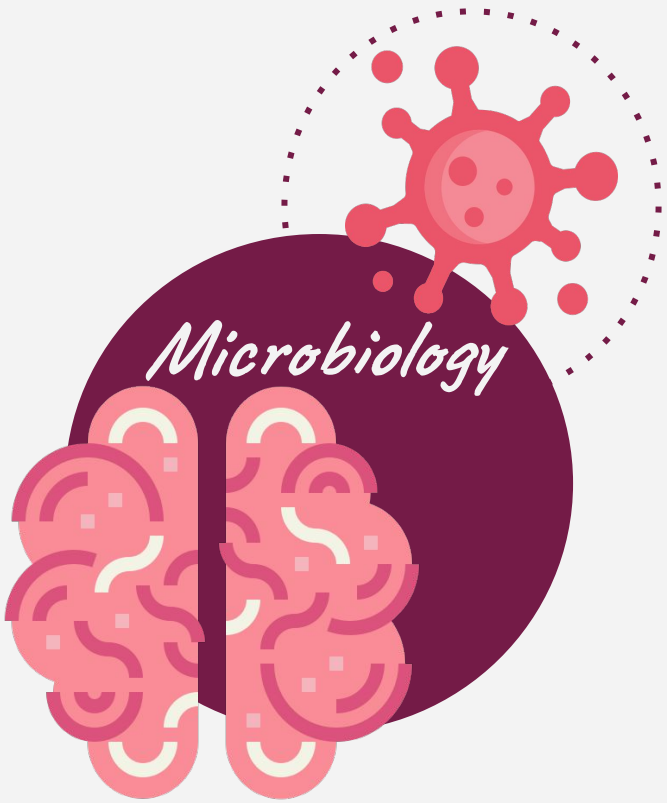
Viral infections

Objectives:

- Understand the different acute viral infections of the CNS (Meningitis, paralysis and encephalitis).
- Differentiate between the clinical presentation and cerebrospinal fluid finding in the viral meningitis (aseptic meningitis) and bacterial meningitis (septic meningitis).
- Understand the common viruses causing aseptic meningitis and encephalitis with regard to classification, structure, epidemiology pathogenesis, infections, clinical presentation, lab diagnosis and prevention.
- Understand general information of arboviruses and giving some example of arboviruses causing CNS infection.



Color index

Girls' slides	Boys' slides
Main content	Extra
Important	Drs' notes

MED439 KING SAUD UNIVERSITY

MICROBIOLOGY team 439

Revised & Approved

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Virus neurological diseases

Acute viral infection of the CNS

- **Meningitis**
- **Encephalitis**
- Paralysis

Chronic virus neurological diseases Not important

Boys slides only

- Subacute Sclerosing Panencephalitis
- Progressive Multifocal Leukoencephalitis
- Creutzfeldt Jakob Disease
- Tropical Spastic paraparesis
- HIV dementia

Neurological diseases precipitated by viral infections. Not important

Boys slides only

- Reye's syndrome
- Guillian-barrè syndrome

Acute viral infections of the CNS

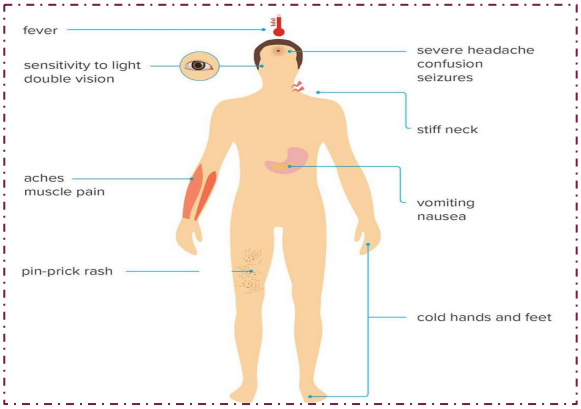
Meningitis

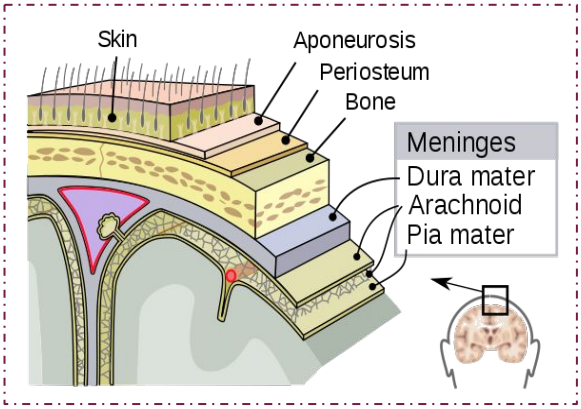
It's Inflammation of leptomeninges (affect Pia, Arachnoid, and Subarachnoid space).

