CENTRAL NERVOUS SYSTEM

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- ○ Anatomy
- ○ Physiology
- ○ Pathology
- ○ Biochemistry
- ● Microbiology
- ○ Pharmacology
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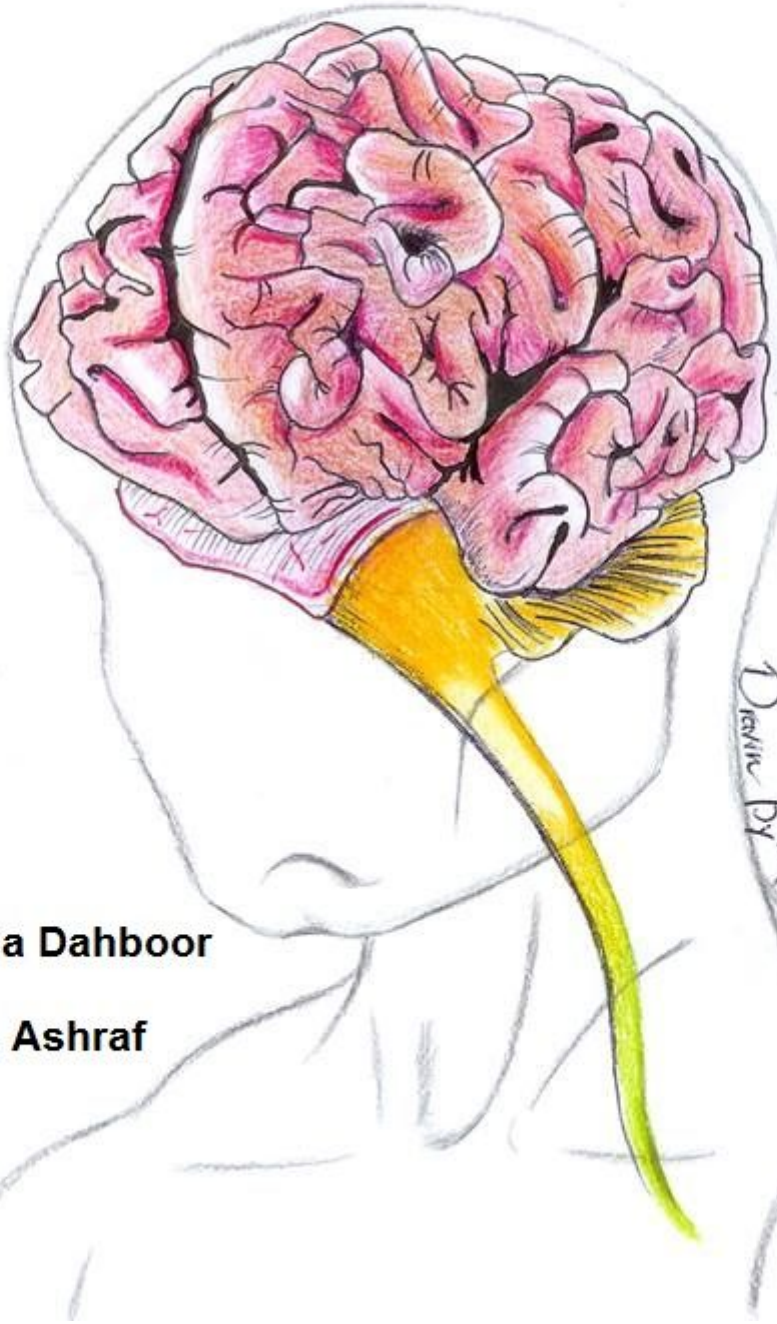

Drawn By Tariq Bushnaq ...

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Lec #: **1**

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Note: The sheet is long because most of the slides' content is incorporated. It's an easy lecture. Good luck!

Aseptic meningitis

Definition of aseptic meningitis:

Asepsis: A condition in which living pathogenic organisms are absent; a state of sterility.	Meningitis: Inflammation of the membranes of the brain or spinal cord.

Aseptic meningitis refers to patients who have clinical signs and laboratory evidence for meningeal inflammation with negative routine bacterial cultures . Let's explain!

If you take CSF sample from a patient and do regular culture for bacteria, the result will be negative (i.e. after 24,48 or even 72 hours have passed, the plates will be empty indicating that no bacterial microorganisms were detected). This finding is highly indicative of aseptic meningitis. From this we conclude that - mostly - the causative agents of aseptic meningitis aren't of the common bacterial pathogens. Indeed , aseptic meningitis can be caused by various agents, but the viral microorganisms are the most common amongst them. Examples of viral etiologies of aseptic meningitis include Echoviruses, Coxsackieviruses and Poliovirus, which belong to the Enterovirus genus that belong to the Picornaviridae family. These viruses and others will be discussed throughout the lecture Inshallah.

