

CNS

Microbiology lecture III

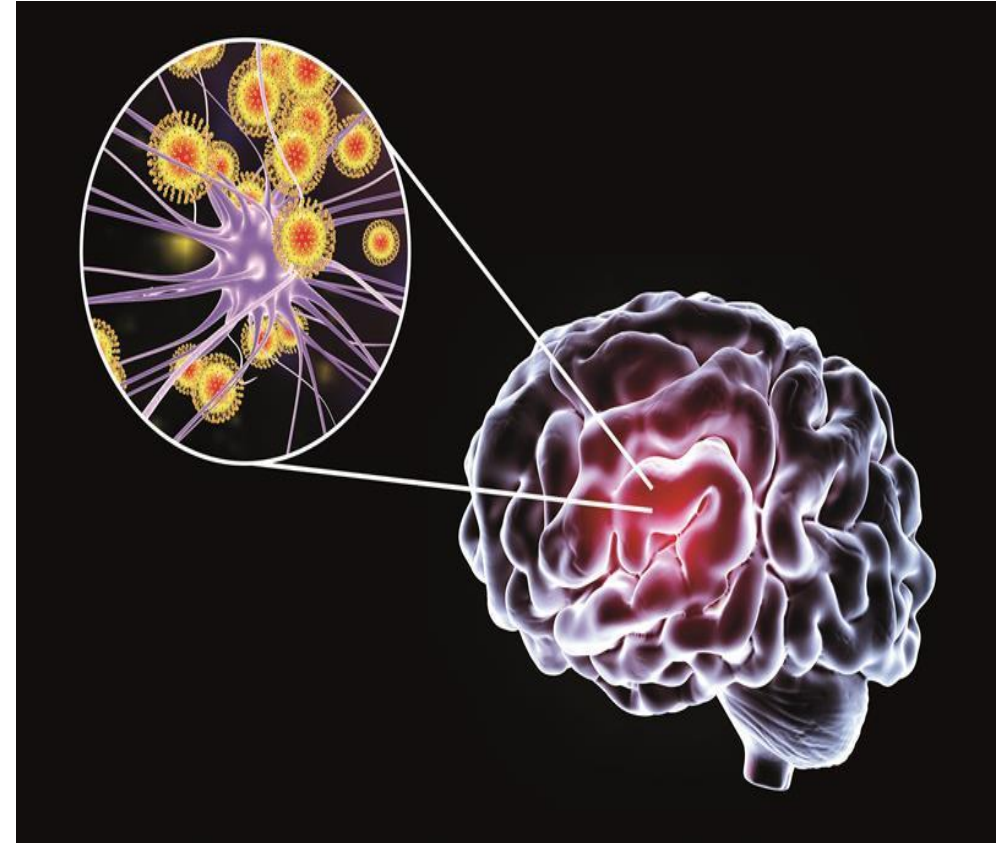
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Encephalitis

- Encephalitis is an inflammation of the of the brain parenchyma caused by:
 - A virus, which is the most common type of encephalitis.
 - Acute or chronic demyelinating diseases, this includes the postinfectious or allergic encephalomyelitis syndromes, in which the cause and pathogenesis are not always clearly defined.



Presentation

- Encephalopathy: altered consciousness persisting for longer than 24 hours, including lethargy, irritability or a change in personality or behavior.
- Encephalitis presents as diffuse and/or focal neuropsychological dysfunction. Although it primarily involves the brain, meninges may be frequently involved as well (meningoencephalitis).
- Focal neurologic deficit: a nerve function problem that affects a specific area. For example, hearing loss or double vision.
- Neuropsychiatric features such as altered mental status, hallucinations, and/or cognitive decline are often seen.



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- Encephalitis: encephalopathy AND evidence of CNS inflammation, demonstrated by at least two of the following:
 - Fever
 - Seizures or focal neurological findings attributable to the **brain parenchyma**.
 - CSF pleocytosis (increased WBCs)
 - EEG findings suggestive of encephalitis
 - Neuroimaging findings (MRI) suggestive of encephalitis



Viral Encephalitis

- Viral encephalitis is a life-threatening process characterized clinically by altered consciousness and frequently by diffuse or focal neurologic signs and behavioral changes.
- Viruses invade the central nervous system (CNS):
 - Hematogenous route
 - In a retrograde manner from nerve endings
- Viral encephalitis tends to be more common in younger people compared to elderly individuals.



