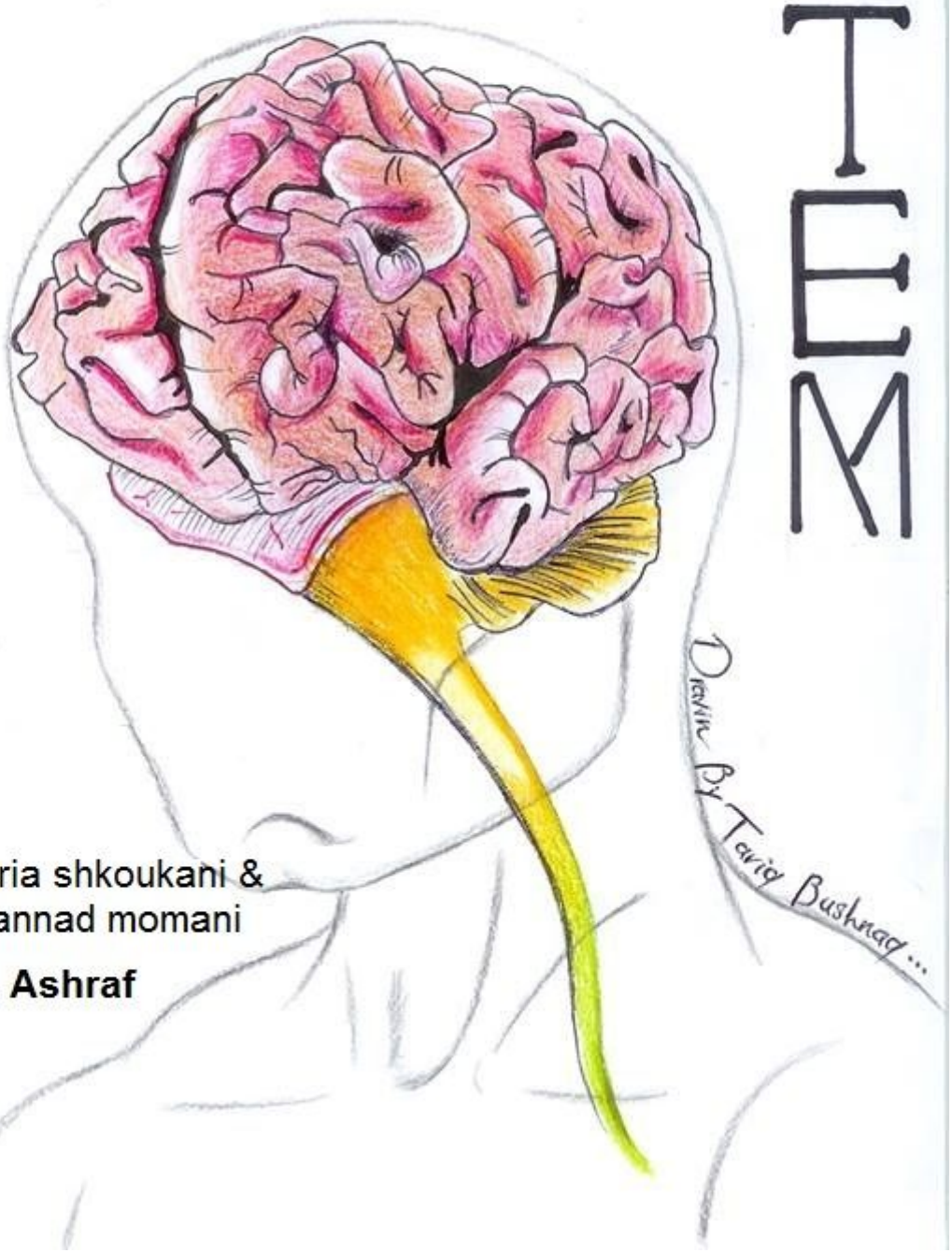
CENTRAL NERVOUS SYSTEM



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- ○ Anatomy
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Lec #: 2

Viral Encephalitis

Hello ☺ due to time constraints this sheet was divided between Zakaria and Mohanned Momani, the first part was written by Zakaria and the second by Mohanned. Kindly note that the doctor spent the majority of the lecture reading the slides with a few explanations here and there, so we apologise in advance for the excessive bullet points.

Part #1

The doctor started off by reading random terminology, so I'll just state these as follows; **viral *meningitis*** is inflammation of the meninges with sterile CSF (cerebrospinal fluid). ***Encephalitis***, on the contrary, is inflammation of the parenchymal tissue of the brain. A combination of the two results in ***meningoencephalitis***. And finally, ***myelitis*** is the inflammation of the spinal cord.

So what is *Encephalitis*?

Encephalitis is inflammation of the brain tissue (parenchyma) due to infection by either viruses or bacteria. It is most commonly caused by infection with a virus, which passes through the blood stream into the CSF leading to the destruction of neural cells and damaging the underlying brain tissue.

Encephalitis can be divided into:
- Primary (Acute)
- Secondary (Post-Infectious)

Let's start with secondary / post-infectious encephalitis first;

The viruses involved in this kind of encephalitis are:

1. **Measles** virus, which causes Subacute sclerosing panencephalitis (SSPE)
2. **Rubella** virus, which causes Progressive post-rubella encephalitis
3. **Polyoma** / **JC virus**, which causes Progressive multifocal leukoencephalopathy (PML)
4. Persistent **enterovirus** infection

1- **Subacute sclerosing panencephalitis** caused by the measles virus .which has CNS involvement through the actions of cytotoxic T-cells (CD8+) which react with and attack the virally infected cells; i.e. the immune system and the body's response to the presence of the virus intracellularly is mediated through activating the CD8+ T-cells, which as we already know are responsible for cell-mediated immunity.