Caused by:

- **Infectious agents:** Bacteria , Fungi , Protozoa.
- **Non-Infectious agents:** Tumor , bleeding , abscess

Signs and Symptoms





1- Viral Meningitis[1]

Type: Aseptic meningitis

Severity: Less severe

Prognosis: resolves without specific treatment within a week or two.[3]

2- Bacterial Meningitis[2]

Type: Septic meningitis

Severity: Quite severe and may result in:

- Brain damage
- Hearing loss[4]
- Learning disability

Prognosis: Medical emergency and would also cause death !![5]

[1] The most common cause of meningitis
[2] The most dangerous cause of meningitis
[3] Self-limiting, but if there is a treatment you should give the patient (ex. Herpes simplex encephalitis)
[4] The inflammation can damage the nerves that run between the ear and brain
[5] Can be fatal if not treated

Viral meningitis

Cerebrospinal fluid (CSF) analysis			
	Normal	**Aseptic meningitis**	**Septic meningitis**
Colour	Clear	**Clear**/Normal	**Cloudy**[1]
Cells/mm^3	<5	↑**Lymphocytes** 100-1000 mm^3	**High Neutrophils** 200-20,000 mm^3
Glucose mg/dl	45-85 mg/dl	Within the **normal** range	**Low** < 45
Protein mg/dl	15-45 mg/dl	**Normal or high** (50-100)	**High** > 100
Causes	-	**Viruses**, others	**Bacteria**

Etiology

Viral (Aseptic) meningitis

- Enteroviruses[2] (most common cause)
- Mumps virus
- Arboviruses
- Herpes Viruses
- Human Immunodeficiency Virus (HIV)
- Lymphocytic choriomeningitis Virus

Viral Encephalitis

- Enteroviruses
- Herpes Viruses
- Rabies Virus
- Arboviruses
- Others

[1] Due to neutrophils' accumulation
[2] Currently, enteroviruses accounts for 70-90% of aseptic meningitis cases

Enteroviruses

Enteroviruses				
Family	**Pico**rnaviridae. pico = small / rna = RNA genome.			
Structural features	○ Non-enveloped ○ Icosahedral capsule ○ +ve Single Stranded RNA genome (+ssRNA).			
Viruses included	**Poliovirus**[1] (1,2&3 types)	Coxsackieviruses (A&B)	Echoviruses	Enteroviruses (68-71)
Epidemiology – **Reservoir**	Humans.			
Epidemiology – **Spread**	○ **Mainly fecal - oral route.**[2] ○ Inhalation of infectious aerosols (In crowded, poor hygiene & sanitation).			
Epidemiology – **Age**	Affect **Children** more than Adults.			
Epidemiology – **Seasonal distribution**	Summer & fall.			
Pathogenesis	★ The main route for enterovirus is the **fecal-oral route** → **replicate in the GIT mucosa and oropharynx** → reaches the blood (viremia) → it targets many organs such meninges, brain, muscles and skin.			

Enteroviruses cause

1 Disease

- **Neurologic Diseases**
  Discussed in next slide
- **Non-Neurologic Diseases:**
  - **- Cardiac and Muscular:**
    - ○ Pleurodynia (epidemic myalgia)
    - ○ Myocarditis, pericarditis.
  - **- Skin and Mucosa infections:**
    - ○ Herpangina
    - ○ Hand-foot and mouth disease
    - ○ Exanthems
  - **- Acute hemorrhagic conjunctivitis**
  - **- Respiratory tract infections**

2 Asymptomatic Infections

[1] The most common one in this group

[2] A particular route of transmission of a disease wherein pathogens in fecal particles pass from one person to the mouth of another person , the main causes of fecal-oral transmission are:

- lack of adequate sanitation and poor hygiene
- Contaminated food due to lack adequate sanitation

Enteroviruses

Dr: numbers are NOT important

Neurologic Diseases:					
Virus / disease	**Polio types 1-3**	**GPA COX. types 1-24**	**GPB COX. types 1-6**	**Echo types 1-34**	**Entero types 68-71**
Aseptic meningitis	1-3	Many	1-6	Many	71
Paralysis	1-3	7,9	2-5	2,4,6,9,11,30	70,71
Encephalitis	-	2,5-7,9	1-5	2,6,9,19	70,71

Lab diagnosis of Enteroviruses

Virus isolation: (old method)

- Samples: **Stool** (best), rectal, throat swabs, & CSF.
- Inoculate in cell culture (MKC & HDF). (all EVs grown except some strains of Cox A viruses)
- Observe for Cytopathic effect (CPE)Cytopathic effect: change in morphological appearance of a cell.
- Identify the type by Neutralization Test.

