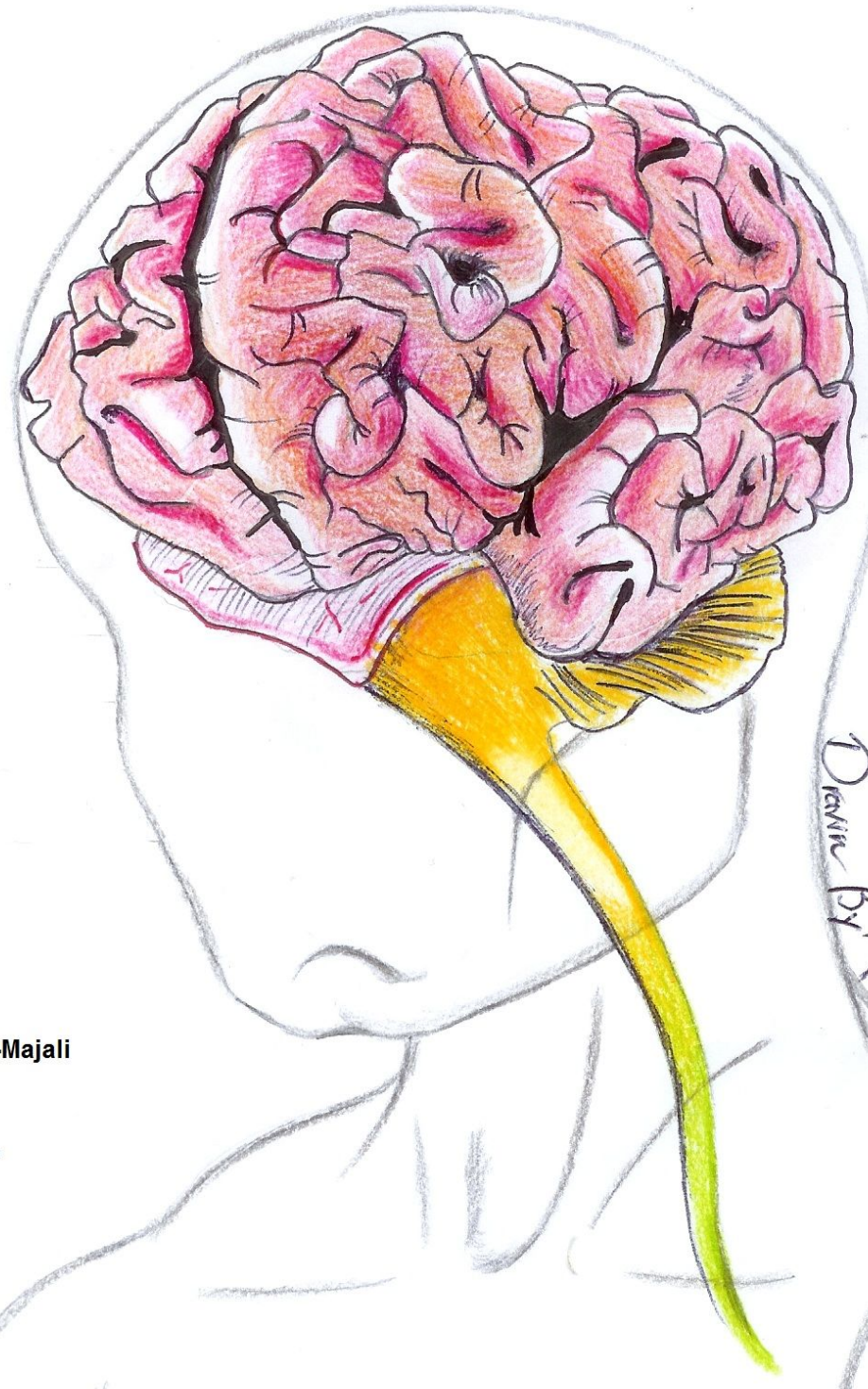
CENTRAL NERVOUS SYSTEM

- ○ Handout
- ★ Sheet
- ○ Slide

- ○ Anatomy
- ○ Physiology
- ○ Pathology
- ○ Biochemistry
- ★ Microbiology
- ○ Pharmacology
- ○ PBL



Drawn By Tariq Bushnaq...