The doctor showed the following table which includes various etiologies of aseptic meningitis. I'll mark the ones he specifically mentioned by a ☆

Differential diagnosis of Aseptic Meningitis†

	Common	Uncommon	Rare
☆ Viral	Echoviruses Coxsackieviruses types A and B Herpes simplex type 2 Human immunodeficiency virus Lymphocytic choriomeningitis virus Arboviruses Mumps Poliovirus	Cytomegalovirus Epstein Barr virus Varicella zoster virus Herpes simplex type I Adenovirus Measles Rubella	Rotavirus Encephalomyocarditis virus Vaccinia Influenza A and B Parainfluenza
Bacterial	Parameningeal bacterial infection (epidural, subdural abscess) Partially treated bacterial meningitis Leptospira sp. ☆ Borrelia burgdorferi (Lyme disease) ☆ Mycobacterium tuberculosis Bacterial endocarditis	Treponema pallidum (syphilis) Mycoplasma pneumoniae Rickettsia sp. Ehrlichia sp. Brucella sp. Chlamydia sp.	Borrelia recurrentis (relapsing fever) Spirillum minor (rat bite fever) Listeria monocytogenes Mycoplasma hominis Nocardia sp. Actinomyces sp.
Fungal		Cryptococcus neoformans Coccidioides immitis Histoplasma capsulatum	Candida sp. Aspergillus sp. Blastomyces dermatitidis Sporothrix schenckii
Parasitic		Angiostrongylus cantonensis Toxoplasma gondii	Taenia solium (cysticercosis) Trichenella spiralis
Drug	☆ Ibuprofen	Trimethoprim-sulfamethoxazole Other NSAIDs Pyridium (phenazopyridine) anti-CD3 monoclonal antibody Azathioprine	
☆ Malignancy	Lymphoma Leukemia Metatstatic carcinomas and adenocarcinomas		
Autoinumme		Sarcoid Behcet's disease Systemic lupus erythematosus	Vogt-Koyanagi-Harada syndrome
Other		Epiden-noid cyst Postvaccination	

† Etiologies are classified according to their relative frequency among all causes of aseptic meningitis.
Modified from Connolly, KJ, Hammer, SM. Infect Dis Clin North Am 1990; 4:599.

Our concern in this lecture will be discussing the viral causes. Let's carry on! ☺

✍ Viral Meningitis:

** Etiological Agents:

- Enteroviruses (Coxsackieviruses and echovirus); most common.
- Arbovirus (Arthropod - borne i.e. transmitted via mosquitoes).
- Measles virus.
- Herpes Simplex Virus.
- Varicella.

- Lymphocytic Choriomeningitis virus (LCM).
- Mumps.
- Other less common causes include West Nile, St Louis Encephalitis, and California Encephalitis.

** Some of these viruses have only human reservoirs (Examples: Enteroviruses, Adenovirus, Measles, Herpes Simplex, and Varicella). Others have natural reservoirs, such as rodent or bird reservoirs. (Examples: Arbovirus, West Nile virus and St Louis virus)

** Modes of transmission:
Primarily person-to-person and arthropod vectors for Arboviruses.

The word *arbovirus* is an acronym (**AR**thropod-**Bo**rne virus).

** Incubation period:
Variable; 2-7 days for enteroviruses, 2 days – 2 weeks for Arboviruses.

** Infectivity:
The proportion of infected persons who develop illness varies from 2-100% depending on serotype or strain and on patient's age.

Doctor Ashraf says that generally, not every viral infection is associated with the appearance of symptoms/illness. This rule applies to all viral infections. He means that the development of symptoms is not necessary for all virally infected people. For some viruses, only a very few percentage of the infected people develop symptoms/illness. We can even make a general rule that states that viral infections - mostly - are asymptomatic ! The viruses that cause viral meningitis don't deviate from this rule as the percentage of developing symptoms among those infected may be as low as 2%.

In a nutshell:

Infectivity ≠symptomaticity(≠ : doesn't necessarily mean).

الإصابة بالعدوى لا تعنى بالضرورة ظهور الأعراض .

Enteroviruses:

** Types:

62 different types are known, distributed as follows:

- 23 Coxsackie A viruses
- 6 Coxsackie B viruses
- 28 echoviruses
- 4 Enteroviruses (68-71). These are relatively new.

** Out of all viral meningitis cases, how many of them are caused by enteroviruses?

90% of all viral meningitis is caused by Enteroviruses.

** Who is at risk?

Everyone is at risk, but children<10 years-old represent 70-75% of the cases (two-thirds of the cases) , so most of the cases are seen in children. Why is that? Remember that the causative agents here are enteroviruses which are naked (un-enveloped) viruses that belong to the Picornaviridae family. The route of transmission for these viruses is primarily fecal-oral which is highly related to hygiene. Children < 10 years have poor hygiene generally as they put everything in their mouths and so on, so they're more prone to being infected with enteroviruses that cause viral meningitis via the fecal-oral route.

(You can add the incompletely developed immune system as another cause for high incidence in children below 2 years).

