



UNIwersytet Medyczny
im. Piastów Śląskich we Wrocławiu

Subject: Faculty Lectures of Virology

Topic: Viral CNS Infections

Academic Year 2024/2025

These educational materials are protected under The Copyright and Related Rights Act of February 4, 1994. Their dissemination and use other than for educational purposes of students of the Wrocław Medical University is forbidden.

Faculty: Medicine
Field of study: Medicine
Level of study (unif. Master's):
Form of study (full time, part-time):
Year of study: III

Academic title/professional title: prof. dr hab.
Name, last name of the lecturer: Beata Sobieszczkańska
Position of person conducting classes: professor
Wrocław Medical University
Copyright ©

**Number of CNS viral infections
each year is greater than all
bacterial, fungal and protozoa
infections combined**



Neurotropic viruses - capable of infecting nerve cells

dsDNA	Adenoviridae	
	Herpesviridae	HSV-1,-2; VZV, CMV, EBV
	Polyomaviridae	JCV
(+)ssRNA	Flaviviridae	WNV, JEV
	Picornaviridae	Polio 1-3; EV71
	Togaviridae	CHIKV
(-)ssRNA	Arenaviridae	LCMV
	Bunyaviridae	LACV
	Orthomyxoviridae	Influenza A
	Paramyxoviridae	MV, MuV, HeV, Nipah
	Rhabdoviridae	RabV
ssRNA-RT	Retroviridae	Lentivirus: HIV, HTLV

Transmission to humans



**Respiratory
route**



**Direct
contact**



**Fecal-oral
route**



**Insect/animal
bite**

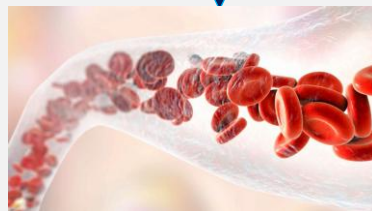
**Paramyxoviruses:
mumps, measles,
Lassa virus**