Done By: **Raya Al-Majali**

Dr. Name: **Ashraf**

Lec #: **3**

Enteroviruses

all enteroviruses :

- ✓ Have +ve sense single stranded RNA.
- ✓ belong to picornaviridae family.
- ✓ naked viruses.
- ✓ transmitted via the fecal-oral route .
- ✓ most cases of infection are seen in children below 10 years due to poor hygienic measures.
- ✓ Pathogenesis starts in the oropharyngeal region when the virus replicates there for a short period of time (2 days-2 weeks). Then virus shedding into saliva occurs and it's then swallowed & goes to the GIT and replicates there. after that, it goes to the blood to cause a **primary viremia**. from there, it goes to other organs depending on the type of enterovirus that we are talking about (examples of organs that can be involved : lungs , kidneys , heart , adrenals , skin & mucus membranes) .then it replicates again in these organs and is being released once again into the blood causing **secondary viremia** .
- ✓ Sometimes , we might not find Ab's against the virus in the serum of the patient even when he's symptomatic . that's because most of the time **symptoms develop before seroconversion**. And that's why we depend mostly on **clinical diagnosis** (history + presentation).

Poliovirus

General Features :

- ✓ It belongs to the Enteroviruses genus of the picornavirus family which replicate mainly in the gut.
- ✓ Single stranded naked RNA virus.
- ✓ Capsid has 60 copies each of 4 proteins, VP1, VP2, VP3 and VP4 which are arranged in icosahedral symmetry around a positive sense genome.
- ✓ stable in acidic pH (3) [this's a characteristic shared among almost all enteroviruses. Since they're transmitted via fecal-oral route they should tolerate high acidity even up to 3 in order to escape the acidity of gastric juices.]
- ✓ first identified in 1909 by inoculation of specimens into monkeys. The virus was first grown in cell culture in 1949 which became the basis for vaccines (as we said growing any microorganism in a culture [cell culture or bacterial culture] would enhance our knowledge about it , and we can further identify the antigenic structures and produce specific vaccines for it).
- ✓ The term derives from the Ancient Greek poliós, meaning "grey", myelós “marrow”, referring to the grey matter of the spinal cord, and the suffix -itis, which denotes inflammation. (so it means inflammation of the spinal cord’s grey matter, although a severe infection can extend into the brainstem and even higher structures).
- ✓ It has 3 serotypes (1, 2, and3) but no common antigen. this means that infection by one doesn't give immunity against the other two (that's why the vaccine should include all the three serotypes) .
- ✓ Serotype #1 (PV1) is the most common form encountered in nature and associated with paralysis, however all three forms are extremely infectious.
- ✓ Have identical physical properties but only share 36-52% nucleotide homology.

- ✓ Humans are the only susceptible hosts (it infects humans only) . though there're certain animal viruses(that infect animals) and causes similar illness in animals but there's no transmission from animals to humans .

Replication :

- ✓ it has the same mechanism of replication of other enteroviruses
  - We always start from attachment of the virus to the receptor. Poliovirus has a canyon which attaches to the receptor on the target cell .
  - After that , the +ve sense single stranded RNA is released to the cytoplasm.
  - Part of this +ve sense RNA then serves as a mRNA and goes directly to the ribosomes to be translated into polyprotein (includes structural & non-structural proteins) .
  - This polyprotein then undergoes further cleavage by proteases to give individual proteins.
  - Then RNA-dependent-RNA polymerase uses part of the +ve sense RNA to give a –ve sense template. Using this template, new copies of +ve sense RNA genome are produced.
  - Finally , these copies of +ve sense RNA together with the structural and nonstructural proteins are going to be assembled into new virions.

Epidemiology :

- ✓ Polioviruses are distributed globally. Before the availability of immunization, almost 100% of the population in developing countries were infected before the age of 5 (before immunization , immunity was conveyed by natural infection .when we say natural infection, does that mean paralysis ? No, 90-95 % of infections are asymptomatic , and only small percentage of those infected [0.1-1%] might develop a major paralytic illness).

