

# INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

## PART 3

### Prion diseases Viral CNS Infections

- Integrated Team Teaching
- Bringing Clinical Aspects and Basic Science together in one lecture



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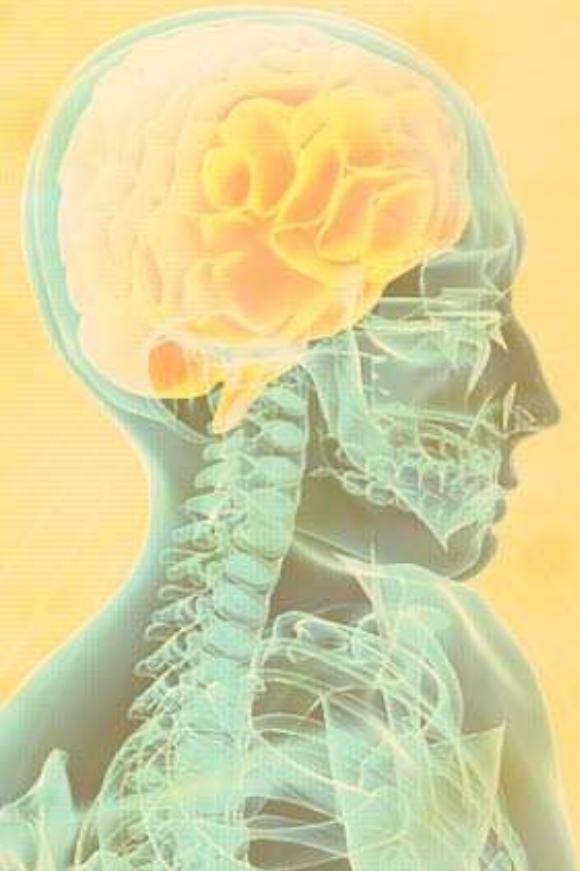
Liisa A. Russell,  
MD



# Objectives (CNS Infections Part 3)

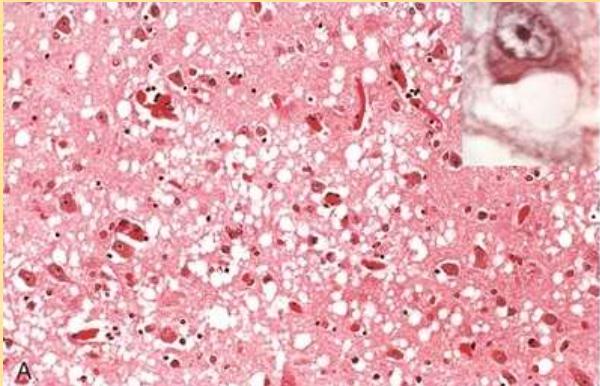
At the end of this lecture students should be able to:

1. Describe prions and the pathogenesis of prion diseases.
2. Enumerate the viruses, causing meningitis and encephalitis
3. Describe the characteristics, epidemiology and pathogenesis of viral meningitis and encephalitis.
4. Describe the pathological and radiological changes seen in encephalitis
5. Describe the diagnosis, laboratory diagnosis, treatment and prevention of viral meningitis and encephalitis





## Prion diseases



Very rare (~1/million) **spongiform encephalopathies** include  
**Acquired forms:** **kuru, iatrogenic Creutzfeldt–Jakob disease.** (~450 historical cases due to use of non-rHGH, re-use of EEG electrodes, dura mater or corneal transplants).

- Degenerative and 100% lethal diseases with decades-long incubation periods.
- Prion diseases known to be caused by ingestion of infected material: vCJD: Consumption of infected beef or mutton or by blood transfusion; Kuru: Ritual cannibalism among tribes in New Guinea.

# Prion diseases: pathogenesis

## Infectious agent is an abnormal protein: PrP<sup>Sc</sup>



# Neurology®

The most widely read and highly cited  
peer-reviewed neurology journal

The characteristics of prion protein.

1.

They are misfolded proteins

INFECTIOUS DISEASE: NEUROINFECTIOUS DISEASES, COMMON ETIOLOGIES, AND RARE DISEASES 2

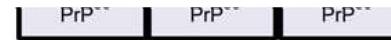
| April 9, 2024 |

Check for updates

## Two Hunters from the Same Lodge Afflicted with Sporadic CJD: Is Chronic Wasting Disease to Blame? (P7-13.002)

Jonathan Trout, Matthew Roberts, Michel Tabet, Ethan Kotkowski, and Sarah Horn | [AUTHORS INFO & AFFILIATIONS](#)

April 9, 2024 issue • 102 (17\_supplement\_1) • <https://doi.org/10.1212/WNL.00000000000204407>



- Symptoms of prion diseases include rapid cognitive decline, a range of neurological manifestations and death often within a few months of Dx.
- Definitive diagnoses are based on pathologic evidence of the variant form of PrP<sup>Sc</sup> in brain biopsy or autopsy.

# IMAGING FINDINGS IN CREUTZFELD-JACOB DISEASE

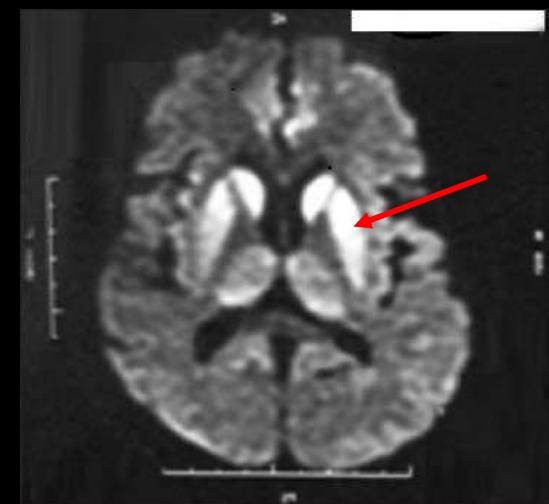


## *Usual Findings*

- Focal or diffuse, symmetric or asymmetric involvement of cerebral cortex, basal ganglia, in particular the corpus striatum, or both basal ganglia and cerebral cortex
- Perirolandic area is usually spared
- Cerebellar atrophy

## *Unusual Findings*

- Involvement of perirolandic cortex
- “Pulvinar” and “double hockey stick” signs can rarely occur in sCJD
- DWI hyperintensity involving cerebellum



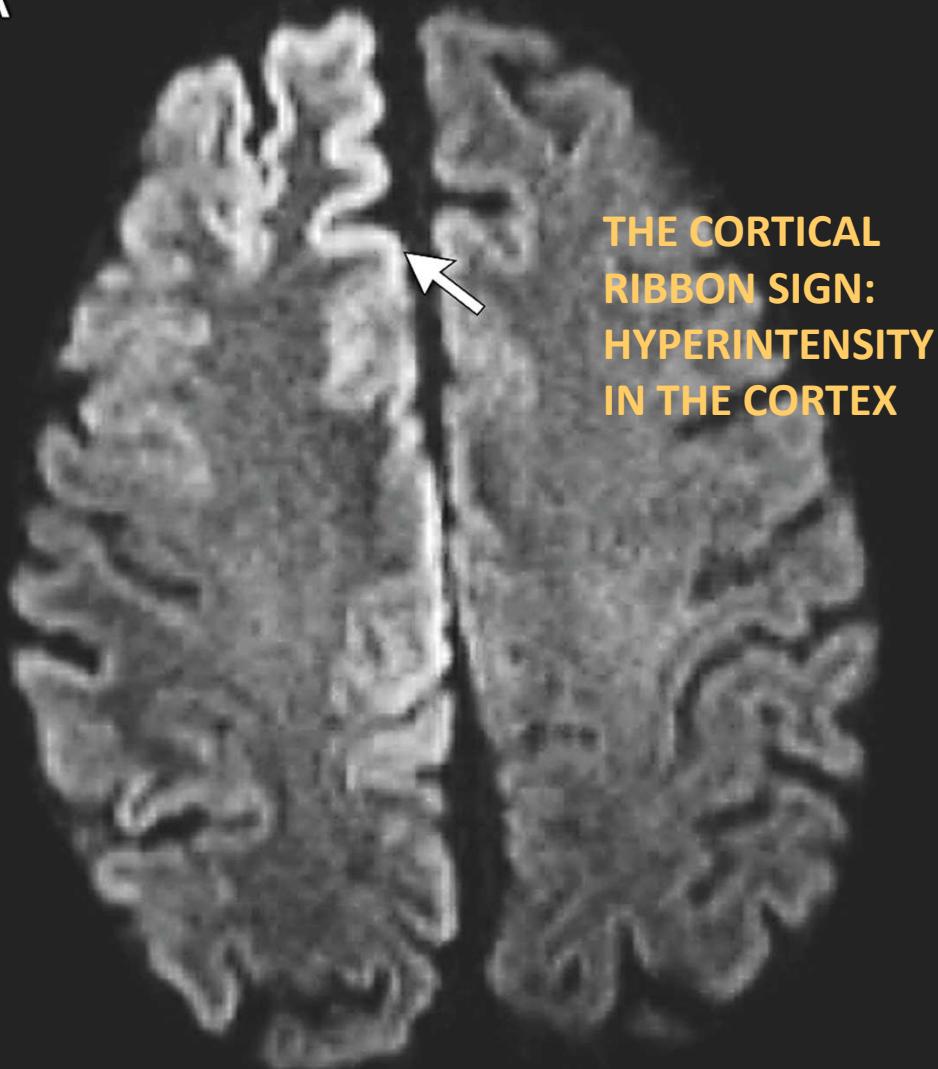
- Unaffected White Matter
- Unaffected BG and Cortex
- DWI restriction



# IMAGING FINDINGS IN CREUTZFELDT-JACOB DISEASE

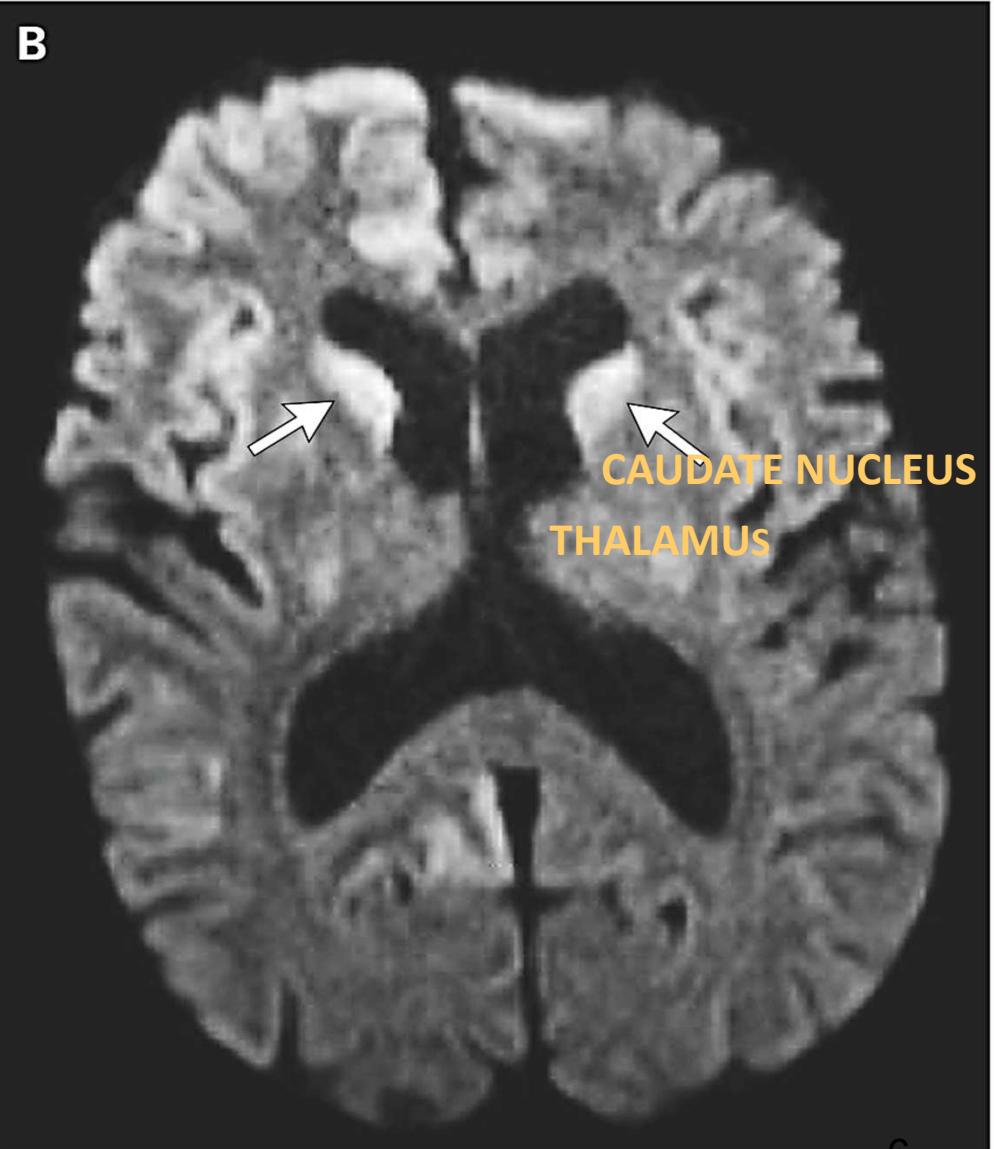
## DIFFUSE-WEIGHTED MRI

A



THE CORTICAL  
RIBBON SIGN:  
HYPERINTENSITY  
IN THE CORTEX

B

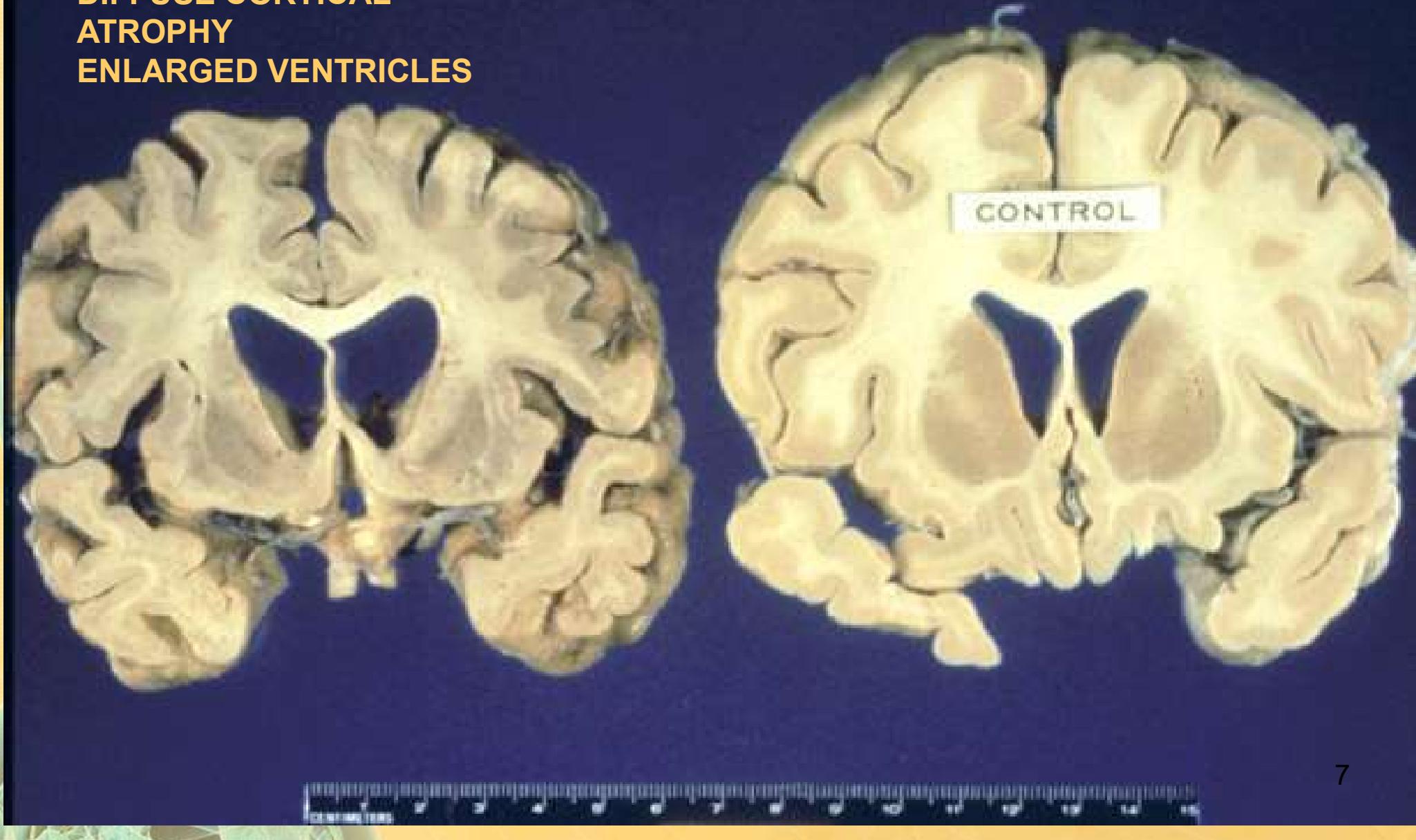


CAUDATE NUCLEUS  
THALAMUS



# BRAIN ATROPHY IN CREUTZFELD-JACOB DISEASE

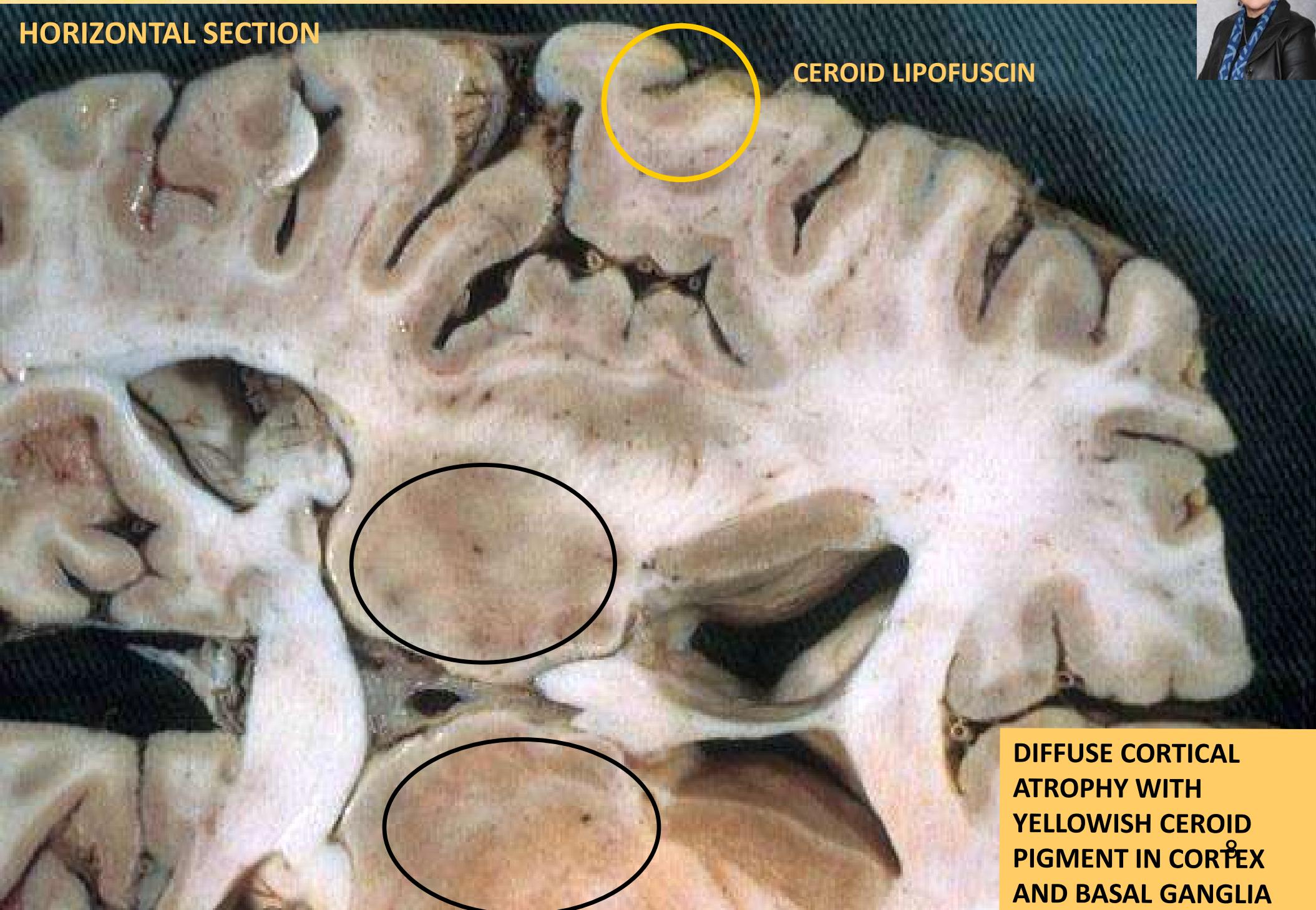
DIFFUSE CORTICAL  
ATROPHY  
ENLARGED VENTRICLES



# CREUZFELDT-JACOB DISEASE CEROID PIGMENT ACCUMULATION



HORIZONTAL SECTION



CEROID LIPOFUSCIN

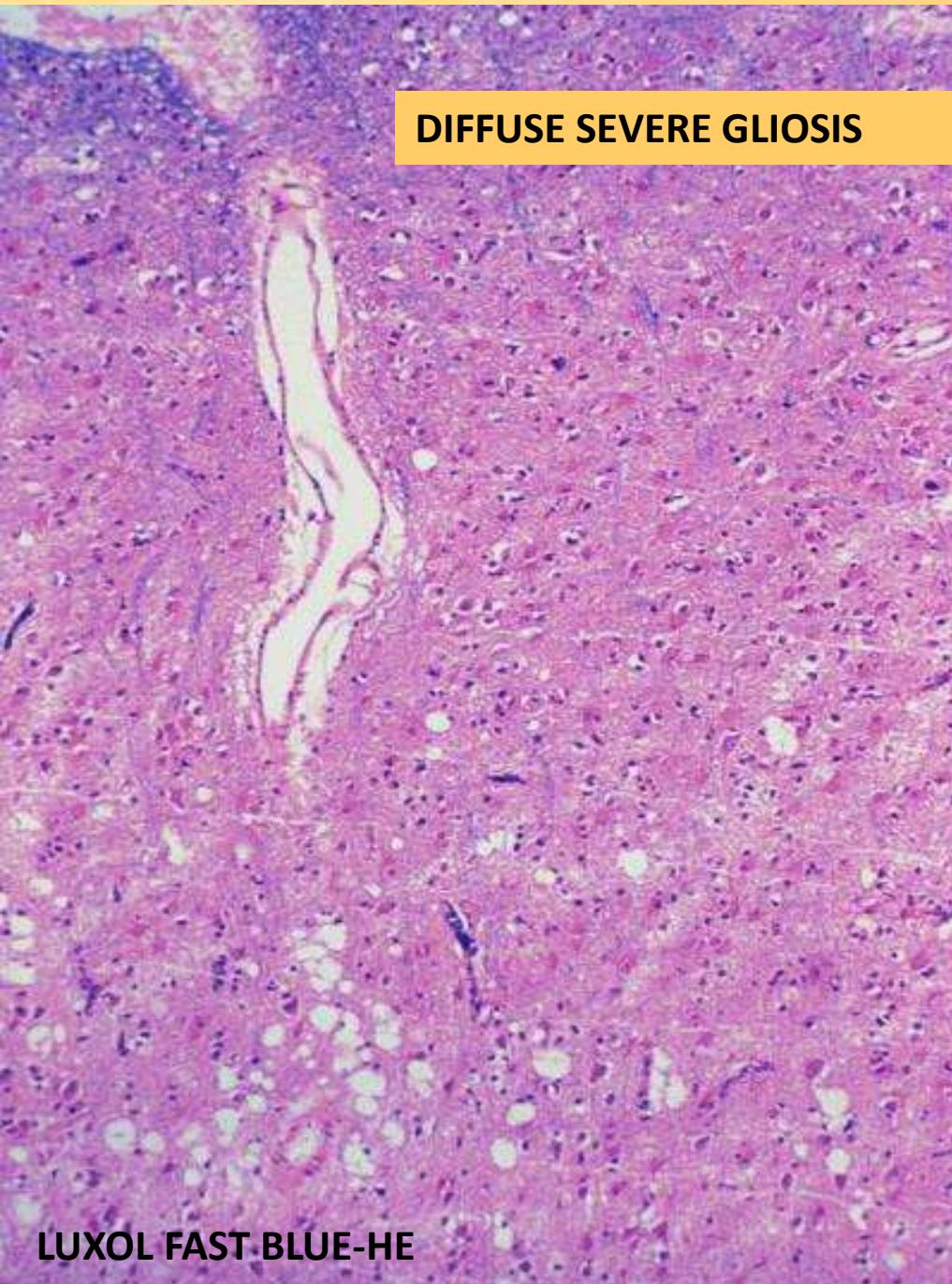
DIFFUSE CORTICAL  
ATROPHY WITH  
YELLOWISH CEROID  
PIGMENT IN CORTEX  
AND BASAL GANGLIA