CSF in Aseptic meningitis:

- Lymphocytosis
- Glucose: Normal to slightly decreased
- Protein: Normal or slightly high.
- Isolation rate is variable.

★ **RT-PCR**[1] **(Reverse transcriptase PCR) to detect Enteroviruses RNA in CSF. (Molecular testing)**

Serology:

- Limited value[2], Preformed antibodies (e.g. due to vaccine) can give false positive results

[1] PCR (Polymerase Chain Reaction) is a matter widely used in molecular biology to rapidly make millions to billions copies of a DNA sample, this allows scientists to take a very small sample of DNA and amplified to a large amount to study it in details. so, some viruses such as corona and enterovirus only contain RNA, this present a problem for the traditional PCR because in the traditional PCR only DNA can be detected. Because of that some viruses such as enterovirus the scientists should convert it to DNA to be detected by the PCR this process called " reverse transcription "

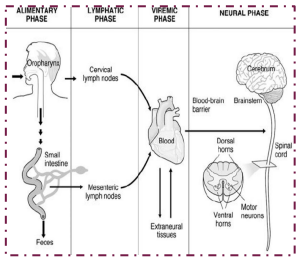
[2] Because so many types of enteroviruses are available & due to the lack of a common antigen in all types.

Poliovirus

Poliovirus

Pathogenesis

- **Pathway to CNS by:**
  - Blood (viraemia).
  - Peripheral nerves.
- ★ **Causing destruction of motor neurons AHCs** (Anterior horn cells) .
- **Rarely affects brain stem (bulbar Poliomyelitis)**
- **Immunity:**
  - IgA & IgG = Lifelong type-specific immunity.



Infections

- **No illness (90-95%):**
  - Asymptomatic
- **Minor illness (4-8%):**
  - Abortive poliomyelitis (No CNS involvement).
- **Major illness (1-2%):**
  - Non-paralytic poliomyelitis (Aseptic meningitis).
  - Paralytic poliomyelitis (Flaccid paralysis). Usually affects the lower limb (no sensation loss)

Management of Poliovirus

Treatment — No antiviral therapy

Prevention: 1 — Sanitation & Hygienic measures

★ **Prevention: 2** — **Poliovirus vaccines**

1. Inactivated polio vaccine (IPV)

- For adults*
- (Salk, Killed), can be injected Subcutaneous, or IM.
- Adverse reactions: Local reactions.
- **Poliovirus vaccines for adults:**
  - **Indications:** Travelers to polio-endemic countries, Health care workers.
  - **Vaccine:** Inactivated polio vaccine (IPV)

2. Live-attenuated polio vaccine (OPV)

- For children*
- Sabin, oral.
- Adverse reactions: Vaccine-Associated Paralytic Poliomyelitis in adult and low immune
- **4 doses**[1] **of Polivitus:**
  2, 4, 6-18 ms, and 4-6 yrs.
- **Pediarix contains:** (just for your knowledge)
  IPV, DTaP, Hib and HB vaccines

[1] WHO recommends that children get four doses of polio vaccine.
They should get one dose at each of the following age :
The first dose : 2 months old
The second dose : 4 months old
The third dose : between 16 - 18 months old
The fourth dose : between 4 - 6 years old

Polio Vaccines

Important Features of Polio Vaccines		
Attribute	**Killed (IPV)**	**Live (OPV)**
3 types (trivalent)	Yes	Yes
Prevents disease	Yes	Yes
Induces humoral IgG	Yes	Yes
Route of administration	Injection	Oral
Induces intestinal IgA*	No	Yes
Affords secondary protection by spread to others	No	Yes
Reverts to virulence Vaccine-Associated Paralytic Poliomyelitis	No	Yes (Rarely) DON'T give it to adults or immunocompromised patients , it's ONLY for children
Causes disease in low immune	No	Yes
Duration of immunity*	Shorter	Longer