- ✓ The availability of immunization and the poliovirus eradication campaign has eradicated poliovirus in most regions of the world except in the Indian Subcontinent and in Africa (still have some focuses of polio infection) .

Pathogenesis:

- ✓ The incubation period is from 1-3 weeks .
- ✓ Infection occurs via the fecal–oral route.
- ✓ Like all enteroviruses , following ingestion, the virus multiplies in the oropharyngeal and intestinal mucosa (so, following the introduction of the virus to the oropharynx , it replicates there for 2 days - 2weeks).then Poliovirus divides within gastrointestinal cells for about a week, from where it spreads to the tonsils, the intestinal lymphoid tissue including the 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 resulting in a transient viremia.
- ✓ Viremia leads to the development of minor influenza-like symptoms and in a minority of cases the virus may involve the CNS following dissemination.(so as a result of viremia there will be nonspecific symptoms characterized by febrile illness)
- ✓ In most cases, this causes a self-limiting inflammation of the meninges, the layers of tissue surrounding the brain, which is known as nonparalytic aseptic meningitis.
- ✓ so where we can find the virus ? feces , saliva , CSF , urine

clinical manifestations :

- ✓ 90-95% subclinical : asymptomatic and pass unnoticed .
- ✓ 2-5% Abortive : will have minor influenza-like illness which recovers within a few days without any treatment (diagnosis can only be made by the laboratory). This minor illness may be accompanied by aseptic meningitis.

- ✓ 0.1-1% major paralytic illness (paralytic polio) : the severe form of illness that's associated with paralysis, may present after 2-3 days of minor illness . Most of the time it is preceded by the minor illness (where there are signs of meningeal irritation and we have flu-like symptoms). signs of aseptic meningitis are common, involvement of the anterior horn cells lead to flaccid paralysis. Involvement of the medulla may lead to respiratory paralysis and death.

Paralytic polio

- ✓ In around 1% of infections, poliovirus spreads along certain nerve fiber pathways, preferentially replicating in and destroying motor neurons within the spinal cord, brain stem, or motor cortex.
- ✓ Early symptoms of paralytic polio include high fever, headache, stiffness in the back and neck, asymmetrical weakness of various muscles, difficulty swallowing, muscle pain.
- ✓ So it starts by the minor illness associated with fever , nosia and vomiting ,then it gives progress to the major illness most of the time with meningeal irritation.
- ✓ Paralysis generally develops 1-10 days after early symptoms begin, progresses for 2-3 days, and is usually complete by the time the fever goes away (this means that once the fever subsides, he has reached the degree of paralysis that he's going to have i.e. the paralysis reaches its peak when the patient becomes afebrile and his condition would not deteriorate beyond this level. [there's some exceptions for this rule]) .
- ✓ The likelihood of developing paralytic polio increases with age:
  - children under five years of age: paralysis of one leg is most common
  - in adults: extensive paralysis of the chest and abdomen also affecting all four limbs is more likely.

So with younger age the extinct of paralysis would be less in comparison with that of adults.

- ✓ Depending on the site of involvement it can be divided into 3 types:
  - Spinal polio: most common
  - Bulbar polio
  - Bulbospinal polio (paralysis of the diaphragm)

Laboratory diagnosis :

- ✓ Virus Isolation :
  - Mainstay of diagnosis of poliovirus infection
  - can be readily isolated from throat swabs, feces, and rectal swabs & CSF as well .
  - can be readily grown and identified in cell culture .
  - Requires molecular techniques PCR to differentiate between the wild type and the vaccine type because for each reported case of paralytic polio caused by wild poliovirus, an estimated 200 to 3,000 other contagious asymptomatic carriers exist.
  - So , does this mean that the vaccine can cause paralytic illness? And how frequent is that ?
    yes there's very very very very minimal and very small chance of paralytic polio in case of giving the oral or the life-attenuated vaccine (1 in every 2.4 million people vaccinated)
  - why do we need to differentiate between the wild type (the infectious virus) and the vaccine type ?
    In certain war countries (like Syria and Iraq), lots of people don't have access to primary health care and to vaccination. as a result of that ,the presence of asymptomatic carriers with non-immunized patients will lead to infection of these non-immunized patients & a small percentage of these develop paralysis. but in areas where there's a good perspective on vaccination there's a little or no risk of these asymptomatic carriers.so, if the disease is as a result of the wild type then there's an outbreak and the infection will be spread from unsettled countries to the nearby region, but if it's as a result