The expression of the viral antigens on the MHC-1 complex of the neural cells causes activation of the CD8+ T-cells, which in turn produce perforating granzymes that destroy the infected cells. This destruction cannot be reciprocated by cellular division ; because neural cells cannot replicate / divide, and hence causes permanent damage to the brain tissue, and inflammation (encephalitis).

SSPE has an incidence rate of 1 in every 100,000 patients infected with measles, it is characterized by changes in personality, intellectual deterioration, myoclonus (spasmodic contractions of muscles), and it usually follows the acute stage of infection with measles by 2-10 years.

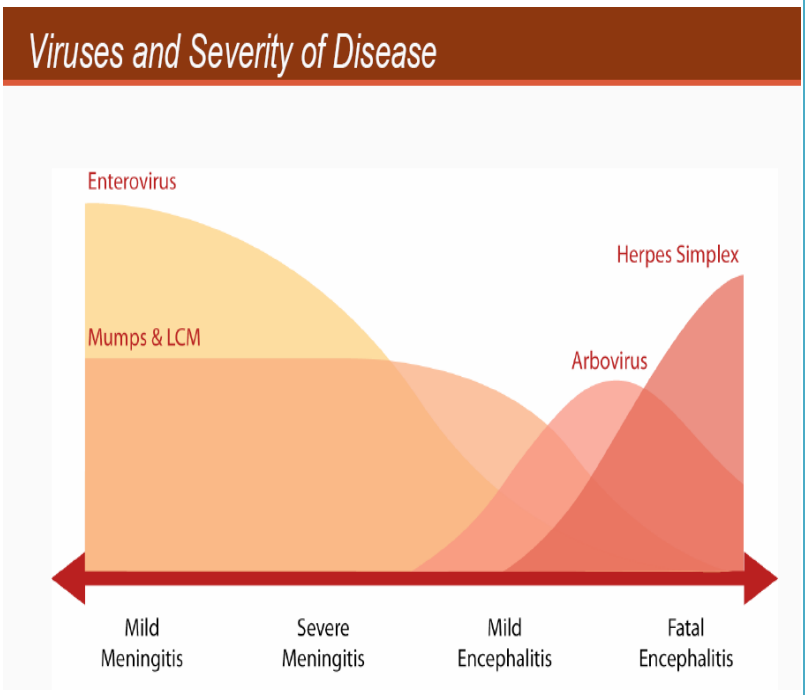
There is NO specific treatment for any of the aforementioned conditions/symptoms.

2- **Progressive post-rubella panencephalitis** mimics SSPE .However, it follows infection with the rubella virus rather than measles. It's associated with either persistent rubella virus infection of the CNS, or less frequently as a congenital infection with rubella which manifests later on in adulthood. There are no specified treatments for this case.

3- **Progressive multifocal leukoencephalopathy (PML)** caused by the JC / polyoma virus; this is usually seen in those who are under immunosuppressive therapy or have an immune-compromising condition e.g. AIDS / malignancies. Once again there is no specific treatment for this condition.

4- **Persistent enteroviral infection** ; as we mentioned in the previous lecture, enteroviruses are usually associated with aseptic meningitis, however a small percentage of those viruses may persist in the body for long periods and cause persistent infection which then develops into encephalitis. In this case the patient presents with confusion, lethargy, seizures, and pleocytosis (increased cell count, particularly WBC count) in the CSF. Although there is again no specific treatment for this condition, researchers found that administration of immunoglobulins specific to the enterovirus involved can improve the patient's state, however once the administration is stopped, the patient relapses and deteriorates once again. →so,there is specific treatment for this condition.

The diagram to the right shows the positive organisms, and the severity of the infection with the virus, and moves from mild meningitis all the way to fatal encephalitis.



- Enteroviruses are generally associated with mild cases of meningitis
- Mumps and lymphocytic choriomeningitis virus (LCV) are also associated with mild to moderate meningitis
- Arboviruses range from severe meningitis to encephalitis
- Herpes simplex virus (HSV), mainly **type 1 HSV**, is associated with moderate-severe encephalitis and can be very fatal, especially in the case of neonates in which the mortality rate can be as high as 100%, while in adults it's around 60-70%.

So how do we differentiate between **viral encephalitis** and **viral meningitis**?

It is generally quite difficult to distinguish between the two conditions ; because the clinical symptoms and presentation of the patient are quite similar. The patient could even present to you with symptoms of both meningitis and encephalitis. Some of the main symptoms include (but are not limited to); headache, vomiting, nausea, confusion, neck stiffness, fever…etc. So a patient with photophobia / stiffness, although you may suspect the diagnosis to be meningitis, may actually have encephalitis.

As a general rule; **check the table in the slides for a summary of these**

1. **Constitutional symptoms** (fever/vomiting/headache…etc) are present in both meningitis and encephalitis
2. **Stiffness and Photophobia** although present in both, we usually suspect meningitis rather than encephalitis; because it is more common in the former
3. **Neurological dysfunction** is more common in encephalitis than meningitis
4. **Cranial nerve palsies / paralysis** is also more common in encephalitis (very rare in viral meningitis)
5. **Coma / seizures** are rarely seen in meningitis, but are common in encephalitis

What are the viruses that cause **meningitis** and **encephalitis**?