# CREUZFELDT-JACOB DISEASE

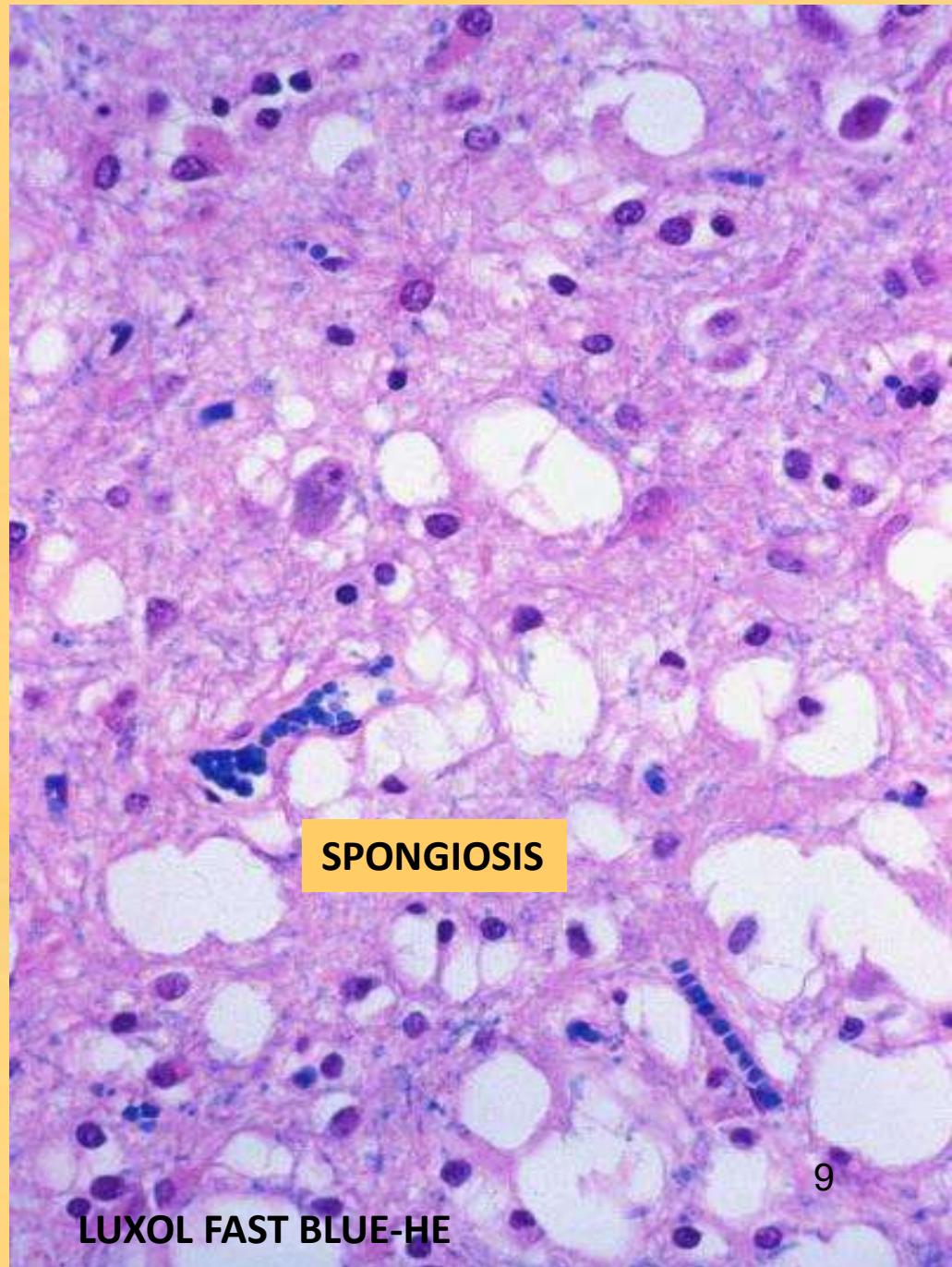
## SPONGIFORM ENCEPHALITIS



DIFFUSE SEVERE GLIOSIS



SPONGIOSIS



**RED = DNA virus**  
**BLUE = RNA virus**



# VIRAL CNS INFECTIONS

**Poliovirus**

**Echoviruses and parechoviruses**

**Coxsackieviruses**

**West Nile virus**

**Eastern equine encephalitis virus**

**HIV**

**Rabies virus**

**SARS-CoV2**

**HSV I & II**

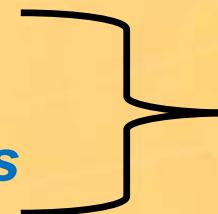
**Cytomegalovirus**

**Varicella zoster virus**

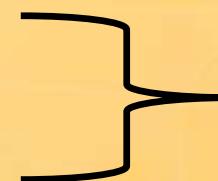
**JC Polyomavirus**



Enteroviruses



Arboviruses



Zoonotic infections

*Neurological disorders, some of which are associated with viral infections, are growing due to the aging and expanding population.*

*Despite strong defenses of the CNS, some viruses have evolved ways to breach them, often with dire consequences.*

# **General virulence mechanisms of CNS viral pathogens: how viruses kill or injure CNS cells**



- **Tropism and cytolysis:**

- Infect only nervous system (polio, rabies, WNV)
- Affect certain areas of the brain more severely (ex. Herpes simplex-1 [HSV1] causes more severe changes in the inferior and medial regions of temporal lobes)
- Infect specific CNS cell types (JC virus: oligodendrocytes)

- **Latency and reactivation**

- VZV, HSV1, HIV

- **Immune mediated CNS injury and/or neuroinflammation;  
with or without damage to vascular endothelium or BBB**

- HIV; SARS-CoV-2, HSV1

- *Congenital malformations*

- Rubella (German measles); other TORCH pathogens*

## *Aseptic meningitis and/or encephalitis:*

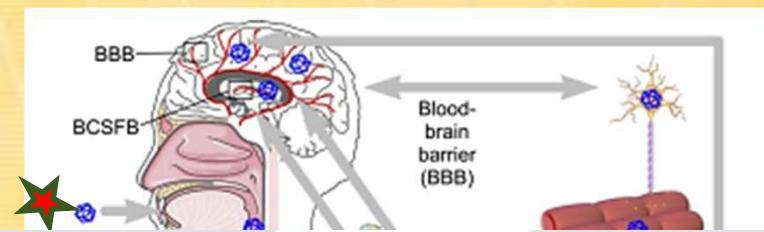
*Over half of aseptic meningitis cases lack an identified cause, but viruses, (esp. enteroviruses) are the most commonly identified pathogens*



- Enterovirus (members of the Picornavirus family) infections are the most common cause (~55-80%) of both meningitis and encephalitis in children 17 years of age and younger.
- ~75,000 cases/year in the US; **90% of cases in pts <1 yr old.**
- **Majority of cases are caused Coxsackie A and B viruses, echoviruses,** with most occurring in late summer and early fall.
- Enteroviral aseptic meningitis usually presents with a gradual onset, with milder symptoms than bacterial, fungal or arboviral meningitis, and is self limiting.
- Cognitive and motor deficits can result, mostly following illnesses that have neurologic findings during acute disease. Parechoviruses (esp. PeV-A3) can cause severe disease in infants, including sepsis, seizures, brain injury, and death.
- **Treatment is symptomatic only.**

# Pathogenesis of picornavirus CNS infections:

There are several routes to the CNS



ElectoralVote x Notes from the Field: Cluster of P x human cosavirus - Search Results x +

ElectoralVote cdc.gov/mmwr/volumes/71/wr/mm7130a5.htm

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## Morbidity and Mortality Weekly Report (MMWR)

### Notes from the Field: Cluster of Parechovirus Central Nervous System Infections in Young Infants — Tennessee, 2022

Weekly / July 29, 2022 / 71(30);977–978

Lili Tao, MD, PhD<sup>1</sup>; Mary-Margaret A. Fill, MD<sup>2</sup>; Ritu Banerjee, MD, PhD<sup>3</sup>; Romney M. Humphries, PhD<sup>1</sup> ([VIEW AUTHOR AFFILIATIONS](#))

[View suggested citation](#)

During April 12–May 24, 2022, 23 previously healthy infants aged 5 days–3 months were admitted to a Tennessee children's hospital for human parechovirus (PeV) meningoencephalitis.\* PeV is a nonenveloped RNA virus of the Picornaviridae family. PeV infections range from mild, self-limiting gastroenteritis to severe sepsis-like disease and central nervous system (CNS) infection, (1) and infants aged <3 months are disproportionately affected. PeV genotype 3 is responsible for the most severe cases, with a pattern of biannual cycle circulation that peaks during summer months (2,3). Although PeV infection is not a reportable disease, the Tennessee Department of Health was notified. An assessment of cases was conducted to better understand this unusually large cluster of infections.

At this children's hospital, a lumbar puncture is performed as part of sepsis evaluation for all infants aged <1 month and for older infants when clinically indicated. Cerebrospinal fluid (CSF) testing includes a multiplex molecular panel (BioFire FilmArray Meningitis/Encephalitis Panel, bioMérieux) for all infants aged ≤3 months and for patients aged >3 months if the CSF white blood cell (WBC) count is >5 cells per high power field. For this investigation, a comprehensive review of electronic health

#### Article Metrics

Altmetric:



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13

**Coxsackievirus A**  
Hand-foot-and-mouth disease  
Rash, herpangina

**Echovirus**  
**Coxsackievirus A and B**  
Myocarditis  
Pericarditis  
Pleurodynia

**Poliovirus**  
**Coxsackievirus A and B**  
Paralytic disease  
Encephalitis

**Poliovirus**  
**Coxsackievirus A and B**  
**Echovirus**  
Meningitis

# *Polio:*

## *THE paralytic disease until the mid-20<sup>th</sup> Century*

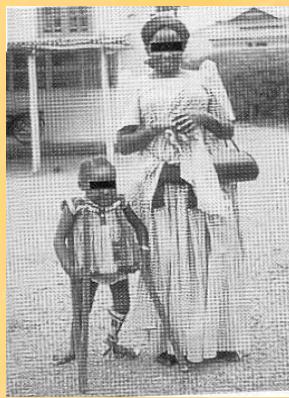


- **Picornavirus family member.** *The three poliovirus serotypes now belong to the species Enterovirus coxsackiepol.* Three serotypes (PV-1-3) known; only active PV-2 poliovirus now remains in the wild.  
*Poliovirus is next major pathogen targeted for eradication by the W.H.O.*

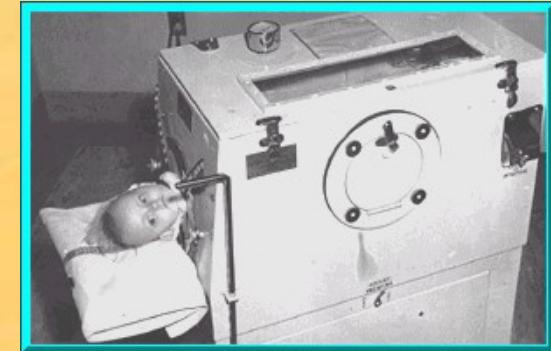
- Former cause of major epidemics in the US. Vaccination and improved hygiene has made this a rare disease, esp. in Europe and the Western Hemisphere.
- *OPV was thought to be safe but contains small amounts of attenuated live virus that can circulate and revert to wild type if communities are undervaccinated.*
- *The first US polio case in nearly a decade was identified in July 2022 in New York State. An unvaccinated man was infected by a virus that had been shed from the recipient of an oral polio vaccine (OPV), which had not been administered in the US since 2000. Polio vaccination rates in NY counties where wastewater samples containing poliovirus were collected were lower (59-79%) than those in the remainder of NY state.*



# Polio-pathogenesis: A motor neuron killer



Child with residual paralysis and wasting in the affected leg after poliomyelitis infection

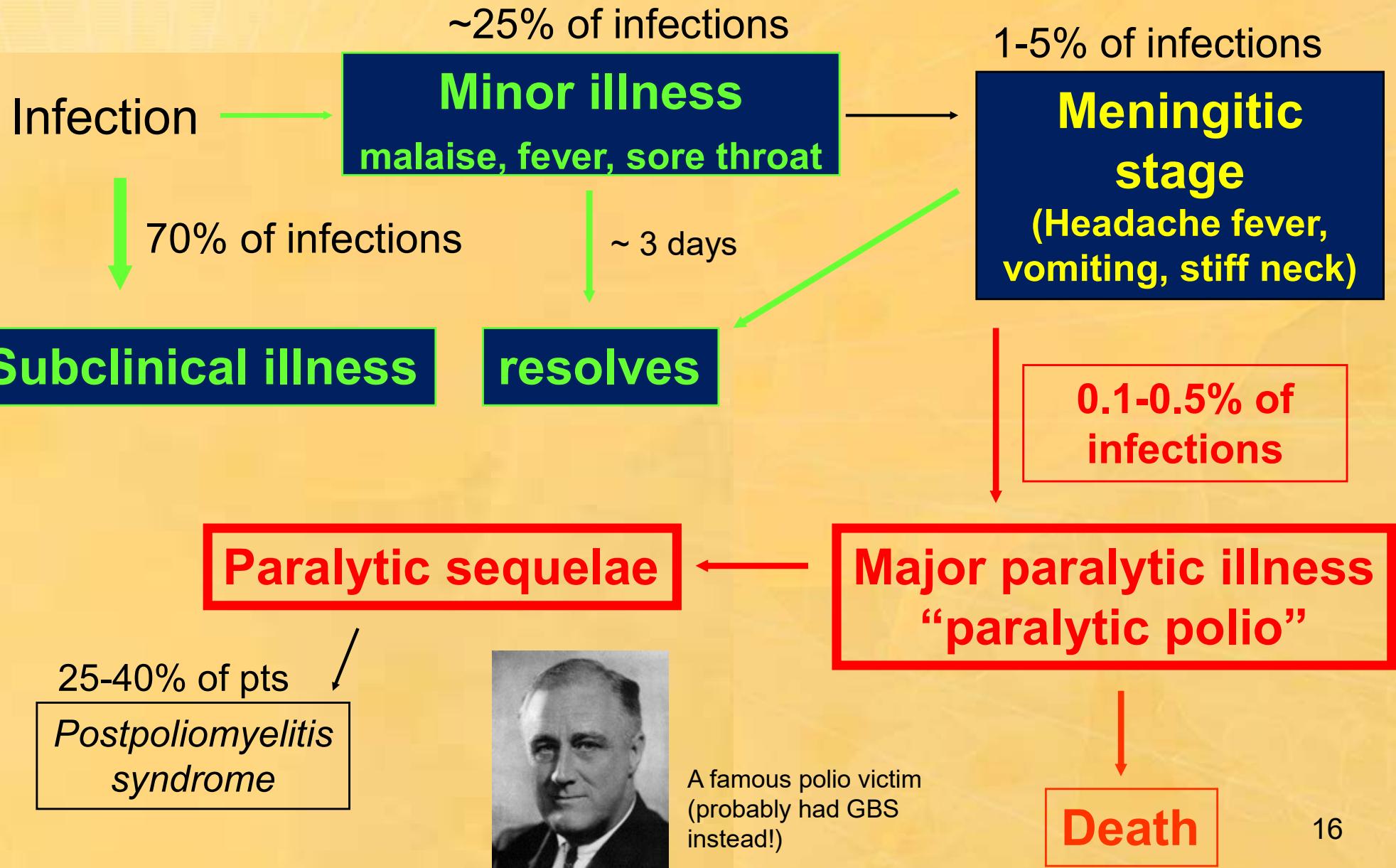


Polio pt in an iron lung. Involvement of the respiratory muscles in the neck and chest (innervated by the third to fifth cervical nerves) can be life threatening, requiring respiratory support in up to 25% of pts.

- **Poliovirus infects and kills motor neurons in the anterior horn of the spinal cord controlling the limbs (spinal/paralytic polio or poliomyelitis) AND/OR cranial nerve motor nuclei leading to dysfunction of the muscles controlling the face, eyes, and respiration (bulbar polio).**
- **Causes an acute flaccid paralysis.** Any or all muscles may be affected. **Sensation is NOT affected.**
- **Poliovirus sheds in stool for several weeks, with the highest concentration in the first week after onset of paralysis.**

# Possible outcomes of poliovirus infection:

Most infections are asymptomatic

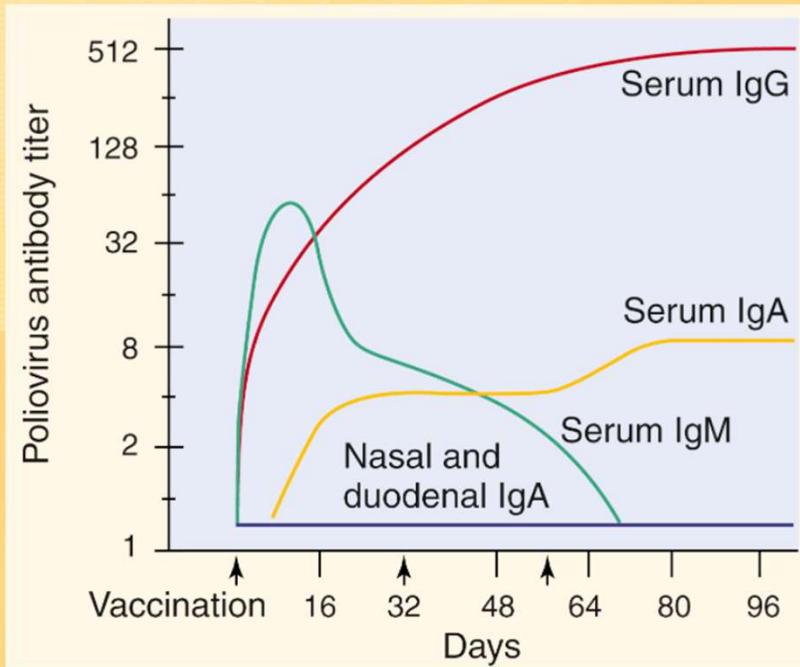


# Polio prevention: vaccines

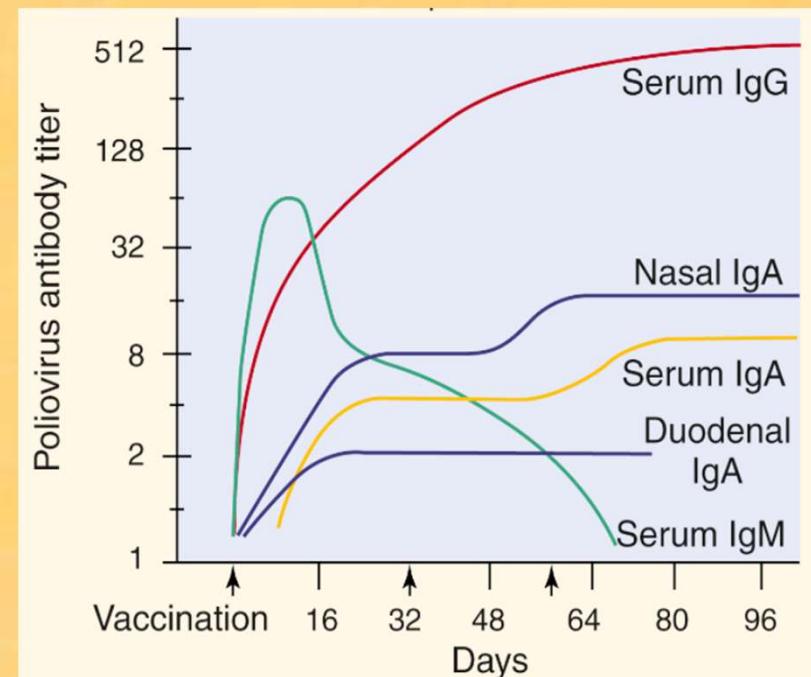


USA

Killed virus vaccine (Salk)  
IPV (inactivated polio vaccine)



Live virus vaccine (Sabin)  
OPV (oral polio vaccine)

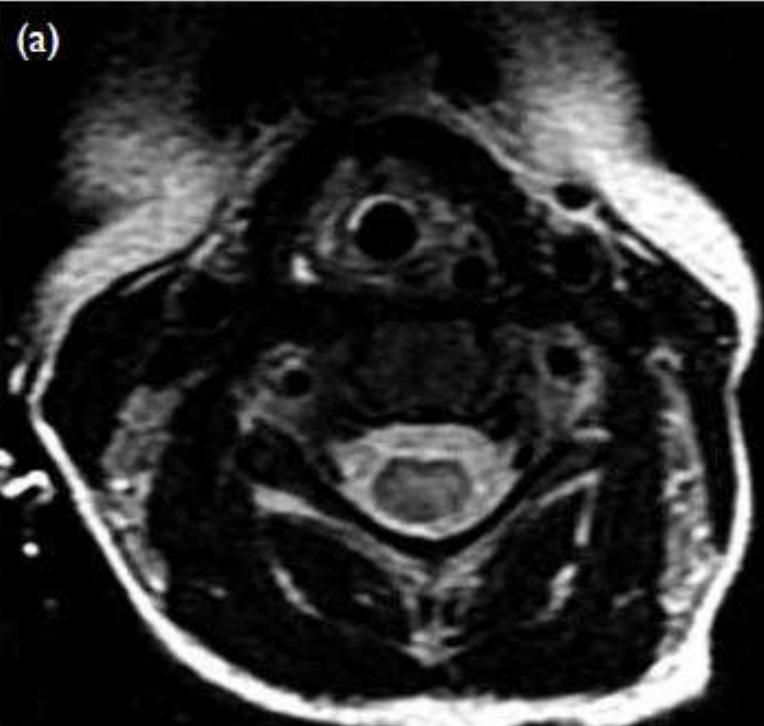


Note how OPV provokes the production of secretory (mucosal) IgA. This provides neutralizing antibody in the gut that blocks viral replication.

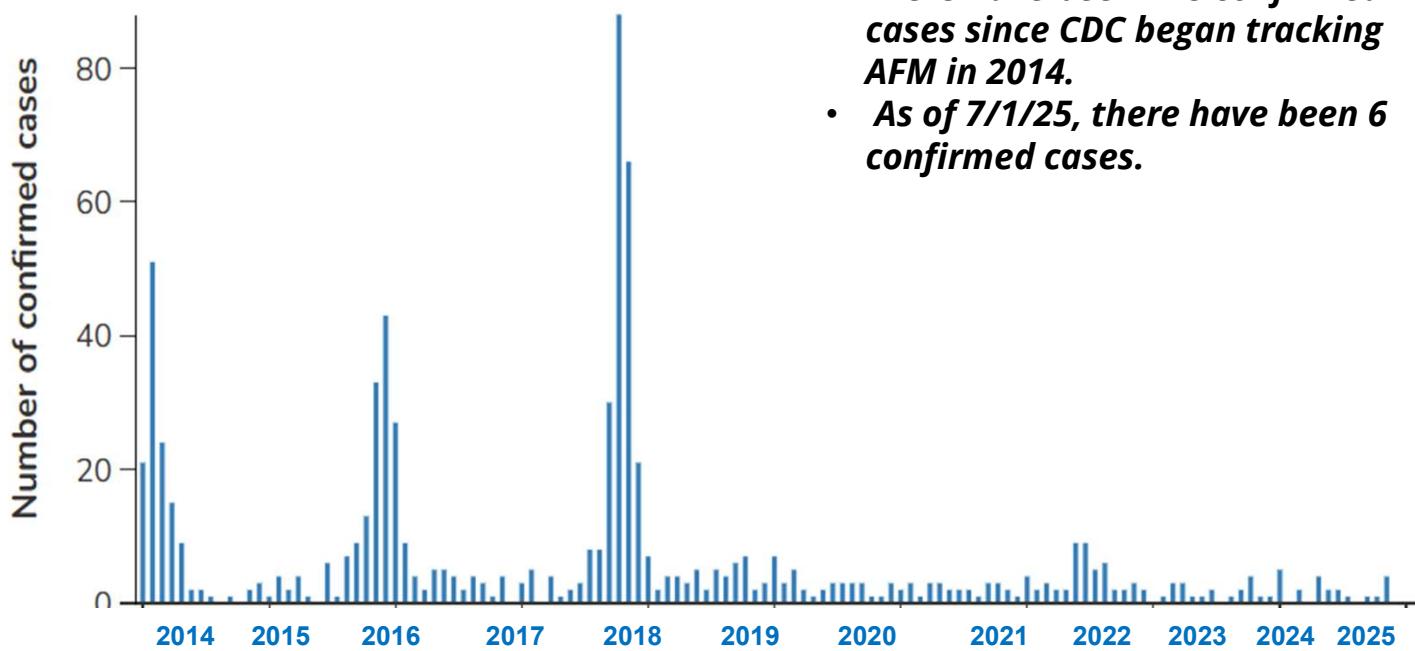
OPV is used when a polio outbreak must be contained, even in countries that typically rely on IPV for routine immunization.

## Risks:

- Can cause disease in immunocompromised or nonvaccinated.
- Recipients can shed live virus, with risks as above.
- Vaccine virus type can revert to virulent type.



## Cases by month, 2014–2025



- *There were 24 cases in 2024;*
- *There have been 778 confirmed cases since CDC began tracking AFM in 2014.*
- *As of 7/1/25, there have been 6 confirmed cases.*

AFM):  
“polio”

in upper  
to moderately

neurological

onset flaccid  
illness, with MRI  
cord gray matter.