Etiology

- The major causes of viral encephalitis:
 - Herpes simplex virus 1 (HSV-1)
 - Arboviruses
 - Measles
 - Varicella-zoster virus
 - Lassa fever encephalitis
 - Human immunodeficiency virus
 - JC virus



HSV-1

- Herpes simplex virus-1 is the most important cause of sporadic viral encephalitis in the United States. It is an enveloped DNA herpesvirus.
- Most **severely-affected** patients are immunologically normal; indeed, an intact immune system may be required for full expression of the disease since immunocompromised patients tend to have a milder course.
- HSV-1 encephalitis can be the result of a primary infection, a reactivation of latent HSV, or a re-infection by a second HSV.
- The most characteristic symptoms and signs of encephalitis due to HSV-1 are attributed to the affinity of the virus for the temporal and frontal lobes. The temporal lobe controls memory and speech while the frontal lobe controls emotions and behavior.
- Encephalitis caused by herpes is dangerous and can lead to severe brain damage and death.



Diagnosis (HSV-1)

- Temporal lobe involvement can be demonstrated by imaging procedures (CT or MRI scan) or by electroencephalography (EEG):
 - MRI scans are more sensitive and specific than CT scans especially during the early phases of the disease.
 - The EEG shows focal abnormalities in more than 80% of cases.
- Lumbar puncture is usually within normal limits.
- The most important specific test on CSF is the polymerase chain reaction (**PCR for HSV-1 DNA**). Reported to be up to 98% sensitive and 100% specific, PCR has replaced brain biopsy as the diagnostic procedure of choice.



Arboviruses

- **Arthropod-borne viruses or 'arboviruses'** are a diverse array of RNA viruses that share the unique characteristic of transmission by hematophagus (blood-sucking) arthropods, including ticks, mosquitoes and sandflies.
- In general, these represent 'dead-end infections' in unnatural vertebrate hosts. Infection with arboviruses can result in a wide range of disease syndromes, including systemic febrile illnesses, encephalitis, and hemorrhagic fevers.
- More than 20 arboviruses that can cause encephalitis have been identified. These arboviruses are enveloped RNA viruses from four different families. Arboviruses that infect the CNS usually cause meningoencephalitis.