1. **Herpesviridae** ; herpes simplex, varicella zoster, EBV, CMV
2. **Paramyxoviruses**; parainfluenza, mumps, measles
3. **Adenoviridae**
4. **Rhabdoviridae** ; the family of viruses that cause rabies (داء الكلب)
5. **Retroviridae** (HIV)
6. **Enteroviruses** ; polio, coxsackie, echovirus
7. **Arboviruses** ; a group of viruses which are **AR**thropod **BO**rne, and are divided into three different families of viruses (togaviridae, flaviviridae, and bunyaviridae), and these are collectively called the Arboviruses; because they are transmitted by mosquitoes / ticks / other organisms. Arboviruses is not a family of viruses ,its a group of viruses which are **Ar**thropod **Bo**rne.

- From these **Arboviruses**;

Viruses causing encephalitis in the *Togaviridae* → **Eastern equine encephalitis (EEE)**, **Western equine encephalitis (WEE)**, and **Venezuelan equine encephalitis (VEE)**.

Viruses causing encephalitis in the *Flaviviridae* → **St. Louis encephalitis**, **West Nile encephalitis**, **Murray Valley encephalitis**, **Japanese encephalitis**…etc. And each of these viruses belongs to a specific geographical location. However in terms of structure, they are very similar since they are considered part of the same family.

As for the viruses causing encephalitis in the *Bunyaviridae* → **California encephalitis**, and **La Crosse encephalitis**.

- While from the **herpesviridae**, we said previously that the herpes simplex virus (**HSV**) **type 1** is mainly associated with **encephalitis**, and **type 2** is mainly associated with **meningitis**. To differentiate between primary / recurrent (secondary) infection with herpes simplex virus, we check whether the patient has any genital lesions; if genital lesions are present, then this means the patient has primary infection with the virus ,{HSV-2 (which produces most genital herpes)}, while if they are not present, then the infection is recurrent.

Herpes simplex encephalitis is one of the most serious complications of herpes simplex disease. There are two forms; *focal disease* related to children/adults, and *neonatal*. In the neonatal cases, the brain is 'globally' involved, meaning all lobes of the brain are affected and this usually leads to liquefaction of the parenchyma of the brain, i.e. liquefactive necrosis, leading to death (100% mortality rates). While in the case of focal disease, the temporal lobe is most commonly affected, it appears in children and adults, and is usually caused by reactivation of the virus. Mortality rates due to focal disease are 60-70%.

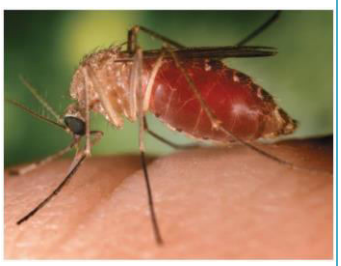
Remember – IF we suspect herpes simplex infection, treatment is **intravenous (IV) acyclovir** without hesitation.

- As for the **paramyxoviridae**, these include the human parainfluenza, measles, and we will also briefly discuss a new virus in this family called the Henipavirus, to which the Nipah virus belongs, and we will also mention the pneumovirus, metapneumovirus, and the human respiratory virus (RSV).

The **Henipavirus** is a newly discovered virus, and can cause severe, rapidly progressive encephalitis in humans, and is associated with high mortality rates, it causes respiratory disease in pigs. So the transmission is from **pigs to humans**. Although they found that the reservoir for the virus is actually the fruit bat, these bats infect the pigs, which in turn infect the humans through direct contact with oral secretions or aerosolization of respiratory secretions. There is **NO** transmission between the fruit bats and humans, nor is there transmission between human-human. And this virus is present most commonly in Bangladesh, Singapore, and Malaysia.

Incubation period is from few days to 2 weeks. It is associated with encephalitis, whereby the person suffers from dizziness, drowsiness, vomiting, seizures, and may even progress to coma within 1-2 days.

Treatment of this virus is supportive/palliative treatment, and since it belongs to the paramyxoviridae family, using Ribavirin *may* prove to be effective.



- Back to the **Arboviruses**, or arthropod-borne viruses, these are viruses which are transmitted to mammals (including humans) by blood-feeding insects called arthropods. Deliberate infection occurs when an infected insect bites an animal/human and takes their blood meal. In the case of mosquitoes, the virus *may* be injected directly into the blood stream when the mosquito attempts to take its blood meal, however as a general rule this is **not** the case. When the mosquito bites the animal/human, it releases secretions around the area where the bite is present. These secretions which contain the virus, cause the bitten human/animal to scratch the area, which causes damage to the skin tissue and breaks the skin barrier, allowing the virus to enter into the bloodstream.

The virus can multiply in the tissue of the arthropod without any evidence of disease or damage. The vectors (mosquitoes/ticks) acquire life-long infection with the virus when they suck blood from an infected viremic vertebrate / mammalian.

All Arboviruses have an RNA genome, and most have a lipid containing envelope and are consequently inactivated by sodium or ether deoxycholate.

It is also worthy to note that ALL of these infections actually primarily arise from **animals**; whether it be birds/cattle/horses…etc, and they are transmitted to humans via the arthropod vectors which caught the virus from those animals when they took a blood meal from them. In which they will become carrier or infected with those viruses .

We have **2 cycles** of infection in the case of Arboviruses; we have the ***Urban***, and the ***Rural* or *Jungle* cycles**. In the case of the *Urban* cycle, transmission occurs from an infected human to the arthropod vector, to another human. While in the case of the *jungle/rural/sylvatic* cycle, transmission occurs from the animal to the vector to the human. Both of these cycles may be seen simultaneously in some Arboviruses such as the yellow fever.