) had a mild  
before they developed

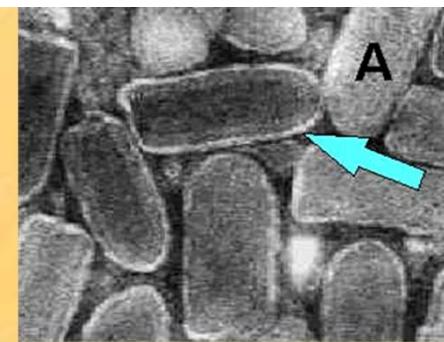
ills of the spinal cord.

therapy.  
consists of five (sero)types





## Rabies



- Member of the *Rhabdoviridae*. Bullet-shaped morphology.
- 100% (only ~31 known survivors!) lethal encephalitis.
- A zoonotic disease, spread mostly via bites from infected animals.
- About 59,000 deaths/year worldwide; only 1-3 deaths/year in the US. However, ~60,000 post-exposure vaccinations are required each year in the US.
- In the US, exposure to bats is the most common cause of rabies. Dog bites are the most common means of transmission worldwide. Always inquire as to pt's travel and animal exposure history when suspecting rabies.

In 2024, there were 2 human rabies deaths in the US. One was in MN, the other was a teacher in Fresno.

# Rabies: transmission



Rabies gets into the body through wounds (i.e., **the bite of a rabid animal** or contamination of a scratch by virus-infected saliva).

Infection may also occur via inhalation of virus-infected saliva (esp. in bat caves) or direct exposure to mucus membranes.



Incubation period: 4-12 weeks. Appearance of symptoms dependent upon proximity of bite to CNS.

*The raccoon is the most common wild vector in the US*

*Map of rabies reservoirs in the US*



## Rabies-pathogenesis

**Virus travels up axons via retrograde movement at a rate of 50-100 mm/day (See Fig. 50.2).** Once inside neurons, the virus replicates, moves trans-synaptically to the brain, and eventually along somatic and autonomic nerves back to the skin, various organs, tissues, the salivary glands, and also to nerve tissue around hair follicles.

**Functional and lethal damage (but with minimal histopathology) is done to the hypothalamus and brain stem, thus influencing cardiac and respiratory control.**

**A final massive replication of virus in the salivary glands leads to the high infectiousness of saliva.**

Despite the severity of the disease, pathology in the CNS is minimal, and pathogenesis is poorly understood.

*There is an almost complete lack of an inflammatory response within the CNS and neuronal dysfunction, rather than neuronal death, is probably responsible for the fatal outcome of rabies*

# Rabies – Clinical Manifestations



**Extent of bites  
Proximity to head  
Amount of secretions**

- Prodromal phase      ~ 1 week
  - Low-grade fever, chills, **malaise**, weakness, anorexia, HA
  - **Paresthesias from wound site**
- Clinical Rabies
  - **Encephalitic ("furious") rabies**      ~80%
    - **Hydrophobia, aerophobia** (pharyngeal spasms after draft of air), **opisthotonus, autonomic instability**, dysphagia, **agitation & combativeness**
    - Hypertonia, increased DTRs, fasciculations, nuchal rigidity
  - **Paralytic ("dumb") rabies**      <20%
    - **Ascending paralysis** (like GBS) (most prominent in bitten limb)
    - Fasciculations, areflexia, nuchal rigidity

**Once symptomatic – progressive encephalopathy & death**

# Rabies – Clinical Manifestations



Once symptomatic – progressive encephalopathy & death

# Rabies – Diagnosis

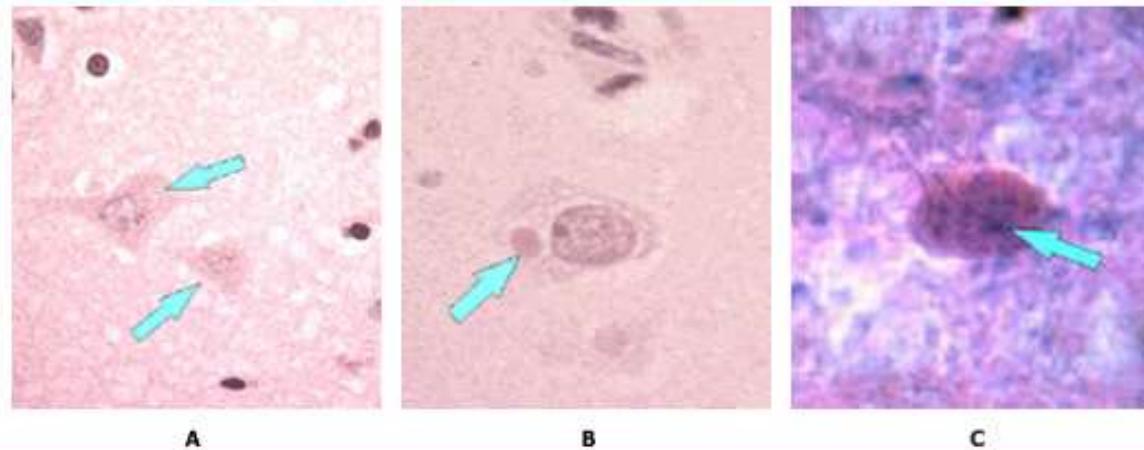


- Thorough pt history & high index of suspicion
  - Paresthesia around an **animal bite**
  - Acute progressive encephalitis (regardless of bite)
  - **Hydrophobia & aerophobia**
- Sample collection:
  - Saliva
  - Skin biopsy (full thickness, posterior neck at hairline)
  - Serum
  - CSF
- Post-mortem:
  - Brainstem and neural tissues
    - Negri bodies & eosinophilic neuronal cytoplasmic inclusions = pathognomonic

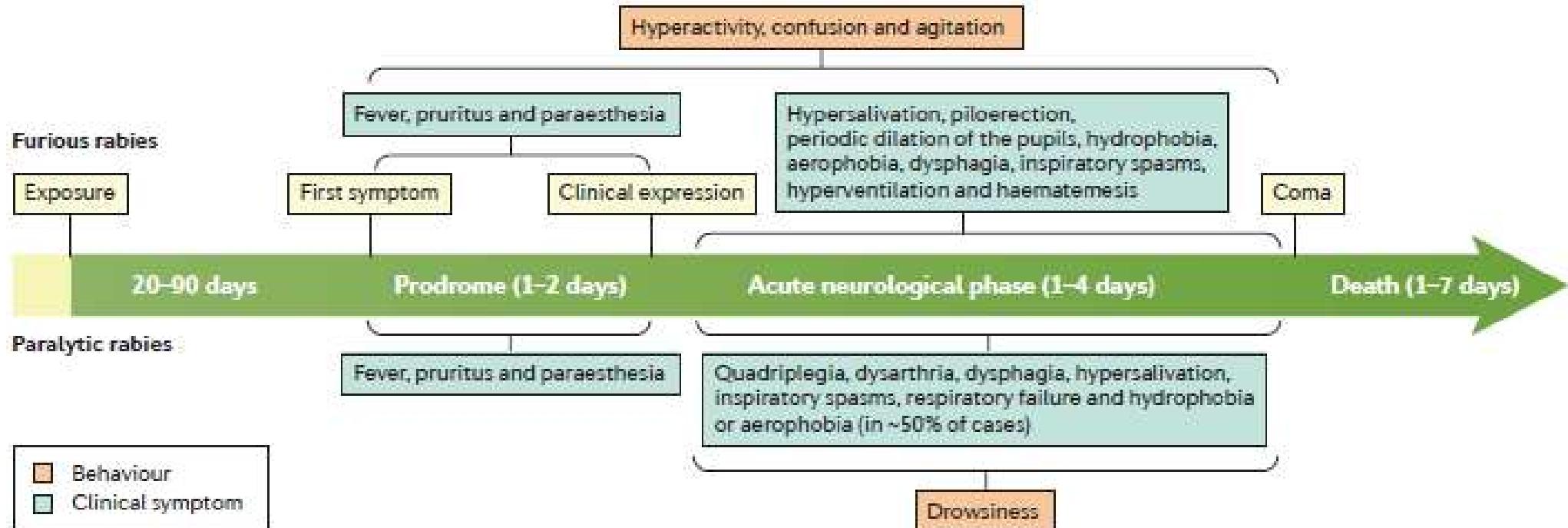
**Immunofluorescence staining**

**Seroconversion for anti-rabies IgM or IgG is seen only late in the disease**

## Negri body in rabies



Panel A shows a neuron without Negri bodies, while panel B shows a Negri body in infected neuron (arrow). Panel C shows a Negri body in Sellers stained brain tissue with dark blue basophilic granules in the inclusion.



# Rabies: Intervention



Treatment: difficult once symptoms start. Palliative vs aggressive approach.

- Palliative → comfort care to alleviate suffering
- Aggressive (accepts severe sequelae) → ICU supportive care + off-label therapies

*Ribavirin, amantadine, and interferon- $\alpha$  have proved to be disappointing agents. Minocycline or corticosteroids should not be used because of concerns about aggravating the disease.*

So.. Post exposure prophylaxis (PEP) is important:



(1) Wash wound thoroughly (soap, water, providone-iodine)

(2) PEP:

- Passive immunization: Human anti-rabies immune globulin should be administered promptly to the bite area
- Vaccine: Inactivated viral vaccine should be used within 8 days of suspected contact. Vaccine is given i.m. in doses at days 0, 3, 7, and 14 days.

(3) antibiotics (amoxicillin-clavulanate) to cover other common bite infection ex: Pasteurella)



# When to give Rabies PEP

**Treatment for bites:**  
Clean wound  
PEP  
**Abx (Augmentin)**



<b>TYPE OF ANIMAL BITE</b>	<b>EVALUATION AND DISPOSITION OF ANIMAL</b>	<b>RECOMMENDATIONS</b>
Dog, cat, ferret	Healthy; observe animal for 10 days	PEP should <b>not</b> be initiated unless the animal develops clinical signs of rabies
	Rabid (or suspected)	<b>PEP should begin immediately</b>
	Unknown (e.g., escaped)	Public health officials should be consulted; <b>immediate PEP should be considered</b>
Raccoon, skunk, fox, other carnivore, bats	Regarded as rabid unless the animal tests negative	<b>Consider immediate PEP;</b> if the animal is being tested, delay PEP until results are available
Livestock, horses	Consider individually	Public health officials should be consulted; most livestock in the United States are vaccinated for rabies
Rodent, rabbit, hare, other mammal	Consider individually	Public health officials should be consulted; bites of rabbits, hares, and small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice) <b>almost never</b> require postexposure rabies prophylaxis

# *Major neurological complications of HIV infection*

*Neurologic complications occur in more than 40% of HIV+ patients*

## **Viral:**

**PML-JC polyomavirus**

**Aseptic meningitis (primary HIV infection)**

**HIV-associated neurocognitive disorders (HAND)**

**CMV encephalitis, retinitis**

**CNS cell types involved in HIV neuropathology:**

**Microglia**

**Monocytes or Macrophages**

## **Bacterial:**

Tuberculous meningitis-*Mycobacteria tuberculosis*

Multiple or recurrent bacterial meningitis

Neurosypilis

**Neurons? NO!**

## **Fungal:**

Cryptococcal meningitis-*Cryptococcus neoformans*

**Pathology results from neuro-inflammation**

## **Parasitic:**

Cerebral toxoplasmosis-*Toxoplasma gondii*

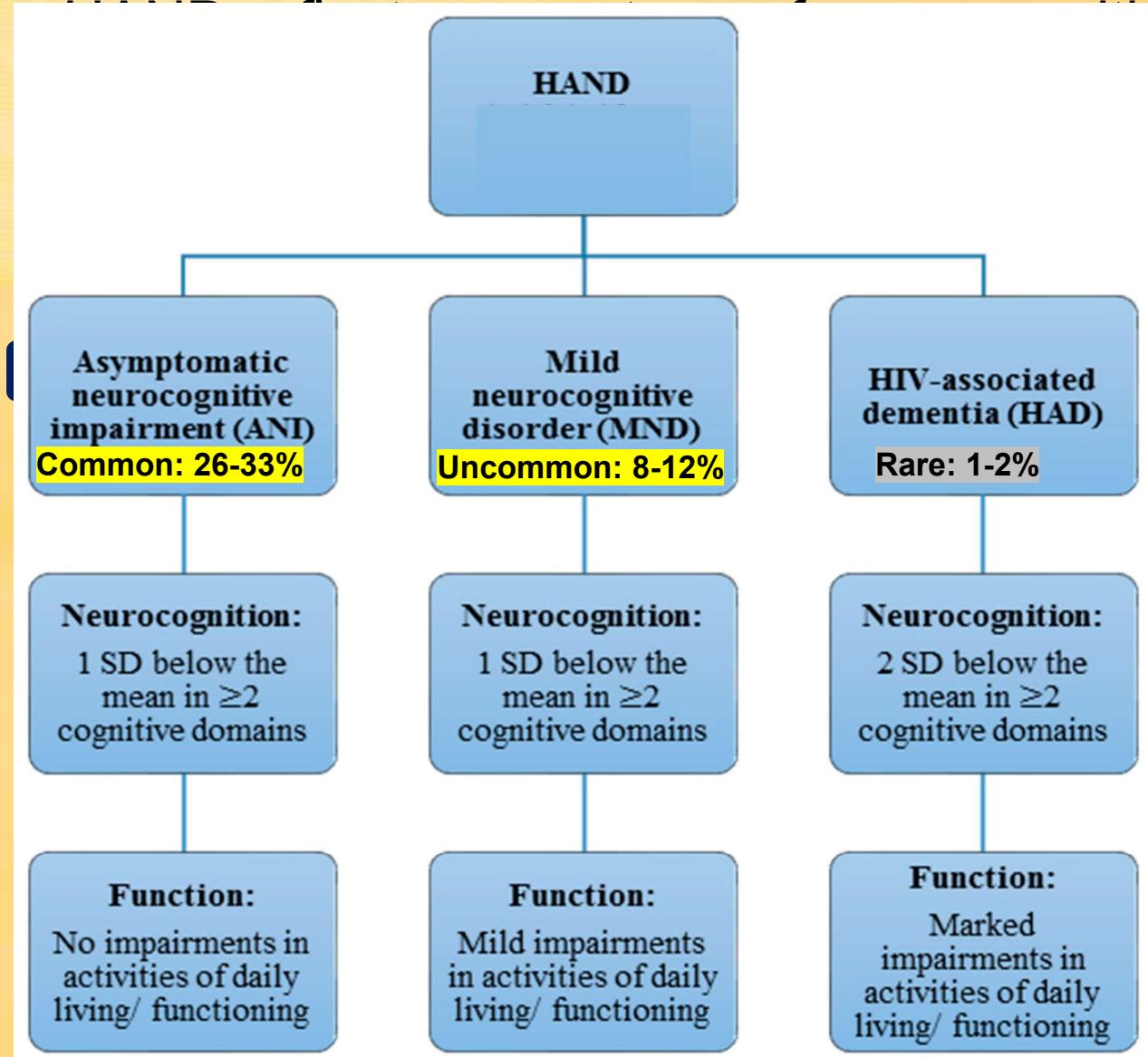
## **Other:**

Primary lymphoma of the brain

**Peripheral neuropathy from medications (didanosine, stavudine)**



# HIV-associated neurocognitive disorder (HAND) a multifactorial cognitive disorder of HIV disease



neurocognitive impairment.

## Aging is the major risk

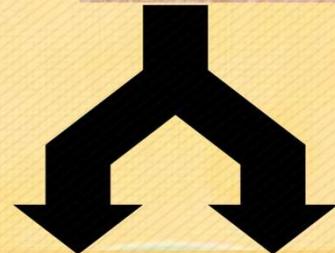
defined as deficits in at least one or more cognitive domains, attention/working memory, language, perceptual abilities, and executive function. Loss of attention, memory, concentration, depression, and slowed

## in the US and developed

D; ART with better BBB

# *Arboviral infections of the CNS: flaviviruses*

*In total, these are dangerous viruses*



Tick-borne  
encephalitis  
(common in  
Eurasia)

Powassan fever  
(~20-60  
cases/year in  
US; 22 in 2025;  
**13% CFR**)

California  
serotype  
arboviruses  
(~50-80  
cases/year in US)

St. Louis  
encephalitis  
(~10-20  
cases/year in  
US; 2 in 2024;  
**6.5% CFR**)

Japanese  
encephalitis  
(common in SE  
Asia)

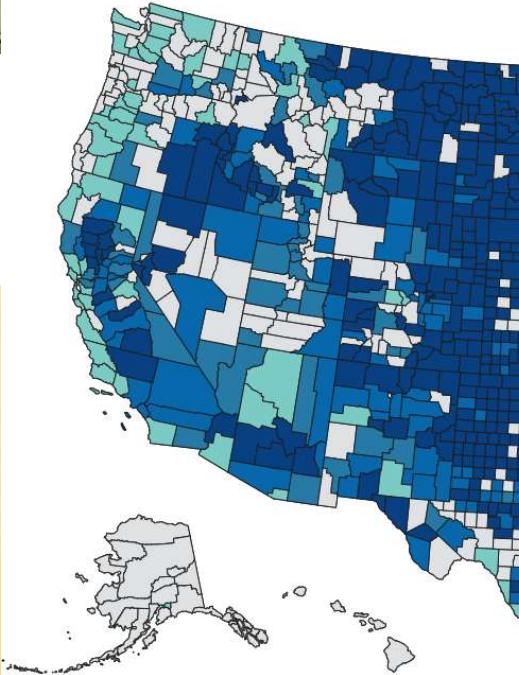
Sad story here (60 sec)



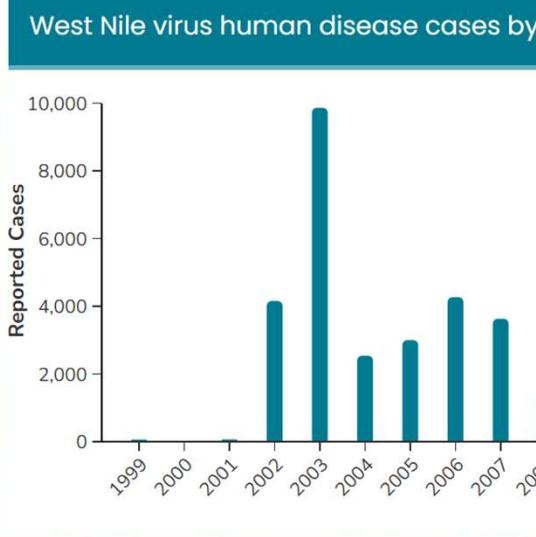
Most human CNS arboviral infections constitute varying degrees and characteristics of **meningoencephalomyelitis** when neuro-invasive disease occurs.

**West Nile  
Virus (WNV)**

The neurological syndrome is preceded by variable combinations of fever, malaise, headache, body aches, nausea, and vomiting, **usually within days of an insect bite**.



vector in the C  
West Nile virus human disease cases by



Health Bird Flu Medicine Mental Health Recalls

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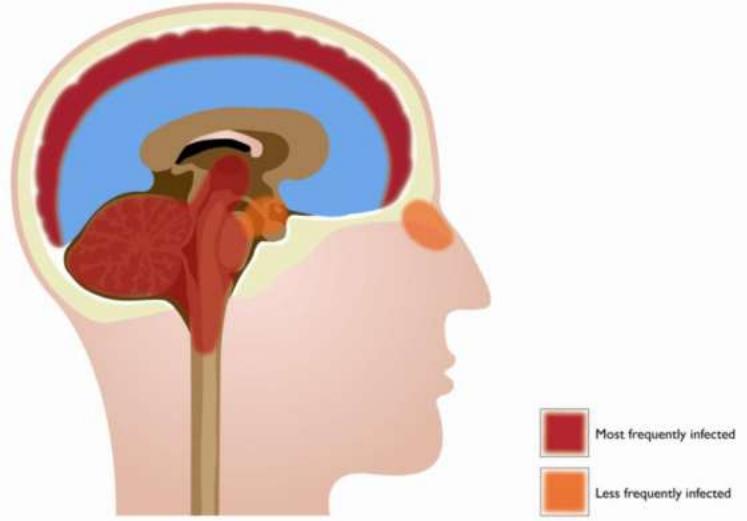


## California's Bay Area reports first West Nile virus death in nearly 20 years

West Nile is transmitted to humans primarily through mosquitoes.



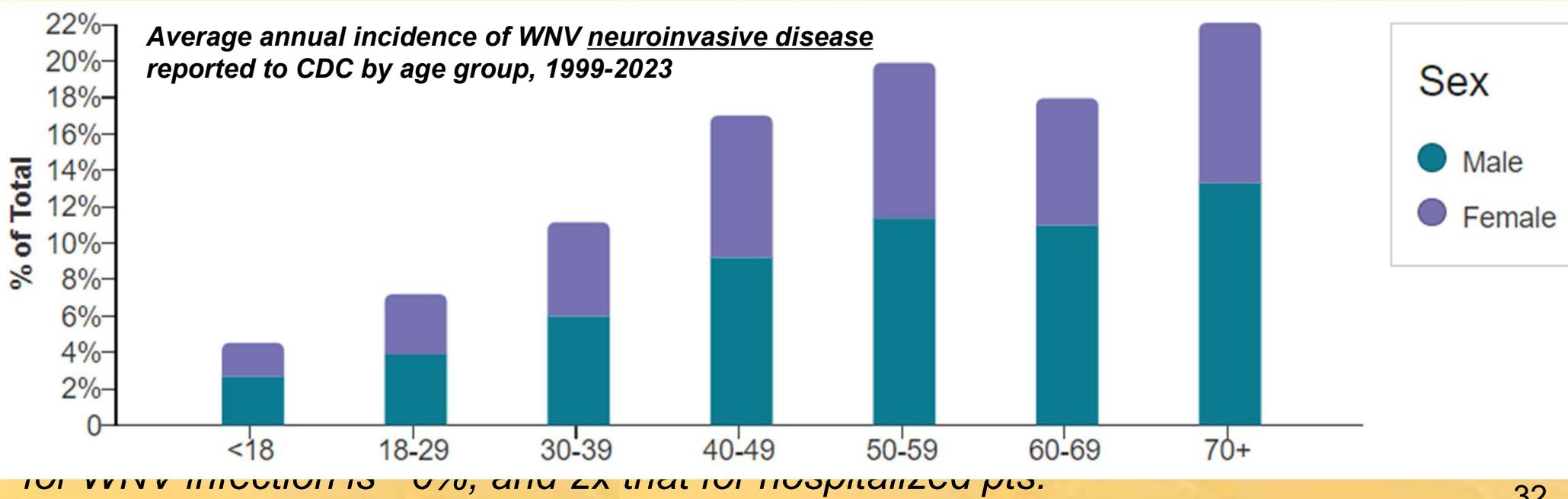
ted in the US, with 3,134 deaths. 2, causing 164 deaths (total CFR of ~9%). neuroinvasive disease in the US.



## WNV pathogenesis: WNV likes to kill neurons



- WNV directly infects neurons, particularly those in the cerebral cortex, thalamus, basal ganglia, brainstem, cerebellum, and spinal cord (anterior horn).



# West Nile Virus – Clinical Outcomes

CNS symptoms are rare, but bad



***Culex  
spp.***



**Mosquito  
bite**

<1%

**Asymptomatic  
infection**

~75%

Significant morbidity?

short-term (30-180 days)

long term

**West Nile  
Fever**

~25%

**Neuroinvasive  
disease**

yes  
no

50-60%

30-40%

**West Nile  
poliomyelitis**

5-10%

**West Nile  
encephalitis**

12-20%

**West Nile  
meningitis**

<1%

**Mortality:**

10-50%

Yes

**Long term morbidity?\***

Yes

Yes

\*Difficulty doing activities of daily living; fatigue (37-75%), neurocognitive impairment, notably memory concerns (11-57%), concentration deficits (17-48%), and depression (17-38%) were also common at post-hospitalization follow-up.

