Pathophysiology of acute infectious encephalitis

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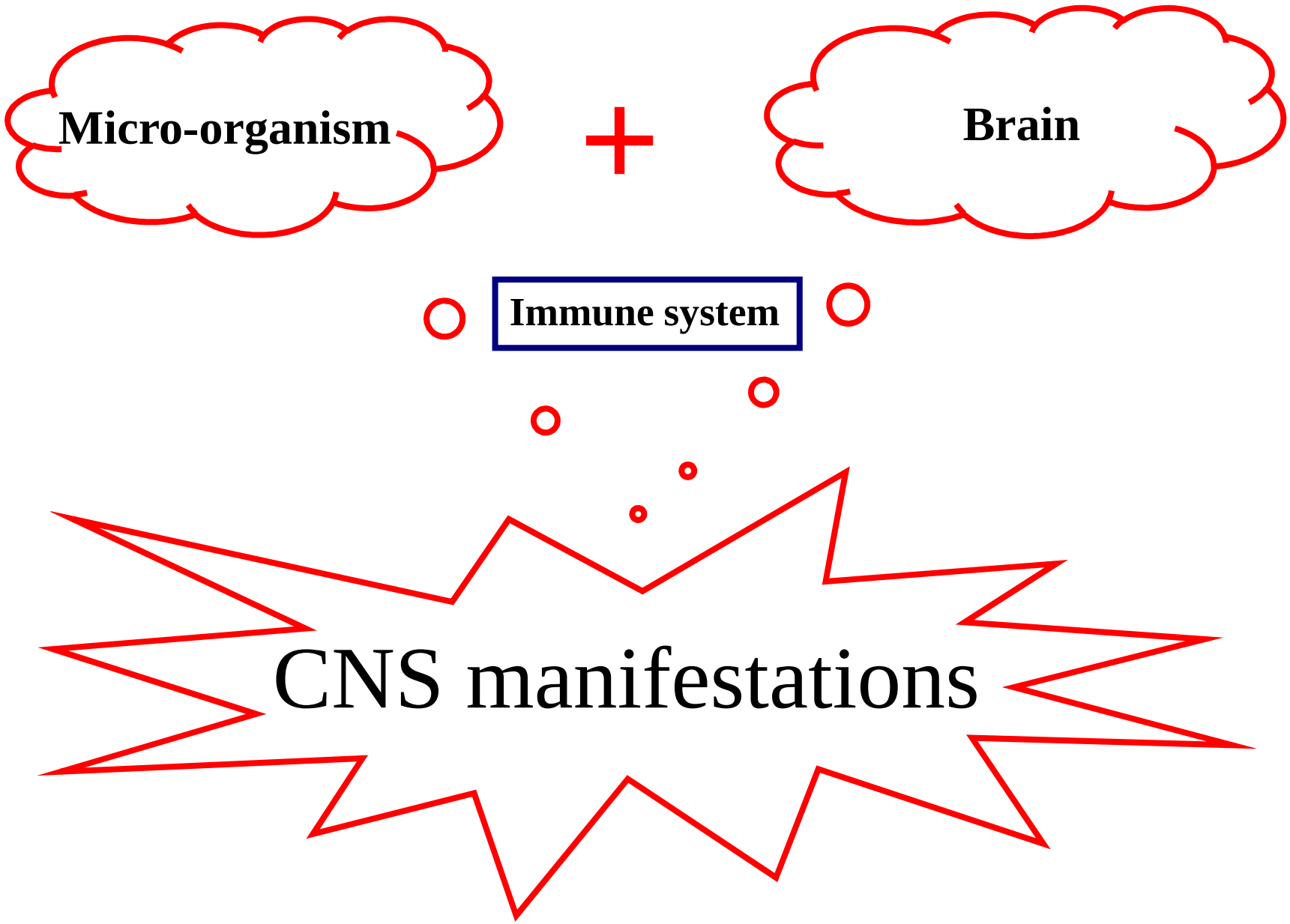
OBJECTIVE

…understand the pathophysiology of acute infectious encephalitis…

- What makes the brain vulnerable to a foreign organism aggression ?
- What makes a microorganism able to infect the CNS (brain & meninges) ?
- What makes a microorganism target specific structures or cell types of the CNS ?
- What are the CNS lesions due to acute encephalitis ?