Arboviruses

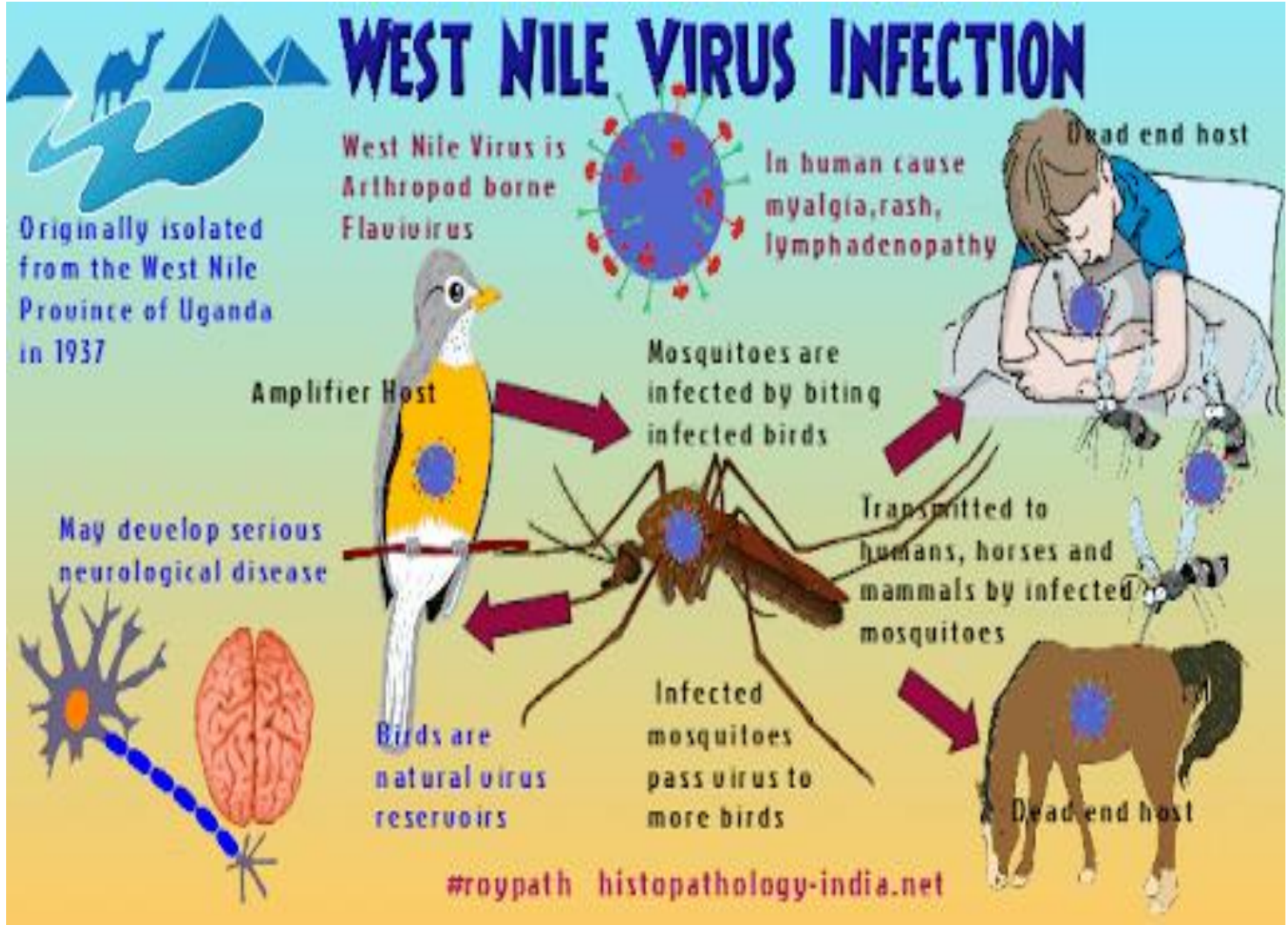
Family	Virus	Arthropod vector	Mortality rate
Togaviruses	Eastern equine virus	<i>Aedes</i> spp.	35%
	Western equine virus	<i>Culex</i> spp.	10%
Flaviviruses	West Nile virus	<i>Culex</i> or <i>Aedes</i> spp.	12% in elderly people
	St Louis encephalitis virus	<i>Culex</i> spp.	2% in young people 20% in elderly people
	Japanese encephalitis virus	<i>Culex</i> spp.	50% in elderly people
Bunyaviruses	La Crosse strain of California encephalitis	<i>Aedes</i> spp.	Low
Reoviruses	Colorado tick fever virus	<i>Dermacentor</i> (tick)	Low



West Nile Virus (WNV)

- Is an RNA virus that belongs to the Flavivirus family.
- WNV infection manifests as two clinical syndromes: West Nile fever and West Nile encephalitis. WNV encephalitis can be defined as a disease that causes encephalitis, meningitis, or acute flaccid paralysis.
- Advanced age is by far the greatest risk factor for severe neurologic disease and long-term morbidity.
- Patients may suffer from severe muscle weakness or flaccid paralysis.





Diagnosis (WNV)

- Viremia is detected as early as 1 to 2 days after the primary mosquito bite and persists for up to 1 week until the development of IgM neutralizing antibodies.
- IgM capture enzyme-linked immunosorbent assay (ELISA) in either blood or CSF during the acute phase is **the gold standard** for the diagnosis of WNV encephalitis and is generally always present by the time neurologic symptoms manifest.
- CSF PCR may be helpful very early in the disease but generally has a low sensitivity (57%).



Other Arboviruses

- **St. Louis encephalitis virus** infection can cause mild febrile illness, aseptic meningitis, or encephalitis. Encephalitis can be accompanied by hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Individual susceptibility to the St Louis virus increases with age.
- **Japanese encephalitis virus** is a neurologic infection with a broad range of manifestations. It can range from subtle changes in behavior to serious problems, including blindness, ataxia, weakness, and movement disorders. Less than 1% of people infected with Japanese encephalitis virus develop symptomatic disease.
- **La Crosse virus** is the most common cause of arboviral encephalitis in the United States and produces seizures and focal neurologic signs, manifested primarily in children, with a mortality of less than 1% and rare sequelae.



Measles

- RNA virus that belongs to the Paramyxoviridae family.
- Measles virus (MeV) infection causes an acute systemic disease; fever, cough, rash, etc.
- Acute measles can be accompanied by early or late CNS complications.
- 2-4 weeks following acute MeV infection some patients develop **acute post-infectious measles encephalitis** (in 0.1% of measles cases). APME is associated with 20% mortality and severe neurological sequelae, mainly in adults. Symptoms include fever, headaches, seizures, and consciousness alterations.
- MeV can also cause **sub-acute sclerosing panencephalitis**. Subacute sclerosing panencephalitis is a very rare, but fatal disease (mortality rate close to 100%) of the central nervous system that results from the persistence of defective measles virus particles in brain cells following an earlier measles infection.