**Ebola virus,
LCMV,
enteroviruses**

Enteroviruses

**Arboviruses,
Rabies virus**

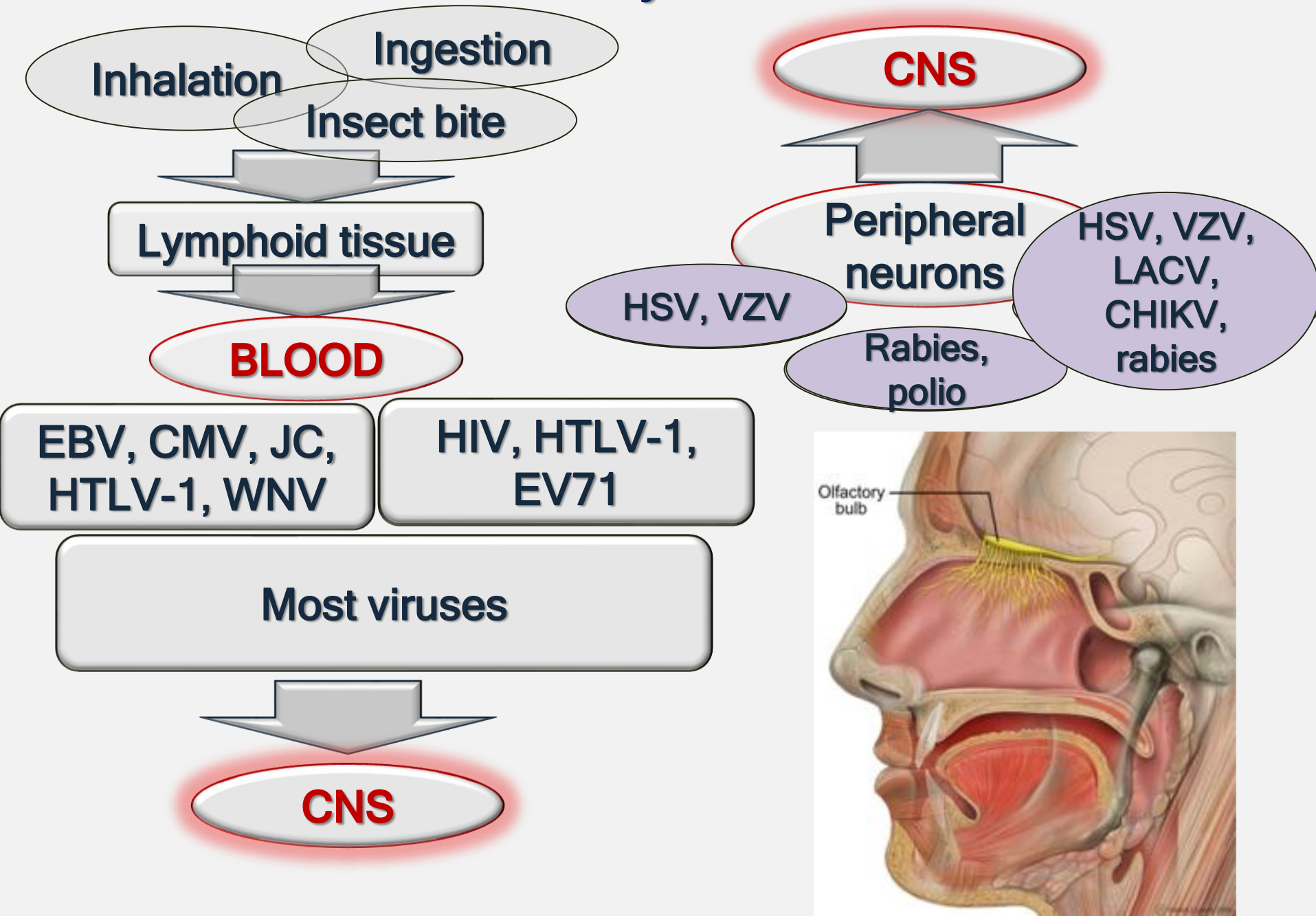
Lymphoid tissue



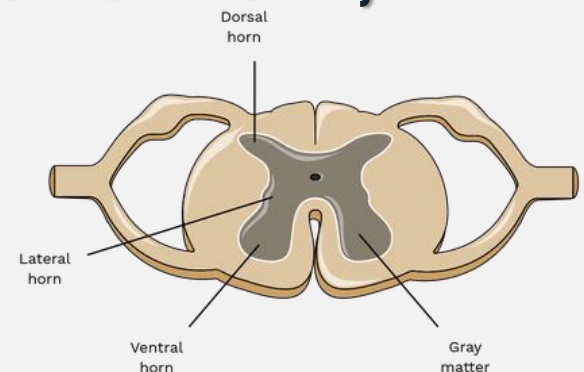
Systemic infection



Viral entry into CNS



- Meninges (**meningitis**): enteroviruses (70-90%), HSV-2, Mumps virus, LCMV
- Brain parenchyma (**encephalitis**): HSV, VZV, EBV, CMV, HHV-6, non-polio enteroviruses, Rabies virus, Mumps virus;
- **Encephalitis limited to certain geographic areas:** Flaviviruses, Alphaviruses (EEE, WEE, VEE, CHIKV)
- Spinal cord (**myelitis**):
- **grey matter** - acute flaccid paralysis: enteroviruses: Polio 1,2,3; Coxsackie A & B; Enteroviruses;
- **white matter**: Herpes viruses



Viral meningitis (aseptic meningitis)

Most common etiologic agents:

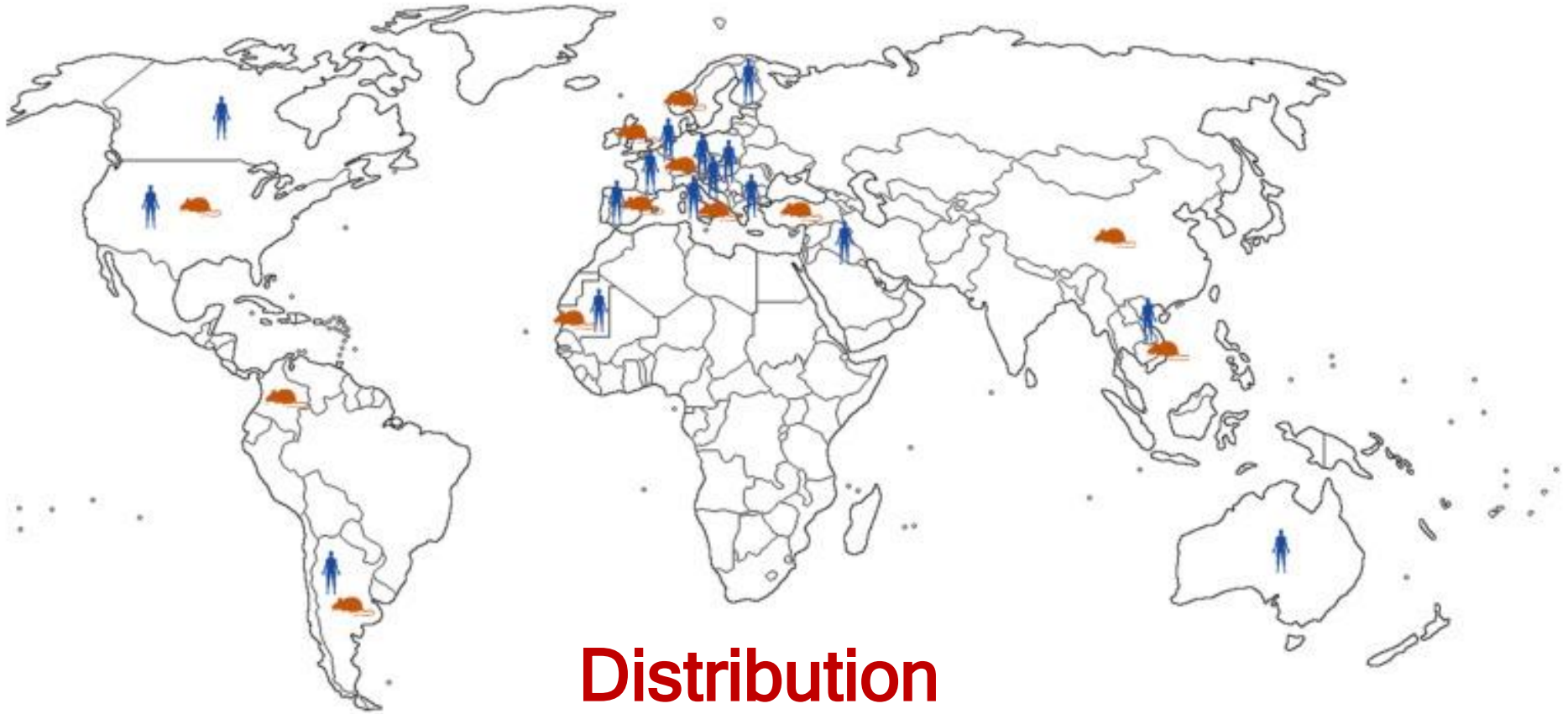
- **Enteroviruses:** EV-D68, EV-A71, EV-D70, EV-B94, EV-B94, ECHO virus 33, Coxsackie A16
- **HSV type 2**
- **Mumps virus**
- **Other:** CMV, EBV, VZV, HIV, arboviruses, LCMV
- **Transmission:** ingestion (fecal contamination of food, water, hands)
- **Symptoms:** acute fever, headache, signs of meningeal irritation, e.g., neck stiffness, photophobia
- **Prognosis - good**
- **Complications:** blindness, deafness, memory troubles, balance issues
- **Treatment:** acyclovir (Herpes viruses), ribavirin, supportive, no specific (mumps vaccine)