# West Nile Virus – Clinical Manifestations



- Most are **asymptomatic** ~75%
- Incubation period of 2-14 days
- **West Nile Fever** ~25%
  - Self-limited
  - **Fever, HA, malaise, back pain, N/V, diarrhea, +/- rash**
  - **Unique to WNV: ~40% of WNV-infected patients complain of painful eyes and chorioretinal target lesions and retinal hemorrhages are common**
- Neuroinvasive disease 1 out 150
  - **Fever, meningitis, encephalitis, flaccid paralysis**



Risk factors for neuroinvasive WNV:

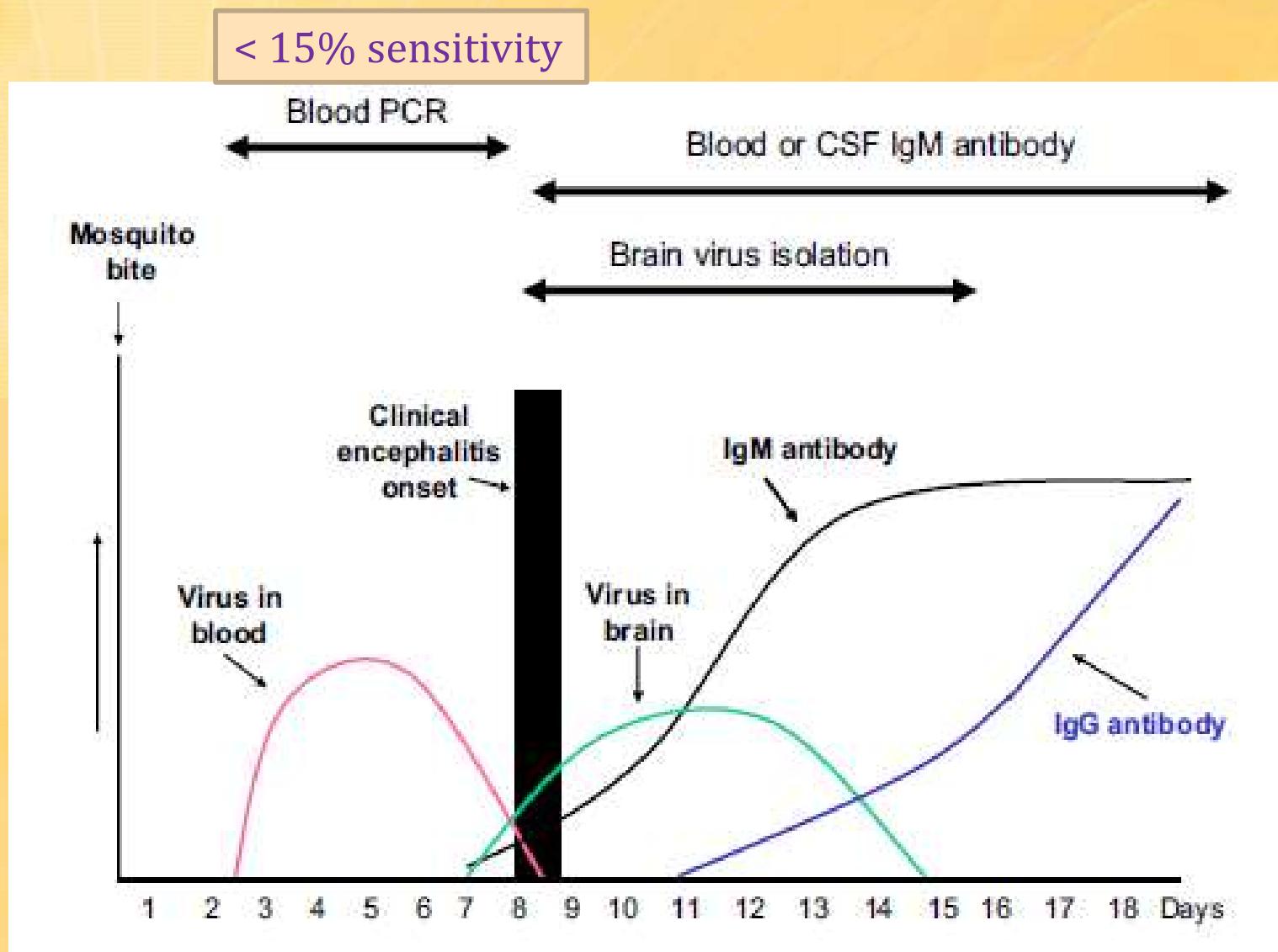
Older Age

Malignancy (hematologic)

Organ transplantation

WNV poliomyelitis

# West Nile Virus Diagnosis



IgM, IgG in serum or CSF

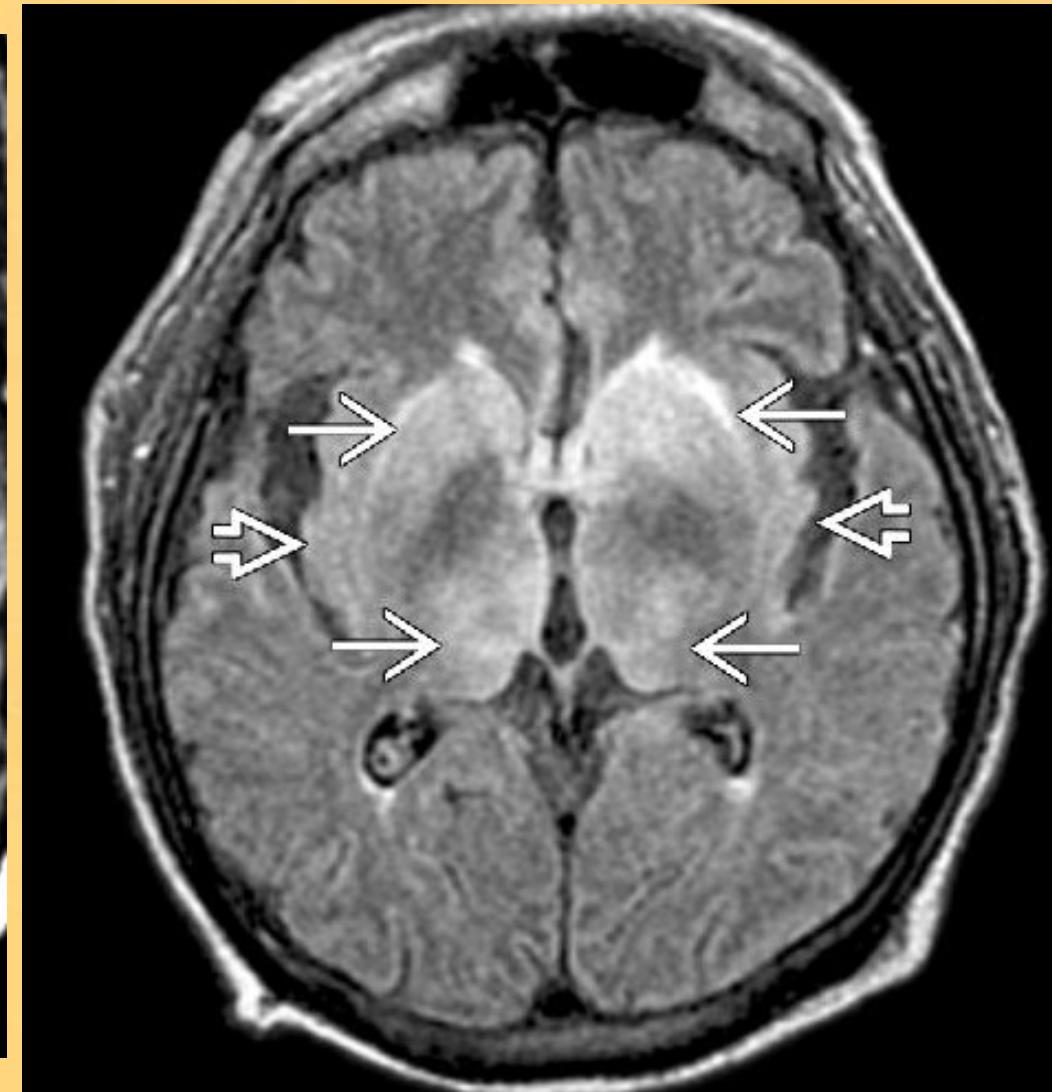
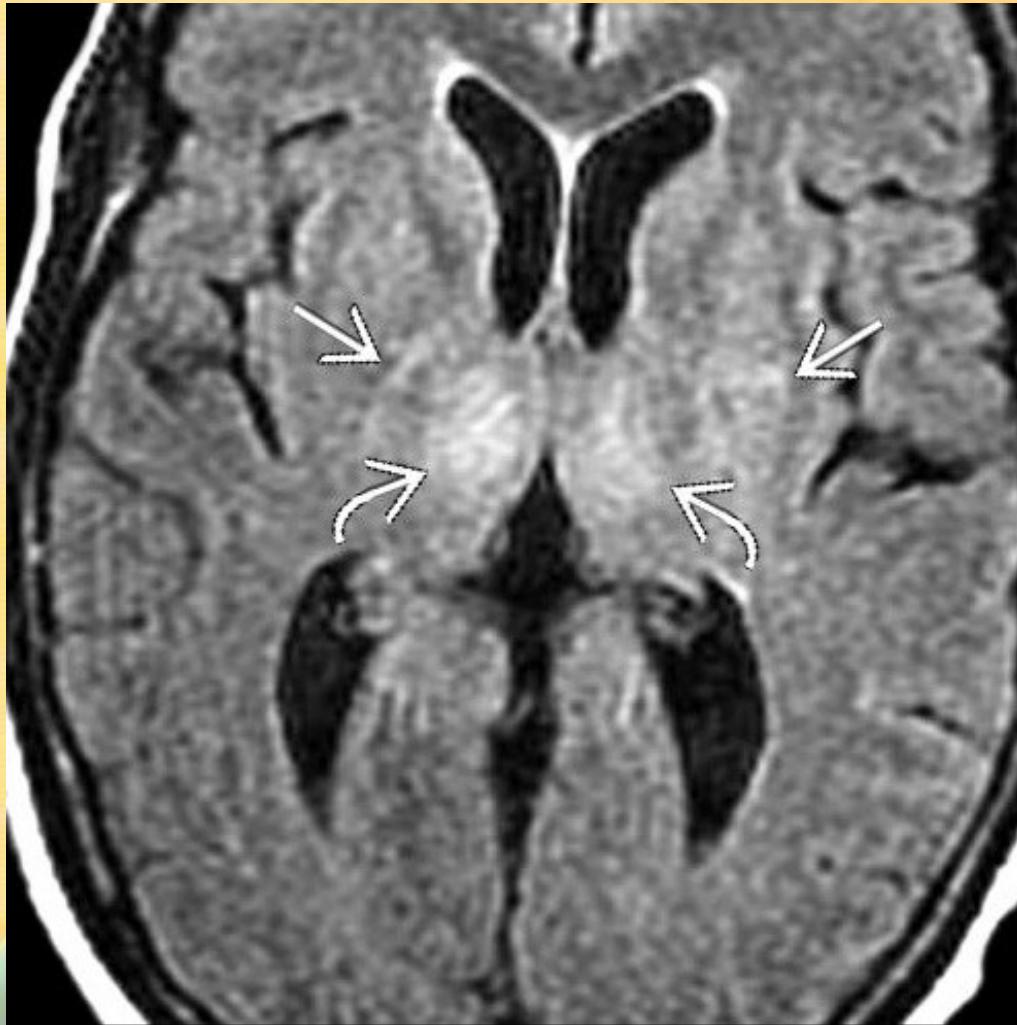
Typical CSF findings show mild pleocytosis, elevated protein and normal glucose

**ELISA for IgM anti-viral antibodies is the mainstay of diagnosis.**

# West Nile Virus-

Basal ganglia and thalamic hyperintensity on MRI

*(may not appear for several weeks after illness onset, and even in severe cases, may have normal imaging)*



# West Nile Virus – Diagnosis & Treatment



- Consider WNV in pts with **unexplained febrile illness, encephalitis, meningitis, and/or flaccid paralysis** during **mosquito season**
- **Serum & CSF WN virus IgM (MAC-ELISA)**
- **Treatment - supportive care**
  - Encephalitis--> monitor for elevated ICP and seizures
  - +/- IVIG, corticosteroids
- **Prevention**
  - **Insect repellent**, mosquito -control programs, blood donor screening (has been reduced though)





# Eastern equine encephalitis (EEE)

## Very bad outcomes!



**Member of the Togavirus family and is the most medically important arbovirus in the US after WNV. Mosquito-borne.**

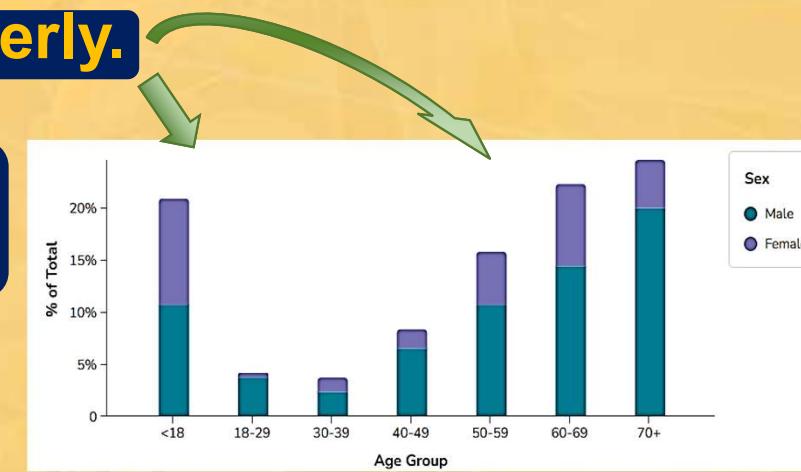
Mostly occurs in the eastern US. Infections are very rare (~5-11 cases/year) **but tend to occur in local outbreaks.** *In a multistate outbreak of EEE in 2019, all 38 patients were hospitalized; 19 (50%) died. 19 cases in US in 2024 with 5 deaths.*

- Most infections are asymptomatic, but **EEE has a mortality rate of ~33-75%.** Like WNV, birds are reservoirs, horses and humans are dead-end hosts.

- **Attack rates highest in children and elderly.**

- Pts who recover from EEE tend to have permanent neurologic sequelae.

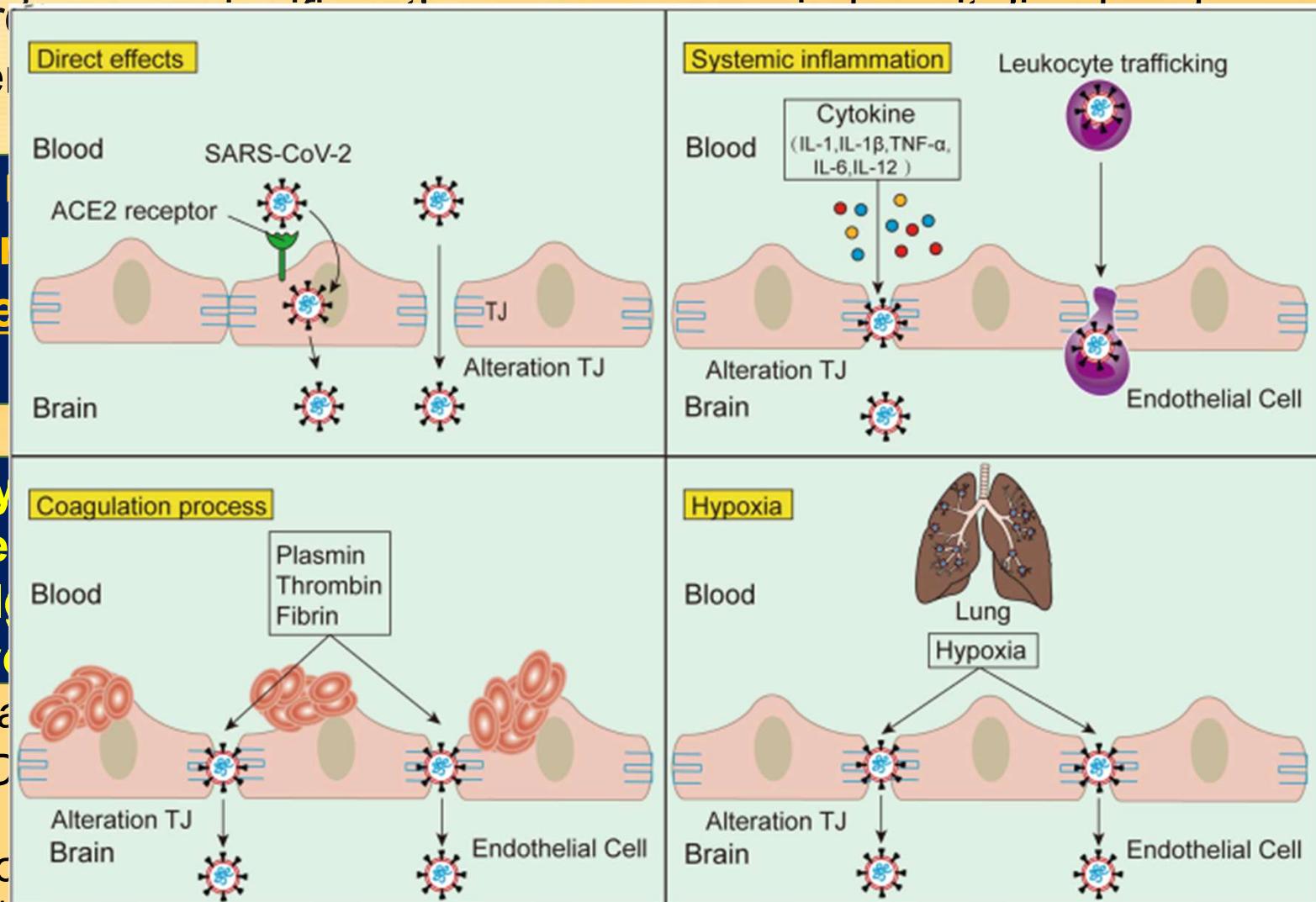
No cases to date for 2025



# CNS manifestations of COVID-19: SARS-CoV-2 affects the CNS in multiple, often severe ways



SARS-CoV-2 is both neurotropic and neurovirulent, and **neurologic complications of COVID-19 are common** [30-80% of pts]. Such disorders include:



The  
19 and  
taste  
part

Many  
suffer  
myalgia  
slower

Mental  
PTSD

Neuro

Encephalitis, demyelination (Guillain-Barré Syndrome), altered consciousness, neuropathy and stroke have also been seen in COVID-19 patients.

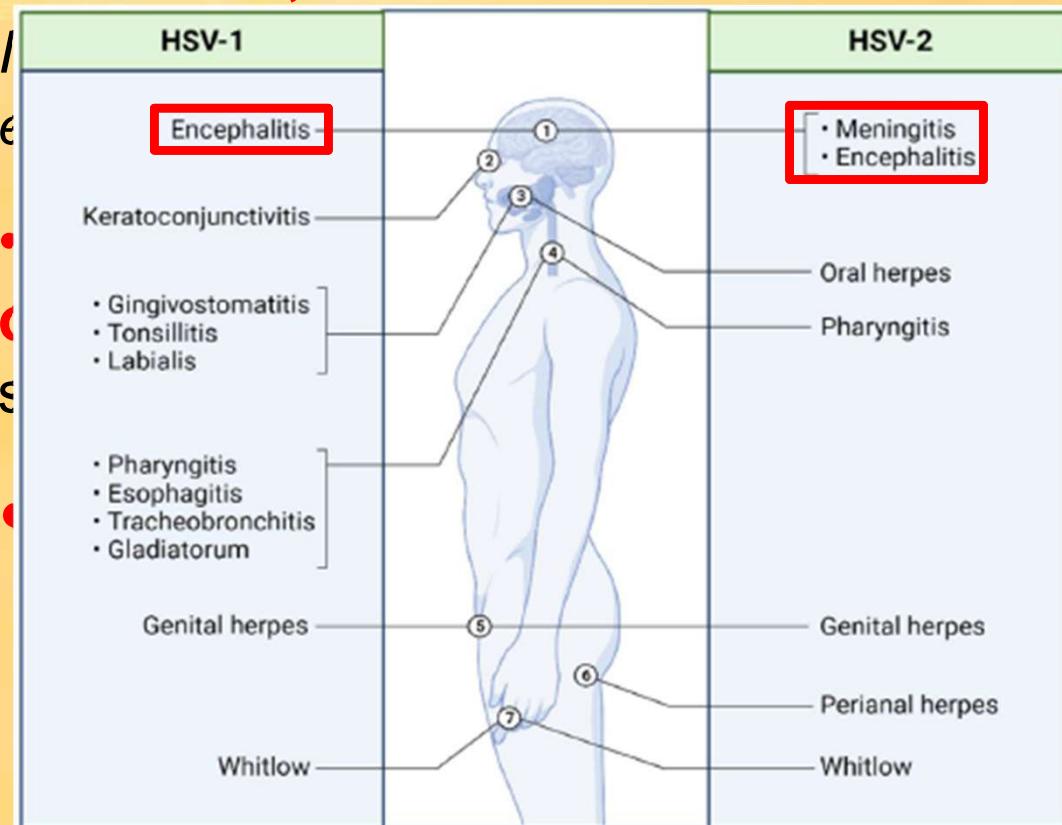


# Herpes simplex virus (HSV) infections of the CNS

## A potentially lethal disease with high morbidity and mortality

HSV, like all other members of the *Herpesvirus* family, cause latent infections. ~6000 encephalitis cases annually in the US.

- HSV encephalitis (HSE) from HSV-1 mainly occurs in adults; HSE from HSV-2 is a disease of newborns.



0-75% of cases of confirmed viral

universal triad of headache (in  
teration in mental status, with  
mental deficits.

ts in adults similarly to other  
application of primary genital  
in course. HSM is a classic

# *HSV infections of the CNS-pathogenesis: HSE is a medical emergency!*



**HSV-1 gains access to the CNS probably by invasion via trigeminal nerve or olfactory tract after primary CNS infection in the oropharynx.**

*Reactivation or viral spread from primary genital infection seems less likely.*

- Untreated, the mortality rate is 70%.
- Even when treated, 40-60% of HSE survivors are left with permanent non-verbal and verbal memory impairment, behavioral abnormalities,, depression, anxiety, insomnia and emotional lability.
- HSE characteristically causes an acute, aggressive, focal inflammatory hemorrhagic necrosis of the temporal or frontal lobes (which contrasts with other viral encephalitides).

# *HSV infections of the CNS- Dx and Tx*



## Diagnosis:

- **PCR for the presence of HSV DNA of the CSF is the procedure of choice.**
- Cranial CT or MRI as soon as possible after presentation.
- CSF pleocytosis is observed in >90% of pts. RBCs in CSF are typical for HSV encephalitis, but NOT diagnostic.

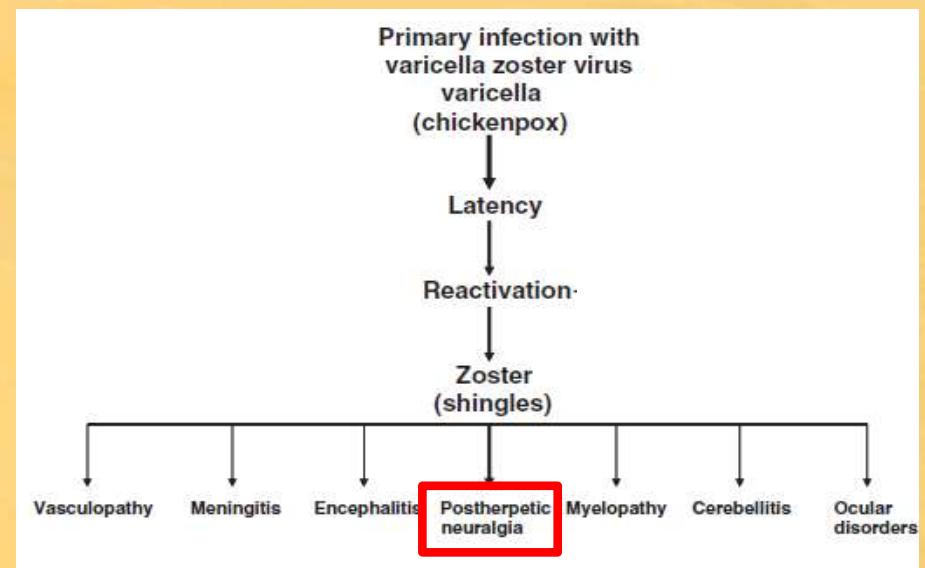
Treatment: **IV Acyclovir** reduces mortality

# *Herpes zoster (HZ) and post-herpetic neuralgia (PHN)*

*PNH is a painful sequelae of HZ*



- **Herpes zoster (shingles) results from the reactivation of latent varicella zoster virus (VZV) infection.** It presents as the painful, often debilitating eruption of a rash, usually unilateral, along a dermatome.
- At least 10% of patients with HZ will progress to PNH ( $\sim 10^6$  people/year; **20-30% of these will be >60**).
- PHN is characterized as **severe, constant burning, throbbing, or stabbing/shooting pain** that persists for at least three months post-resolution of the HZ skin lesions.



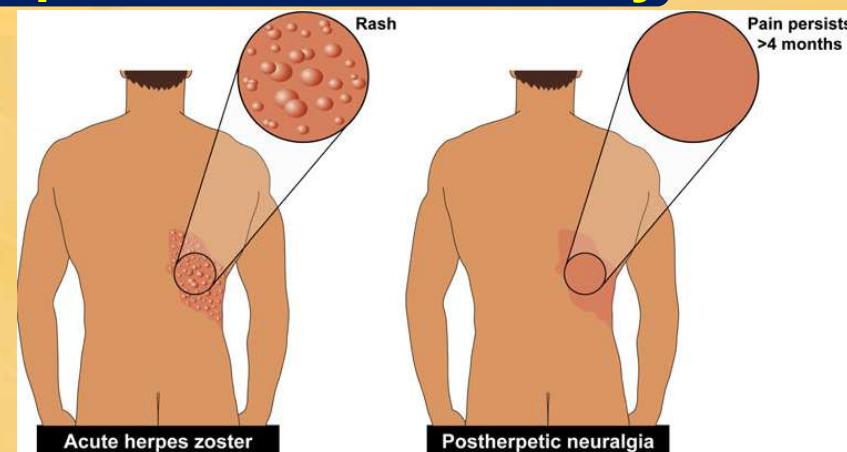
# *HZ and PHN-pathogenesis*

*PNH is one of the most common forms of neuropathic pain*



- **PHN symptoms can also include allodynia** (pain evoked by normally non-painful mechanical stimuli, such as light brushing of the skin).
- **Risk factors include older age**, greater acute pain during HZ; greater severity of rash.
- **The most frequent sites affected are the thoracic nerves, followed by the ophthalmic division (V1) of the trigeminal nerve.**
- Because VZV is latent in most ganglia, HZ can occur anywhere on the body.
- **Reactivation results from a decline in VZV-specific T cell immunity.**

- Following VZV reactivation, the nerve ganglion typically exhibit intense inflammation, accompanied by hemorrhagic necrosis of nerve cells.



# *PHN-intervention:*

## *PHN is treated as neuropathic pain*



**Dx:** Typically, via pt history and physical exam.

**Treatment:** First-line treatments include tricyclic antidepressants (like nortriptyline > amitriptyline) or \*SNRIs (like duloxetine or venlafaxine) and gabapentinoids (gabapentin or pregabalin).