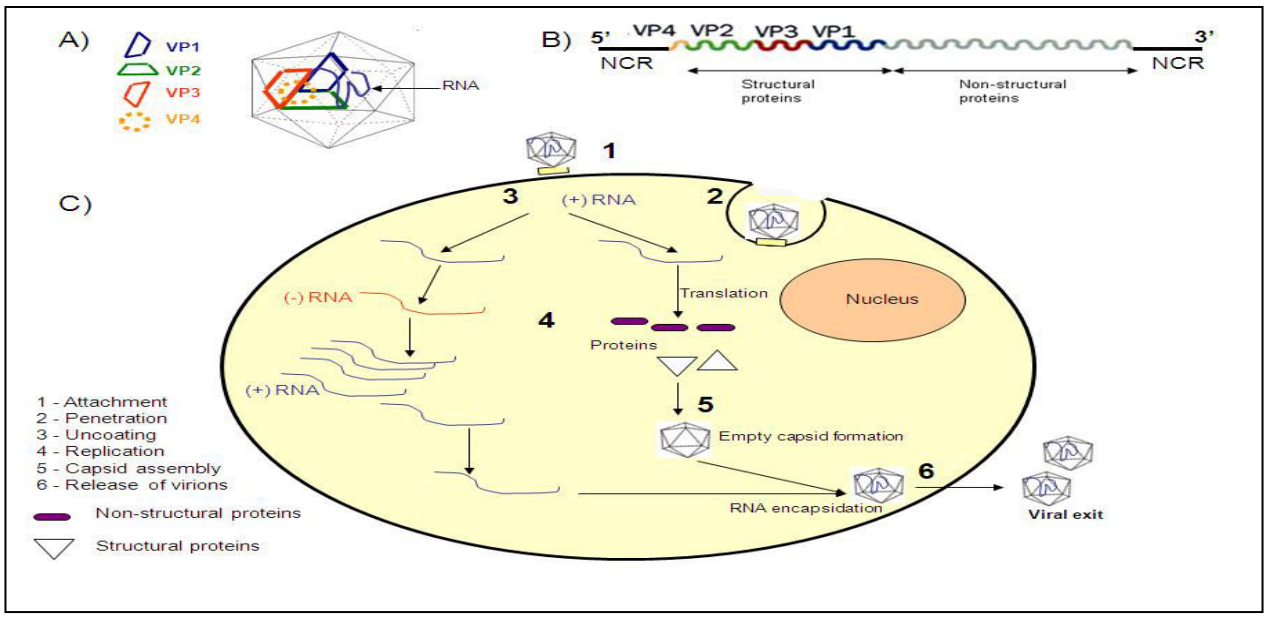
** Features of enteroviruses:

- Positive sense, naked, ssRNA viruses.
- Have an icosahedral capsid that is composed of 4 proteins (VP1, VP2, VP3, VP4).
- Replicate in the cytoplasm (since they're RNA viruses) leading to host cell protein synthesis cessation and cell lysis.
- Resistant to acidic pH and 70% ethanol and ether. This is because they're naked. Naked viruses usually resist harsh environmental conditions like heat and sterilizing agents.

- Genetic variation as a result of mutation and antigenic drift occurs in some strains, altering cellular tropism sometimes. So enteroviruses are prone to antigenic drifts (point mutations that cause variations in viruses due to lack of proof reading that allows mutations to accumulate), but to a lesser extent than in influenza virus i.e. enteroviruses may undergo antigenic drifts , but compared to influenza virus, they are considered stable!

** Replication of +ve sense ssRNA viruses:

Enteroviruses are +ve sense ssRNA viruses; let us remember how this family replicate ☺



Starting from outside the target cell, any virus - whether naked or enveloped - need to attach to receptors on the target cell in order to enter that cell. Enveloped viruses achieve this via glycoproteins known as spikes. Naked viruses such as enteroviruses achieve this via surface proteins or what's known as slits (synonyms: grooves, fissures, canyons), so these canyons attach to receptors on target cells to initiate virus entry into it.

Now the virus is in the cytoplasm. Here, un-coating occurs so that the +ve sense RNA is released into the cytoplasm. Part of this +ve sense RNA

goes directly to ribosomes in order to be translated into structural and non-structural proteins. ❶

What about the genome? How does it replicate? RNA-dependent-RNA polymerase uses part of the +ve sense RNA genome that was released by un-coating to give a –ve sense template. Using this template, new copies of +ve sense RNA genome are produced.❷

The newly produced viral proteins❶ and the new copies of the +ve RNA ❷assemble to produce new virions.

Assembly of ❶+❷ gives new virions.

Notice that the original source of both ❶ and ❷ is the +ve RNA of the infecting virus after being un-coated (❶ by direct translation in ribosomes, ❷ by processing via RNA polymerase as we explained).

Virion - defined by Britannica: an entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid (either RNA or DNA).