Bacterial versus Viral Meningitis

SYMPTOMS	Bacterial Meningitis	Viral Meningitis
 Fever.	✓	✓
 Chills.	✓	✓
 Headache.	✓	✓
 Neck stiffness.	✓	✓
 Nausea/vomiting.	✓	✓
 Sensitivity to light.	✓	✓

CAUSES	Bacterial Meningitis	Viral Meningitis
 <i>S. pneumoniae</i>, Group B strep, <i>N. meningitides</i> and others.	✓	✗
 Enteroviruses, herpesviruses and others.	✗	✓
TREATMENT	Bacterial Meningitis	Viral Meningitis
 Treated with Antibiotics.	✓	✗
 Risk of severe complications	✓	Rare.

Lymphocytic choriomeningitis virus (LCMV) = rodent-borne meningoencephalitis



Host/reservoir: rodents
(mice, hamsters, guinea pigs)



Lymphocytic choriomeningitis virus (LCMV)

Non-fatal, influenza-like illness with occasional aseptic meningitis, but can be fatal if transmitted in utero or through organ transplantation

TRANSMISSION

HORIZONTAL



Direct contact with
infected material or
inhalation
Organ transplantation

Transplant recipient: intracerebral hemorrhages, death, or recovery - mortality rate >70%

VERTICAL



First trimester
= fetal death

From mother to fetus

Congenital infection:
hydrocephalus, chorioretinitis,
mental retardation, abortion,
blindness, seizures, brain
perivascular calcifications

The mortality rate is 35% by 21
months of age

Lymphocytic choriomeningitis virus (LCMV)

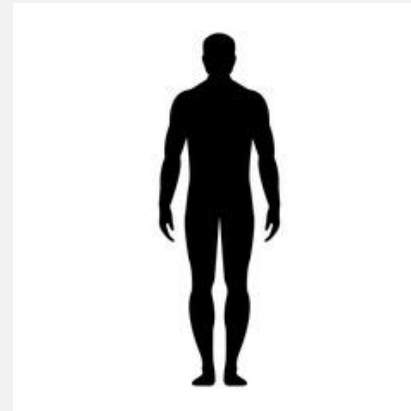
TRANSMISSION



HORIZONTAL



Direct contact with rodents - broken skin, mucous membranes, bite
Indirect - urine, droppings, saliva, nesting material
Inhalation of aerosolized excreta



Lymphocytic choriomeningitis virus (LCMV)

BIPHASIC FEBRILE ILLNESS

- Symptoms: 8-13 days after exposure

Initial phase: flu-like symptoms

Second phase (viremia): meningitis (lymphocytic infiltration of the choroid plexus), **encephalitis**

- Neurologic sequelae: chronic headache, deafness, myelitis, Guillain-Barre syndrome

Transmission of Lymphocytic Choriomeningitis Virus by Organ Transplantation

Authors: Staci A. Fischer, M.D., Mary Beth Graham, M.D., Matthew

J. Kuehnert, M.D., Camille N. Kotton, M.D., Arjun Srinivasan, M.D., Francisco

M. Marty, M.D., James A. Comer, Ph.D., and the LCMV in Transplant Recipients

Published May 25, 2006; N Engl J Med 2006;354:2235-2249; DOI: 10.1056/NEJMoa053240

Lymphocytic choriomeningitis virus (LCMV)

Initial phase: no or minimal symptoms - flu-like symptoms (fever, malaise, weakness, myalgia - especially lumbar, retro-orbital headache, photophobia, anorexia)

