

MICROBIOLOGY

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Number

1

Subject

Aseptic Meningitis

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Aseptic Meningitis

This sheet was written according to the record of section 1, the order is very different from the record and hopefully made easier.

Some terminology:

Asepsis – It means sterility (absence of microorganisms)

Aseptic Meningitis: Refers to patients who have clinical signs & laboratory evidence for meningeal inflammation with **negative** routine bacterial cultures (from CSF or blood).

What's the difference between meningitis and encephalitis?

- Meningitis: Inflammation of membranes of brain or spinal cord.
- Encephalitis: Inflammation of brain matter itself.

It's hard to differentiate between meningitis and encephalitis and there is an overlap between them both and is diagnosed as “meningoencephalitis” in most of the times.

- One of the findings that are found in **encephalitis** and not in meningitis is “altered level of consciousness”.

What are the causes of aseptic meningitis?

- ❖ Viruses (most common cause)
- ❖ Atypical bacteria (e.g. Borrelia, Mycobacteria)
- ❖ Drugs (e.g. NSAIDs)
- ❖ Malignancies (e.g. Lymphomas, Leukemias)

What are the viruses that cause aseptic meningitis?

Enteroviruses, Arbovirus, Herpes Simplex virus, Lymphocytic Choriomeningitis (LCM), Measles, Mumps, and others...

Enteroviruses

- Most common cause of viral meningitis (90%), 50% cause of overall meningitis.
- Coxsackie's & Echovirus are the most common
- Humans are reservoir for these viruses
- Can infect anyone, but mostly in children with bad hygiene.
- Transmission is fecal-oral; (Occurs in babies that wear diapers when the person taking care of them change the diaper for one baby and then feed the other)
- Transmission can also be via direct contact with another person's RS secretions
- Incidence increase in summer months
- Incubation period: 2-6 days

(Enteroviruses is NOT a family, it is part of RNA viruses family called Picornaviridae)

Arbovirus

- It is part of the arthropod-borne viruses
- Transmission: Animal viruses (transmitted to human when coming into contact with animals via arthropod, bird **or** tick vector)
- Incubation period: 1-2 weeks

*(When talking about arthropod-borne viruses, we must concern about **encephalitis**, but in case of Arbovirus we take meningitis into consideration.)*

- ❖ The proportion of infected people developing illness varies from 2-100%.
- ❖ Infections with enteroviruses or arbovirus are mostly asymptomatic.

Let's talk more about the Enteroviruses in general...

Enteroviruses are classified into:

- **Polio enteroviruses** (We will talk about them in the coming lectures...)
- **Non-polio enteroviruses** – and these include:
 - Coxsackievirus A (23 types)
 - Coxsackievirus B (6 types)
 - Echovirus (32 types)
 - New Enteroviruses 68, 69, 70, 71

Picornaviridae family includes:

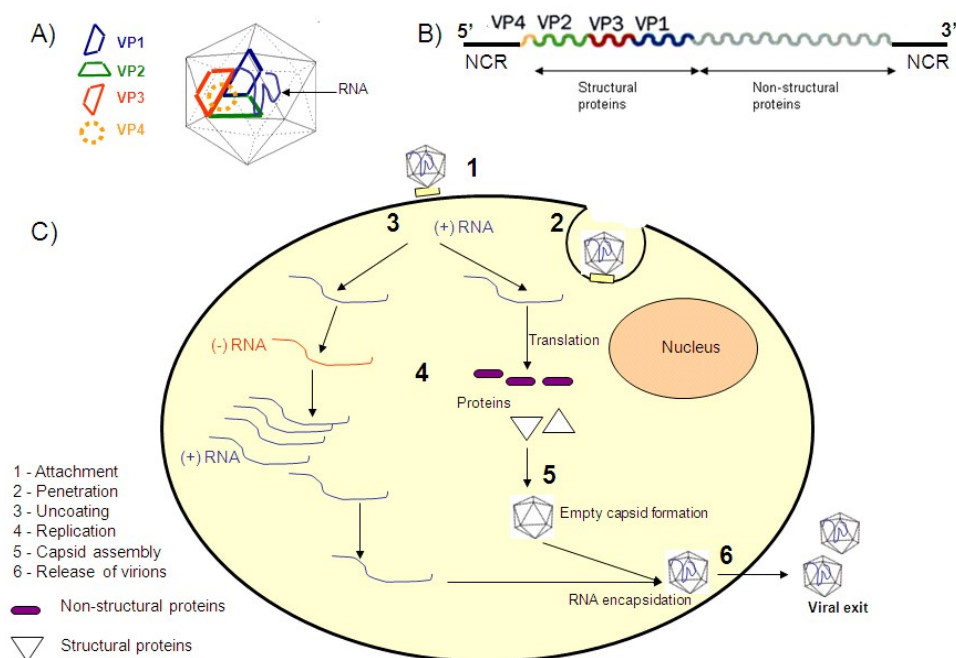
- 1) Enteroviruses
- 2) Rhinovirus
- 3) Hepatitis A (ex-enterovirus 72)