** Pathogenesis:

The doctor read the following slide; here's the slide and the doctor's comments about it:

Pathogenesis

- Primary replication occur in epithelial cells and lymphoid tissue of RS and GI, 1ry Viremia
- Spread to CNS, heart, liver, vascular endothelium, lungs, gonads, pancreas, skeletal muscles, synovial tissues, skin and mucous membrane. 2ry viremia may occur.
- Initial tissue damage result from lytic cycle of virus replication.
- Viremia undetectable by the time that symptoms appear
- Termination of virus replication associated with appearance of Abs, interferon and PMNs in infected tissue.
- IgM followed 6-12wks by IgG
- Secondary tissue damage may be immunologically mediated. (pericarditis, nephritis, and myositis) Serology +ve, virus rarely isolated. Tissue damage due to host immune response against the virus or viral antigens that persist in affected tissues.
- Molecular mimicry: viral epitope peptide sequence shared with host tissue/s.

(RS = Respiratory system, PMNs = Polymorphonuclear cells)

Molecular mimicry: Once a person gets infected by an enterovirus, the body starts to produce antibodies (IgM is produced at first, followed by IgG weeks later. Remember that IgG has a role in life-long protective immunity). The antibodies produced attack the virus antigens as well as closely related structures in the body that highly resemble the antigen. That's why the heart, kidneys and muscles may be attacked in certain enterovius infections.

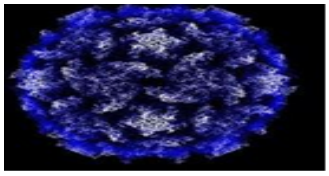
Viremia (primary vs. secondary): The virus enters the primary site of infection (via RS & GIT) and replicates there, then the virus particles are released into the blood stream →primary viremia.

After that, the virus enters secondary sites to replicate again (Each type of enteroviruses has its preferred secondary sites of infection. The ones mentioned in the slide are the secondary sites of infection for ALL enteroviruses collectively; in other words, not every enterovirus replicates secondarily in all these places). After replicating in the secondary site of infection, the virus is released again into the bloodstream →secondary viremia.

An important point is that viremia is undetectable by the time of symptoms appearance. The patient may come to you with certain symptoms that indicate an enterovirus infection, so you send him to the lab for investigation in order to test for viremia to confirm the diagnosis. The results at the time of symptoms onset will be negative, i.e. NO enteroviruses are found in the blood of the patient. This does not exclude the causative agents we're thinking about (i.e. enteroviruses in this scenario). To confirm diagnosis, you should re-do the investigations 24-48 hours later and the microorganism will be detected in the blood clearly.

Enteroviruses cause 50% of all meningitis cases and 90% of aseptic meningitis cases.

** The doctor read the following slide:



Enteroviral Meningitis

- Enteroviruses are thought to be the most common cause of viral meningitis
- Are a diverse group of RNA viruses including Coxsackie A & B, Echoviruses, and polioviruses.
- Account for >50% of cases and approximately 90% of cases in which no specific etiologic agent is identified. Majority of cases are in children or adolescents, but patients of any age can be affected.
- As many as 75000 cases occur in US yearly
- Transmitted primarily by fecal-oral route, but can also be spread by contact with infected respiratory secretions.
- The incidence is increased in the summer months, but cases occur throughout the year.

** Now we'll be discussing some types of enteroviruses in details.

✍ Coxsackieviruses:

The doctor read the following slide; here's the slide with the additional info underlined:

- Coxsackieviruses are distinguished from other enteroviruses by their pathogenicity for suckling rather than adult mice. They are divided into 2 groups on the basis of the lesions observed in suckling mice.
  - Group A viruses produce a diffuse myositis with acute inflammation and necrosis of fibers of voluntary muscles.
  - Group B viruses produce focal areas of degeneration in the brain, necrosis in the skeletal muscles, and inflammatory changes in the dorsal fat pads, the pancreas and occasionally the myocardium.

  Since there are too many coxsackieviruses , a classification for them into two groups was made to make their study easier . This classification is based on the major pathologic effects of the virus after being inoculated into mice . Group A coxsackieviruses is related to myositis , while group B is related to brain degeneration .
- Each of the 23 group A and 6 group B coxsackieviruses have a type specific antigen .Cross-reactivities have also been demonstrated between several group A viruses but no common group antigen has been found.

(Unique antigens for each coxsackievirus with minimum cross-reactivity between them) .

✍ Echoviruses:

The doctor read the following slide; he said that the details mentioned in it are not very important:

Echoviruses

- The first echoviruses were accidentally discovered in human faeces, unassociated with human disease during epidemiological studies of polioviruses. The viruses were named echoviruses (enteric, cytopathic, human, orphan viruses).
- These viruses produced CPE in cell cultures, but did not induce detectable pathological lesions in suckling mice.
- Altogether, There are 32 echoviruses (types 1-34; echovirus 10 and 28 were found to be other viruses and thus the numbers are unused)
- There is no group echovirus Ag but heterotypic cross-reactions occur between a few pairs.

Note: CPE = **C**yto**p**athogenic **E**ffect.