Part #2

Three families of arboviruses

- Togaviridae ->Genus Alphavirus
- Flaviviridae -> Genus Flavivirus
- Bunyaviridae ->Genus Bunyavirus

Approximately 80 arboviruses known to cause human disease. This number is increasing due to scientists discoveries every year.

Transmission Cycles

•Man -> arthropod -> man (urban cycle)

- e.g. dengue, urban yellow fever.
- Reservoir may be in either man or arthropod vector.
- In the latter transovarial transmission may take place.

•Animal -> arthropod -> man (*jungle/rural/sylvatic* cycle)

- e.g. Japanese encephalitis, Eastern equine encephalitis(EEE), Western equine encephalitis (WEE), jungle yellow fever; so as you can see yellow fever can be transmitted by both urban and rural cycle.
- The reservoir is in an animal.
- The virus is maintained in nature in a transmission cycle involving the arthropod vector and animal. Man becomes infected incidentally.
- Both cycles may be seen with some arboviruses such as yellow fever.

Animal Reservoirs (The dr. said that there will be a question on this point)

In many cases, the actual reservoir is not known. The following animals are implicated as reservoirs

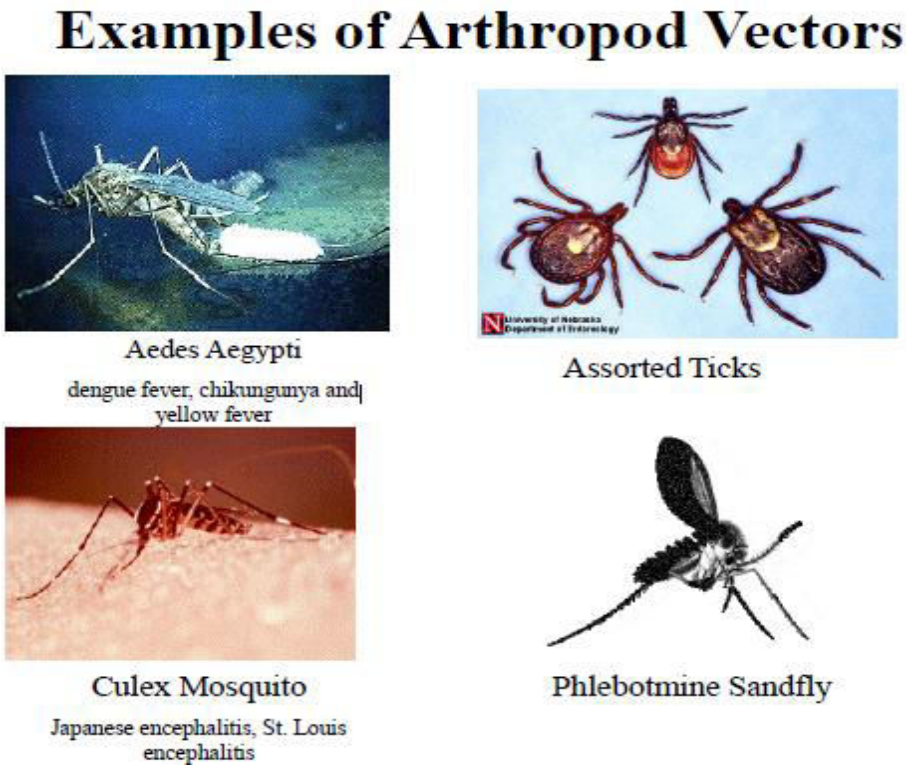
•Birds; Japanese encephalitis, St Louis encephalitis, EEE, WEE

•Pigs ;Japanese encephalitis

•Monkeys; Yellow Fever

•Rodents ;VEE, Russian Spring-Summer encephalitis

The virus is carried by a vector from an infected animal, and then transmit it to human; directly(biting the human) or indirectly.



Keep in mind, zika virus (the recent outbreak) is also transmitted by aedes egypti

