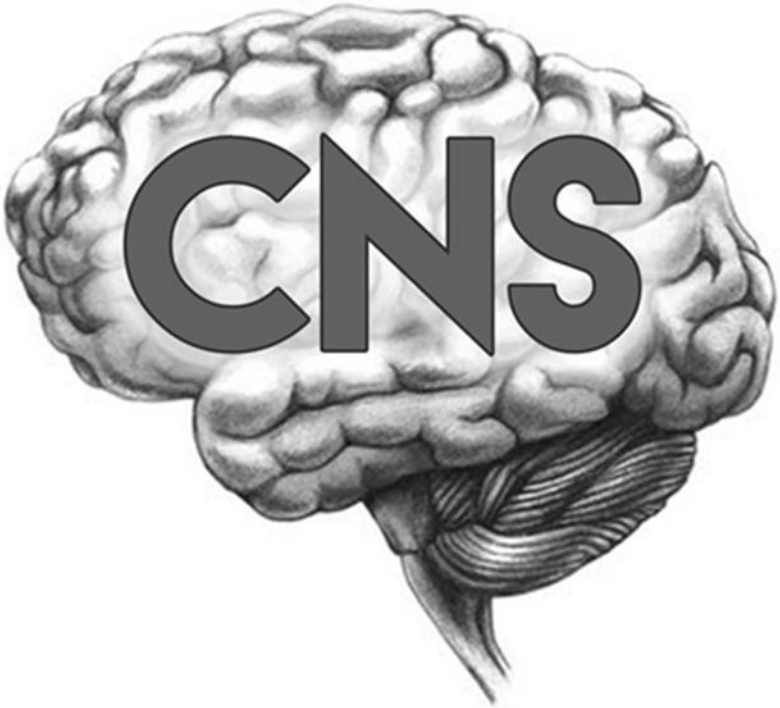

MICROBIOLOGY

☑ Sheet ○ Slide ○ Handout

Number

3

Subject

Poliovirus & Rabies virus

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Poliovirus & Rabies virus

This is really one of the most interesting and easy lectures for Dr. Ashraf :')
The sheet was written according to the record of section 3, the order is very different from the record and hopefully made easier.

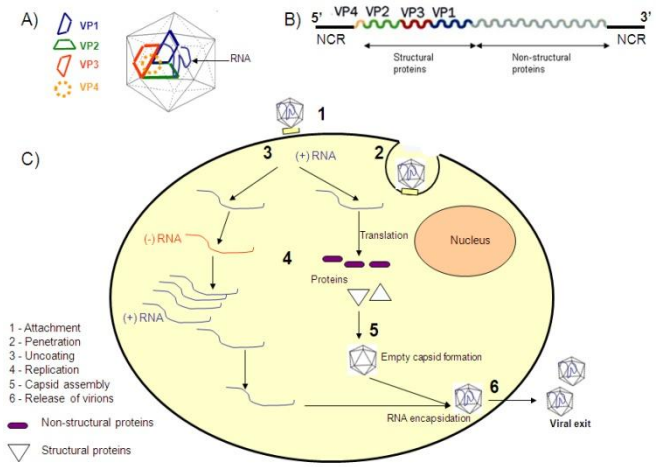
❖Polioviruses (شلل الأطفال)

They belong to Picornaviridae family, to the genus Enteroviruses.
(Remember: Enteroviruses is NOT a family)

As all enteroviruses, polioviruses are transmitted via a fecal-oral route.

Let's remember some general information about Enteroviruses…

- Humans are the only reservoir for these viruses
- Can infect anyone, but mostly in children with bad hygiene.
- Transmission is fecal-oral; (Contaminate food & water).
- (+sense) ssRNA
- Icosahedral capsid with 4 proteins; VP1, VP2, VP3, VP4.
- Naked → Unenveloped viruses are resistant to environmental changes, e.g. acidic pH.
- **Stable viruses** generally talking, although genetic drifts might occur but rarely.
- 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 generate (- sense) RNA as templates for many copies of +sense RNA.

4) Assembly, then release of the virus into blood.

Let's get back talking specifically about polioviruses…

- It was first identified in 1909 by inoculation of specimens into monkeys.
- The term derives from the Ancient Greek word "polios" meaning "grey", myelós meaning "marrow", referring to the grey matter of the spinal cord, and suffix -itis, which denotes inflammation. (so it's **inflammation of the grey matter of CNS**)
- It has 3 serotypes (1, 2, 3), they all share the same physical properties but there is no common antigen; That means that infection by one doesn't give immunity against the other two. (The vaccine should include all three serotypes).