Diagnosis and Prevention (Measles)

- Diagnosis of measles:
 - Serologic testing for measles-specific IgM or IgG titers
 - Isolation of the virus in culture
 - Polymerase chain reaction (PCR) evaluation. Blood, throat, nasopharyngeal, or urine specimens can be used.
- Measles has decreased in incidence due to the introduction of the live-attenuated MMR vaccine. CDC recommends that people get MMR vaccine to protect against measles, mumps, and rubella. MMR is part of the Jordanian children vaccination program.



Varicella-zoster virus

- Varicella zoster virus (VZV) is a DNA virus.
- Primary infection causes chickenpox.
- If the virus is not fully eradicated from the body, it travels and lies dormant in the dorsal root ganglia. Secondary VZV skin eruption demonstrates a characteristic unilateral, vesicular, and painful eruption that follows a distinct dermatomal distribution (Shingles).
- VZV can also cause many different central nervous system pathologies if the infection invades the spinal cord or cerebral arteries, including cerebellar ataxia, arteritis, myelitis, meningitis, and encephalitis. CNS infection can occur with primary or secondary reactivation of the virus.



Diagnosis (VZV)

- Diagnosis:
 - VZV IgM and IgG serum titers.
 - Positive PCR testing in CSF confirms VZV encephalitis.
- VZV serum immunoglobulin M (IgM) appears within 2 to 5 days of symptom onset. Therefore, a positive serum IgM is usually indicative of active infection
- IgG levels decrease with time but generally remain positive for life. Indicating a person's immunity to the disease.
- VZV PCR may be dependent on the time of symptom onset and the time of CSF acquisition with decreasing sensitivity of PCR after 1 week.
- VZV IgG levels have higher sensitivity in comparison to PCR, 93% versus 30%, respectively.



Prevention

- VZV encephalitis has become increasingly prevalent in the era of acquired immunodeficiency syndrome (AIDS). VZV encephalitis mortality rate for immunocompetent patients is approximately 15% and almost 100% in an immunosuppressed patient.
- VZV has a vaccine. Two doses of the vaccine are about 90% effective at preventing chickenpox. Some people who are vaccinated against chickenpox may still get the disease. However, it is usually milder with fewer blisters and little or no fever. This vaccine is optional in the Jordanian children vaccination program.



Lassa fever encephalitis virus

- RNA Arenaviruses usually infect rodents. Thus, infection most commonly occurs during the winter, when mice are indoors, and humans have contact with their excreta.
- Lassa fever (LF) is a West African disease that starts with gastrointestinal (GI) and respiratory complaints and progresses to hemorrhagic shock.
- In severe cases, LF may present with central nervous system (CNS) features and is usually associated with bleeding and poor prognosis. Unilateral or bilateral deafness may follow the period of encephalitis. Mortality is in the range of 8-52%.



Rabies virus

- Bullet-shaped RNA virus of the Rhabdoviridae family.
- Rabies virus is transmitted through saliva of infected animals, usually after a bite.
- Rabies is an important pathogen in developing countries, where endemic canine infection still exists (dogs). Rabies is also present in wild animals (skunks, foxes, raccoons, bats). It can be controlled in domestic animals with vaccination.
- After a bite, Rabies virus travels to the CNS by migrating in a retrograde fashion up nerve axons after binding to acetylcholine receptors. It replicates in the neurons of the brain and spinal cord.
- Rabies has a long incubation period (weeks to months) before symptom onset.