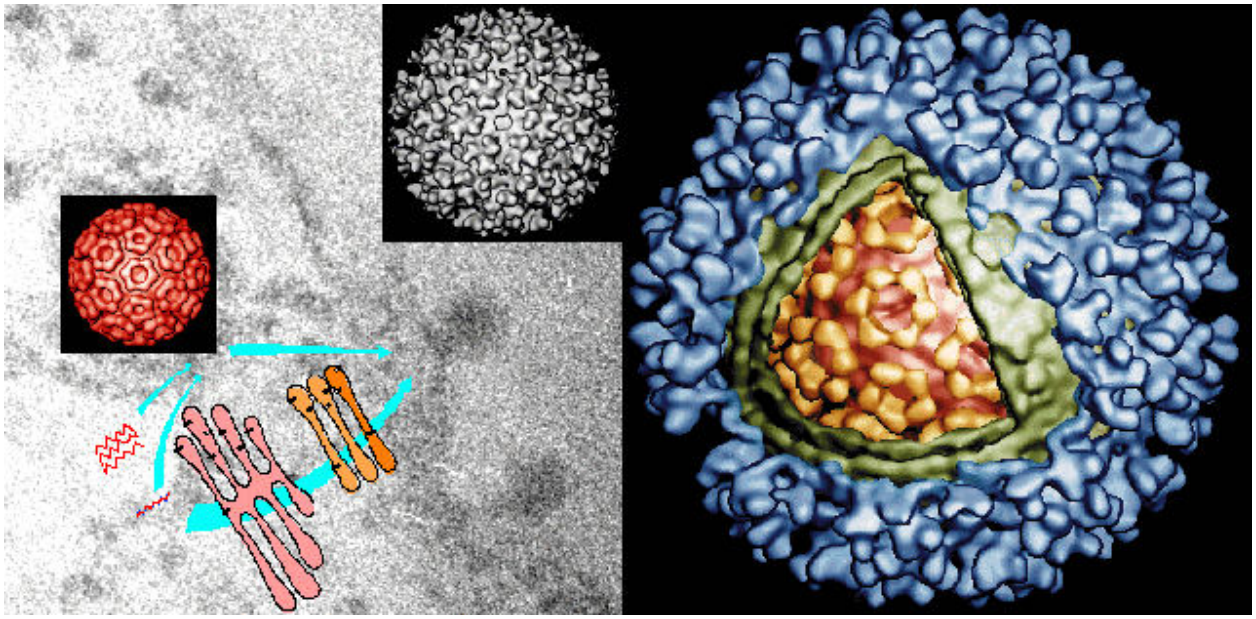
Diseases Caused

- **Fever and rash** - this is usually a non-specific illness resembling a number of other viral illnesses such as influenza, rubella, and enterovirus infections. The patients may go on to develop encephalitis or haemorrhagic fever.
- **Encephalitis** - e.g. EEE, WEE, St Louis encephalitis, Japanese encephalitis.
- **Haemorrhagic fever** - e.g. yellow fever, dengue, Crimean-Congo haemorrhagic fever.

Those patients develop Haemorrhagic fever then will start to bleed internally or externally. Loss of blood (external bleeding) is not a main cause of death.

The patient die from internal bleeding in most cases, in which there will be organ failure ,where the bleeding occurs in. which causes death .

Structures of Alphaviruses



•Single stranded, +ve sense, enveloped RNA virus with Icosahedral capsid

•it has 2 Glycoproteins E1 and E2

•Hemagglutinate via fusion of E1 with lipids on erythrocyte membrane.

What is the different between hemagglutination and agglutination? Both result in clotting ;but Hemadsorbtion is done in lab (cell) cultures, also is used in culturing influenza and measles .

hemagglutination →the Ag on the virus (in this case E1 glycoprotein) is the one responsible for attachment of receptor to target cell. The virus naturally is a free virus which has E1 all around its surface ,and is going to bind the RBCs and cause something similar to clot formation (agglutination).

Hemadsorbtion →attachment of RBCs to surface glycoprotein of the virus E1 .and this is done in a cell culture so you inoculate the virus in a cell culture (eg; influenza and measles).once the virus enters, and you put RBCs in the cell culture. The RBCs are going to bind the glycoprotein on the surface of the virus.

Principal medically important Alphaviruses

Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution
Eastern equine encephalitis	Encephalitis (EEE)	Mosquito	Birds	Americas
Western equine encephalitis	Encephalitis (WEE)	Mosquito	Birds	North America
Venezuelan equine encephalitis	Febrile illness, encephalitis (VEE)	Mosquito	Rodents, horses	Americas

Here you can see the route of transmission→rural cycle

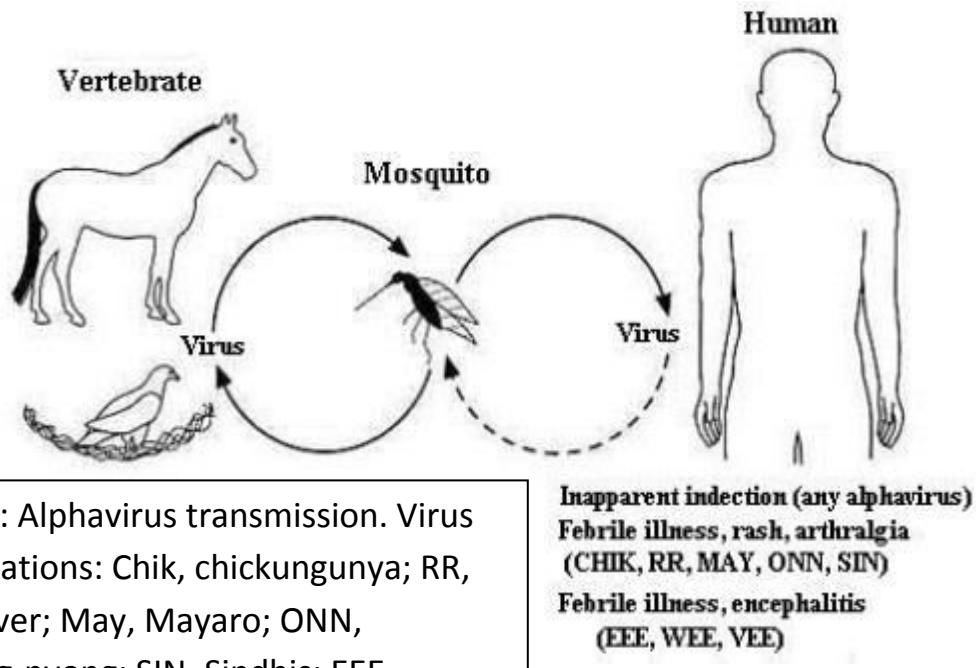
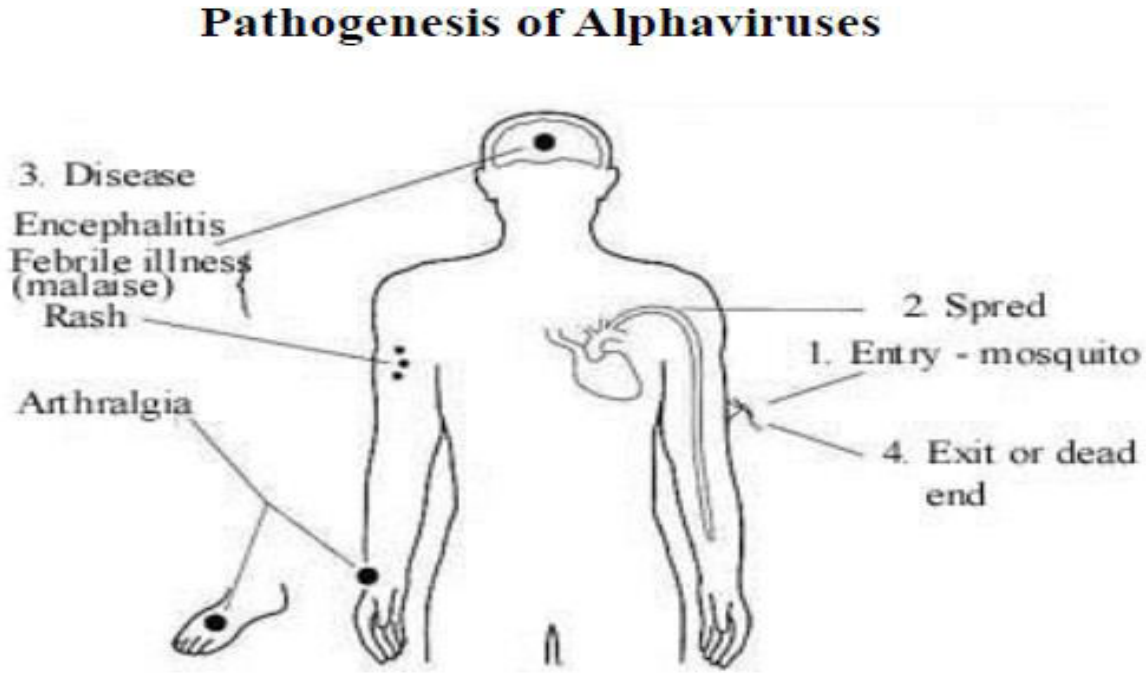