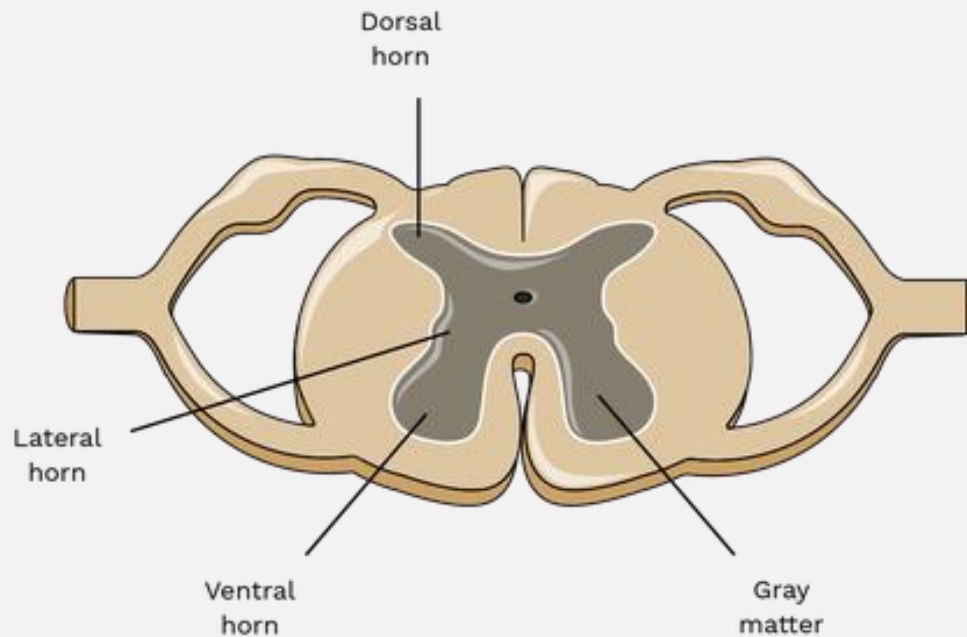
Improvement after 5 days to 3 weeks, but then **relapses** with recurrent symptoms (additionally, orchitis, parotitis, alopecia, joint swelling, rash, meningeal signs)

Second phase (viremia): aseptic meningitis (a minority of patients), rarely frank encephalitis, ascending paralysis, bulbar-paralysis or other neurological signs

- **Neurologic sequelae** (rare in meningitis but occur in 33% of encephalitis cases): chronic headache, deafness, myelitis, Guillain-Barre syndrome
- **Treatment** - supportive; meningitis - ribavirin
- **Diagnosis** - PCR, serology, virus isolation from CSF and/or blood

Viral myelitis

Spinal cord (myelitis): **grey matter** - acute flaccid paralysis: enteroviruses: Polio 1,2,3; Coxsackie A & B; Enterovirus 71;
white matter: Herpes viruses



Symptoms of Acute Flaccid Myelitis (AFM)

AFM is a rare but serious condition that affects the Nervous System of young children