  Serotype #1 (PV1) is the most common form in nature and associated with paralysis, however all three forms are extremely infectious and can cause paralysis.
- Humans are the only host for the virus, and that makes it easier to eradicate it.

  There has been some campaigns launched by the WHO in order to eradicate it, but there are some asymptomatic carriers that can carry the infection but fortunately, they transmit the virus to immunized people,
  If someone who is <u>immunized</u> got infected with the virus:-

  - 90-95% of infected people will be asymptomatic carriers
  - 5-10% will develop acute, minor flu-like illness, or minor non-paralytic meningitis
  - 0.1-1% will have a chance to develop paralysis. *(So even with the vaccine, there is a very small percentage that the person will develop paralytic polio disease).*

  There haven't been any reported cases in the last 20 years in our country, but if any interruption occurs that prevent people from visiting health centres in order to get the vaccine, for example (wars & high costs), asymptomatic carriers will transmit the virus to <u>un-immunized</u> people, therefore, there will be a higher percentage for the infected persons to develop paralysis.
- It was globally distributed before the development of immunization, and almost all the population did get infected before the age of 5 years.
- Nowadays, the vaccine is applied worldwide and covers almost the whole globe, except for 4 African countries, Pakistan, and the new outbreaks in Iran & Syria due to war conflicts and refugee crisis.

Pathogenesis

- Incubation period: 6-20 days
- Transmission is fecal-oral; (replicates in the oropharynx or GI tract)

It replicates in the oropharynx then is transmitted to the saliva that enter your GI tract upon swallowing, Poliovirus divides within gastrointestinal cells for about 1 week, from where it spreads to the tonsils, intestinal lymphoid, M cells of Peyer's patches, and the deep cervical and mesenteric lymph nodes, where it multiplies abundantly.
The virus is subsequently absorbed into the bloodstream (transient viremia).

As we said, in 90-95% of the viremic cases it's asymptomatic, and a chance of 5-10% that viremia will cause **abortive infection**, characterized by minor flu-like symptoms which is self-limiting and in a minority of cases the virus may involve the CNS, causing non-paralytic aseptic meningitis. And only 0.1-1% develop major illness.

♧ Paralytic polio (The major illness, 0.1-1% of infections)

- ✓ It presents 2-3 days after abortive infection (minor symptoms) **or** it can present suddenly without any minor symptoms.
- ✓ Poliovirus spreads along certain nerve fibre pathways, preferentially replicating, destroying motor neurons within the spinal cord, brain stem, or motor cortex.
- ✓ **Early symptoms** include high fever, headache, stiffness in the back and neck, asymmetrical weakness of various muscles, difficulty swallowing & muscle pain.
- ✓ Paralysis generally develops 1-10 days after early symptoms begin, progresses (keeps increasing) for 2-3 days.
- ✓ Progression is complete by the time the fever goes away
  (once the fever subsides, degree of deterioration/paralysis has reached its peak).
- ✓ The likelihood of developing paralytic polio increases with age and the paralysis is more severe in adults;
  - In children: Paralysis of one leg is most common.
  - In adults: Extensive paralysis of the chest and abdomen, also affecting one side of his body (hemiplegia) or all four limbs (paraplegia).
- ✓ It can be divided into 3 types, depending on sites involved:
  Spinal polio, **Bulbar** polio & **Bulbospinal** polio (paralysis of diaphragm)

Diagnosis

- Diagnosis can be deduced from the clinical picture
- Look for outbreaks
- Travelling to areas that are still endemic with poliovirus can be a clue
- Isolation in cell culture
- You have to do molecular techniques, like **PCR**;
  It differentiates between the "wild-type" and the "vaccine-type" poliovirus, because for each reported case of paralytic polio (major disease) caused by the wild poliovirus, there are 200 to 3,000 other contagious asymptomatic carriers.

  Why do you have to differentiate between both types?

  It's a country thing (الشؤون الصحية للدولة); If the patient has vaccine-type polio then it's not a problem because they already know there is a very very small chance that poliovirus vaccine can cause the disease limited to that person only, while if the case is a wild-type polio then this indicates that it might be due to an outbreak and that the virus can spread, so they have to stop that.
- Serology is very rarely used.