of vaccination we should not care so much because it is going to be limited to him.

- due to unsetteled situations in Syria poliovirus has emerged once again after being totally eradicated. So, a serious of campaigns of poliovirus vaccination were held & they vaccinated all children below 5 years . there were also other campaigns that targeted people up to 20 years.

✓ Serology:

- Very rarely used for diagnosis (as we said, most of the time when we are talking about enteroviruses, the appearance of the symptoms precedes the seroconversion against the virus)

Treatment:

✓ is there any specific anti-viral drug?

No ,there is no specific antiviral drug for any of the enteroviruses including poliovirus .

✓ Is there a treatment for those who became paralytic ?

it often requires long term rehabilitation, including occupational therapy, physical therapy and sometimes orthopedic surgery.

✓ We said that once the patient becomes afebrile, then this's the degree of paralysis or disability that the patient is going to have . is there a chance of recovery following that ?

The patient still have a chance up to 6 months and sometimes up to 1 year . patients might recover with rehabilitation because the partially damaged nerves might regain their function . after 1 year the degree of paralysis is going to stay as it is .

Prevention :

✓ we have two types of vaccines :

- IPV : Intramuscular Poliovirus Vaccine (other name : Salk vaccine)
- OPV : Oral Poliovirus Vaccine (other name : Sabin vaccine) .

>> Salk & sabin are the names used by the scientists.

- ✓ Comparison between the two :
  - both have all three serotypes.
  - both are given as three doses: two doses 6-8 weeks apart, 3rd given after 8-12 months.
  - both are going to give us a high protection (IPV 99% , OPV 95%) after the three doses.
  - IPV consists of formalin inactivated/killed virus , OPV consists of Live attenuated virus
  - IPV is going to confirm only serum immunity (IgG) , but the OPV is going to confirm a serum immunity(IgG) & local immunity (IgA) because it's oral / live attenuated and mimics the actual infection . (local means in the GIT & RT where there is secretions and non-mobile lymphatic organs and it's in the form of IgA).
  - Don't forget the point that the OPV may cause paralytic polio rarely (1 in 2.4 million people vaccinated).
- ✓ Most countries use OPV because of its ability to induce local immunity and also it is much cheaper to produce than IPV (the normal response rate to OPV is close to 95%)
- ✓ Because of the slight risk of paralytic poliomyelitis, some countries have reverted to using IPV.
- ✓ OPV is used for the WHO poliovirus eradication campaign.
- ✓ Nowadays , a combination of both is used in the national vaccination program (4 doses ,when we use only one of them we give 3 doses- this is what the doctor said!) :
  - at the beginning of the 3rd month they start by giving the IPV.
  - at the beginning of the 4th month they give IPV & OPV
  - at the beginning of the 5th month they give IPV & OPV
  - after 9th months (the beginning of 10th month) they give OPV.
  - At the 18th month they give OPV.
- ✓ Poliovirus was targeted for eradication by the WHO by the end of year 2000. To this end, an extensive monitoring network had been set up.

- ✓ Poliovirus has been eradicated from most regions of the world except the Indian subcontinent and sub-Saharan Africa.

Prognosis:

- ✓ Patients with abortive polio infections recover completely (abortive polio as we said is a febrile illness, sometimes they might have aseptic meningitis . In those who develop only aseptic meningitis, the symptoms can be expected to persist for two to ten days, followed by complete recovery.)
- ✓ In cases of spinal polio, if the affected nerve cells are completely destroyed, paralysis will be permanent; cells that are not destroyed, but lose function temporarily, may recover within 6 months to 1 year after onset:
  - Half the patients with spinal polio recover fully
  - one-quarter recover with mild disability
  - quarter are left with severe disability.