New enteroviruses:

In the late 20th century, 4 new enteroviruses (enteroviruses 68-71) were identified/discovered. The doctor read the following slide , the additional points will be underlined :

- 4 new enteroviruses have been identified (68 - 71). Enterovirus 68 is associated with respiratory illness and share Enteroviral and Rhinoviral structures (Remember that Rhinovirus causes respiratory tract infections manifested as common cold . Rhinovirus belongs to Picornaviridae family which is the family of enteroviruses as well and that's why they are related .) Enterovirus 70 is the causative agent epidemics of acute hemorrhagic conjunctivitis that swept through Africa, Asia, India and Europe from 1969 to 1974. The virus is occasionally neurovirulent.
- Enterovirus 71 appears to be highly pathogenic and has been associated with epidemics of a variety of acute diseases, including aseptic meningitis, encephalitis, paralytic poliomyelitis-like disease and hand-foot-mouth disease.
- Enterovirus 72 was originally assigned to hepatitis A virus, but it had now been assigned to the genus hepatoviruses of the Picornaviridae family (this virus is no longer classified as enterovirus) .

Let's revise!

New Enterovirus	Manifestations
68	Respiratory tract infections
70	Hemorrhagic conjunctivitis
71	A range of diseases: • Aseptic meningitis • Encephalitis • Paralytic poliomyelitis – like disease • Hand – foot – mouth disease
72	This is hepatitis A! Thus no longer classified as enterovirus. It's a hepatovirus of the Picornaviridae family.

Disease associations:

** The following table shows different diseases and their degrees of association with different enteroviruses. The doctor mentioned them ALL:(cox here refers to coxsackieviruses)

Diseases associated with Enteroviruses

Syndrome	Polio	Cox A	Cox B	Echo
Paralytic disease	+	+	+	+
Meningitis-encephalitis	+	+	+	+
Carditis	+	+	+	+
Neonatal disease	–	–	+	+
Pleurodynia	–	–	+	–
Herpangina	–	+	–	–
Rash disease	–	+	+	+
Haemorr. conjunctivitis	–	+	–	–
Respiratory infections	+	+	+	+
Undifferentiated fever	+	+	+	+
Diabetes/pancreatitis	–	–	+	–

It's clear from the table that paralytic disease, meningitis-encephalitis as well as undifferentiated febrile illness are seen in all types of human enteroviruses.

The doctor commented that diabetes and pancreatitis are seen in cox B infections due to molecular mimicry. The antibodies produced against cox B antigens might attack the pancreas leading to pancreatitis and diabetes.

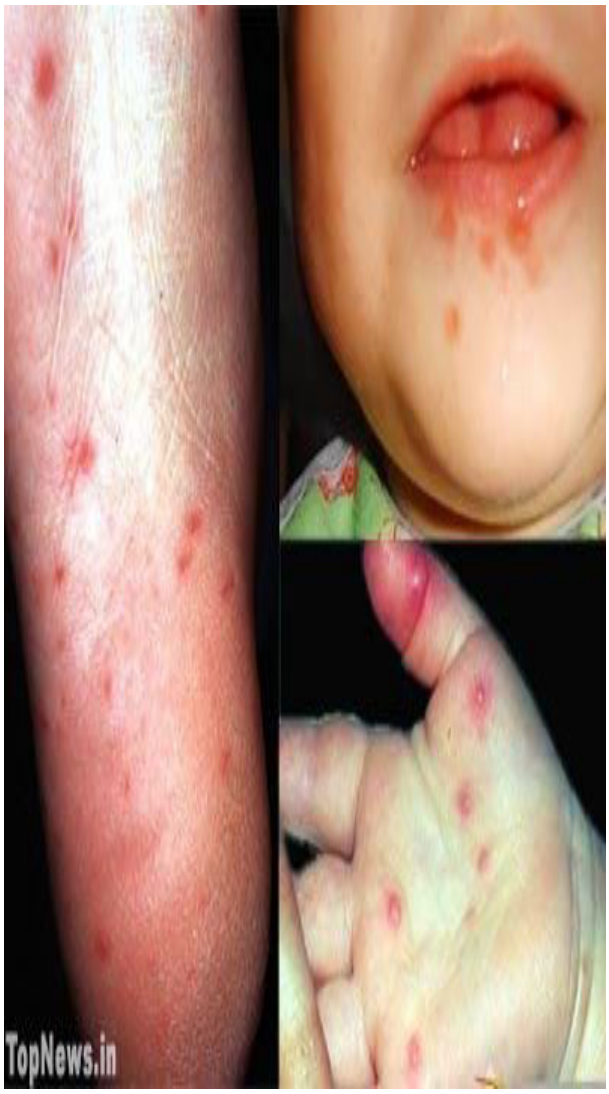
**Note from Greenwood: The Enterovirus genus is classified into Human Enteroviruses and Human Rotaviruses. Human enteroviruses are classified into 4 subgroups: Coxsackieviruses A & B, Polioviruses, and echoviruses.

Hand – foot – mouth disease: Usually caused by group A Coxsackieviruses. Other less common microorganisms that can cause this disease are group B coxsackieviruses and enterovirus 71. This disease is manifested by rash in the palms of the hands, the soles of the feet and around the mouth (oral cavity) – see the figure.