Rabies

Vaccinate your pet



Vampire bats in Latin America



Dog, wolf, fox are principal reservoirs



1) Man bitten by rabid animal (dog)

2) Virus from infected saliva enters the wound



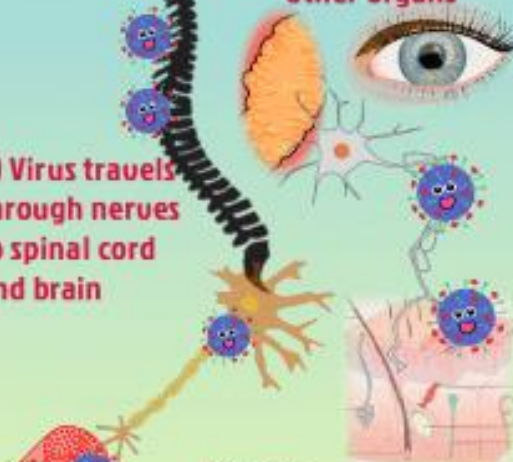
Rabies is a Rhabdovirus

5) Infection of brain neurons



6) Virus spread along nerves to salivary glands, cornea, skin & other organs

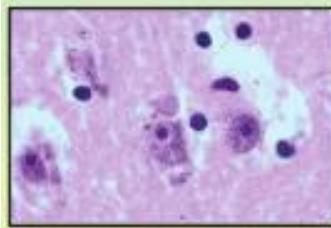
4) Virus travels through nerves to spinal cord and brain



3) Virus multiplies in muscle



Disease progresses to death within one to several weeks



Diagnosis and Prevention (Rabies)

- Progression of disease:
 - fever, malaise, tingling sensation at the site of the bite
 - agitation, photophobia, hydrophobia, hypersalivation
 - paralysis, coma
 - death
- Rabies is usually diagnosed by postmortem examination. PCR could be done for confirmation.
- **Postexposure prophylaxis** is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. There is no treatment for rabies after the neurological symptoms start, only six cases worldwide have survived and most have significant neurological damage.



HIV

- While HIV can sometimes cause a type of subacute encephalitis, it is important to mention it here because its associated immunosuppression predisposes the individual to viral encephalitis caused by HSV-1, VZV, or cytomegalovirus (CMV).
- Certain forms of encephalitis are observed almost exclusively in patients with HIV. Among those, cytomegalovirus (CMV) encephalitis has emerged as a unique entity in patients with advanced HIV infection.



JC virus (John Cunningham virus)

- A naked DNA virus that belongs to Polyomaviridae family.
- JCV causes a disease known as **Progressive Multifocal Leukoencephalopathy** (PML).
- PML is a rare, subacute, degenerative disease of the brain found primarily in adults with **immunosuppressive diseases**, especially AIDS and hematologic malignancies, or those receiving immunosuppressive agents.
- The disease is characterized by the development of impaired memory, confusion, and disorientation, followed by a multiplicity of neurologic symptoms and signs that include hemiparesis, visual disturbances, incoordination, seizures, and visual abnormalities.
- PML is progressive, with death usually occurring 3 to 6 months after the onset of symptoms.



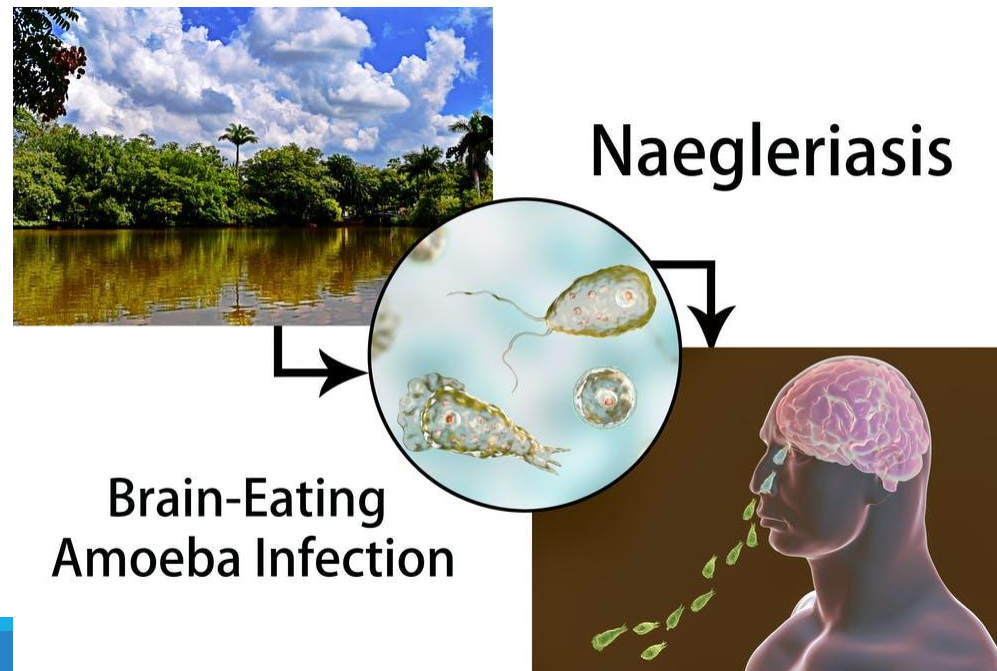
Diagnosis (JC virus)