➔ Clinical Correlate: When a patient presents with early symptoms of poliovirus what will you, as a physician do?

- The patient will present with minimal meningeal-like symptoms (fever, headache, stiff neck, etc…), when a patient presents with such symptoms, you always have to consider it as **meningitis**.
- You should instantly start the patient on empirical anti-biotic therapy
- Take a CSF sample using a lumbar puncture (LP), then send it to the lab for culturing & sensitivity test and wait for the results in about 48 hours.

  ⇨ **If the culture came back positive**, then it's bacterial therefore, you switch from empirical treatment into a specific antibiotic.

  ⇨ **If the culture came back negative**, then it's viral (aseptic).
  You will even notice that in the moment culture results come back, the patient will already be doing good and feeling better than when he presented, as viral cases of meningeal symptoms are mostly self-limiting.

Paralysis can be improved by 6-12 months of rehabilitation & physiotherapy. Mostly, improvement will stop once finished 6 months of physiotherapy.

Prevention

There is no specific antiviral drug for poliovirus.

The vaccine works by Sensitization, formation of antibodies & memory B-cells.

There are 2 types of poliovirus vaccine, they both are being used since 1960s when they were first introduced:-

- **OPV: Oral Poliovirus vaccine** (Live-attenuated) ➔ **95% efficacy – which is high**
  - Also called Sabin vaccine. (according to the scientist who invented it)
  - It's the main polio-vaccine that WHO use for polio eradication campaigns as it is cheaper than IPV.
  - There is a chance of [1 in 2-3 million] to cause paralytic polio disease, and this has limited its use in certain countries.
  - It should never be given to immunocompromised patients.
  - USA stopped giving OPV since the year 2000.
  - It is given in the form of droplets, which replicates in the mouth then goes down the GI tract, mimicking the normal virus pathway, therefore giving the patient both systemic & local (IgA) immunity.

- **IPV: Inactivated Poliovirus vaccine** (Killed) ➔ **99% efficacy**
  - Also called Salk vaccine. (according to the scientist who invented it)
  - Only gives systemic immunity. (No local immunity/IgA).

✓ Due to the Syrian crisis, many polio outbreaks have occurred, therefore there were many campaigns in Jordan since then in order to prevent any unwanted outbreaks, and these campaigns involved college students in 2012/2013.

✓ In Jordan, when the vaccination first started they used only OPV.
Nowadays they give multiple **booster** doses using a combination of both OPV + IPV.

✓ The National vaccination program in Jordan:
In the beginning of 3rd month: IPV
In the beginning of 4rd month: IPV + OPV
In the beginning of 5rd month: IPV + OPV
In the beginning of 10rd month: OPV
In the 18th month: OPV

In the USA:

Only IPV is given, the vaccine is given in the 2nd, 4th and 6th months.

❖Rabies virus (داء الكَلَبْ)

A disease characterized by severe neurologic symptoms due to an animal bite/scratch, such as dogs, cats and wild animals.

- It causes a wide-spread encephalitis along the brain matter & myelitis of spinal cord.
- It's not in natural sense a disease of humans, it's a **zoonotic infection (animals)**
- Urban animals, e.g. Home-cats are being vaccinated, especially in western countries.

CNS Symptoms

Progressive excess in motor activity, agitation, hallucination & salivation as a result of virus spread to autonomic nervous system (ANS).

If a person was bitten by an infected animal and then presented with CNS symptoms → عظم الله أجركم It's a terminal case and he's going to die in 1-2 weeks no matter what.

How would you, as a physician prevent him to reach this stage?

Once a patient comes to you and tells you that he was bitten or scratched by a dog or a wild animal you should have high suspicions that the animal might've been infected with rabies and give the patient the rabies vaccine instantly even before doing any tests.

Diagnosis of Rabies in animals

To find out if the biting animal was infected with rabies or not:

- You kill it and open its head
- Have a look on its CNS and find out if there's **Negri bodies**

Negri Bodies:
Cytoplasmic eosinophilic inclusion bodies
(A diagnostic feature of rabies)

➔ If the animal was infected then you must give the vaccine to the patient
➔ If the animal was not infected, then you don't have to give the patient the vaccine

But is this practical? No. Always give the vaccine before even checking if the biting animal is infected or not, and that is in order to be on the safe side. Even if the animal is not infected, giving the vaccine to non-infected patients is of no harm.