Current status of Wild Poliovirus Transmission:

Still found in Afghanistan , India, Nigeria and Pakistan.

Summary:

- ✓ Enteroviruses genus ,picornavirus family, replicate mainly in the gut, ssRNA, naked, icosahedral ,capsid has 60 copies each of 4 proteins: VP1, VP2, VP3 and VP4 , stable in acidic pH (3),3 serotypes, no common antigen(infection by one doesn't give immunity against the other two, vaccine should include all the three serotypes), all three forms are extremely infectious,PV1 is the most common, humans are the only susceptible hosts.
- ✓ distributed globally,100% of the population in developing countries were infected before the age of 5 before immunization ,eradicated in most regions of the world except in the Indian Subcontinent and in Africa ,Afghanistan, Nigeria and Pakistan.
- ✓ incubation period 1-3 weeks, fecal–oral route, virus found in: feces , saliva , CSF & urine(throat swabs + rectal swabs).
- ✓ 90-95% subclinical , 2-5% Abortive (diagnosis only by laboratory /may be accompanied by aseptic meningitis / recover without treatment), 0.1-1% paralytic polio(present after 1-10 days of minor illness, progress 2-3 days, complete by the time the fever goes away, likelihood of developing paralytic polio increases with age ,3 sites of involvement :Spinal –

most common: Half patients recover, quarter mild disability, quarter severe disability - + bulbar + bulbospinal ,aseptic meningitis is common)

- ✓ Lab : virus isolation (cell culture) ,molecular techniques PCR to differentiate wild from vaccine (OPV cause paralytic polio in 1 in every 2.4 million people vaccinated) ,Serology (rare)
- ✓ no specific anti-viral drug , who became paralytic : long term rehabilitation (chance from 6 months – 1 year) .
- ✓ two types of vaccines: IPV (Salk),OPV(Sabin) .
    - both: all three serotypes , three doses: two doses 6-8 weeks apart, 3rd given after 8-12 months, high protection (IPV 99% , OPV 95%)
    - IPV> formalin inactivated, OPV >Live attenuated .
    - IPV :serum immunity (IgG) ,OPV: serum immunity(IgG) & local immunity(IgA).
    - Most countries +WHO use OPV(local immunity+ cheaper)
    - Some countries use IPV (Because of the slight risk of paralytic poliomyelitis of OPV).
    - Combination of both : 4 doses >> 3rd : IPV , 4th : OPV +IPV , 5th: OPV +IPV, 9th : OPV.

Rabies Virus

General features:

- ✓ Helical capsid
- ✓ Nonsegmented genome
- ✓ "Bullet" shaped **- Rhabdovirus**
- ✓ -ve sense single stranded RNA genome
- ✓ Has G glycoprotein on the surface (the doctor means trimeric spikes)
- ✓ genome encodes 6 proteins (in the slides : 5 >> Nucleoprotein, Phosphoprotein, Matrix protein,glycoprotein & Polymerase).

Rabies virus replication:

✓ Attachment to the receptor > release of –ve sense ssRNA into the cytoplasm, RNA-dependent RNA-polymerase convert it into a +ve sense strand which can be translated by cell ribosomes into structural and nonstructural proteins. Then the +ve sense RNA is used as a template to produce many copies of the viral genome (-ve sense RNA). Then the proteins and the new genome are assembled into a new virion.

What's Rabies ?