Difficulty moving the eyes or drooping eyelids



Facial droop or weakness

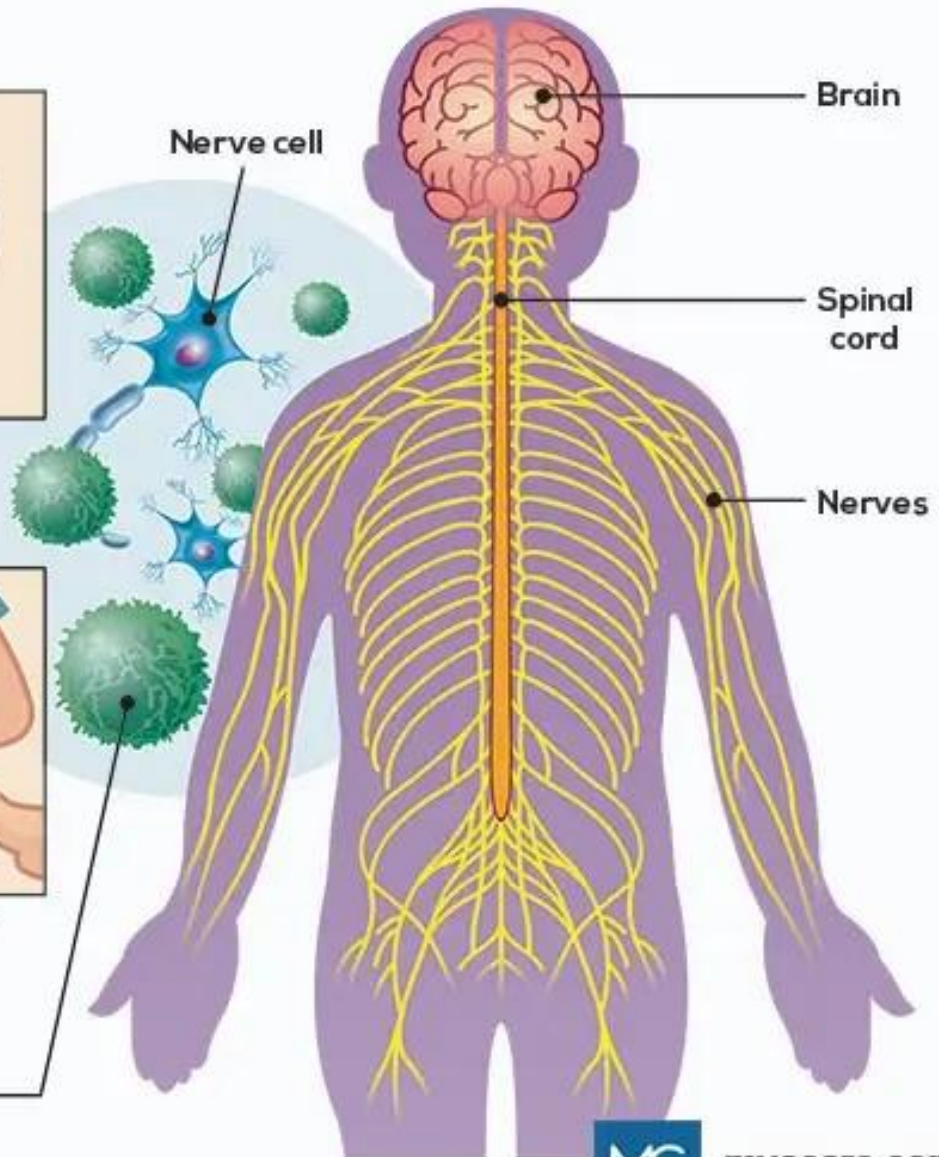


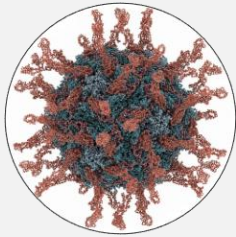
Difficulty swallowing or slurred speech



Sudden arm or leg weakness

Linked to viral infections
(The exact cause remains unknown)





POLIOVIRUS



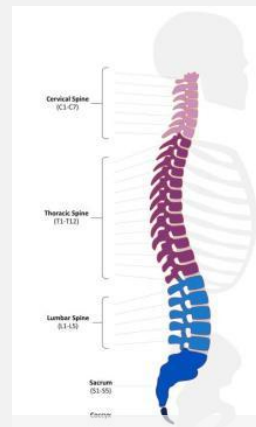
AFP = acute flaccid paralysis



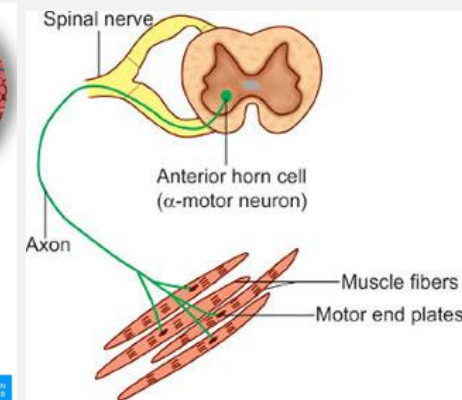
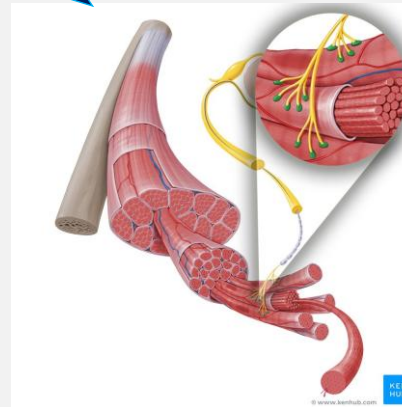
AFM



Spinal cord



Peripheral nerves



Neuromuscular junctions and muscles

POLIOVIRUS



Echoviruses



Enteroviruses



AFM = acute flaccid myelitis

Paralysis and limb weakness occurring within a week of respiratory symptoms of fever caused by a non-polio viral infection

> 500 cases worldwide since 2012

EV-D68 >50% of cases

Classic diagnostic characteristics:

Acute limb weakness

Lesion in the spinal cord

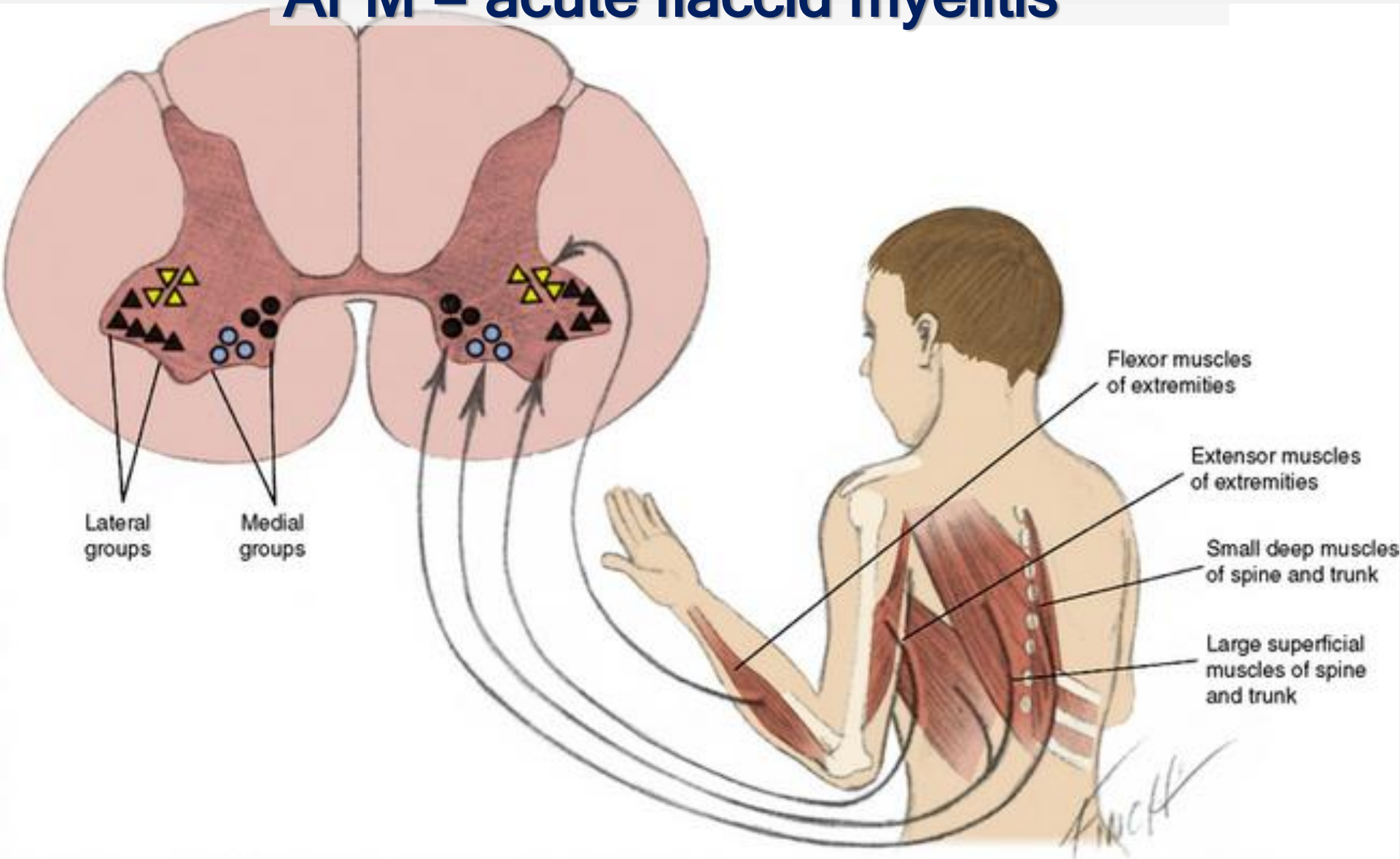
Elevated leukocyte counts in CSF



Inflammation, motor neurons loss within the brain stem and spinal cord

BUT no signs of generalized encephalitis

AFM = acute flaccid myelitis



Family: Picornaviridae

- Genus: Enterovirus
- Subgroups: Poliovirus types 1-3
- Coxsackie virus group A (types 1-22, 24) and group B (types 1-6)
- Echoviruses (types 1-9, 11-27)
- Newer enteroviruses 68, 71 (types 29-34, 68-72)

