-2 recurrent chronic meningitis with recurrence of genital lesions

Mumps causes acute or chronic meningitis

Protozoal: Toxoplasma gondii

Helminths: Cysticercosis →larva of Taenia solium infect the meninges through ingestion of raw pork, and is spread feco-orally →CSF contains mononuclear cells and eosinophils in order to fight the infection

Clinical Approach to Chronic Meningitis:

Once we have a **suspicion** of chronic meningitis due to **clinical symptoms** (chronic headache, hydrocephalus, cranial neuropathies, cognitive decline), we want to try to **take a sample of CSF via lumbar puncture**. **Remember, be wary of increased intracranial pressure** because of the risk of brain herniation. In this case we do a cranial CT or MRI before administering the lumbar puncture. After analysis of CSF is done and we have confirmed chronic meningitis, we start **identifying the cause.** In many of these cases the **history and epidemiology is important** and can narrow the differential down to a few causative agents. After narrowing down the differential we **conduct lab studies** in order to **confirm diagnosis** (eg. Tuberculin skin test & chest X-ray for Mtb). After identifying the causative agent we then **begin therapy** (drugs for Mtb, amphotericin for fungal infections, dexamethasone for non-infectious chronic meningitis). In some cases, because the infection is rapid and destructive (**Mtb and fungal**) we **begin empiric treatment based on clinical suspicion**, instead of waiting on confirmation from the lab.