(“Enterovirus 72” was considered a non-polio enterovirus in the past but not anymore, although it's still in the picornaviridae family as “Hepatitis A”)

Genetic features of Enteroviruses:

- (+sense) ssRNA
- Icosahedral capsid with 4 proteins; VP1, VP2, VP3, VP4.
- Naked → Unenveloped viruses are more resistant to environmental changes.
- Resistant to acidic pH
- **Stable viruses** generally talking, although genetic drifts might occur sometimes (*RNA viruses replicate by “RNA-dependant RNA polymerase” enzyme which lacks proofreading and introduces a single mutation every 2,500 - 10,000 bps*)

Replication cycle



- 1) **Attachment:** Naked viruses don't have spikes/glycoproteins, they have grooves on their capsid called canyons (or slits), these interact with receptors on cell surface
- 2) The virus will enter the cell via receptor-mediated endocytosis
- 3) **Replication:** The virus will release (+sense) RNA that will undergo two processes:
 - ➔ Part will be used as mRNA and be translated into proteins by the ribosomes.
 - ➔ Part will be used to generate (- sense) RNA that will act as a template to form many copies of (+sense) RNA.
- 4) **Assembly**
- 5) **Release of the virus into blood**

Spreading (Fecal-Oral route) & Pathogenesis

- Primary replication occur in epithelial cells & lymphoid tissue of RS & GI tracts (e.g. In the oropharynx) then they leave to the blood. (**Primary viremia**)
 - **All enteroviruses** can cause the following diseases meningitis, encephalitis, carditis, paralytic disease, Upper RS tract infections, & undifferentiated fever.
- Some other organs are targeted only by specific types of enteroviruses; they replicate in these organs and leave to the blood again. (**Secondary viremia**)
- **Initial tissue damage:** Naked viruses prevent protein synthesis in the host cell, and by shedding out of the cell they cause cell lysis.
- **Secondary tissue damage:** They also use molecular mimicry; the virus mimics antigens in your own body resulting in cross-reaction of antibodies attacking proteins in your own organs.

Diagnosis

- ❖ When the symptoms start to appear, viremia will no longer be detected in blood, so using PCR to check virus levels in blood will be useless.
- ❖ Antibodies against enterovirus antigens will start to appear during seroconversion (once the virus has stopped replication).
 - IgM followed by IgG after 6-12 weeks.

Seroconversion: when antigens of the virus become detectable by the body, thus stimulating the immune system to produce Abs.

Now let's talk about different types of Enteroviruses...

Coxsackieviruses

- Coxsackie A has 23 types while Coxsackie B has 6 types, each with a specific antigen (There is no antigen that is common in all coxsackieviruses).
- Diagnosis: These viruses are hard to be found by cell culturing, so they are distinguished by introducing the virus into suckling mice:
 - ➔ If the mouse showed symptoms of myositis or muscle necrosis then it's **coxsackievirus A**.
 - ➔ If the mouse showed symptoms of brain damage or meningitis then it's **coxsackievirus B**.