- ✓ A disease characterized by severe neurologic symptoms and signs as a result of an animal bite (not only an animal bite, it can also be an animal scratch and in some cases it was as a result of inhalation of bat dropping).
- ✓ This disease is characterized by progressive excess in motor activity, agitation, hallucination and salivation as a result of virus spread to autonomic nervous system.
- ✓ So, the virus starts peripherally (or locally) in the muscles and the supplying nerves, and then it replicates there and travels along the peripheral nerves into the CNS, spinal cord , and then into the grey matter of the brain and then once again it descends to the ANS to infect other organs (such as salivary glands , adrenals & kidneys)

Epidemiology :

- ✓ Rabies is not, in the natural sense, a disease of humans. It's wide-spread and infect animals .Raccoons, skunks, foxes, coyotes, and several species of insectivorous bats have been identified as reservoirs for the disease. and it can infect humans in two ways (or exist in two epizootic forms) : rural & urban .
  - urban : unimmunized dogs or cats
  - rural: other animals such as skunks, foxes and raccoons.

And once humans get accidentally bit or scratched by these animals they will become infected with the virus .

- ✓ Since the introduction of the vaccine against rabies , the number of cases has been reduced dramatically and no death has been reported in the past couple of years.
- ✓ Is there serotypes of rabies virus ? it's considered stable though there is strain variation limited to certain geographical locations . for example , in the USA , in certain locations they know that rabies infections is low .but they found that due to the behavioral of the hunters who go to the wild and hunt foxes or raccoons and bring them

back to this geographical area and the number of rabies infections increased. Also ,in cases of failure of vaccine , there might be a slight modification or a new strain has been emerged .

Pathogenesis:

- ✓ Rabies virus replicates in striated muscle tissue and peripheral nerves at the site of inoculation. Then it goes along the peripheral nerves into the CNS . Immunization at this stage will prevent viral migration to neural tissues (once the patient get bitten or scratched by an animal , the virus has been produced into the muscles , so we need to give the vaccine because they've found that the rabies virus is characterized by long incubation period [10 days -1 year]).
- ✓ But when the immunity is absent the virus enter peripheral nervous system at neuromuscular junction then spread to the CNS , pass across autonomic nerves to reach salivary glands, adrenal medulla, kidneys and lungs.
- ✓ There will be infiltration by lymphocytes and plasma cells to the infected tissue and nerve cell destruction
- ✓ we know that viral infection to humans will confirm immunity , once you become infected with certain virus the immune system is going to respond by the production of IgM & IgG and IgG is going to confirm immunity . in the case of the rabies virus why inoculation of virus into tissues doesn't confirm protection ?
  Because of the poor access of the T-lymphocytes into the peripheral nerves and muscle tissue which is the initial site of replication of the virus . so, we need to give the vaccine subcutaneous in order to confirm immunity and protection against the virus .

Pathogenicity

- ✓ Defined by encephalitis and myelitis
- ✓ Perivascular infiltration throughout entire central nervous system
- ✓ Causes cytoplasmic eosinophilic inclusion bodies, which are the remnants of the capsid protein in the cytoplasm and are called **Negri bodies** (a diagnostic feature of rabies).

- ✓ Long incubation period (10 days – 1yr).
- ✓ Several factors may affect outcome of rabies exposure:
  - Dose: amount of virus, amount of tissue involved
  - Route: bite, scratch or inhalation of droppings
  - Location of exposure: distance traveled to CNS (this means that a bite in the leg isn't like a bite in the shoulder , incubation period is less when the bite is closer to the CNS)
  - Individual host factors: immunity (immunocompetent patients have a long incubation period , immunosuppressed patients will have short incubation period).

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 may infect humans .
- ✓ humans are considered a dead end . they don't transmit the infection to others .

Stages of rabies virus infection :

- ✓ 3 stages (here the virus has already reached the CNS): Prodromal stage , acute neurological stage , coma / terminal phase .

1- Prodromal stage is characterized by:

- ☒ mild and 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 :

- ☒ lasts 2-7 days, can be divided into further two phases:
- ☒ Furious phase : hyperactivity , excitement , disorientation , hallucination , hydrophobia & convulsions.

☒ Paralytic phase : lethargy & paralysis .

3- coma / terminal phase :

☒ flaccid paralysis , coma , death within 4-20 days (If the disease manifests in the CNS fate is ultimate death).