Herpes Simplex Encephalitis

Herpes simplex Encephalitis (HSV)	
Family	Herpesviridae family
Caused by	○ **Herpes simplex virus -1 (HSV-1)** ○ Double Stranded DNA genome (dsDNA) ○ Enveloped. notice that all the viruses that will cause encephalitis are enveloped ○ Icosahedral virus
Clinical presentation/Feature	○ Fever, headache, vomiting, seizures & altered mental status ○ High mortality rate[1]
Pathogenesis	1. Primary infection: Virus enters via cutaneous or mucosal surface → infect sensory or autonomic nerve endings → transport to the cell body in ganglia before establishing latent phase 2. Latent phase 3. Reactivation (lytic phase): deactivation of HSV in trigeminal ganglion can result in spread to temporal lobe via meningeal branch of CN-V (trigeminal nerve)
Treatment[2]	**Acyclovir**

Diagnosis of HSV

MRI
(Magnetic resonance imaging)

For temporal lobe lesion

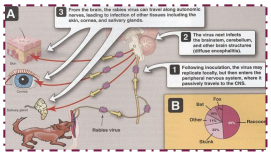
CSF

-↑ in Lymphocytes, glucose is normal & protein is↑

- Detection of HSV-1 DNA by PCR

[1] Especially in children with low immunity
[2] There's no vaccine yet

Rabies Encephalitis

Rabies Encephalitis		
Caused by:	○ Rabies virus ○ It's **zoonotic** disease (infection that spread between animals & human) ○ A fatal acute encephalitis	
Family	○ Rhabdoviridae	
Epidemiology	**Reservoir**	○ Major: Raccoons, Foxes, Wolves, & **Bats** ○ Imp: Cats & Dogs
	Transmission	○ **Common route: bite of rabid animal** ○ Uncommon route: 1- Inhalation while in a bat infested cave 2- Corneal transplant
Pathogenesis	After getting a bite from a rabid animal that is infected rabies → the virus will enter the PNS → reaches spinal cord, medulla & brain → from the brain it travel down to infect other tissues like the cornea, skin & salivary glands Dr: note that there is no viremia stage	

Phases

The incubation period[1]	The prodromal phase	Neurological phase	Recovery
1-3 month	Fever, Nausea, Headache, Vomiting, Malaise, Anorexia, ★Abnormal sensation around the wound	1- Encephalitis: Nervous, lacrimation, salivation, hydrophobia (fear of water), convulsion, coma & death 2- Paralytic illness: Ascending, death, associated with Bat bite	Extremely rare

Structural Features of rabies encephalitis

- Helical nucleocapsid
- Enveloped virus
- -ve Single Stranded RNA genome (-ssRNA)
- Bullet shaped virus

[1] Duration of incubation period depends on the site of the bite. To illustrate: when the bite is in the head, the incubation period is shorter than the incubation period of a leg bite. This is because the distance to CNS is shorter in the first case, and vice versa..

Rabies Encephalitis

Laboratory diagnosis

1:	**RT-PCR**[1]	Rabies RNA in saliva
2:	Virus cultivation[2]	
3:	Histopathology[3]	Neuronal brain cell Intracytoplasmic inclusions (negri bodies)
4:	Serology	
5:	**Rapid viruses antigen detection (IF)**	Neck skin biopsy ,Corneal impressions ,Brain tissue

Prevention

Pre-exposure prophylaxis (vaccine)[4]

- For persons at increased risk of rabies (e.g. vets, animal handlers etc.)

Control measures against canine rabies includes:

- Stray animals control
- Vaccination of domestic animals

Post-exposure prophylaxis

- Wound treatment
- Passive immunization:
  human anti-rabies immunoglobulin applied around the wound & IM
- Active immunization:
  Human Diploid Cell Vaccine (HDCV) 5-6 dose

[1] Most sensitive and rapid

[2] ممكن نسوي culture للفيروس، لكن المريض لما يجي وعنده إصابة يعملون له PCR على طول (قبل ظهور الأعراض لأنها لو ظهرت الأعراض يكون الفيروس قد تمكن من الشخص، فلا يوجد طريقة تمنع المضاعفات و ممكن يموت،، أساسًا الشخص المصاب سواء ظهرت الأعراض أو لم تظهر يجب أن يأخذ ال vaccine - [Team 435]