- Adjunctive treatments include topical capsaicin and topical lidocaine 5% patches. Opioids and tramadol are less favored due to risks associated with these drugs. NSAIDS are ineffective.
- There is no evidence that anti-virals are useful in the TX of PNH.
- OMT can be viewed as an adjunctive therapy for PHN.

**Prevention:** Recombinant protein vaccine (**Shingrix**) is given for the prevention of HZ/PHN in persons  $\geq 50$  years of age.

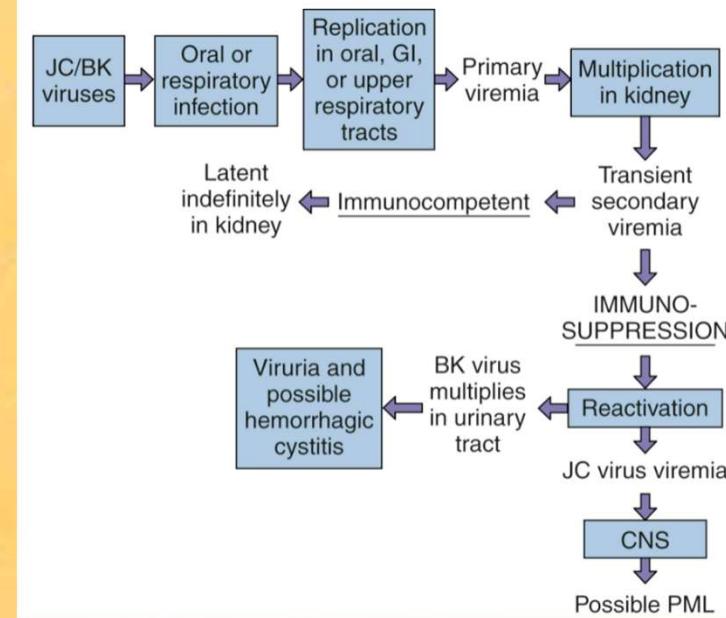
Given 2x, 2-6 months apart.

\*serotonin-norepinephrine reuptake inhibitors



# *JC polyomavirus (JCV) infection:*

*Commonly innocuous virus that causes a mouthful of a bad disease*



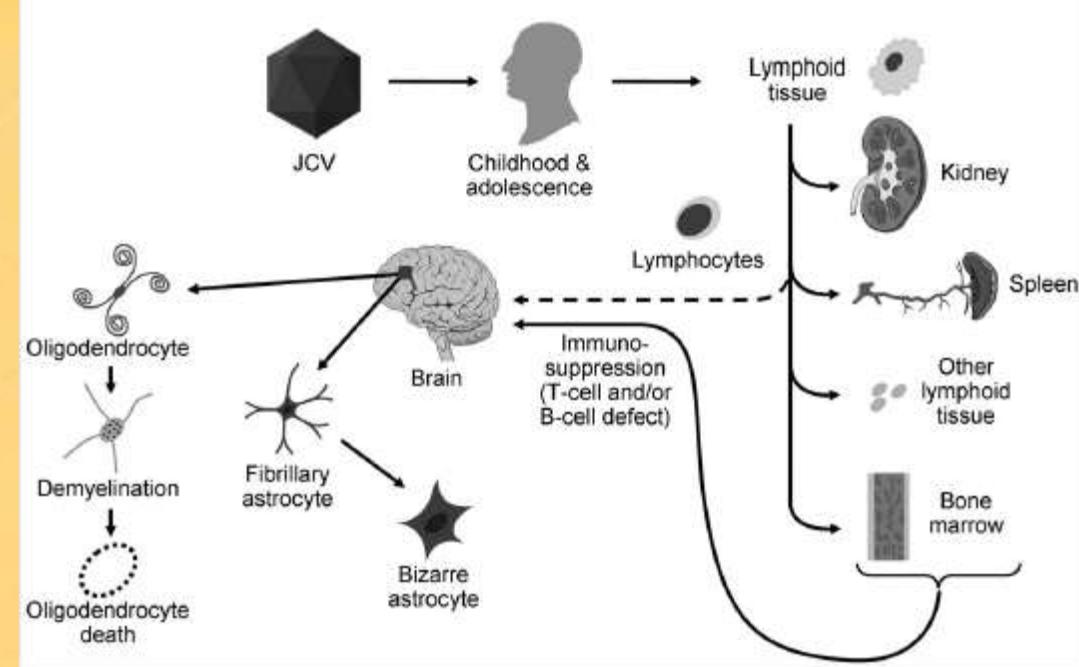
- Member of the **Polyoma virus family**.
- Infection is widespread (50-90% of the population is antibody-positive) and nearly all infections are asymptomatic.
- Causes **latent infections** in the kidneys and other sites; may infect tonsils first. How it enters the brain is still unknown.
- **JCV is an opportunistic pathogen and is the cause of progressive multifocal leukoencephalopathy (PML), a disease involving degenerative demyelination of white matter in severely immunosuppressed pts.**
- **80% of PML pts have HIV/AIDS.**

# PML-pathogenesis:

*PML is a dangerous disease of the profoundly immunosuppressed*

- **After toxoplasmosis,**

**PML** is the most common opportunistic infection to affect the CNS (~10-14% of pts, even in the age of HAART).



- **JCV is cytolytic for astrocytes and oligodendrocytes.**

- **PML is characterized by motor weakness often with hemiparesis, speech disturbances including aphasia and dysarthria, vision abnormalities, gait instability, cognitive deterioration, sensory and visual field loss, with rapid progression to coma and death.**

- Mortality rate is for HIV+ pts is 30-50%; survivors have devastating neurologic deficits.

- **CD4 counts <200/uL indicate a poor prognosis.**



## *PML-intervention: Get the T cell count up!*



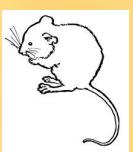
**Diagnosis of PML is based on:**

- Clinical presentation along with neuroimaging (see next slide), and
- qPCR on CSF for JCV
- HAART and immune reconstitution are the only effective treatments for PML in HIV+ pts. For AIDS pts already receiving HAART, therapy should be changed to optimize immune restoration and normalization of CD4 counts.
- Make Dr Mookerjee happy! Agents with highest CNS penetration = Zidovudine, Nevirapine, Indinavir

# Other viruses affecting the CNS



- *Cytomegalovirus: (as retinitis or encephalitis in the immunocompromised).*
- *HHV-6: common pediatric rash causing virus; causes encephalitis in 0.5–6% of cases.*
- *Measles: encephalitis.*
- *Mumps: deafness, encephalitis.*
- *Nipah and Hendra viruses: zoonotic encephalitides with high mortality rates*
- *LaCross and Jamestown Canyon viruses: most commonly reported pediatric arboviral encephalitides in North America. <100 cases of mild encephalitis/yr in the US for each.*
- *Oropouche virus: In Florida, there have been ~100 travel-associated cases of this flavivirus. Is a pathogen of concern due to global warming.*
- *Lymphocytic choriomeningitis virus: associated with rodent exposure; mild disease; prevalence of LCMV infection in humans is 2-5%.*
- *Influenza: acute encephalopathy/encephalitis is a rare sequelae of flu.*
- *Powassan virus: only tick-borne encephalitide in the US; very rare but has estimated CFR is 10–30%. Cases have been increasing over the past 10 years.*



# VIRAL MENINGOENCEPHALITIS: MORPHOLOGIC FEATURES



## COMMON TO ALL:

- Both meningeal and parenchymal changes
- Most viruses cause similar morphologic changes with varying severity
- Viral meningoencephalitis is typically lymphocytic with perivascular distribution of mononuclear inflammatory infiltrates
- Individual neuronal necrosis with neuronophagia and microglial nodules
- In more severe cases multifocal gray and white matter necrosis, necrotizing vasculitis and focal hemorrhages
  - Neutrophils are often present, but fewer than in bacterial meningitis

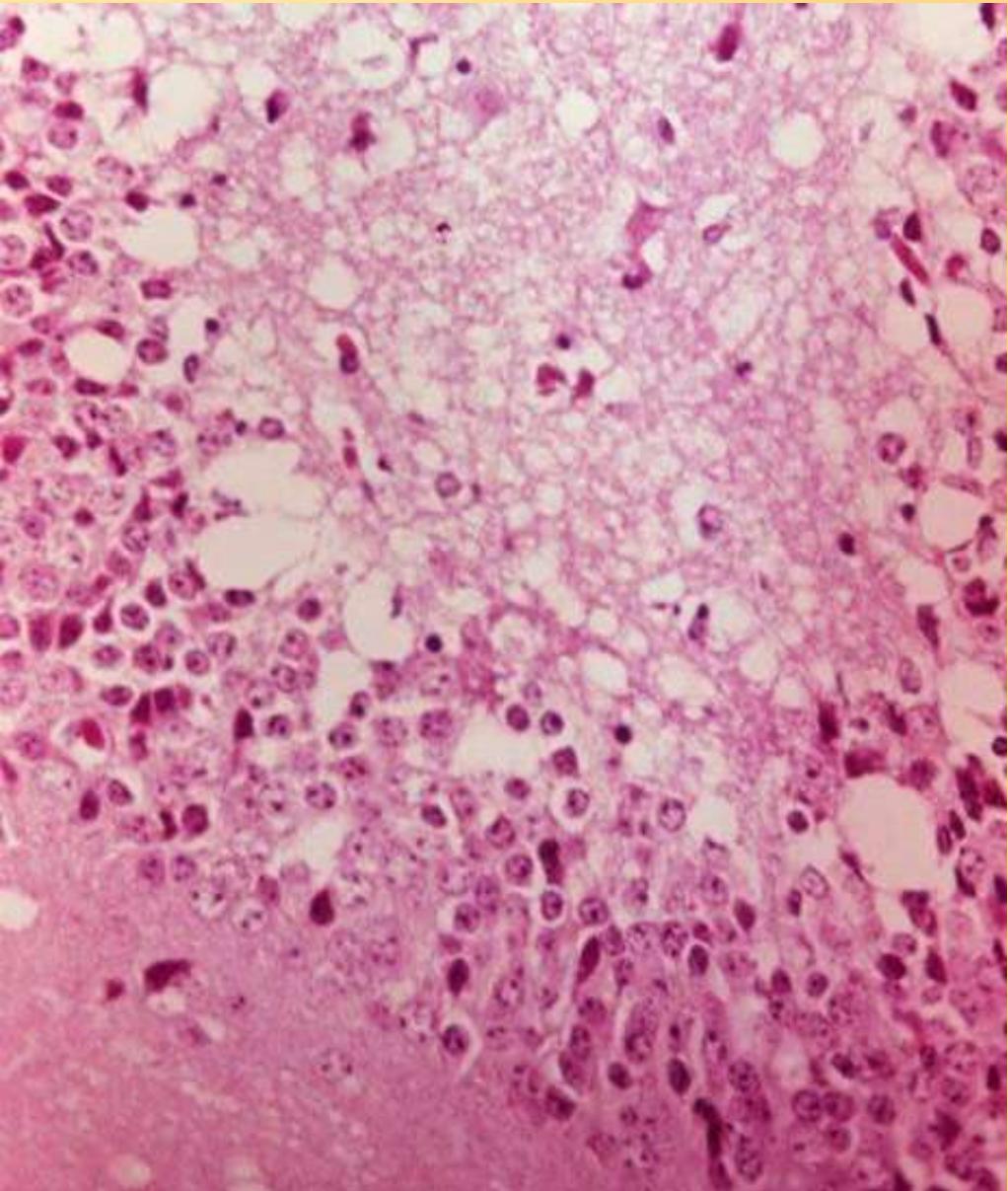
## CYTOPATHIC CHANGES CAUSED BY CERTAIN VIRUSES:

- Cowdry type A nuclear inclusions in HSV infection
- Negri bodies in rabies
- Cytomegaly and intranuclear and cytoplasmic inclusions in CMV infection
- Nuclear inclusions in oligodendrocytes in progressive multifocal leukoencephalopathy (PML) caused by JC virus (polyomavirus) infection

# TYPICAL MICROSCOPIC FEATURES OF VIRAL MENINGOENCEPHALITIS



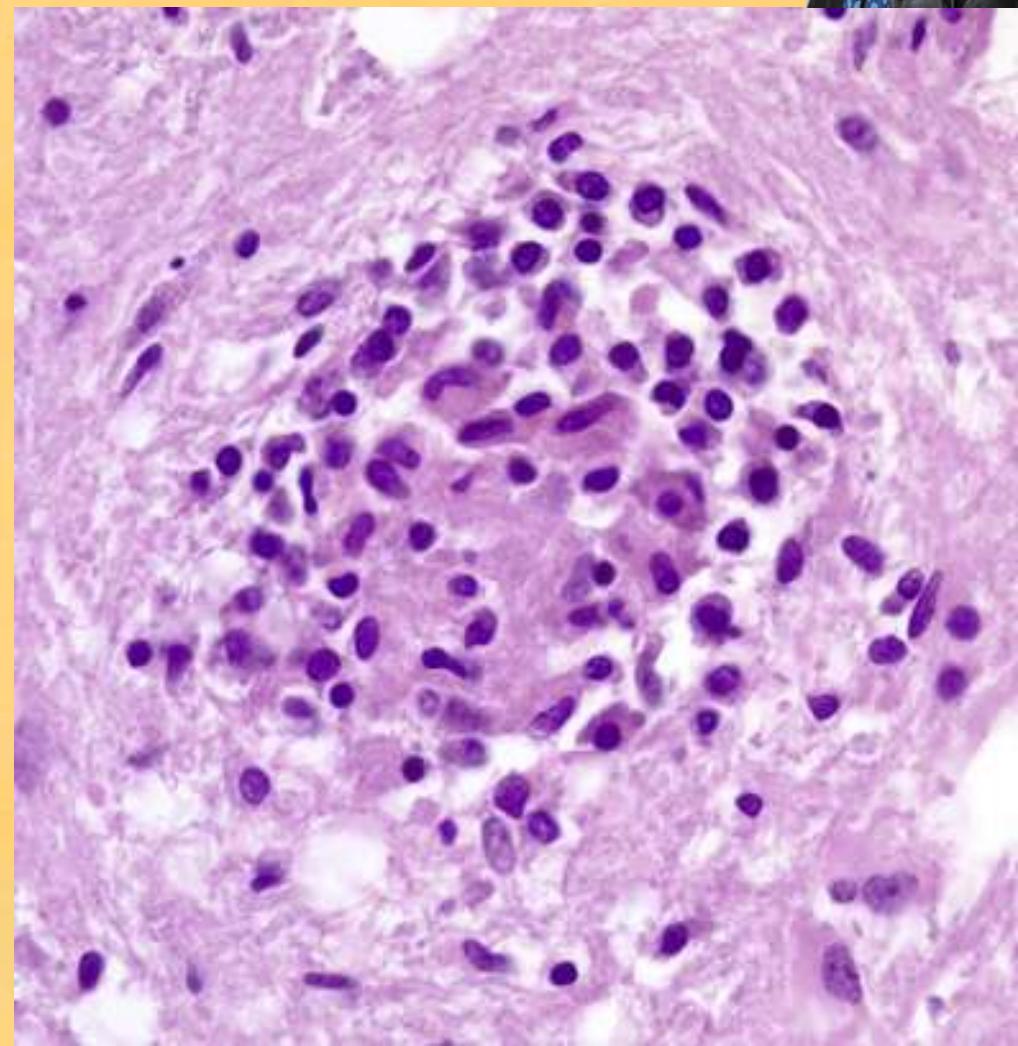
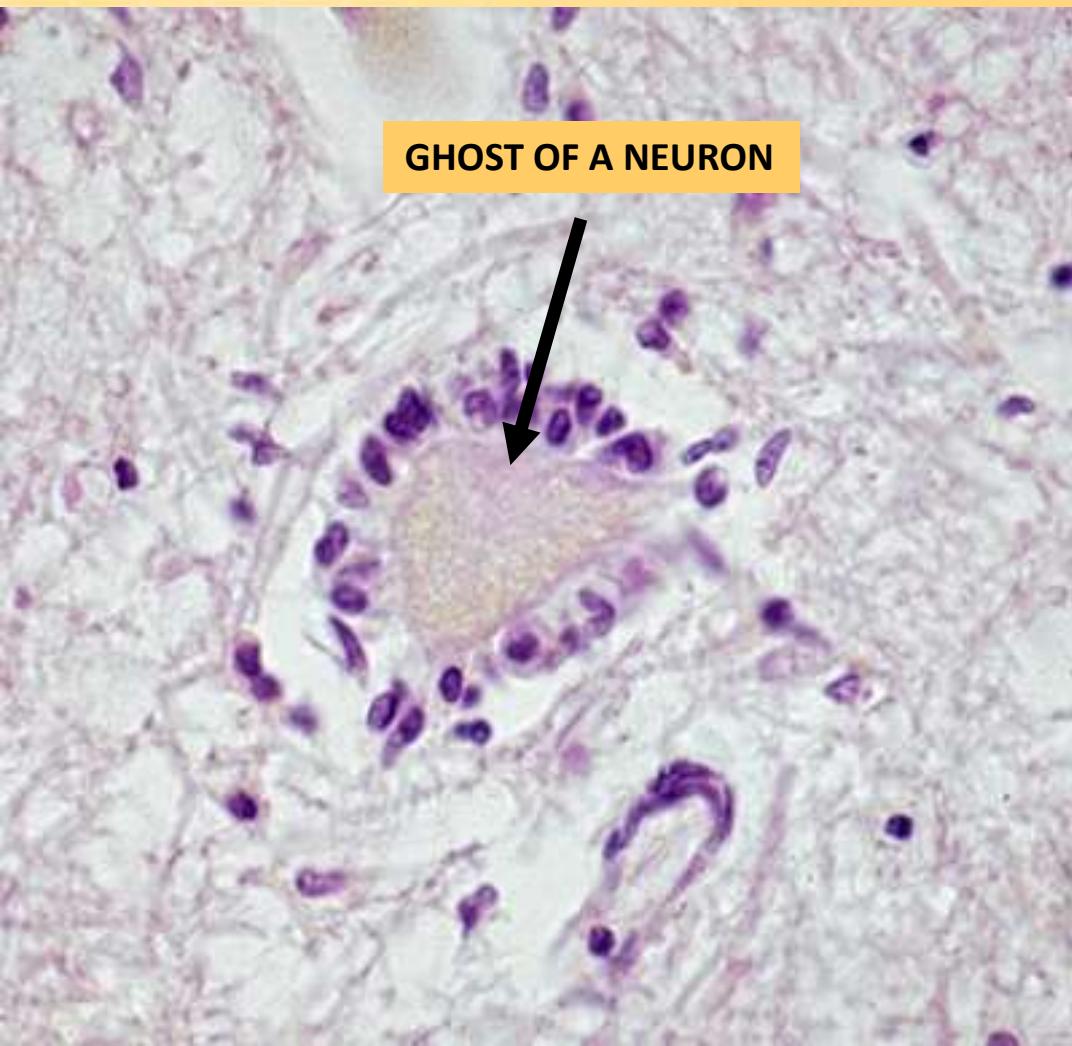
MONONUCLEAR INFLAMMATORY INFILTRATES



PERIVASCULAR CUFFING BY MONONUCLEAR CELLS



# NEURONOPHAGIA AND MICROGLIAL NODULES IN VIRAL MENINGOENCEPHALITIS



NEURONOPHAGIA = PHAGOCYTOSIS:  
DAMAGED NEURON IS SURROUNDED BY  
MACROPHAGES

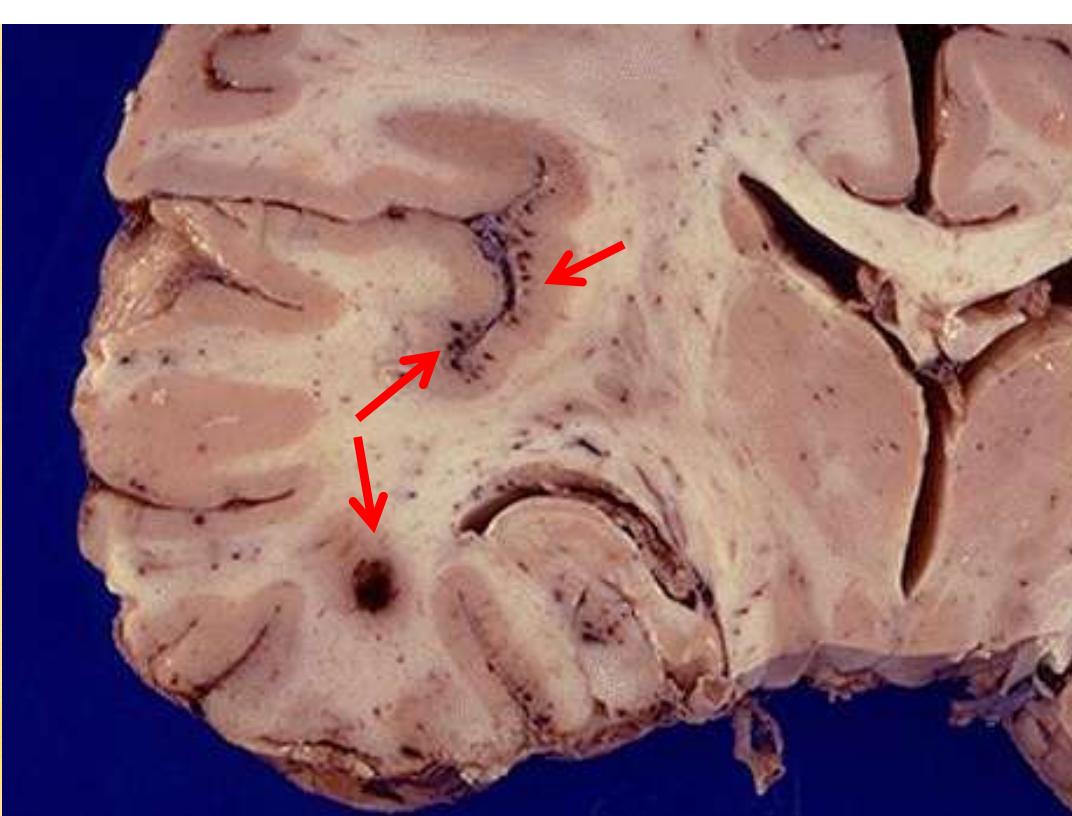
MICROGLIAL NODULE:  
MACROPHAGES AND LYMPHOCYTES  
SURROUND DAMAGED NEURONS



# HERPES SIMPLEX ENCEPHALITIS CAUSED BY HSV-1

## TOP:

- Hemorrhages in the temporal lobe due to herpes simplex virus infection
- Temporal lobes are typically most affected
- Multiple hemorrhagic lesions
- Viral infections produce mononuclear cell infiltrates microscopically.
- In severe infection causing neuronal necrosis neutrophils are also present, but not in the same numbers as in bacterial meningoencephalitis.