FIGURE: Alphavirus transmission. Virus abbreviations: Chik, chickungunya; RR, Ross River; May, Mayaro; ONN, O'nyong-nyong; SIN, Sindbis; EEE, eastern equine encephalitis; VEE, Venezuelan equine encephalitis



The virus will enter from the mosquito directly by injection into blood or by putting secretions on the skin and indirectly enter the skin by scratching .After that it will spread by blood and cause encephalitis ,febrile illness and arthralagia.

exit →another mosquito take blood from the infected human and spread the virus to others.

dead end→the infected human recover from the disease or die .

Symptoms : EEE

•Most people have no symptoms, mainly depends on the immunity of the patients and the amount (dosage) of the virus in their body

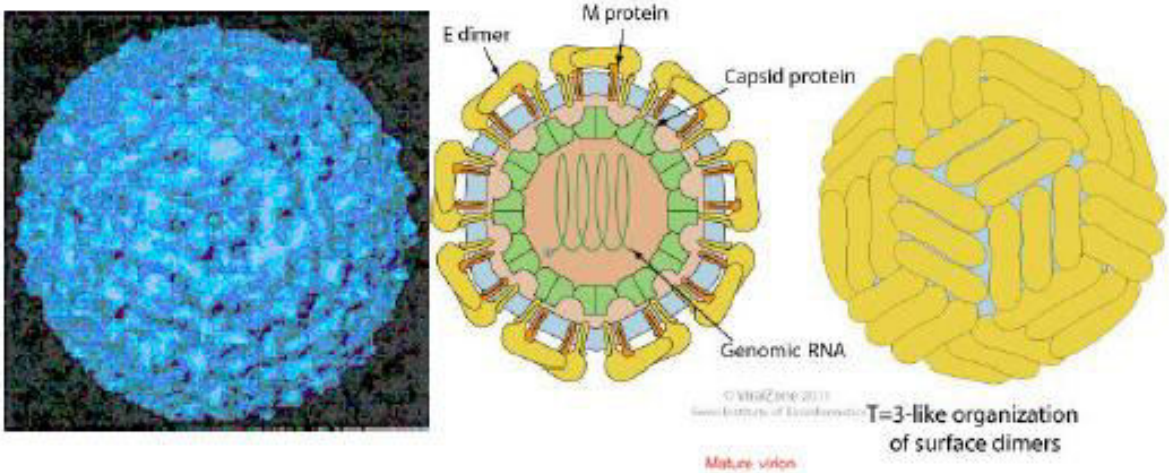
•Central Nervous system symptoms develop 4-10 days after being bitten

•Sudden onset of fever, muscle aches, headache

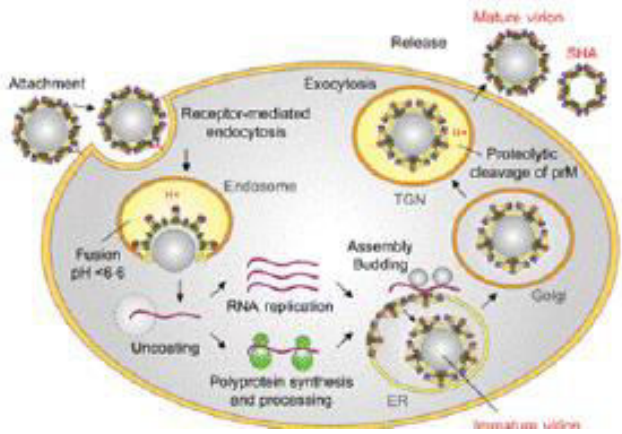
•May progress to more severe symptoms such as seizure and coma (encephalitis)

•30 to 50% of patients with encephalitis die of the disease

Structure of Flaviviruses



Positive sense, single stranded, enveloped RNA viruses with icosahedral capsid.