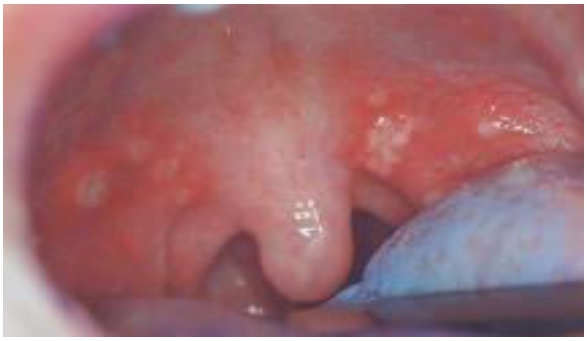
على باطن الكف و القدم و حول الفم

It's associated with fever, sore throat, loss of appetite and diarrhea. It's a self – limiting disease, thus, there is no need for medical intervention or treatment. Symptomatic treatment/relief can be provided to alleviate symptoms, such as fever, that requires antipyretics. It resolves within 7-10 days without any sequela. {Sequela – defined by Wiki and Merriam-Webster: it is an aftereffect of a disease/injury. It usually manifests late after the initial acute condition}.

** Note: the rash developing around the mouth or oral cavity can be given the term "circumoral". Circumoral rash is a rash surrounding the mouth.



Herpangina: Caused by group A coxsackievirus. It's characterized by lesions in the upper palate, pharynx, and tonsillar area. These lesions start off as vesicles that ulcerate with time. Herpangina is associated with fever and sore throat. It's a self-limiting condition that heals in 1 week.



✎Epidemic Pleurodynia (Bornholm disease) is normally caused by group B coxsackieviruses. It's characterized by fever, sudden pain in lower abdomen or thoracic region. It lasts for 14 days.

✎ Myocarditis → Group B coxsackieviruses mainly but may be caused by other enteroviruses.

✎ Respiratory infections → several enteroviruses, especially enterovirus 68.

✎Rubelliform rashes: a rash disease resembling rubella may be seen with several coxsackie A, B, and echoviruses.

✎Neonatal infection → A few coxsackie B viruses.

✎Conjunctivitis →Coxsackievirus A and enterovirus 70 (causes hemorrhagic conjunctivitis).

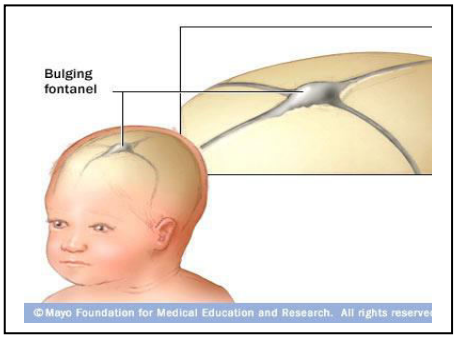
✎Pancreatitis and diabetes →Coxsackievirus B.

✍ Common symptoms noticed in meningitis:

- Fever
- Headache
- Stiff neck
- Photophobia
- Nausea/vomiting
- Can also include rash, URT symptoms preceding the illness (a viral example is enterovirus 68), abdominal pain, and diarrhea.

Remember that any one is prone to meningitis and these are the symptoms that will appear, but as mentioned previously, children<5years are at more risk . In newborns and children ≤2 years, other signs are present; such as poor feeding, irritability, crying all the time as well as bulging fontanel noticed after physical examination – see the figure below .

A fontanelle (or fontanel) is an anatomical feature of the infant human skull comprising any of the soft membranous gaps (sutures) between the cranial bones that make up the skullcap of a fetus or an infant. Fontanels close months after delivery.



Physical exam:

Can vary depending on the etiology (+/- means might or might not be present):

- +/- Fever
- +/- Lethargy
- +/- Kernig's sign
- +/- Brudzinski's signs

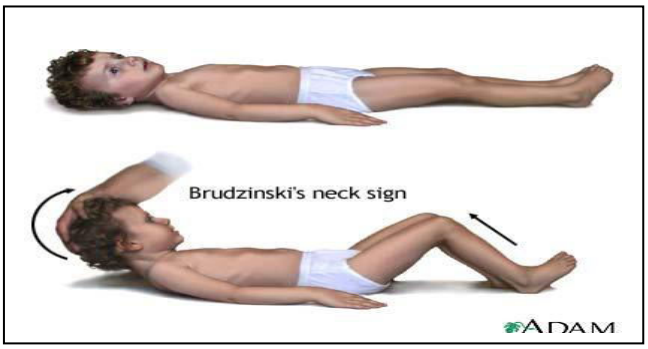
This angle doesn't exceed 135 in meningitis and if the case is severe, it won't exceed 90 (this is +ve Kernig's sign indicating meningitis).

Kernig's sign:

The patient must be in the supine position (lying flat on one's back). You try to extend the knee at the knee joint while the thigh is flexed at the hip joint (notice the figure). In case of meningitis, knee extension will lead to meningeal irritation and pain so that the patient will resist the movement you're trying to do. As a result, in case of meningitis, the angle (marked in the figure) will NEVER EVER reach 180° i.e. complete knee extension will not take place. If the meningeal irritation was slight, the angle may reach a maximum of 135°. In cases of severe meningeal irritation, the angle will not go beyond 90°.