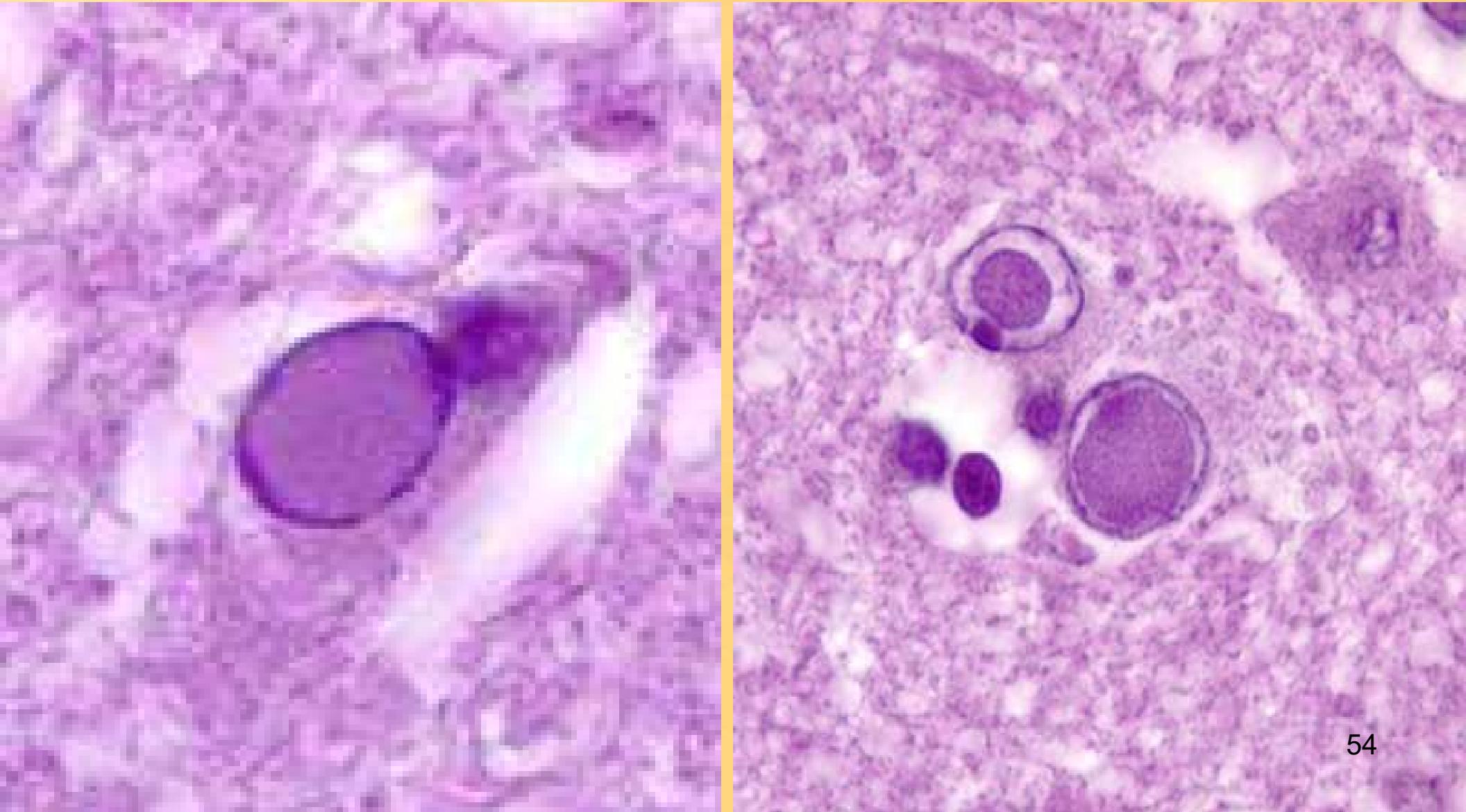
## BOTTOM:

- HSV encephalitis in an adult HIV+ patient resulted in hemorrhagic necrosis on the ventral aspect of frontal and temporal lobes

# VIRAL MENINGOENCEPHALITIS: CYTOPATHIC EFFECTS OF HSV



COWDRY A TYPE INTRANUCLEAR INCLUSIONS BOTH IN  
NEURONS AND GLIAL CELLS





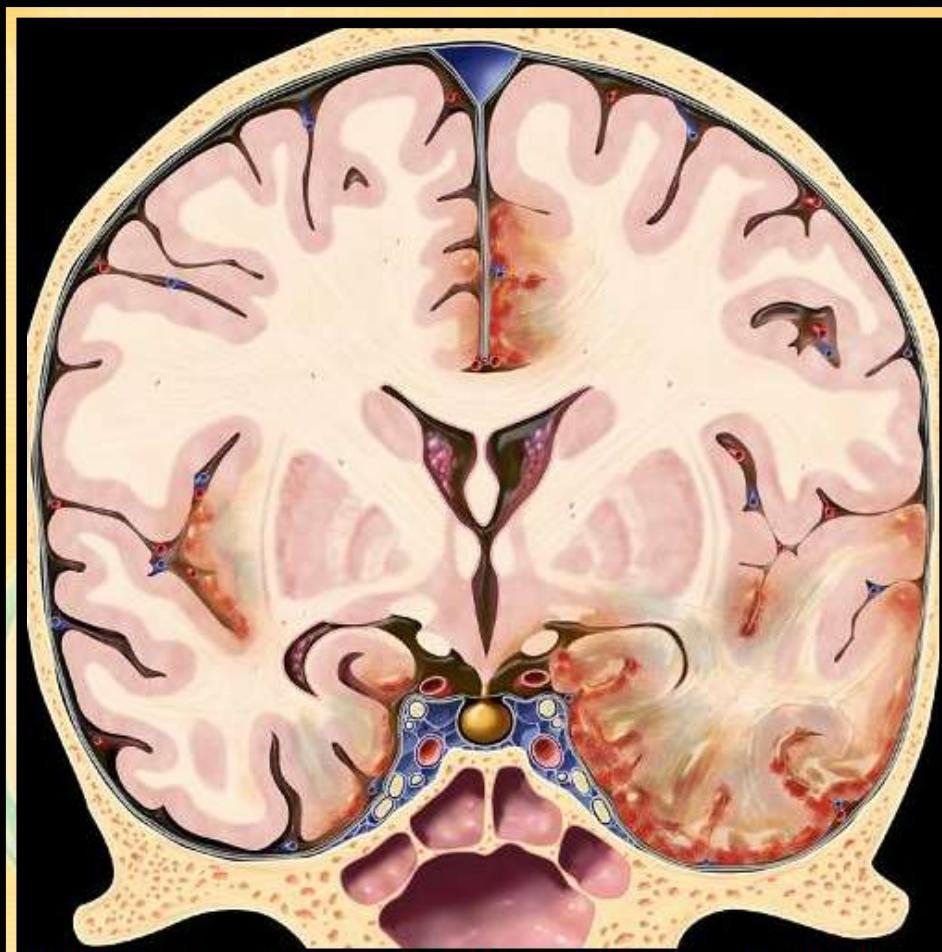
# HERPES SIMPLEX IN NEONATES\*

- HSV-1
  - Infero-medial **temporal** lobes
  - Insular cortex
  - Inferior lateral **frontal** lobes
  - **Frequently associated with cortical hemorrhage**
  - Basal Ganglia typically spared- distinguished from MCA infarct
    - (Periventricular white matter changes)
- HSV-2 Neonatal and probable self-limiting

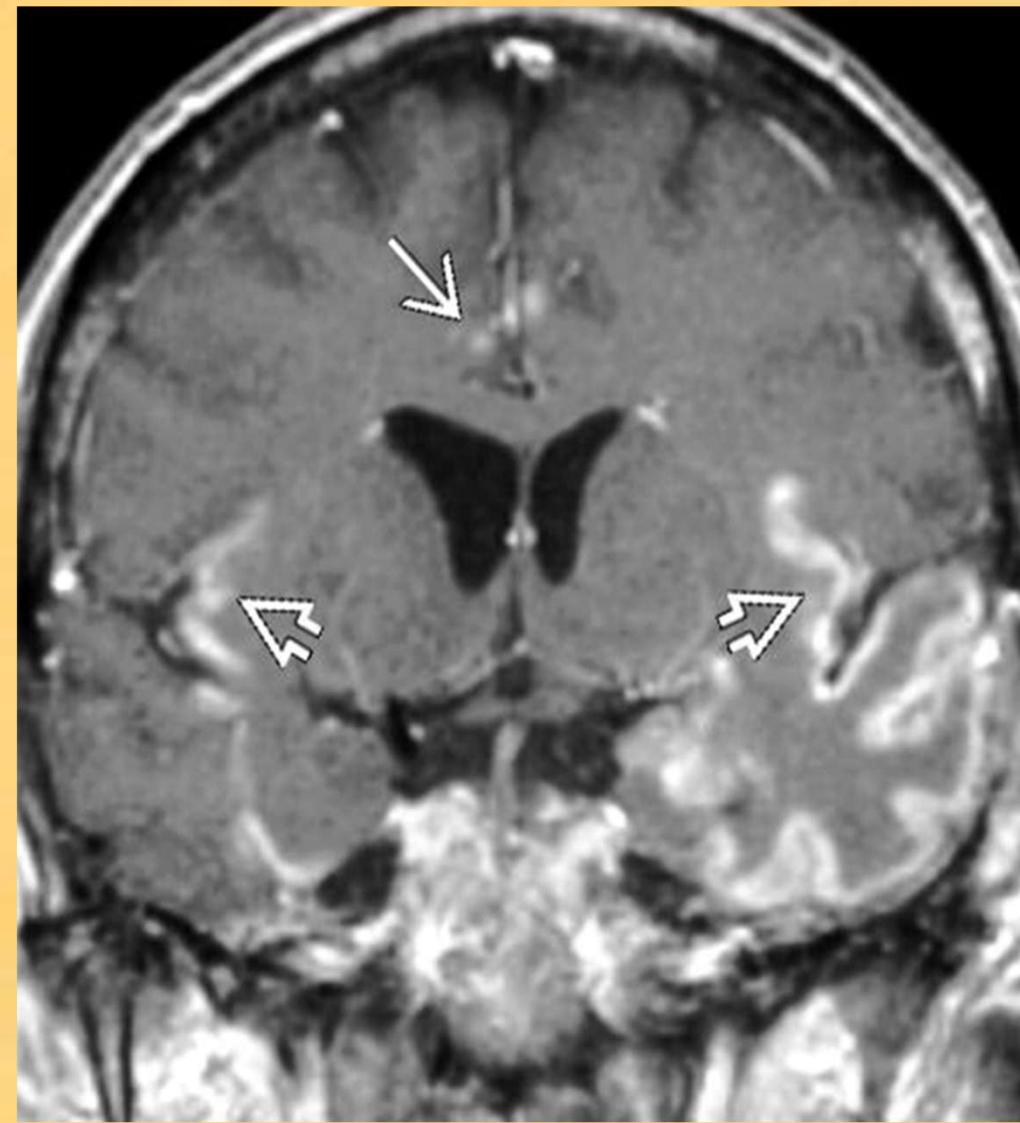
\*Edited by LAR. Original slide created by Dr. Tami Hendriksz<sup>35</sup>



# HERPES SIMPLEX TYPE -1 IN NEONATES\*



Coronal graphic shows the classic features of herpes encephalitis with bilateral but asymmetric involvement of the limbic system. There is inflammation involving the temporal lobes, cingulate gyri, and insular cortices.

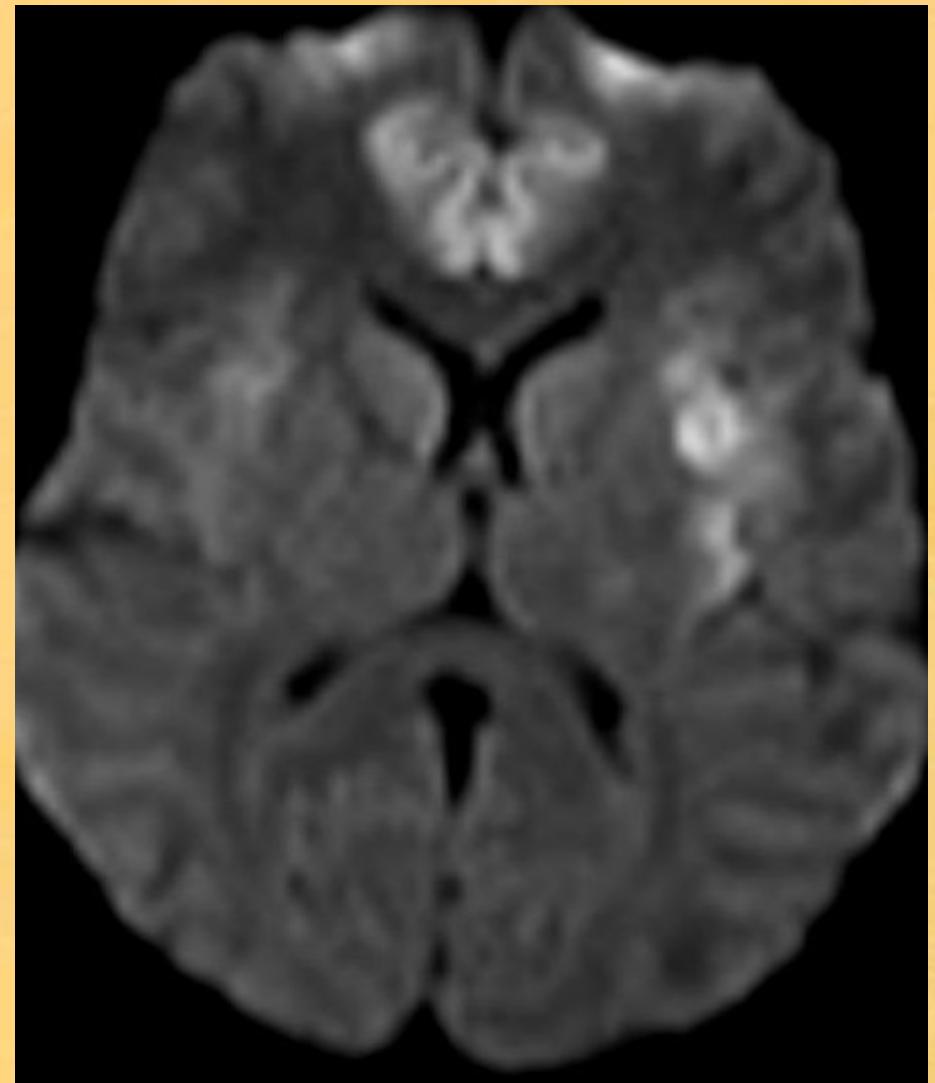
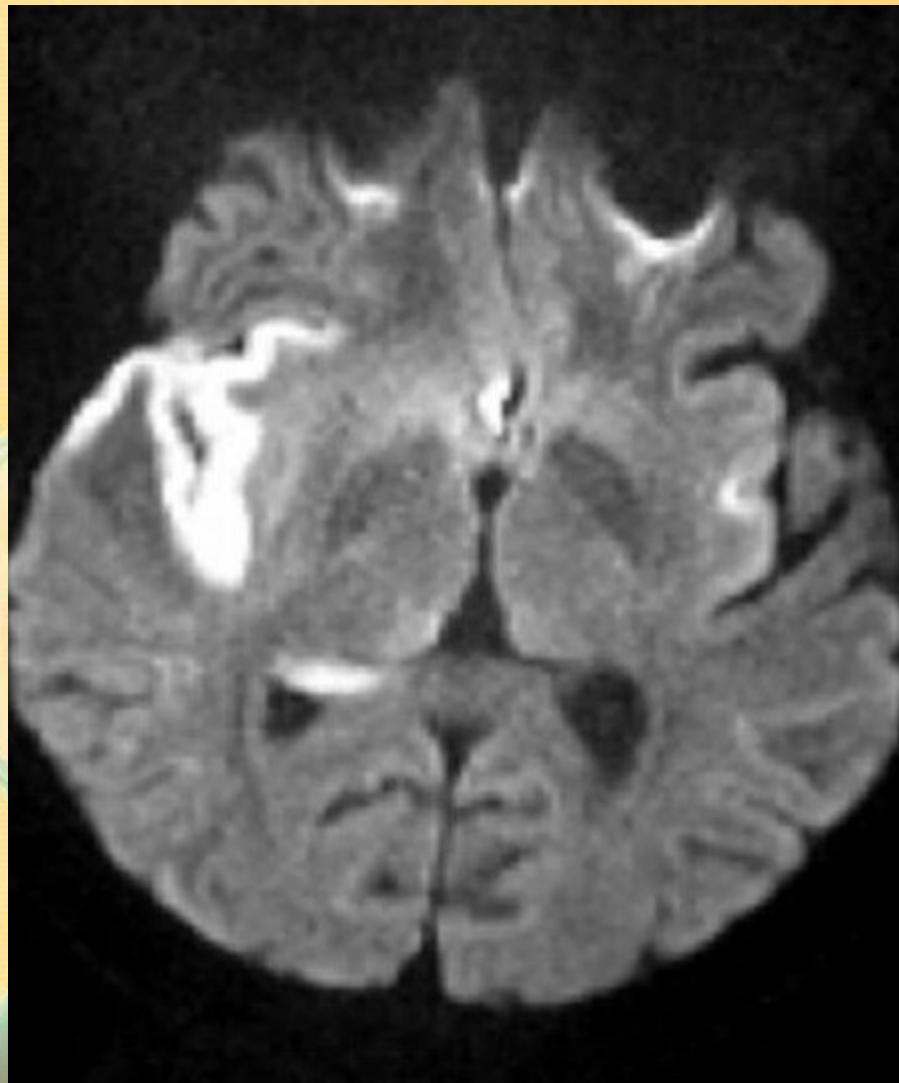


**Edema, hemorrhage, and necrosis in the inferomedial temporal lobe are common findings.  
Brain involvement may be unilateral or bilateral.**



# HERPES SIMPLEX TYPE -1 IN NEONATES\*

Changes in the insular cortex and inferior frontal lobes



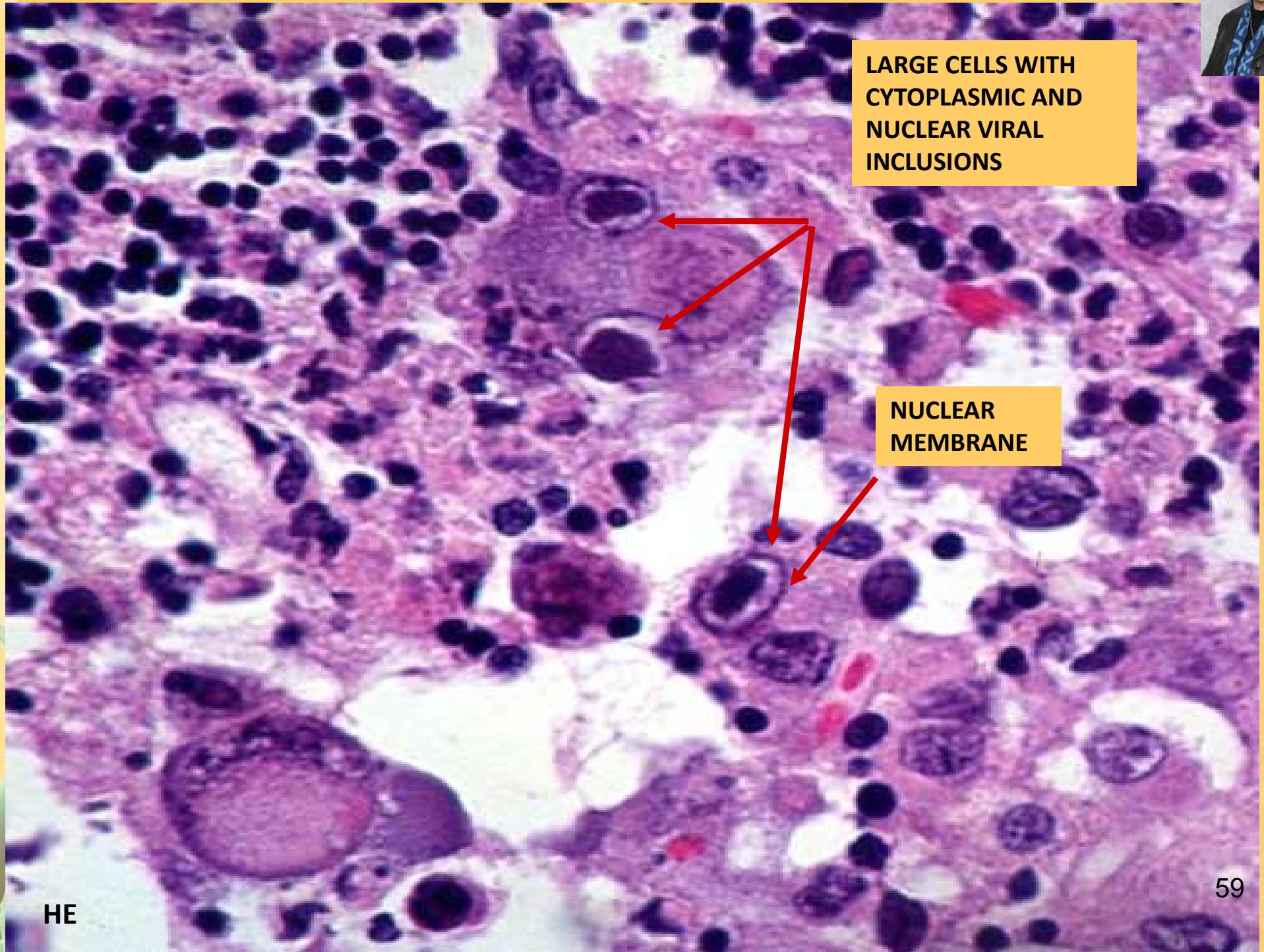
# NEONATAL NECROTIZING HEMORRHAGIC HSV PANENCEPHALITIS CAUSED BY GENITAL HSV (HSV-2)



58

70% OF CASES ARE ACQUIRED DURING VAGINAL DELIVERY AND CAUSED BY GENITAL HSV.

# CMV ENCEPHALITIS: CYTOPATHIC EFFECTS

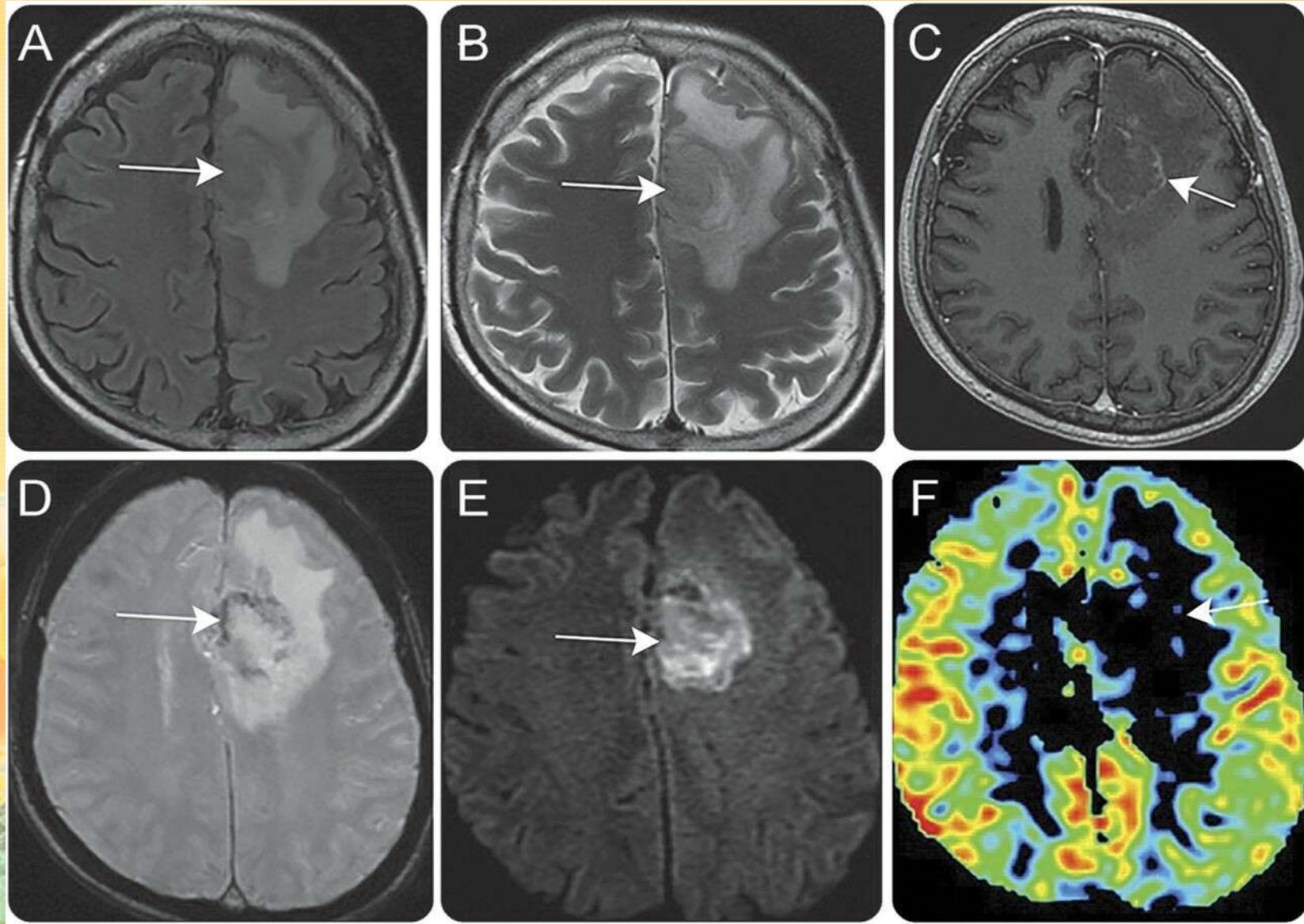


# CMV-INFECTION IN A KIDNEY-TRANSPLANT PATIENT



BRAIN  
MASS

TUMOR?