Poliovirus

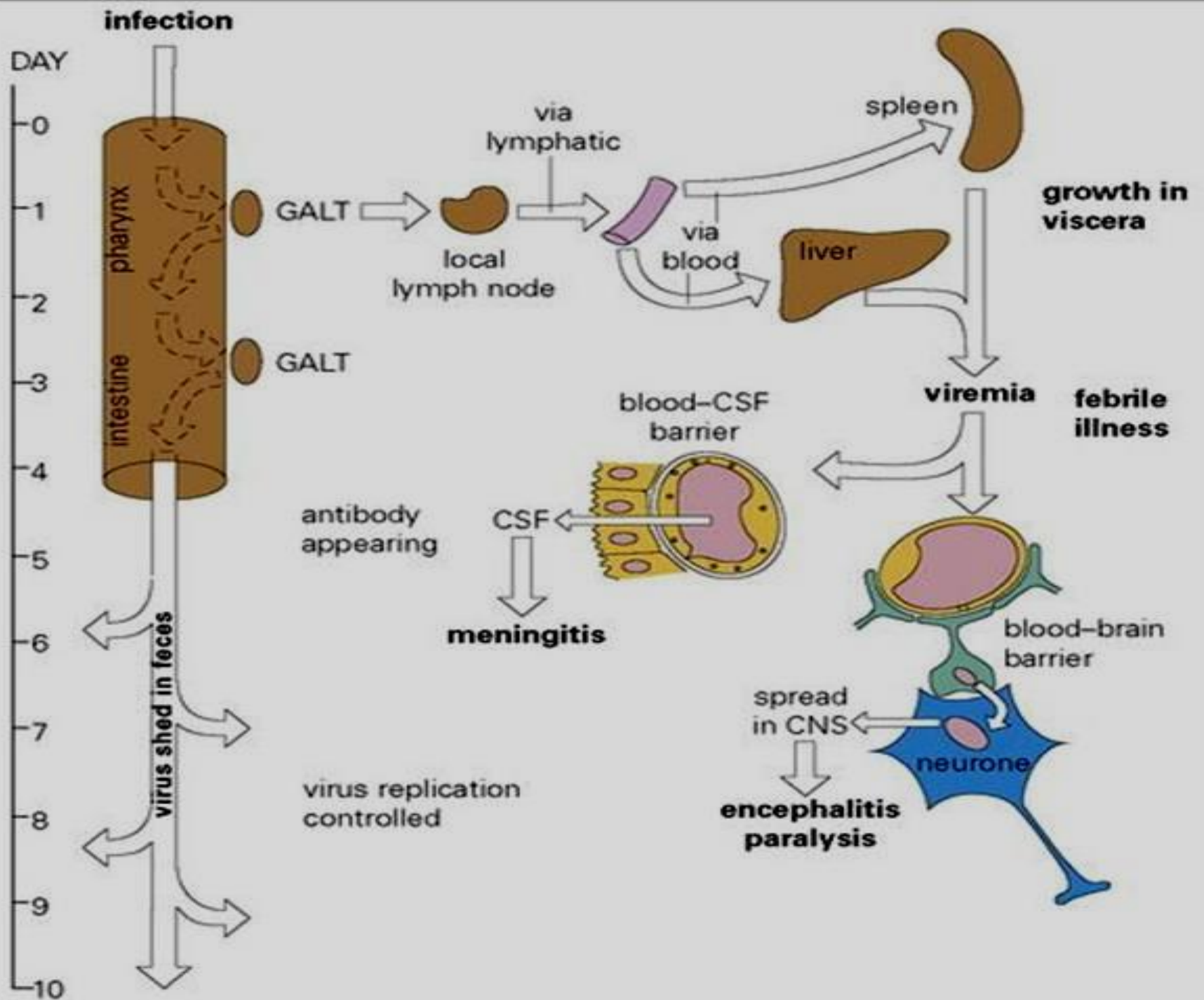
- ssRNA virus with icosahedral capsid, naked
- Stable at pH 3-9 (remains infectious for several days in water, milk, food, etc.)
- **Temperate climate**: disease mainly occurs during summer and autumn
- **Tropical and subtropical climates** - disease throughout the year
- **Antigenic serotypes**: 1, 2, 3
- **Reservoir**: humans
- **Transmission**: fecal-oral route; rarely respiratory
- **Communicability**: 7-10 days before onset (virus present in stool 3-6 weeks)

Poliovirus

Myelitis (poliomyelitis, Heine-Medin disease) - disease of the anterior horn motor neurons of the spinal cord and brain stem (grey matter) - motor neuron destruction causes typical manifestations of poliomyelitis

The virus replicates in the oropharynx and the intestinal tract - viremia may result in infection of CNS cells

Infection with poliovirus results in lifelong, type-specific immunity



Poliovirus type 1 is still **endemic** in **Pakistan and Afghanistan**

1988

Countries with polio cases

**There is no cure for polio
It can be only prevented**

Countries that have never eliminated polio

Countries that have eliminated polio

Data not available

Polio elimination status as of 1988 is based on multiple sources, because the quality and methods of data collection varied widely at that time. Current boundaries are shown on both maps. Boundaries shown do not imply the expression of any opinion concerning the legal status of any country or territory.

**As long as a single child remains infected with
poliovirus, children in all countries are at risk of
contracting disease**

POLIO

Asymptomatic 70-75%

Symptomatic

**Abortive
4 - 8%**

**Non-paralytic
2 - 10 %
Aseptic meningitis**

**Paralytic
< 1%
Aseptic meningitis
+ AFP**

Spinal cord

Bulbar: cranial nerves

Spinal-bulbar

Years-decades

Post-poliomyelitis syndrome

Paralytic poliomyelitis



Complications

- Encephalitis and myocarditis
 - Respiratory failure, airway obstruction
 - **Post-poliomyelitis syndrome (PPS)** - muscle atrophy several decades after paralytic poliomyelitis
 - **Specific prevention - vaccines:**
 - a) inactivated (IPV, Salk)
 - b) live attenuated (OPV, Sabin)
- cVDPV2=circulating vaccine-derived poliovirus**
- in 2012, it was reported in 15 countries, with 93% of cases attributed to cVDPV type 2

Live attenuated (OPV, Sabin) vaccine

- cVDPV=circulating vaccine-derived poliovirus
 - in 2012, it was reported in 15 countries, with 93% of cases attributed to cVDPV type 2

Although the vaccine-derived strains are weakened if allowed to circulate in under- or unimmunized populations for long enough, or replicate in an immunodeficient individual, the weakened virus can revert to a form that causes illness and paralysis