[3] After death

[4] Active immunization

Arthropod-borne Viruses

Arthropod-borne Viruses		
Include	Arboviruses >500 viruses.	
Epidemiology	**Reservoir**	**Wild birds & Mammals**
	Vector	**Mosquito**, Tick, & Sandfly
	Transmission	Bite of infected vector
Infections	Asymptomatic infections	
	Diseases: - Fever, Rash, & Arthralgia - Hemorrhagic fever ± hepatitis. - CNS diseases (in the next table, and they are not imp) (meningitis & encephalitis)	

Dr. All black is NOT IMPORTANT

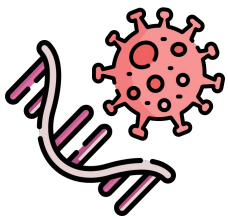
Virus	Vector	Reservoir	Distribution
Eastern equine (encephalitis EEEV)	Mosquito	Birds	America
Western equine (encephalitis WEEV)	Mosquito	Birds	America
Venezuelan equine (encephalitis VEEV)	Mosquito	Rodent	America
Japanese encephalitis V	Mosquito	Birds, Pigs	Orient
Murray Valley (encephalitis V)	Mosquito	Birds	Australia
West Nile Virus	**Mosquito**	**Birds**	**Middle East,** Europe, Africa, Asia, America

West Nile Virus

West Nile Virus	
Family	Flaviviridae **(Zoonotic virus)**
★ **Diagnosis of Arboviruses**	○ Reference lab ○ Lab Methods : **1- Isolation (Gold standard)** Samples: blood, CSF, Viscera Cell culture → CPE (cellular pathological effect)→ Identify by IF **2- IgM -AB, ELISA, IF (most used)** 3- Arbovirus RNA by RT-PCR

Structural Features of West Nile Virus:

- Enveloped virus
- Febrile illness → meningitis, encephalitis
- +ve Single Stranded RNA genome (+ssRNA)



Prevention Of Arboviruses:

1. Vector control

- Elimination of vector breeding sites
- using insecticides
- Avoidance contact with vectors (repellants, net)

2. Vaccines

- Tick-borne encephalitis vaccine
- Japanese encephalitis vaccine

Dr. Malak

- Acute viral infections of the CNS usually present as (1) aseptic meningitis, (2) paralysis, and (3) encephalitis. They have varying degrees of severity which depend on host/viral factors.
- Viruses are the most common cause of meningitis. Viral meningitis is usually benign and self-limited whereas bacterial meningitis is less common but more severe. Bacterial meningitis is also usually treated as a medical emergency with empiric treatment. Another way to differentiate between aseptic/viral and septic/bacterial meningitis is through CSF analysis.
- Aseptic meningitis: inflammation of meninges with lymphocytes (unlike bacterial with neutrophils), and the causative agent in this case is not identified after routine stain and culture of CSF (gram stain & culture will be negative as the cause is a virus). Usually, aseptic meningitis is associated with a fever, headache, photophobia, and neck stiffness. It is usually benign & self limited, except when it is accompanied by encephalitis (becomes severe).
- Encephalitis occurs when brain parenchyma is infected (a serious disease). It is characterized by changes in the level of consciousness, seizures, and neurological signs.
- Enteroviruses: Entero means that it replicates in the enteric tract(GIT), so they are transmitted through fecal oral route.

★ **Important to know:** (1) The mode of transmission/spread? Fecal-oral route. (2) Where does it replicate? GIT mucosa. (3) What does it cause? Aseptic meningitis, paralysis, and encephalitis.

- **Poliovirus** (a type of Enteroviruses):- It transmits through **fecal-oral route** → **GIT invasion/replication**→ passing to lymph nodes → causing viremia → CNS infection that leads to destruction of motor neurons of **anterior horn cells (AHCs)**→ **paralysis** of the muscles innervated by affected neurons.
- Current gold standard for diagnosis of Enteroviruses (aseptic meningitis) is (1) Enterovirus RNA detection in CSF using **RT-PCR**. (PCR is a method used to make billions of copies of a specific DNA sample, RT–PCR has an added step of reverse transcription of RNA to DNA) (2) virus isolation.

★ **The only Enterovirus with available vaccine is poliovirus, with two types of vaccines: (Extremely important)**
1- Killed, inactive: salk. (Given by injection).
2- Live attenuated: sabin. (Given orally).