Brudzinski's sign:

The patient is in the supine position. Try to flex the head of the patient. If there's meningitis, head flexion leads to meningeal irritation and placing high pressure on the meninges. The patient responds by bending his knee in order to relief this pressure and irritation.



The doctor reminds you that other tests and investigations must be done to confirm the diagnosis precisely. Positive Brudzinski's sign or Kernig's sign alone isn't enough. The presence of other symptoms must also be confirmed for proper and accurate diagnosis.

✍ Laboratory findings:

These are the contents of CSF after being sent into labs in different cases. I incorporated doctor's comments in the table and modified it a bit compared to the one in the slides, so please study it carefully ☺(arrows indicate increase or decrease compared to normal value).

	Leukocyte/mm3	% PMN	Glucose % of blood	Protein (mg/dl)
Normal	0-5	0	≥ 60	≤ 30
Viral infection	↑ 2-2000 (avg is 80)	≤ 50	≥ 60	↑ 30-80

Bacterial infection	↑ 5-5000 (avg is 800-1000 i.e. ten times more than in viral infection)	≥ 60	↓ ≤ 45 (less than in viral infection thus this feature differentiates between them)	↑ >60
TB and fungal	↑ 5-2000 (avg is100)	≤ 50	↓ ≤ 45(less than in viral infection so this feature differentiates between them)	↑ >60
neonate	0-32 (avg is 8) Leukocyte number is not increased because the immune system isn't well – developed thus it won't respond appropriately by increasing WBCs as occurs in adults.	≤ 60	≥ 60 (might be elevated)	↑ 20-170 (avg is 90) Very high protein level, the HIGHEST compared to elevation due to other causes and to elevation in other age groups.

Diagnosis:

- Virus isolation.
- PCR: The most specific and common diagnostic tool.
- Serology: Very rarely used for diagnosis.

✍ Management and prevention: involved in viral aseptic meningitis ☺

The doctor read the following slide; additional info will be underlined:

- There is no specific antiviral therapy available against enteroviruses other than polio (He than said that even for polio there's no specific antiviral treatment) .
- Some authorities use IVIG (intravenous immunoglobulin) in the treatment of neonatal infections or severe infections in immunocompromised individuals. However, the efficacy is uncertain.
- IG has been used to prevent outbreaks of neonatal infection with good results (Intravenous immunoglobulins are used in outbreaks to minimize the number of cases) .
- For severe enteroviral infections a new investigational drug named Pleconaril (YOU HAVE TO KNOW THE NAME OF THIS DRUG) which works by integrating into the capsid of picornaviruses, including enteroviruses and rhinoviruses, preventing the virus from attaching to cellular receptors and uncoating to release RNA into the cell, has been shown in limited

We have finished enteroviruses and now we'll discuss another viral etiologies of aseptic meningitis :

✍ Herpes simplex meningitis:

The doctor read some slides then he explained some concepts, this is the slides' content with the additional info underlined:

- Generally caused by HSV-2 (as opposed to encephalitis, which is mostly caused by HSV-1)– We'll compare encephalitis and meningitis next lecture
- dsDNA virus
- The main route of transmission for HSV-2: Sexual transmission.
- Increasingly recognized as a cause of aseptic meningitis, with improving diagnostic techniques and a continued increase in the transmission of HSV-2
- Can be due to primary or recurrent HSV infection
- Between 13 and 36% of patients presenting with primary genital herpes have clinical findings consistent with meningeal involvement including headache, photophobia, and meningismus. The genital lesions are typically present (85% of the time), and usually precede the CNS symptoms by seven days.
- HSV meningitis can be recurrent; these patients may not have clinically evident genital lesions. For patients with benign recurrent lymphocytic

meningitis, careful analysis has revealed that over 80% are due to HSV meningitis. Explanation: There are two scenarios; the first case describes meningitis that is associated with primary herpes infection in which genital lesions (ulcers and vesicles) are always present making the identification of the causative agent easy. Once you see genital lesions in a patient with meningitis you can easily conclude that the causative agent is HSV-2. The second case is meningitis that's associated with recurrent herpes infection in which the genital lesions are not always present and accordingly the identification of the causative agent will be more difficult.

- CSF- typical of viral meningitis, with lymphocytic pleocytosis, modest elevation in protein, and normal glucose. Viral cultures are + in approx. 80% of patients with primary HSV meningitis, but less frequently positive in patients with recurrent HSV meningitis.
- HSV PCR of the CSF is the single most useful test for the evaluation of a patient with suspected HSV meningitis (we conclude that PCR is the most reliable way of diagnosis in both enteroviruses and herpes viruses).
- Most cases are self-limited and will require only symptomatic treatment.