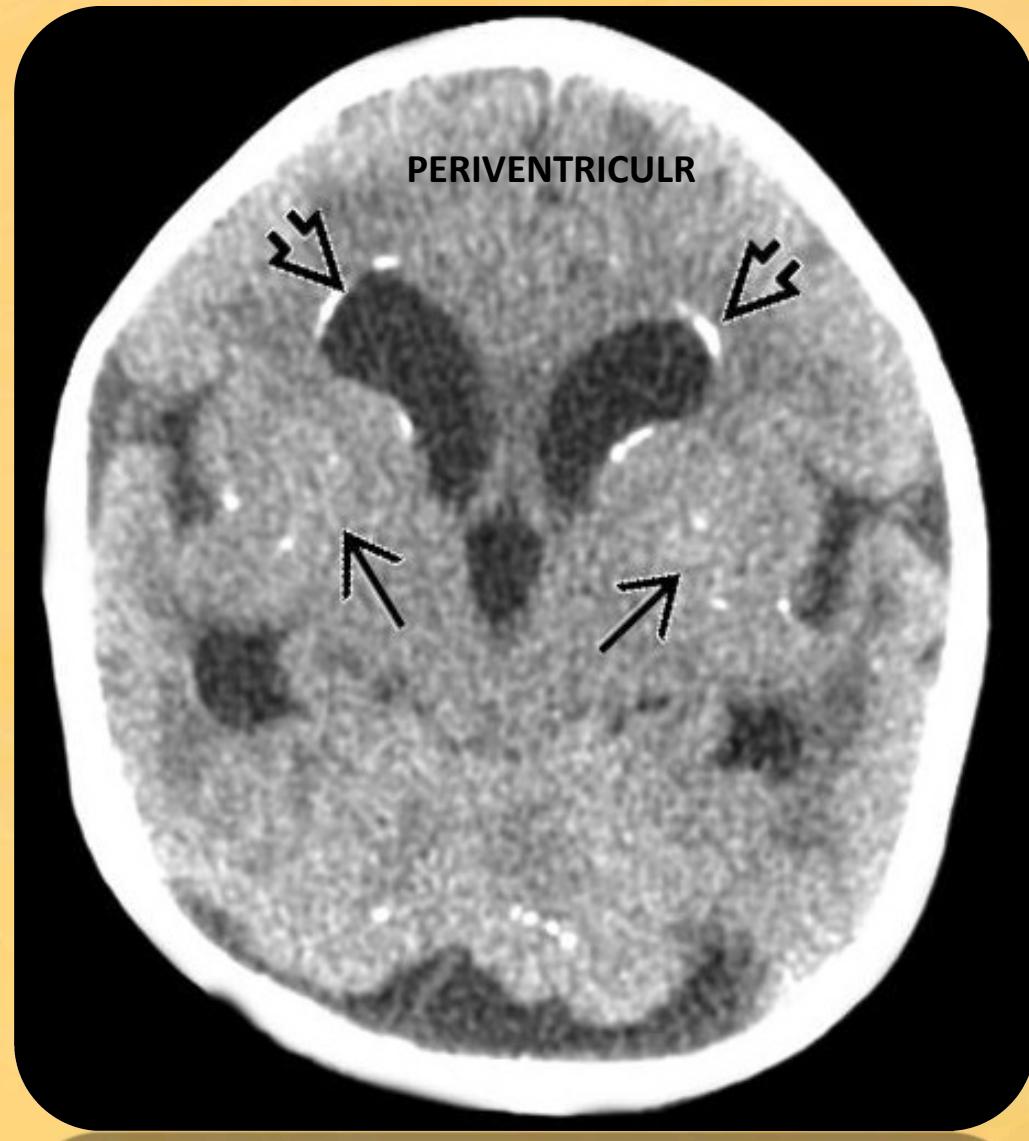
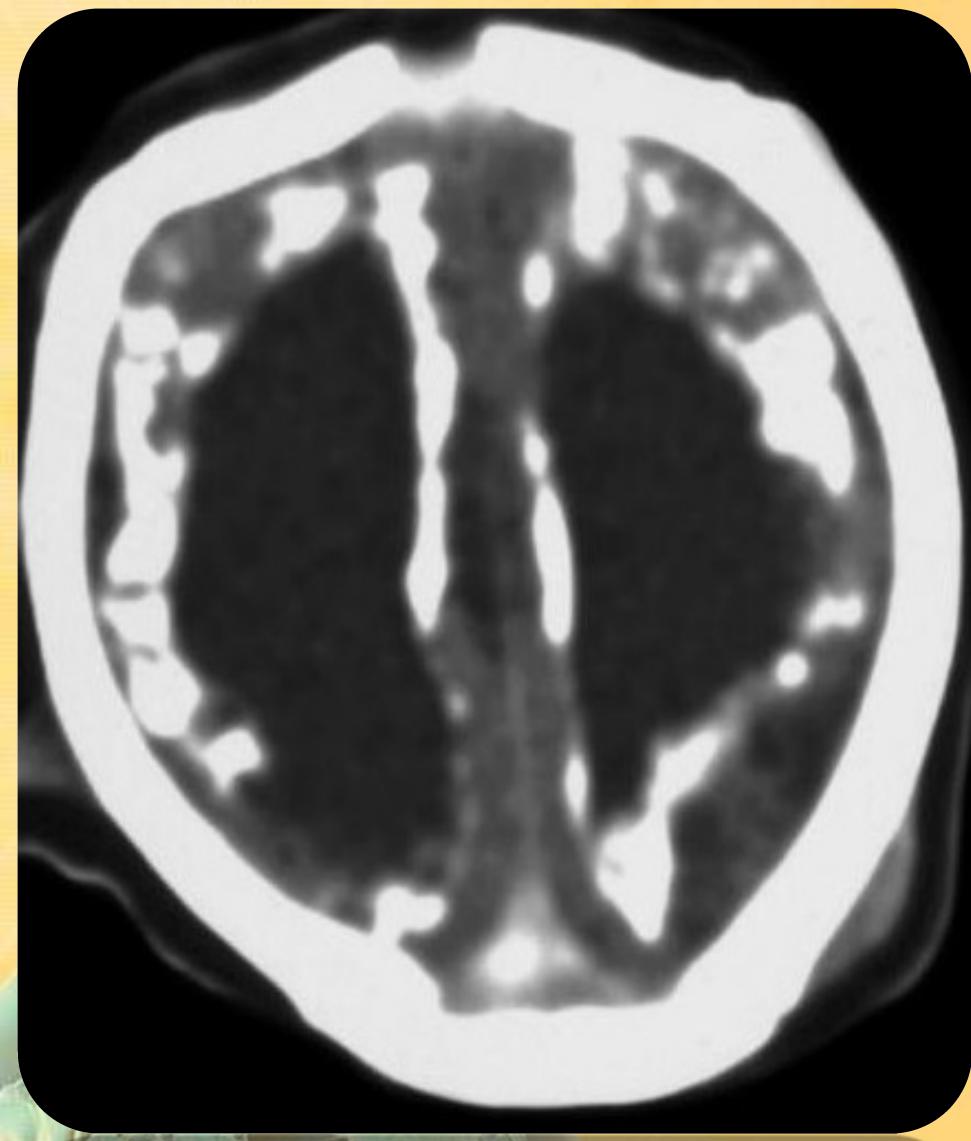


Axial fluid-attenuated inversion recovery MRI (A) and axial T2 MRI (B) reveal a large brain mass in the left frontal lobe. Axial postcontrast T1 (C) shows marked peripheral enhancement by gadolinium. Axial susceptibility weighted imaging (D) shows a hemorrhage. Axial diffusion (E) shows restriction diffusion: ?tumor? Axial arterial spin labeling perfusion (F) reveals low perfusion -> no tumor.



# CT ALTERATIONS DUE TO CONGENITAL CMV INFECTION

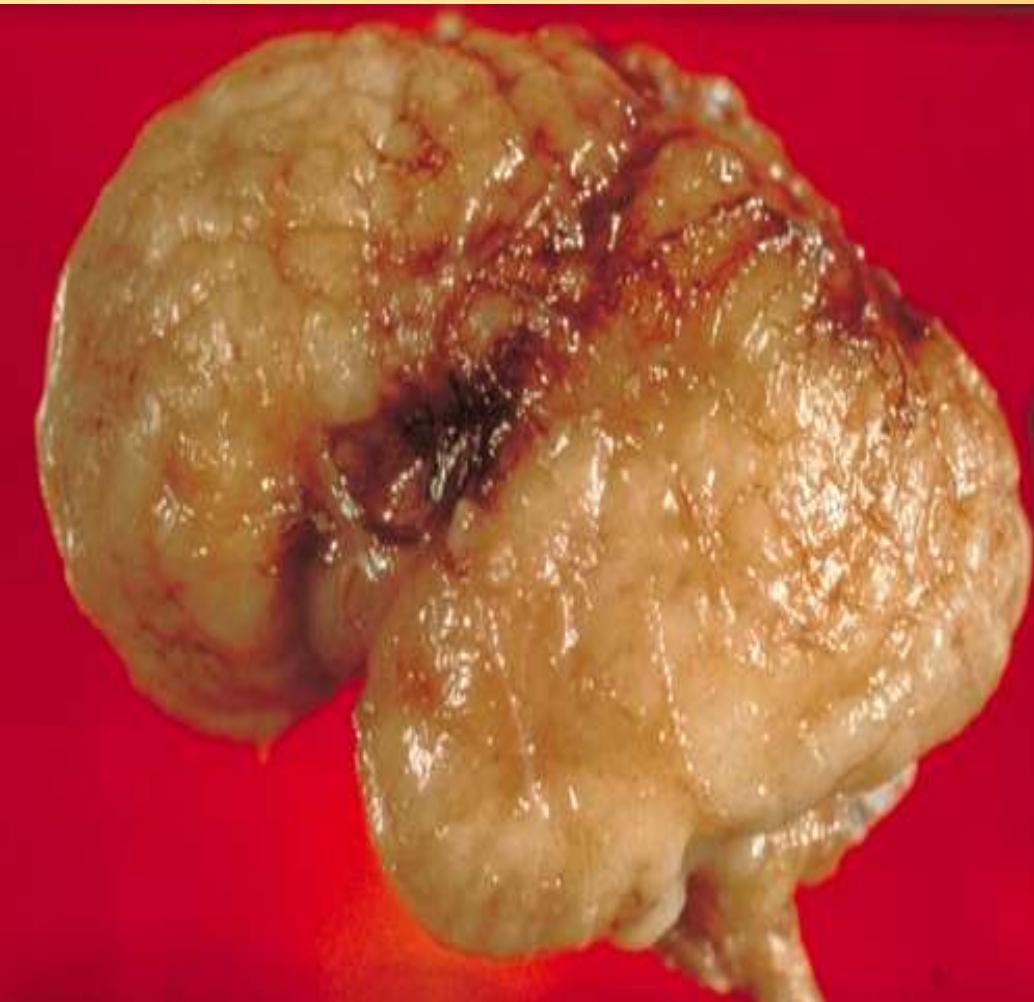
- MICROCEPHALUS
- PERIVENTRICULAR CALCIFICATIONS
- ENLARGED VENTRICLES



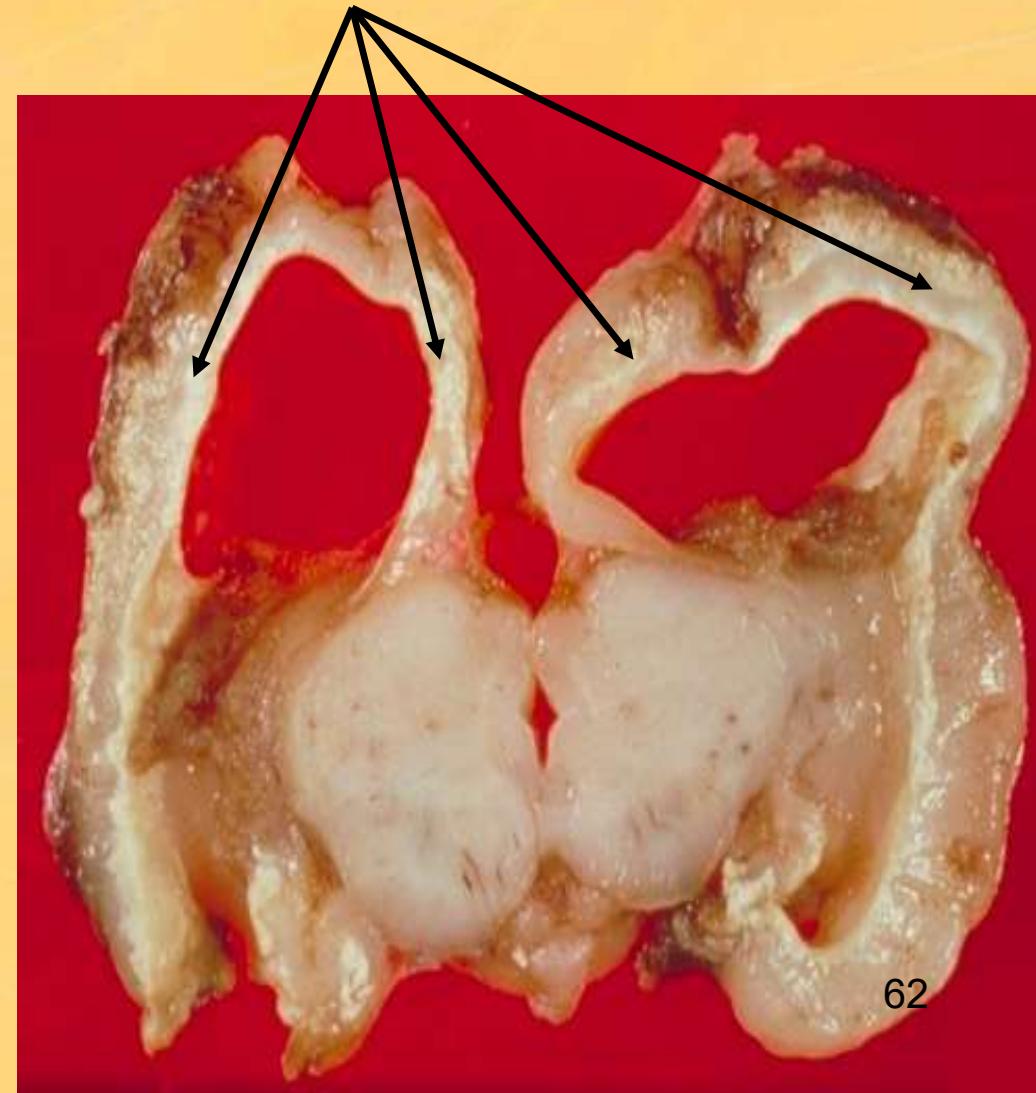


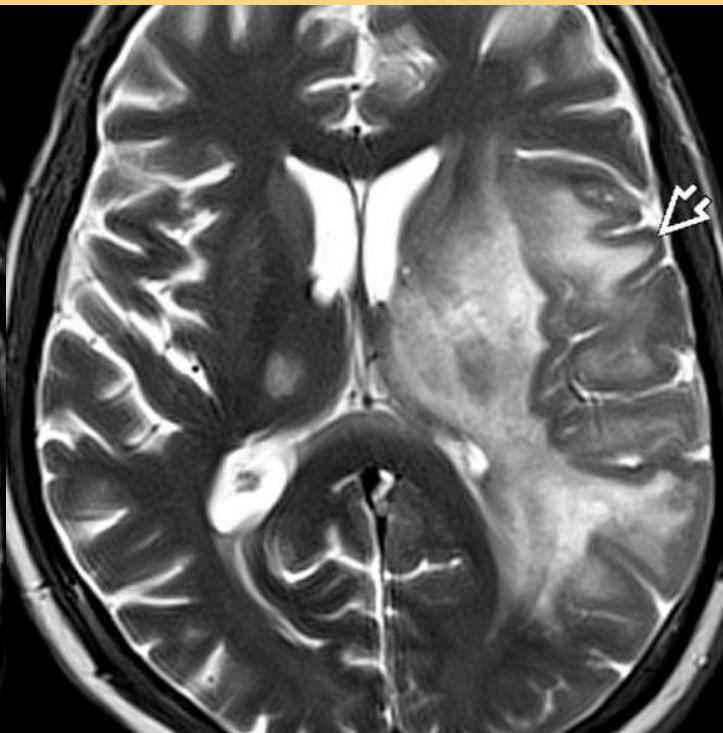
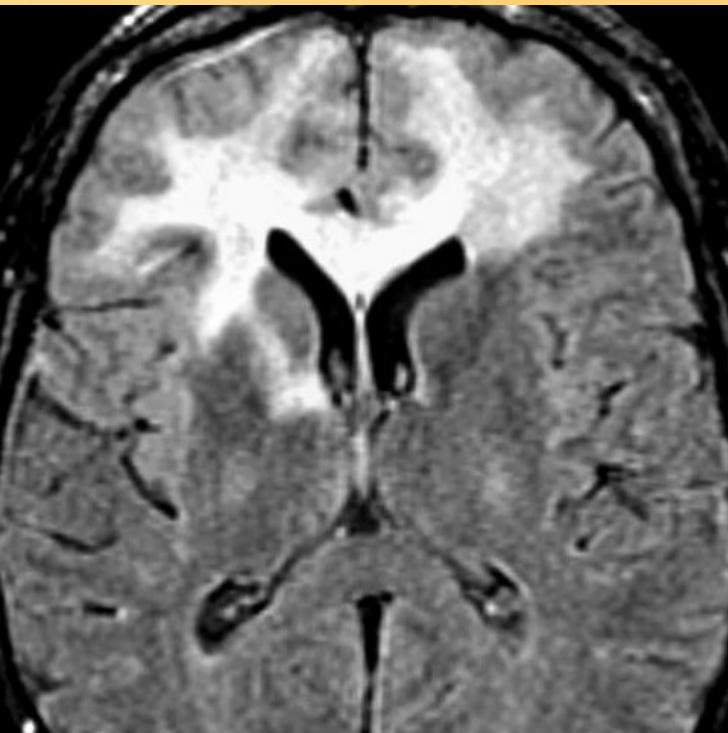
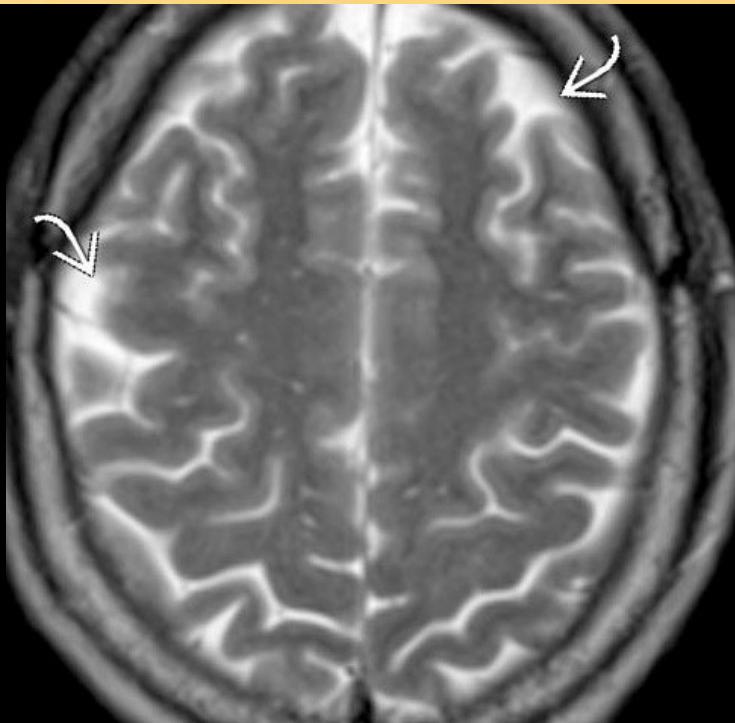
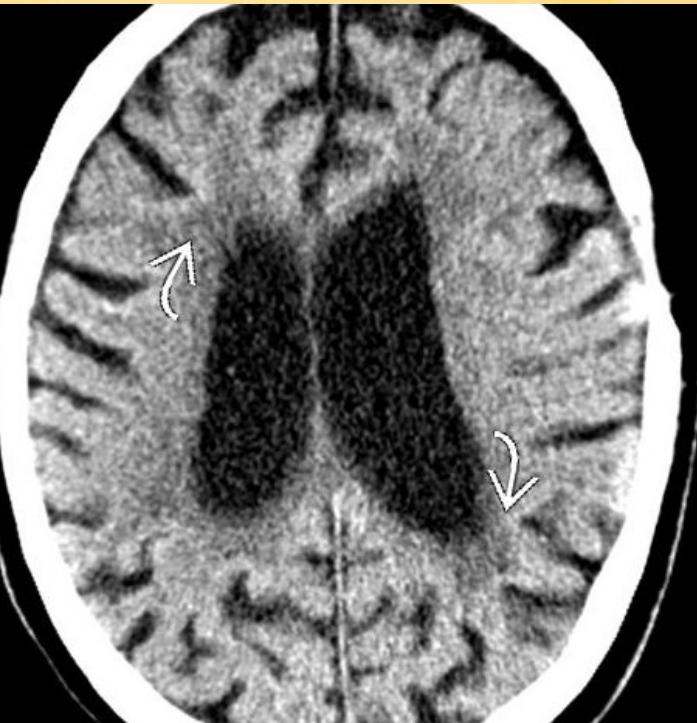
# COMPLICATIONS OF NEONATAL CMV INFECTION:

MICROCEPHALUS



CORTICAL ATROPHY AND  
PERIVENTRICULAR  
CALCIFICATIONS





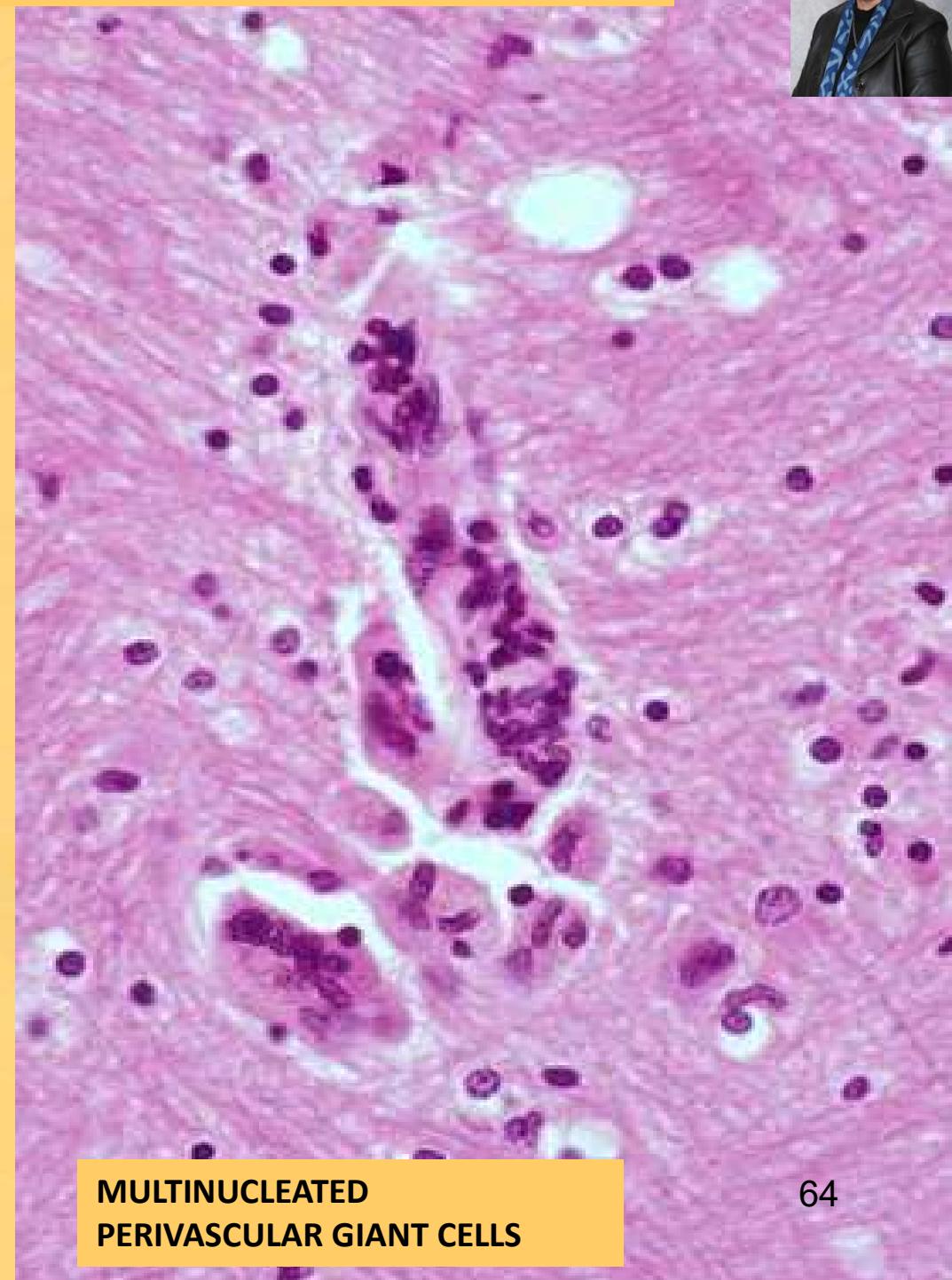
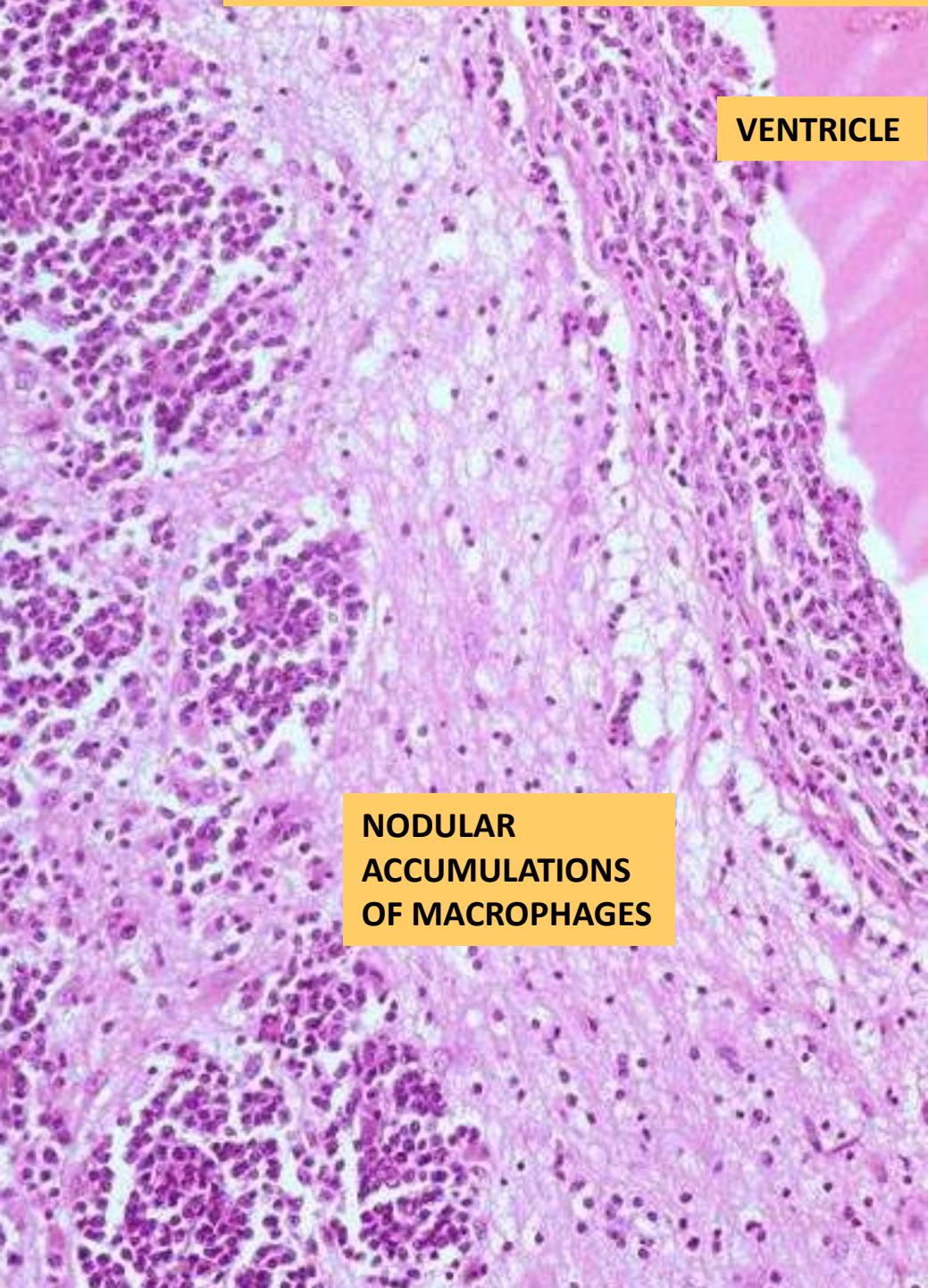
## HIV-ASSOCIATED CHANGES:

- THE MAIN IMAGING FINDING IS ATROPHY

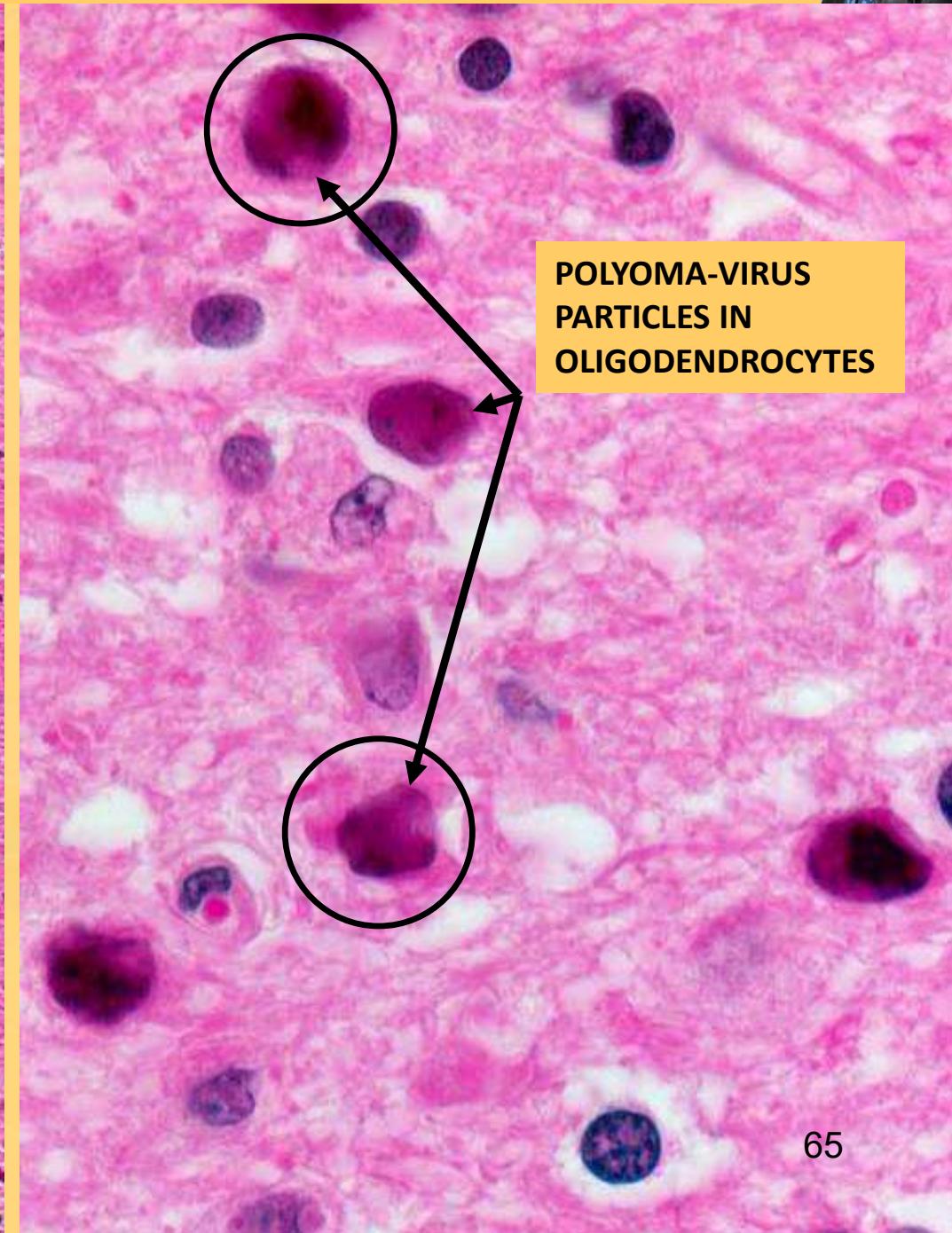
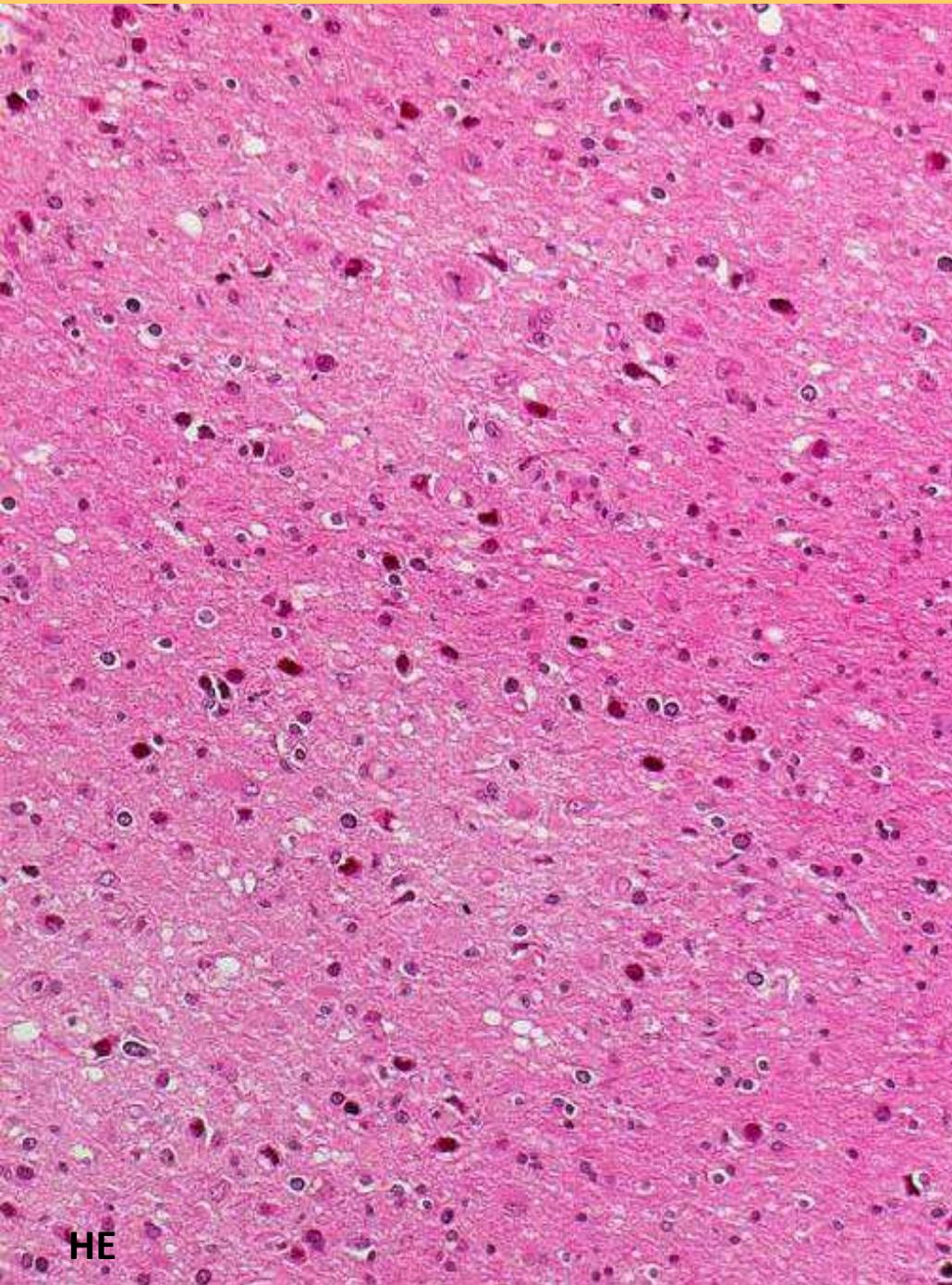
## PML in HIV+ and IMMUNOCOMPROMIZED PATIENTS:

- PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
- CAUSED BY JC VIRUS
- MULTIFOCAL SUBCORTICAL AREAS OF INVOLVEMENT

# HIV-ASSOCIATED ENCEPHALOPATHY

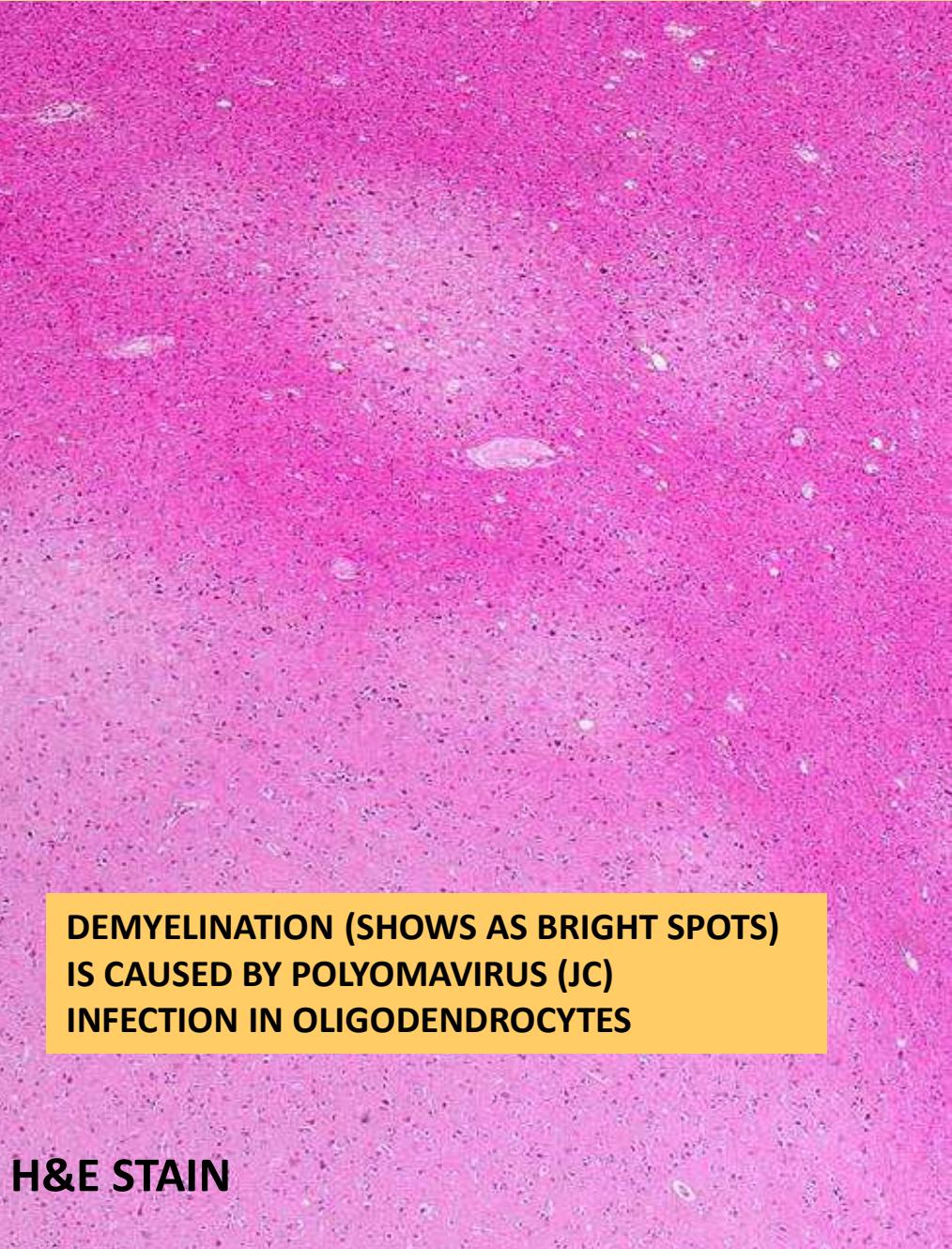


# PML IN A BREAST CANCER PATENT POST CHEMOTHERAPY: JC VIRUS INCLUSIONS IN OLIGODENDROCYTES



POLYOMA-VIRUS  
PARTICLES IN  
OLIGODENDROCYTES

# PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) WITH DEMYELINATION (BREAST CANCER PATIENT)



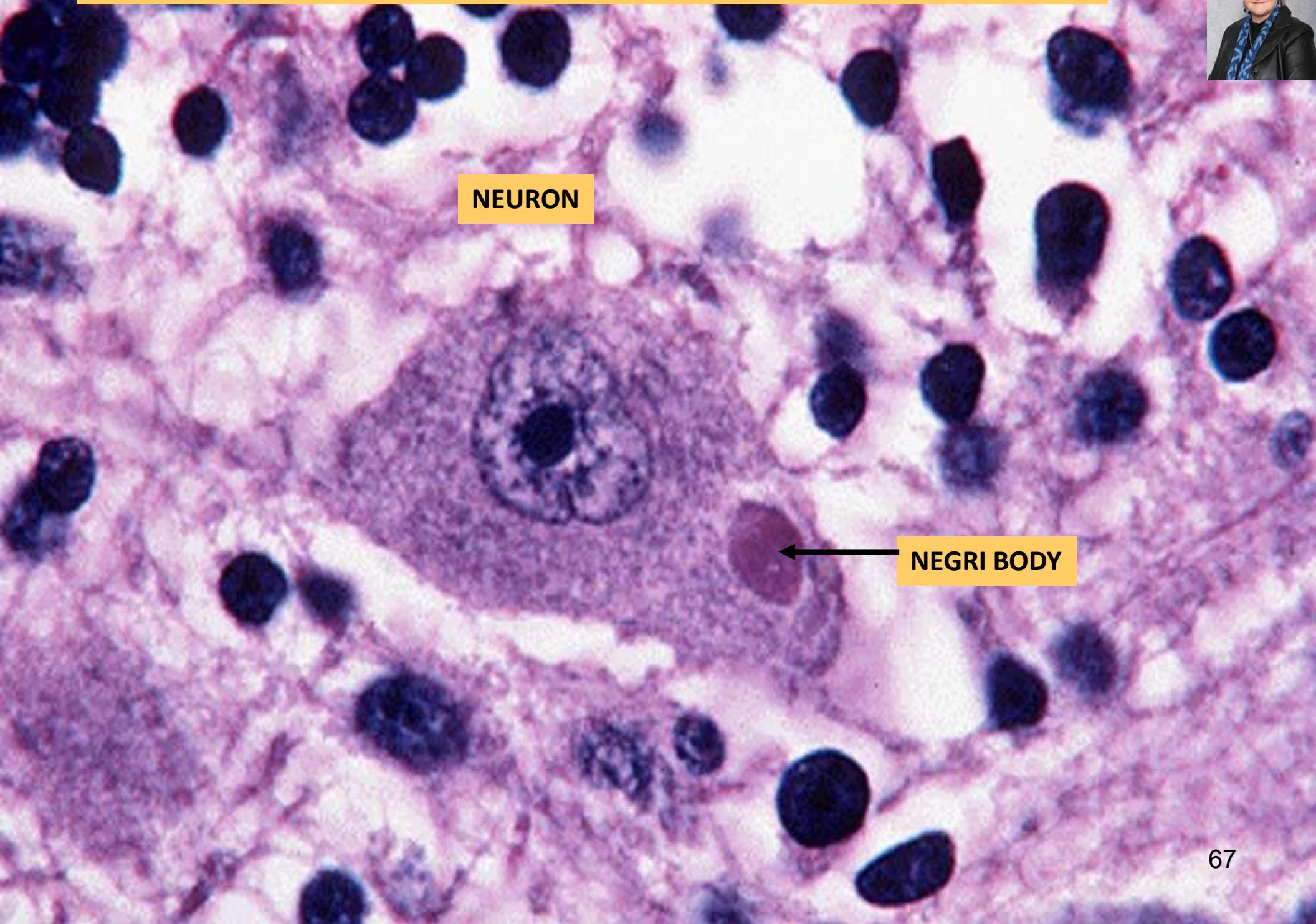
DEMYELINATION (SHOWS AS BRIGHT SPOTS)  
IS CAUSED BY POLYOMAVIRUS (JC)  
INFECTION IN OLIGODENDROCYTES

H&E STAIN



MYELIN STAIN

# RABIES ENCEPHALITIS WITH NEGRI BODIES



# POLIOMYELITIS

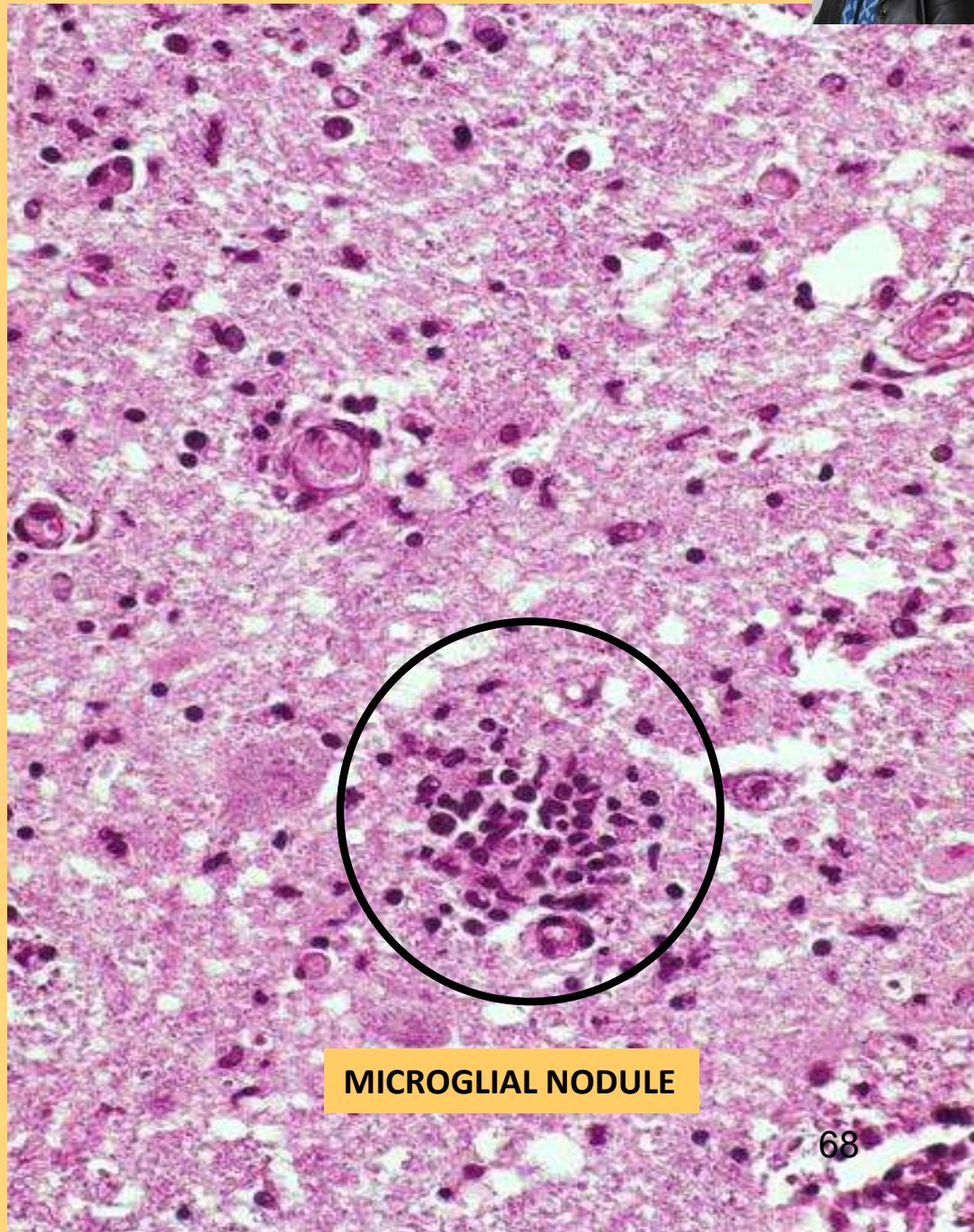
## ANTERIOR HORN OF THE SPINAL CORD



PROMINENT EDEMA AND NEURONOPHAGIA



MICROGLIAL NODULE



# VIRAL MENINGOENCEPHALITIS: MORPHOLOGIC FEATURES\*



## COMMON TO ALL:

- Both meningeal and parenchymal changes
- Most viruses cause similar morphologic changes with varying severity
- Viral meningoencephalitis is typically lymphocytic with perivascular distribution of mononuclear inflammatory infiltrates
- Individual neuronal necrosis with neuronophagia and microglial nodules
- In more severe cases multifocal gray and white matter necrosis, necrotizing vasculitis and focal hemorrhages
  - Neutrophils are often present, but fewer than in bacterial meningitis

## CYTOPATHIC CHANGES CAUSED BY CERTAIN VIRUSES:

- Cowdry type A nuclear inclusions in HSV infection
- Negri bodies in rabies
- Cytomegaly and intranuclear and cytoplasmic inclusions in CMV infection
- Nuclear inclusions in oligodendrocytes in progressive multifocal leukoencephalopathy (PML) caused by JC virus (polyomavirus) infection



# Viral Meningitis – General Treatment, Prognosis & Prevention

- **Treatment:** primarily **supportive** care
  - **Antivirals** for some (acyclovir = HSV), passive immunity & vaccine for rabies, ± steroids for inflammation
- **Prognosis:** good, for a self-limited Viral Meningitis
- **Prevention:** limited vaccines available
  - **Vaccines:** MMR, influenza, varicella, herpes zoster, rabies, Japanese encephalitis
  - **Good hygiene** (frequent hand washing), avoiding crowded living spaces (prisons, dorms), avoid mosquito bites





## *The case of the TUCOM medical student..*

- A 25-year-old male medical student with a one-week history of headache and slightly stiff neck presents to the ER at a nationally renowned hospital. He was on his second rotation in family practice near Detroit. On arrival, vitals were normal. There was no significant medical history. He admitted to having a headache (diffuse but mostly towards the back of his head), neck stiffness, as well as general weakness and lethargy.
- Being an astute scholar (a TUCOM student), he suggested to the nurses and doctor that maybe he had meningitis, but the reply by the staff was unequivocally "not possible." Nobody, they said, with meningitis presents in this stable condition and drives themselves to the hospital. They decided against a lumbar puncture. He was given a prescription for Vicodin and returned home.



## *The case of the TUCOM medical student-II*

- That night he experienced high fever, headache and sweating and woke up unable to get out of bed. The headache worsened to a 10/10 and the room was spinning. Neck stiffness was increased as well. Luckily, his parents lived nearby, and his mother was able to take him to the hospital.
- He was admitted and an LP was ordered. His temperature was 103°F and he was given pain meds along with Vancomycin, Rocephin and Acyclovir. Lumbar puncture followed by CSF analysis reported mildly elevated WBCs, normal levels of glucose and elevated proteins. No organisms were grown from blood or CSF. A CSF PCR was positive.

What's your diagnosis?

What is the likely etiologic agent?

How does meningitis differ from encephalitis?



## *The case of the TUCOM medical student-III*

- Due to the presentation (insidious onset, mildly elevated WBCs and normal glucose , slightly raised proteins in CSF) he was diagnosed with viral meningitis and given acyclovir. He was kept on Vancomycin for two more days, especially because of the high fever and the fact that the WBCs were a little too high initially, to be definitely viral. The source was probably from a child who went through his clinic.
- He was sent home after three nights.
- He still experienced residual headaches for two weeks as well as generalized weakness, but ultimately was fine and is currently doing well in his career as an osteopathic physician.

# REVIEW: CSF FINDINGS IN MENINGITIS



	CSF cellularity	Cell type	CSF protein	CSF glucose
Normal	0-5	mononuclear	15-45 mg/dL	40-70 mg/dL
Bacterial meningitis	elevated	neutrophils	elevated	decreased
Aseptic meningitis	elevated	mononuclear, neutrophils early	normal or elevated	normal
Tuberculous meningitis	elevated	mononuclear +/- neutrophils	elevated	decreased
Viral meningo-encephalitis	elevated	mononuclear	normal or elevated	normal
Brain abscess	elevated	mononuclear +/- neutrophils	elevated	normal
Cryptococcal meningitis	elevated	mononuclear	elevated	decreased in 50% of cases <sup>74</sup>

# WATCH WITH WHOM YOU PLAY!