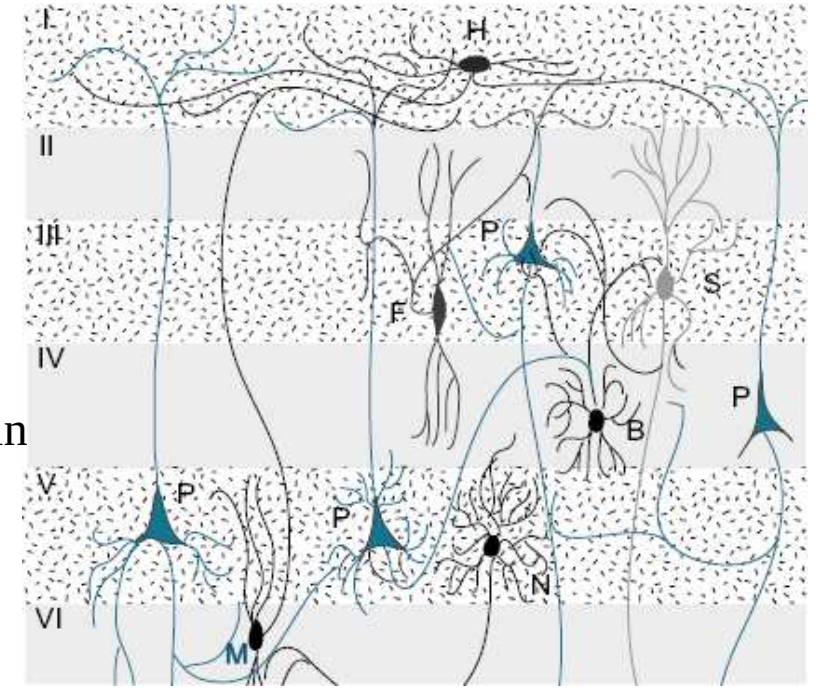

Micro-organism
+
Brain
Immune system
CNS manifestations

1. The brain, its accessories and the immune system

The CNS cells (1/2)

- Neurons
  - Specialized cells in specialized areas

- Neuroglial cells
  - Astrocytes participate
    - To the maintenance & structure of the brain
    - To the neuromediator homeostasis
    - To the blood-brain barrier (BBB)
    - To the innate host's immune response
    - To the wound healing (astroglial scar)
  - Oligodendroglial cells : myelin sheath
  - Ependymal cells : ventricular lining
  - Microglial cells
    - Resident antigen-presenting cells
    - Participate to the innate and adaptative immune responses