There is some cross-reactivity between some types of coxsackieviruses due to similarity between their antigens. → *e.g. Giving antibodies to treat coxsackievirus A16 can be used to treat illnesses caused by coxsackievirus B3.*

Echoviruses (Orphan viruses)

- Enteric, cytopathic, human, orphan viruses.
- There are 32 types and cross-reactivity can happen between some types.
- There is no group antigen that is common for all types.
- They were discovered accidentally when a research about polio viruses was carried on.
- Called orphan viruses because they were not linked to any illnesses in that time. (Although they are linked to some illnesses now).
- Diagnosis: They produce cytopathic effect in cell cultures.

New Enteroviruses

What illnesses do these enteroviruses cause?

Enterovirus 68 → Upper RS tract infection (due to structural similarity with rhinovirus)

Enterovirus 69 → No illness

Enterovirus 70 → Haemorrhagic conjunctivitis

Enterovirus 71 → Meningitis, encephalitis, poliomyelitis-like disease, hand-foot-mouth disease

Hand-foot-mouth disease

There have been some reported cases in the last few (2-3) years.

The typical picture presentation:

- Rash on the oral region, on the palms of hands & soles of foot
- Ulcerative lesions in the oral cavity (sore-throat) → Severity varies between children; these lesions make it painful to swallow food in some patients.



It can affect any person who has never been infected with the virus and then came in contact with an infected one, but it mostly affects children (<5 years).

* In adults → afebrile

* In children → febrile illness (with fever)

P.S.) It's not always the typical picture!

e.g. The rash might be on the dorsum of hands/feet, fever might or might not be present, variety in number of lesions, etc...

Causes:

- 1) Coxsackievirus A (most common cause)
- 2) Coxsackievirus B
- 3) Enterovirus 71

The disease is self-limiting and treatment is symptomatic (antipyretics, painkillers, etc..)

Herpangina



A disease that resembles hand-foot-mouth disease by having the lesions inside the oral cavity (especially in the upper palate), but with **no rash**.

* Caused by coxsackievirus A.

* The disease is self-limiting.

Other diseases associated with Enteroviruses:

Pleurodynia – Coxsackievirus B

- (Inflammation in the pleural space)
- Fever, sudden pain in lower abdominal or thoracic region.
- Self-limiting and resolves in 1-2 weeks.

Myocarditis – Coxsackievirus B

Rubelliform rashes – Coxsackieviruses A, B, and echoviruses.

- (rash resembling rubella)

Pancreatitis/Diabetes - Coxsackievirus B (molecular mimicry)

Neonatal infections

Viral Meningitis

Now we will start talking about meningitis caused by different viral agents...

Symptoms

Fever • Headache • Lethargy

Stiff neck • Photophobia

Nausea/vomiting • Abdominal pain • Diarrhea

In children: Fever can be the only presentation and sometimes accompanied by irritability, poor feeding & poor sleeping.

→ When a child presents with fever, you have to locate the inflammation in (lungs, pharynx middle ear, urinary tract, etc...) if inflammation is excluded from all these areas then go for an LP (Lumbar puncture) to check for meningitis.

Physical examinations

If a child presents to you with fever & lethargy and you suspect meningitis you do these physical examinations on him:

❖ **Kernig's sign**

Look at the photo in order to be able to imagine and understand...



- 1) You tell the patient to lie supine (يتمدد)
- 2) Flex his hip & flex his knee
- 3) Now keep the hip flexed and try to extend his knee to make knee angle **180°**
- 4) If the patient resists this movement due to pain then he got meningitis;

(This pain is a result of the inflammation and by extending his knee you put pressure on this inflammation and the patient relieves that pain by not letting you extend it.)

❖ **Brudzinski's sign**



- 1) You tell the patient to lie supine
- 2) Flex his neck → If he elevates his knees to relieve the pain then he got meningitis.