A polio outbreak, specifically of circulating vaccine-derived poliovirus type 2 (cVDPV2), was confirmed in Gaza in July 2024. The first case of paralysis in a child was reported in August, and the virus has been found in environmental samples since then. While no new cases have been reported since August, ongoing vaccination campaigns aim to end the outbreak by reaching all children under 10, says the World Health Organization (WHO)

The detected strain is genetically linked to a strain found in Egypt in 2023

Enteroviruses associated with AFM

- **EV-D68** - outbreaks in 2014, 2016, 2018

Less frequently

- EV-A71, EV-D70, EV-B94, EV-B94,
- ECHO 33
- Coxsackie A16

Poor prognosis - less than 20% of children will fully regain neurological function within 6 months

No specific treatment - physical rehabilitation (nerve transfer procedures)

PLoS Pathog. 2017 Feb 23;13(2):e1006199. doi: [10.1371/journal.ppat.1006199](https://doi.org/10.1371/journal.ppat.1006199)

A mouse model of paralytic myelitis caused by enterovirus D68

[Alison M Hixon](#)^{1,2}, [Guixia Yu](#)^{3,4}, [J Smith Leser](#)⁵, [Shigeo Yagi](#)⁶, [Penny Clarke](#)⁵, [Charles Y Chiu](#)^{3,4}, [Kenneth L Tyler](#)^{5,7,8,*}

Animal study - intraperitoneal inoculation of EV-D68 into neonatal mice recapitulates clinical AFM symptoms

Enterovirus A71 (EV-A71)

EV-A71: hand, foot, and mouth disease (HFMD), aseptic meningitis, brainstem, cerebellar encephalitis, acute flaccid paralysis (AFP)

Infections - worldwide, with large epidemics occurring in the Asia-Pacific region and Eastern Europe

The majority of enterovirus infections are self-limiting or resolve spontaneously

Complications are very rare but can lead to serious neurological diseases or even death

Enteroviruses in CNS become neurotropic

Replication in CNS generates quasispecies of enteroviruses

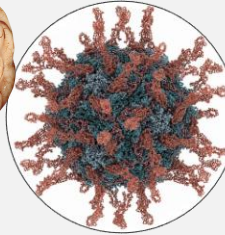
genetic diversity of produced during enterovirus replication induce neuroinvasive capabilities

Low fidelity of RNA-dependent RNA polymerase in enteroviruses

Research - high fidelity of polymerase decreases enteroviruses fitness under selective pressure

Once virus gets to CNS - ,burned-bridge' phenomena - limits subsequent virus strains from entering the CNS

AFP
AFM



mutation
neuroinvasive
quasispecies

burned-bridge = selective pressure

STOP! NO PASS

IMMUNE SYSTEM CELLS



monocyte



macrophage



mast cell



dendritic cell



natural killer
cell



neutrophil



eosinophil



basophil



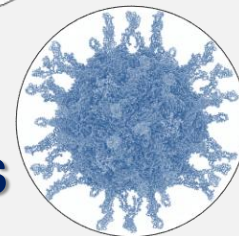
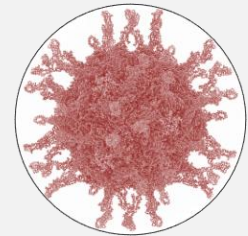
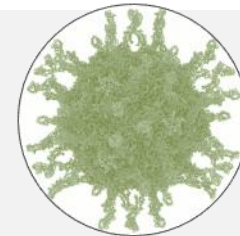
T cell



B cell

respiratory, gastrointestinal tracts -
quasispecies with no neuroinvasive
capabilities

lack of
neuroinvasive capabilities



Viral encephalitis

The majority of pathogens that cause encephalitis are viruses

- **Encephalitis** - inflammation of the brain with clinical evidence of neurological dysfunction
- Symptoms: fever, headache, disturbances in higher mental function (behavioral changes, seizures, focal paresis or paralysis)
- Most common viruses involved: **HSV type 1** (sporadic fatal meningitis)
- Treatment - acyclovir, cidofovir
- Other: Herpes virus family: VZV, EBV, CMV, HHV-6, Rabies virus, Mumps virus

Viral encephalitis

- Endemic: **Flaviviruses**: West Nile virus (WNV), Japanese encephalitis virus (JEV), St. Louis encephalitis (SLEV), tick-borne encephalitis (TBEV), and **Alphaviruses**: Western (WEEV) & Eastern Equine Encephalitis viruses (EEEV)
- **Chronic encephalitis**: SSPE - subacute sclerosing panencephalitis (**Measles virus**), primary lymphoma (**EBV**), HIV-associated neurocognitive disorder, progressive multifocal leukoencephalopathy (PML) - **JC virus**, **HTLV**- myelopathy

Check yourself

- Viral entry to CNS - give examples of routes of transmission
- LCMV - in whom does the virus cause the most severe course of infection?
- List the most common AFP-associated viruses
- Why does the polio virus still threaten the world?
How can its spread be stopped?
- What virus most commonly causes encephalitis?
- Which meningitis causes more complications - viral or bacterial?



UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Thank you for your attention!

In order to get information on the presented content,
please send messages to the e-mail address:

beata.sobieszczanska@umw.edu.pl