Methods of cure (**Vaccination + Immunoglobulins**)

Rabies vaccine is a "killed-virus" vaccine grown in human fibroblasts.

The vaccine is given either pre-exposure or post-exposure.

The **pre-exposure** vaccine is given in 4 doses:

** Day 0, Day 7, Day 21, Day 14.

The **post-exposure** vaccine is given in 4 doses:

** Day 0 (The day that patient presents to you), Day 3, Day 7, Day 14.

Previously-vaccinated patients are given only two booster doses:

** Day 0 & Day 3

General features of Rabies virus

- Bullet-shaped - **Rhabdovirus**
- (-sense) ssRNA
- Helical capsid
- Non-segmented genome
- It has more than 400 spikes (glycoproteins) of its surface
- Genome encodes for 5 proteins:
  Nucleoprotein (RNA) / Phosphoprotein / Matrix protein / Glycoprotein / Polymerase.

Replication cycle

Attachment of spikes to the receptor → Release of (–sense) ssRNA into the cytoplasm
→ The enzyme "RNA-dependent RNA-polymerase" convert it into (+ sense) then:-

- Part will be used as mRNA and be translated into proteins by the ribosomes.
- Part will generate (- sense) RNA as templates for many copies of +sense RNA.

→ The proteins and the new genome are assembled into a new virion → Viremia.

Epidemiology

They exist in 2 epizootic forms:

- ⌘ Urban: In unimmunized cats & dogs.
- ⌘ Sylvatic (jungle): Racoons, skunks, foxes, coyotes & bats

➔ It's transmitted via the wild animal's bite or scratch.
➔ Another form of transmission is via inhalation of droppings of cave bats (very rare).

Pathogenesis

- The virus replicates in striated muscles, it will then look for peripheral nerves, and it will go there then move retrogradely towards the CNS.
- It can pass across autonomic nerves to reach salivary glands, adrenal medulla, kidneys & lungs.
- There will be infiltration by lymphocytes and plasma cells to the infected tissue and nerve cell destruction.
- Incubation period: [1 day -1 year] which is very long.

  The length of incubation period depends on several factors, including:

  1) The site of bite/scratch (The more further the infection from the CNS, the longer it's going to take to develop the disease. e.g. A bite in the shoulder would develop the disease faster than if the bite was on the hand distally).
  2) The dose of the virus that infected the patient
  3) The immunity of the patient
  4) The bite is associated with a shorter incubation period than a scratch

  Ps.) The type of the host animal does not make any difference.

Discharge and Intermediate Hosts (we are talking about the animals here):

- ✓ Infection of new host via saliva
- ✓ Death of host
- ✓ Wild rabid animals may infect domestic animals & people
- ✓ Rabid domestic animals (e.g. A rabid dog – كلب مسعور) may infect humans.
- ✓ Humans are considered a dead end; they don't transmit the infection to others.

Other manifestations

As we said that the infection in the ANS goes to the salivary glands & increase salivation + these patients will have involuntary contraction of the respiratory laryngeal and pharyngeal muscles responding to the presence of excess saliva > no swallowing.

Final result is a combination of excess salivation (foaming at the mouth) & difficulty swallowing produce the fearful picture (fear of water)

Stages of infection

There are 3 stages of infection, and all these three stages appear **AFTER** the end of the incubation period (here, the virus has already reached the CNS):

1) **Prodromal stage:**

- Mild & non-specific symptoms (slight fever, chills, malaise, headache).
- Occur between 2-10 days.
- Specific early symptoms: local, radiating pain in the location of the bite.

2) **Acute neurological stage (excitation stage):**

- Lasts 2-7 days
- Can be divided into further two phases:
    - Furious phase
    - Paralytic phase: lethargy & paralysis.

3) **Coma / Terminal phase:**

- Flaccid paralysis, Peripheral vascular collapse, Coma, Death within just 4-20 days (median survival period).

Diagnosis in humans

- Immunofluorescence : Take a sample from the back of the neck and look for antigens
- RT-PCT (Reverse Transcriptase PCR)
- Serum & CSF are tested for antibodies
- Skin biopsy, examined for specific rabies antigen
- Once the patient has died, brain autopsy will show Negri bodies.

Control of rabies

Control dogs and wild animals, vaccinate them in the urban places, and logically you should try to avoid wild animals.

Good luck

#HalaMadrid