- ✓ Combination of excess salivation and difficulty swallowing produce the fearful picture “foaming at the mouth”.(we said that the infection in the ANS goes to the salivary glands & increase the amount of saliva + these patients will have involuntary contraction of the respiratory laryngeal and pharyngeal muscles responding to the presence of excess saliva > no swallowing. The result of these two is "foaming at the mouth") .
- ✓ Median –survival 4-20 days .

Rabies Diagnosis in animals:

- ✓ By Immunofluorescence
- ✓ you need to kill the animal to look for the presence of the virus .
- ✓ If the animal is infected >you have to vaccinate the patient , if not > you don't need to (this's not practical , any patient present to you with an animal bite or scratch you should give him the vaccine to stay in the safe side).

Rabies Diagnosis in humans :

- ✓ if the human is dead: look for negri body or by immune staining of the CNS.
- ✓ If the patient is alive : sample from the saliva or the CSF and detect the virus by the PCR or form the back of the neck to detect the virus by immune staining . (we can use skin biopsy also). Saliva, serum and spinal fluid can be tested.

Methods of cure:

- ✓ No specific antiviral
- ✓ Long incubation period , so interference should be in the form of giving a vaccine and Ig:

4- We have two cases : pre-exposure vaccination , post-exposure vaccination .

- ☒ Pre-exposure vaccination :
  - ↵ for people who works with animals and have high chance of being bitten by rabid animal .
  - ↵ given as 3 doses :one ate day 0,the second at day 7, the third at day 21 or 28
  - ↵ no need for Ig , just the vaccine .
- ☒ Post-exposure vaccination : it's further divided into two cases :
  - ↵ pre vaccinated patient (who has taken the vaccine before: boost his immune status by giving 2 doses (one at day 0,the other at day 3)
  - ↵ a patient who has never been vaccinated against rabies: give him 4 doses : one at day 0 ,the second at day 3 ,the third at day 7 ,the last one at day14. with an Ig that can be given systemically or intralesionally- the Ig would neutralize the virus within the lesion)..

✓ Limited exposure to animals would also help in protection from Rabies .

Summary:

- ✓ Helical, Nonsegmented ,Bullet shaped ,-ve sense ssRNA, genome encodes 6 proteins (in the slides : 5).
- ✓ virus starts peripherally in the muscles and the supplying nerves & travels to CNS then descends to ANS(salivary glands , adrenals & kidneys will be affected.)/ Immunization at the stage of replication in muscles prevent viral migration to neural tissues/ There will be infiltration by lymphocytes and plasma cells to the infected tissue and nerve cell destruction/3 Stages: Prodromal stage , acute neurological stage , coma or terminal phase / excess salivation + difficulty swallowing > “foaming at the mouth” /If the disease manifests in the CNS fate is ultimate death.
- ✓ long incubation period (10 days – 1yr). affected by : dose, route , location of exposure individual host factors)
- ✓ not a disease of humans. exist in two epizootic forms : urban (unimmunized dogs or cats) & rural(other animals)/ humans are a dead end host / in animals :Infection of new host via saliva , results in death of host .
- ✓ Rabies Diagnosis:in animals: Immunofluorescence, not practical so give the vaccine to all patients / in humans :negri body or by immune staining of the CNS(patient is dead) . sample from the saliva or the CSF [PCR] ,from the back of the neck [immune staining] (patient alive)
- ✓ pre-exposure vaccination:3 doses (0,7,21 or 28), no Ig .

Post-exposure vaccination: Pre-vaccinated> 2 doses (0,3) / not pre-vaccinated > 4 doses (0 , 3,7,14) + Ig (systematically + intralesionally).

.. يا بلادي

.. مثلما يكبرُ فيكِ الشَّجَرُ الطيّبُ

.. نكبرُ

فازرعينا .. فوقَ أَهدابكِ ،

.. زيتوناً .. وزعتر

.. واحملينا أملاً ، مثل صباح العيدِ ، أخضر

واكتبي أسماءنا

في دفترِ الحب : نشامى

.. يعشقون « الوردَ » ، لكن

.. يعشقون « الأرضَ » .. أكثر

Raya Abdalhameed Almajali

This sheet is dedicated to Deema al qawasmeh & Zain Al-khamaiseh <3