- Antiviral therapy is recommended in patients with primary HSV infection or with severe neurological symptoms. Treatment depends mainly on the presentation of the patient, but ONCE you suspect herpes virus infection, you should IMMEDIATELY administer IV acyclovir. Why is that? Herpes virus (especially in infants) might lead to meningoencephalitis (encephalitis + meningitis). Although meningitis may not be that severe in this case, the brain could be damaged **(liquefied – كأنّ الدماغ يذوب)** due to encephalitis. Brain liquefaction seen with encephalitis is associated with high mortality rate. The problem is that you can't clinically differentiate meningitis from encephalitis i.e. you can't expect at which time the virus may spread to the brain parenchyma and liquefy it, that is why immediate acyclovir administration must be done.

  Keep in mind that both meningitis and encephalitis can be caused by any of the herpes viruses (HSV1 and HSV2), however; meningitis is **mostly** caused by HSV-2 and encephalitis is **mostly** caused by HSV-1 (There are NO generalizations in medicine).

✍ HIV meningitis:

The doctor read some slides; this is the slides' content with the additional information underlined:

- A subset of patients with primary HIV infection will present with meningitis or meningoencephalitis, manifested by headache, confusion, seizures or cranial nerve abnormalities.
- ssRNA retrovirus
- Serum might reveal an atypical lymphocytosis, leukopenia, and elevated serum aminotransferases. Documentation of seroconversion or detection of HIV plasma viremia by nucleic acid techniques can be used for diagnosis.
- CSF- might show a lymphocytic pleocytosis, elevated protein, and normal glucose. CSF cultures are often positive, but are not available in most centers.
- The meningitis associated with primary infection resolves in most patients without treatment, and patients are typically assumed to have benign viral meningitis. This occasionally leads to missing the diagnosis of HIV.

Explanation: HIV infection is characterized by a primary (early) stage during which flu-like symptoms and other non-specific symptoms might appear. This early stage is followed by long incubation period (10-15 years). HIV meningitis may occur during the early stage of HIV infection. It could be the only thing the patient complains of during this stage! Commonly it's mistakenly diagnosed as transient viral meningitis irrelevant to HIV and thus the diagnosis of HIV will be missed. If it's correctly diagnosed as HIV-related meningitis, early detection of HIV will improve its prognosis and anti-retroviral drugs will be administered.

✍ Lymphocytic Choriomeningitis Virus (LCM):

The doctor read some slides; this is the slides' content with the additional info underlined:

- LCM is thought to be an underdiagnosed cause of viral meningitis, in one review it was noted to be responsible for 10-15% of cases.

- ssRNA virus of the arenavirus group
- LCM is excreted in the urine and feces of rodents, including mice, rats, and hamsters (that probably includes Jorge's hamster Houdini). It is transmitted to humans by either direct contact with infected animals or environmental surfaces. Infection occurs more commonly in the winter months.LCM is mainly a virus of rodents; an infected rodent transmits the virus to its offspring (i.e. vertical transmission). Humans get infected by contact of feces that belong to the infected rodents. The chance of rodent-to-human transmission increases in poor hygienic conditions.
- Symptoms generally include influenza-like illness accompanied by Headache and meningismus. A minority of patients develop orchitis, parotitis, myopericarditis, or arthritis.
- CSF- typical of other viral meningitis causes except that 20-30% of the time low glucose levels are present, and cell counts of > 1000/mm3 are not unusual (Referring to the table about CSF findings, we'll notice that the number of leukocytes count is increased in viral infections to reach 80-100 in average, here in LCM it's about 1000 i.e. increase is above the average. A drop in glucose level is also noticed in LCM infection).
- Diagnosis is made by documentation of seroconversion to the virus in paired serum samples.
- Most patients will recover spontaneously.
- There is no specific anti-viral therapy available presently.

✍ Mumps meningitis:

The doctor read the following:

- Caused by paramyxovirus which is a ssRNA virus
- Prior to the creation of the mumps vaccine in 1967, it accounted for 10-20% of all cases of viral meningitis.
- Even now this virus causes a significant minority of cases in unvaccinated adolescents and adults.
- In patients who do acquire mumps, CNS infection occurs rather frequently, with CSF pleocytosis detected in 40-60% of patients, and 10-30% of those have clinical signs and symptoms of meningitis.
- CSF- similar to other viral causes, but like LCM it can induce a lymphocytic pleocytosis with cell counts >1000/mm3 or a decreased glucose <50mg/dl, can isolate the virus from the CSF

- Can document seroconversion.
- Clinical correlation is very helpful, ex. If the patient has parotitis or orchitis.
- Most cases resolve without serious sequelae, and there is no specific therapy available.

Miscellaneous viruses:

- West Nile Virus, St Louis Encephalitis, California Encephalitis, primary VZV, outbreaks of herpes zoster ,EBV ,CMV, and adenoviruses.
- Less common causes of meningitis, but they do occur. In most cases the course is self-limited, and the treatment is supportive in nature.

End of the sheet ! If you find any mistake or imprecise information feel free to inform me ☺ Good luck !

" خطوة واحدة، واحدة فقط، كان عليه أن يمشيها بَعدُ ، كي يرى "