Advantages of sabin/live attenuated vaccine: (1) It is given orally. (2) Since it has a live but attenuated virus, it might replicate in GIT and spread to close contacts (people), immunizing and re-immunizing them. This helps in prolonging and maintaining the efficacy of the vaccine. **(Should only be given for children)**

Disadvantage of sabin/live attenuated vaccine: There is a potential risk of the attenuated virus reverting to its virulent form and causing paralysis. This is rare and is more likely to happen in an adult/immunocompromised person; **Therefore, adults, immunocompromised people, and their relatives in general must receive the killed/salk vaccine. (IMPORTANT)**

- Herpes simplex encephalitis: Transmitted by saliva and direct contact with herpes lesions. After recovery, the virus travels through peripheral nerves to ganglia, and remains latent in the trigeminal ganglia. When the patient becomes immunocompromised, the virus will travel to the temporal region, causing an acute lesion. **Note that this is the only treatable virus in CNS** (but it cannot be prevented). If not treated, it might lead to death or cause severe complications in those who survive. (1) What is its best diagnostic method? PCR

★ Rabies virus: (1) Main reservoir? Bats. (2) Common route of transmission to human? Animal bite. (3) Where does it replicate? Locally in wound area. (Note that it has no treatment. However; it can be prevented with post-exposure prophylaxis). (4) Best diagnostic method? RT-PCR and IF.

★ West nile virus: (1) Main reservoir? wild birds (2) Common route of transmission to human? a vector which is mosquito. The majority of infected people are asymptomatic; however, some show symptoms of non-specific acute viral infections, and less than 1% will present with CNS involvement. Note that the West Nile virus is not treatable, nor can it be prevented by a vaccine.

Dr. Abdulkarim

- Arboviruses are originally animal viruses (zoonotic), but they can cause an infection if they are transmitted by a vector eg. mosquito.
- Poliovirus can cause aseptic meningitis, encephalitis, and **poliomyelitis**. The problem with polio infections of the CNS is that they are irreversible (meaning that if a patient becomes paralyzed, he/she will not recover).
- Virus isolation is an old method for diagnosing Enteroviruses. Presenty, RT-PCR are used (Serology has a limited value in diagnosing Enteroviruses because we already have a vaccine and preformed antibodies which will give a false positive).
- HSV encephalitis has a high mortality rate (especially in children because they have weak immunity).

Quiz

Click on the icon to check out the team's summary

MCQ

Q1: Which one of the following is true about polioviruses?

A- Causes destruction of motor neurons of posterior horn cells.
B- Gold standard for the diagnosis is by IF
C- Its route of transmission is by animal bites
D- Leads to paralysis of the muscles innervated by AHCs

Q2: What is the most common etiology for meningitis?

A- Viral infection
B- Bacterial infection
C- Fungal infection
D- A & B

Q3: Which of the following viral CNS infection is treatable?

A- Brucellosis
B- Rabies Encephalitis
C- Herpes Simplex Encephalitis
D- Enterovirus

Q4: Which one of the following is considered to be wrong about enteroviruses?

A- RT-PCR is the gold standard of diagnosis.
B- Serology is a widely used diagnostic method.
C- Cytopathic effect will be observed upon viral isolation.
D- CSF analysis will reveal lymphocytosis.

Q5: Which one of the following should be avoided in cases of immunocompromised patients?

A- Salk Vaccine
B- Sabin Vaccine
C- Killed Vaccine
D- Human Diploid Cell Vaccine

Q6: Main reservoirs for west nile virus and rabies virus respectively are?

A- Wild birds, mosquitos
B- Wild birds, bats
C- Bats, Wild birds
D- Bats, dogs

Answers: Q1:D | Q2:A | Q3:C | Q4:B | Q5:B| Q6:B

SAQ

CASE: A 73-year-old man had pain in his left shoulder and severe dehydration because he was phobic to water. He looked very sick. Initial evaluation showed irritability and lethargy. After 48 hours, the patient exhibited multifocal myoclonus and decorticate posturing. Intubation, and mechanical ventilation were performed. He was given vasopressors, corticosteroids and broad-spectrum antibiotics. His family confirmed that he had sustained a bat bite on his left shoulder 6 months previously but had not sought treatment.

Q1: What is the most likely diagnosis?

A: Rabies Encephalitis

Q2: What is the most likely causative agent?

A: Rabies virus

Q3: What are the best diagnostic methods for this case?

A: RT-PCR and Immunofluorescence.

Q4: What is the prognosis and treatment in this case?

A: Prognosis is poor, no treatment (exposed individuals must seek medical care right after after exposure, to be given post-exposure prophylaxis vaccine before the incubation of virus).

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