Lab findings in the CSF

	Leukocytes	Polymorphonuclear cells (PMNs)	Glucose (% in blood)	Proteins (mg/dL)
Normal	0	0	> 60	30
Viral	100	< 50	> 60	Remain or increase
Bacterial	1000	> 60	< 45	Increase
TB & Fungal	100	< 50	< 45	Increase
Neonates	0			<u>V. HIGH (>90)</u>

Diagnosis

The diagnosis of meningitis is by clinical symptoms.

To know that causative agent of meningitis, you take a CSF sample and send it to the lab for culturing → The gold standard for diagnosis is PCR.

Serology: rarely used.

Treatment & Prevention

- ❖ There are no specific antiviral drugs for enteroviruses, so treatment is symptomatic.
- ❖ There are no vaccines for enteroviruses, except for polio.
- ❖ Immunoglobulins can be given to immunocompromised.
- ❖ ***Pleconaril***: A new antiviral drug that works against picornaviridae viruses;
 - In rhinoviruses: inhibits the uncoating step.
 - In enteroviruses: it prevents their attachment to cell-surface receptors.

Now, we'll talk about meningitis caused by other viruses...

Herpes Simplex Meningitis

- ds-DNA virus
- HSV-1: More associated with encephalitis.
- HSV-2: More associated with meningitis.
- (Although both viruses can cause either illnesses)
- Can be primary or recurrent HSV infection (HSV is characterized by latency);
 - ⇒ ***In primary infection:*** There will be genitals infections, making it easier to diagnose meningitis that is caused by HSV.
 - ⇒ ***In recurrent infection:*** No genitals infection so it's going to be harder for the physician to diagnose HSV-meningitis.
- Diagnosis: CSF findings typical of viral meningitis, PCR to determine the viral agent.
- Treatment: In most cases just symptomatic treatment will be enough, **but** whenever you diagnose meningitis caused by HSV then give him “**IV acyclovir**”, that is because HSV-meningitis might lead to encephalitis (which causes brain liquefaction with very high mortality rate).

HIV Meningitis

- (+sense) ss-RNA retrovirus
- Diagnosis: Serum → lymphocytosis, leukopenia, high protein level.
CSF → typical of viral meningitis.
- Treatment: Self-resolving, symptomatic treatment.

Important) One of the presentations of primary HIV infection is severe flu-like symptoms, but as we said it's not always the typical picture when it comes to presentation, sometimes meningitis can be the only presentation of HIV! So if someone having unprotected sex presented to you with meningitis, you as a physician should highly expect HIV and dig deeper to find the causative agent of meningitis.

(His meningeal symptoms & you being a clever physician helped in diagnosing HIV in a person with no HIV symptoms)! :))

Lymphocytic Choriomeningitis (LCM) Meningitis

Excreted in urine or faeces of rodents (فئران); faeces can dry out and become air-borne and you might inhale them without even noticing. Always link the symptoms of meningitis with history/environmental factors (e.g. In India, rodents live side-by-side with people).

- ss-RNA arenavirus
- Biphasic infection stages:
 - ⇒ Phase 1, patient will present with flu-like symptoms.
 - ⇒ Phase 2, while the patient is recovering from phase 1 or 2-3 days after recovery, he'll start to develop meningitis symptoms.
- Diagnosis: CSF → Typical viral findings (except sometimes with leukocytes >1000 and low glucose level). Serum can also help in diagnosis.
- Treatment: Self-limiting, symptomatic treatment.

Mumps Meningitis

- ss-RNA paramyxovirus
- Mumps can cause **parotitis** (unilateral or bilateral inflammation of the parotid gland) or **orchitis** (inflammation of the testis) which can complicate into meningitis.
- Diagnosis: CSF → Typical viral findings (except sometimes with leukocytes >1000 and low glucose level).

CSF pleocytosis in 40-60% of patients & 10-30% of those have meningitis symptoms.

Seroconversion is present; mumps antigens can be detected by antibodies.

- Treatment: Self-limiting, symptomatic treatment.

Other viruses that cause meningitis but very rarely:

Varicella Zoster Virus, EBV, CMV, Measles, etc...

Treatment for all these viruses is just symptomatic.

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Good luck :')