Pay attention to the parts shown in this picture

#febrile illness →fever, general symptoms of arthralgia and myalagia without developing encephalitis.

Principal medically important Flaviviruses

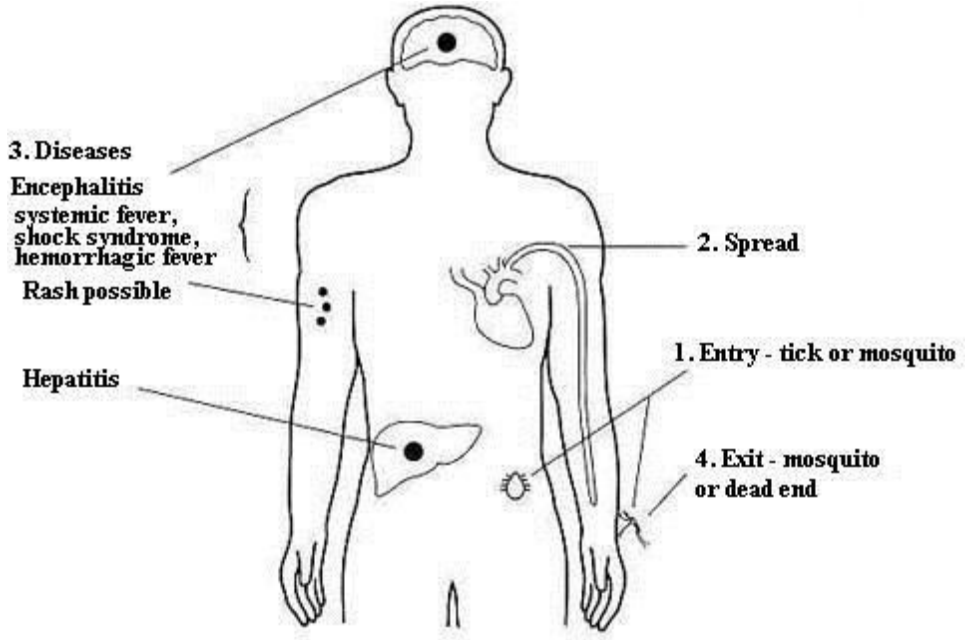
Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution
Murray valley	Encephalitis	Mosquito	wild water birds	Australia
Powassan	Encephalitis	Tick	Squirrels snowshoe hare Rabbit	Canada
St. Louis encephalitis (SLE)	Encephalitis	Mosquito	Birds	Americas

Principal medically important Flaviviruses

Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution
Japanese encephalitis (JE)	Encephalitis	Mosquito	Pigs, birds	India, China, Japan, South-East Asia
West Nile	Febrile illness or encephalitis	Mosquito	Birds	Africa, Middle East, Europe
Tick-borne encephalitis (TBE)	Encephalitis	Tick	Rodent	Europa, Asia

((Human infection with both mosquito-borne and tick-borne flaviviruses is initiated by deposition of virus through the skin via the saliva of an infected arthropod (Fig).)). As described before;" Deliberate infection occurs when an infected insect bites an animal/human and takes their blood meal. In the case of mosquitoes, the virus *may* be injected directly into the blood stream when the mosquito attempts to take its blood meal, however as a general rule this is **not** the case. When the mosquito bites the animal/human, it releases secretions around the area where the bite is present. These secretions which contain the virus, cause the bitten human/animal to scratch the area, which causes damage to the skin tissue and breaks the skin barrier, allowing the virus to enter into the bloodstream."

#This point was repeated a lot in the lecture. (important)



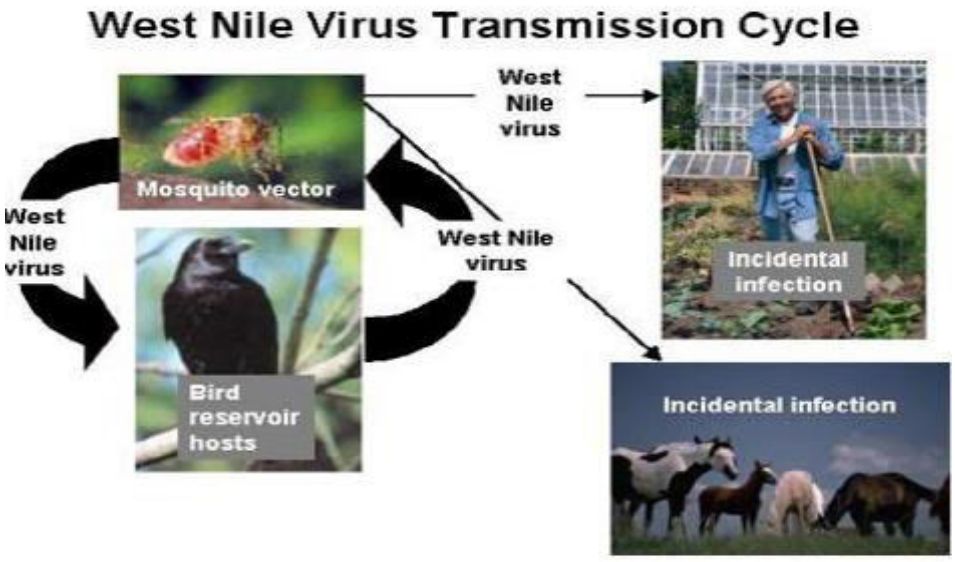
Japanese Encephalitis

- First discovered and originally restricted to Japan. Now large scale epidemics occur in China, India and other parts of Asia.
- Most human infections are subclinical: the inapparent to clinical cases is 300:1
- In clinical cases, a life-threatening encephalitis occurs.
- The disease is usually diagnosed by serology.