- CSF findings are often normal, although some patients show a slight increase in lymphocytes, and protein levels may be elevated.
- Histopathology: foci of demyelination are found, surrounded by giant, bizarre astrocytes containing intranuclear inclusions.
- Electron microscope: Abundant JCV particles can be seen in the brain by electron microscopy and may be concentrated within the nuclei of oligodendrocytes.
- There is **no** specific treatment for PML, although reducing the immunosuppression, if possible, may have some clinical benefit.



Parasitic causes of encephalitis

- *Acanthamoeba* species: granulomatous amebic encephalitis
- *Naegleria fowleri*: primary amebic meningoencephalitis (PAM); rapidly progressive fatal disease acquired by entry of *N. fowleri* into the body during swimming in freshwater lakes.



Differential diagnosis of encephalitis

- **Autoimmune:**
 - Antibodies against neuronal surface antigens, mainly associated with tumors:
 - NMDAR antibody encephalitis (ovarian teratoma)
 - LGI-1 antibody encephalitis (thymoma)
- **Infective causes that mimic encephalitis:**
 - Systemic sepsis with encephalopathy.
 - Bacterial meningitis.
- **Inflammatory diseases:** vasculitis, systemic lupus erythematosus with CNS involvement.
- **Metabolic:** hypoglycemia, toxins (drugs, alcohol).
- **Neoplastic:** primary brain tumor (low grade glioma mimicking CNS inflammation).
- **Psychiatric disease**



Diagnosis of encephalitis

- Imaging studies
- Lumbar puncture
- CSF PCR for viral DNA/RNA detection usually yields results within 24–48 hours in most laboratories.
- Serum serological tests
- Viral cultures



Imaging studies

- Either a computed tomography (CT) scan or, ideally, magnetic resonance imaging (MRI) should be obtained urgently. Following this, if there are no radiological contraindications, LP should be performed as soon as possible.
- Brain imaging serves three purposes:
 - to look for changes of encephalitis.
 - to exclude alternative diagnoses.
 - to assess patency of the basal cisterns and an absence of mass effect so that LP can proceed without risk of herniation.



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- **Magnetic resonance imaging (MRI)** is the gold standard technique for brain imaging in encephalitis and is abnormal in 90% of cases of HSV encephalitis but may be normal or subtly abnormal in autoimmune encephalitis.
 - Further imaging techniques including ultrasonography, CT of the body and positron emission tomography (PET) imaging may be indicated if a paraneoplastic cause is suspected.
 - **Electroencephalography (EEG)** is useful in identifying and monitoring seizure activity but is non-specific and can be abnormal in several other causes of encephalopathy.



Lumbar puncture

- **Lumbar puncture (LP):** the key to establishing evidence of central CNS inflammation is the analysis of CSF.
- Ideally, LP should be performed immediately in patients with suspected brain infection, and empirical treatment started immediately thereafter.
- The CSF usually shows:
 - Normal glucose
 - Moderately elevated proteins
 - CSF pleocytosis (>5 white cells $\times 10^9/L$), comprising predominantly lymphocytes
 - About 10% of patients will have normal CSF studies



Management and treatment

- The treatment of viral encephalitis is primarily supportive as there is no specific medical therapy for most central nervous system viral infections.
- Certain viral encephalitis cases may respond well to antiviral therapies.
 1. When started early, **acyclovir** has been shown to significantly decrease mortality and morbidity and limit the severity of long-term behavioral and cognitive impairment of HSV encephalitis.
 2. Acyclovir with possible adjunctive corticosteroids in immunocompetent patients, is recommended for varicella-zoster virus encephalitis.
 3. The recommended treatment for CMV encephalitis is a combination of **ganciclovir** and foscarnet.



Empirical treatment

- Empirically, it is recommended that physicians start all patients with suspected encephalitis on **acyclovir**.
- If LP is delayed for more than 6 hours, empirical acyclovir may be given before the LP. An LP is often excessively delayed, primarily due to performing brain imaging to exclude raised intracranial pressure.



Complications

- Encephalitis may be associated with a number of complications, including the following:
 - Seizures.
 - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
 - Increased intracranial pressure.
 - Coma
 - Death



Thank you 😊