• No specific therapy is available.

• Since Culex (the vector of the virus) has a flight range of 20 km, all local control measures will fail. An effective vaccine is available.

Transmitting WNV infection



Symptoms : West Nile virus

•Most people do not develop symptoms, an estimated 20% become ill 3-15 days after being bitten

–Mild illness: fever, headache, body aches, and sometimes skin rash and swollen glands

•An estimated 1 in 150 (more than Japanese encephalitis) persons infected develop a more severe form of the disease

–West Nile encephalitis: inflammation of the brain, high fever, stiff neck, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis; few cases have been fatal

It occurs in the form of outbreaks, e.g. 3-4 years ago there was an outbreak in North America especially in hot humid states like Texas.

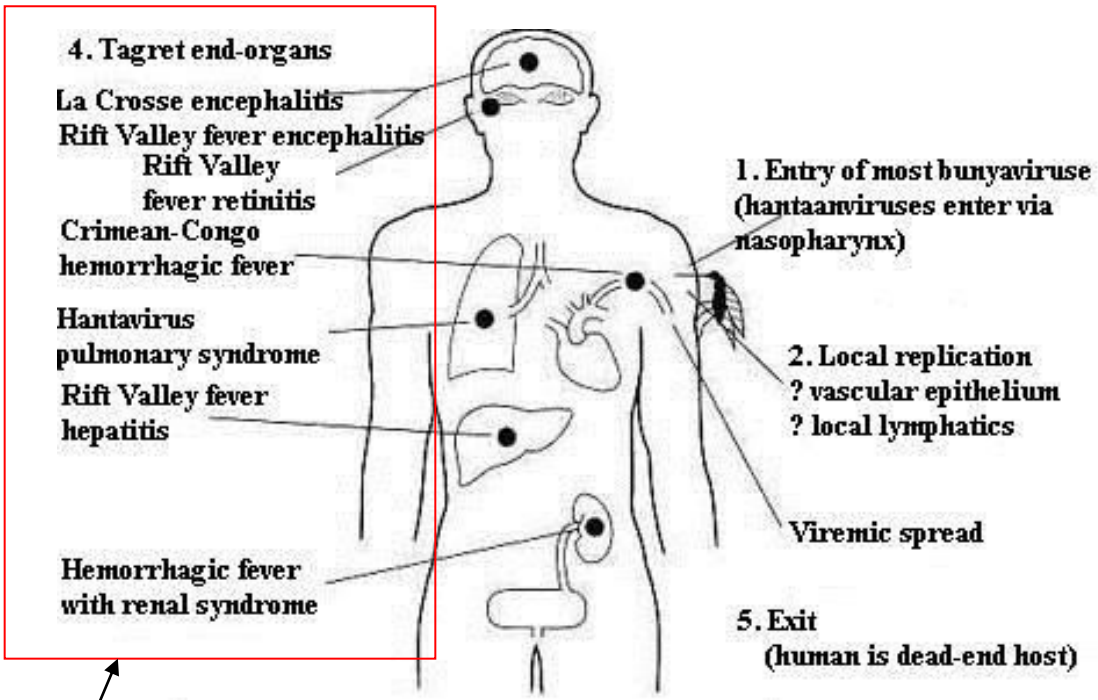
Bunyaviridae is the last family of viruses; it is a family of arthropod borne viruses, spherical, enveloped, single stranded negative sense RNA, with two types of glycoproteins G1 and G2, with 3 nucleocapsids (S=small, M=medium, L=large). Some may think that bunyaviridae are segemented viruses ,however they do not completely fulfill the requirements to be a segmented virus.

(A segmented virus is a virus with a segmented RNA molecule in which each segment produces its own protein)

Examples of segmented viruses are influenza virus and rotavirus.

The reason bunyaviridae isn't considered a segmented virus; because these fragments (small/medium/large) code for more than one protein each. For example the medium fragment codes for G1/G2 and nonstructural proteins. The L fragment codes for the L protein, and the S fragment encodes for nonstructural proteins too.

Bunyaviruses are responsible for a number of febrile diseases in humans, and other vertebrates. Examples are California encephalitis, Rift valley fever, and La Crosse which are also associated with encephalitis.



Pathogenesis of bunyavirus infections

The dr. read those in the box

Serology is the best tool to be used to diagnose bunyavirus infections. Since the viruses are considered very harmful, cultures need to be done at biosafety lab levels of 3-4 and so isn't done routinely.

Prevention – eradication of the vectors (mosquitoes/ticks), control of vector by pesiticides, personal protection of humans through cleaning houses, bed nets, insect repellants, and wearing protective clothing.

Vaccination is rare, only present for yellow fever, Japanese encephalitis and Russian tick-borne encephalitis do have vaccines .

Treatment is palliative/supportive, with good nursing care. There is No specific therapy.

Arboviral encephalitis treated by hospitalization, intravenous fluids, respiratory support, prevention of secondary infections, and good nursing care

Thank you ☺

¬ Dedicated to Q and C.H