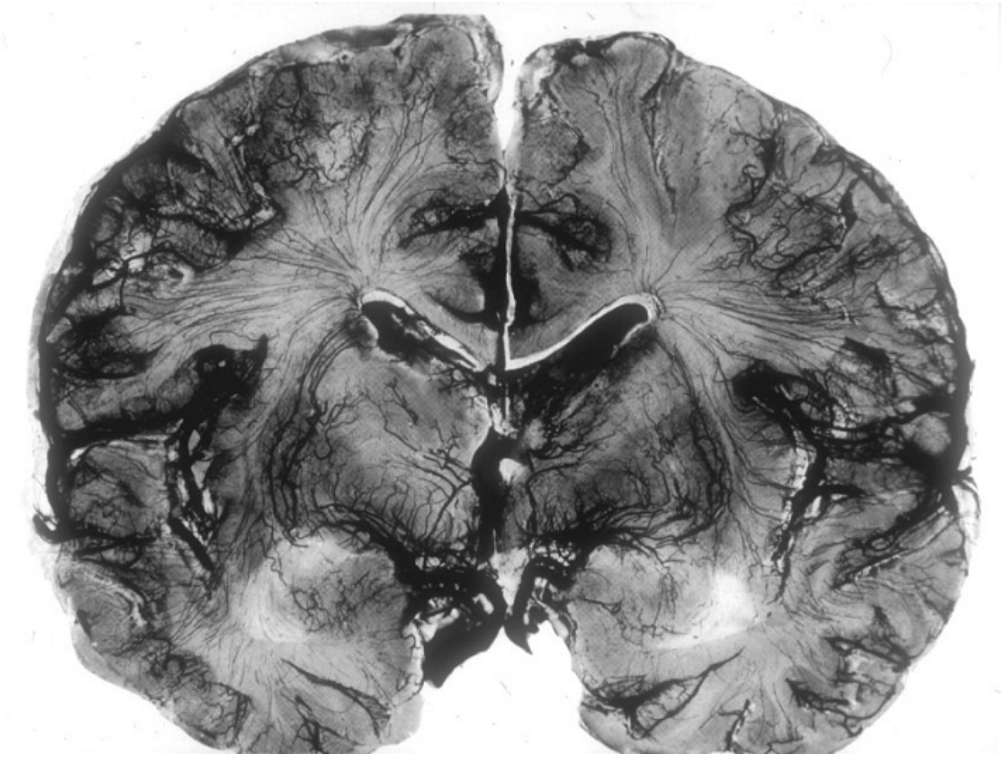


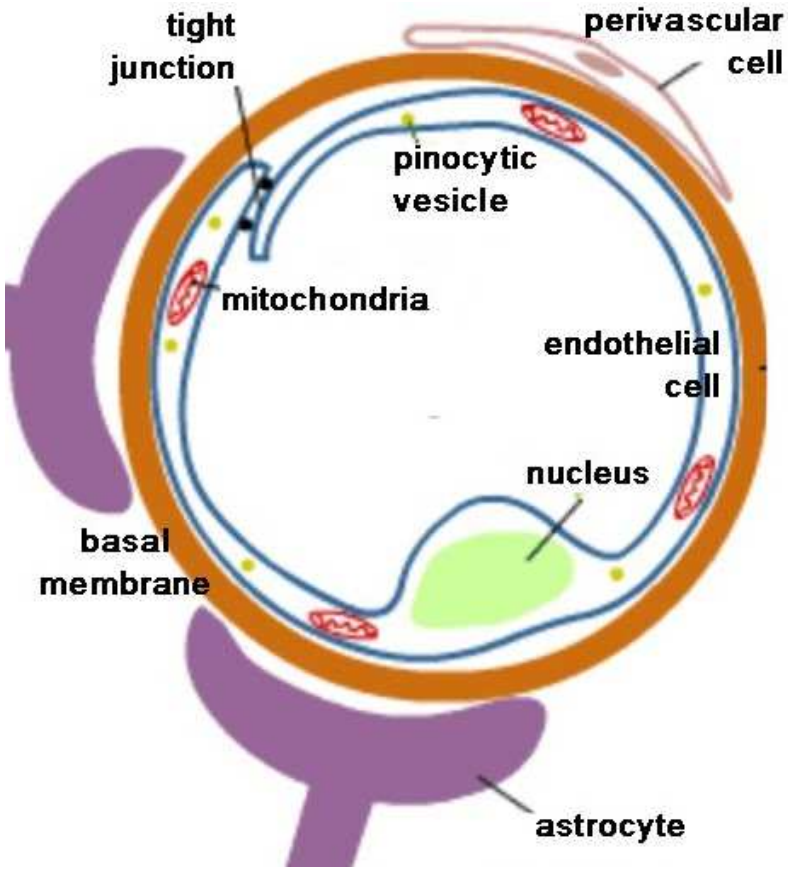
The CNS cells (2/2)

- Nonglial cells
  - Cerebrovascular endothelial cells (CVE)
  - Perivascular and plexus choroid endothelial cells
  - Macrophages and dendritic cells
  - Leptomeningeal cells

- Blood-derived leukocytes trafficking cells
  - Lymphocytes

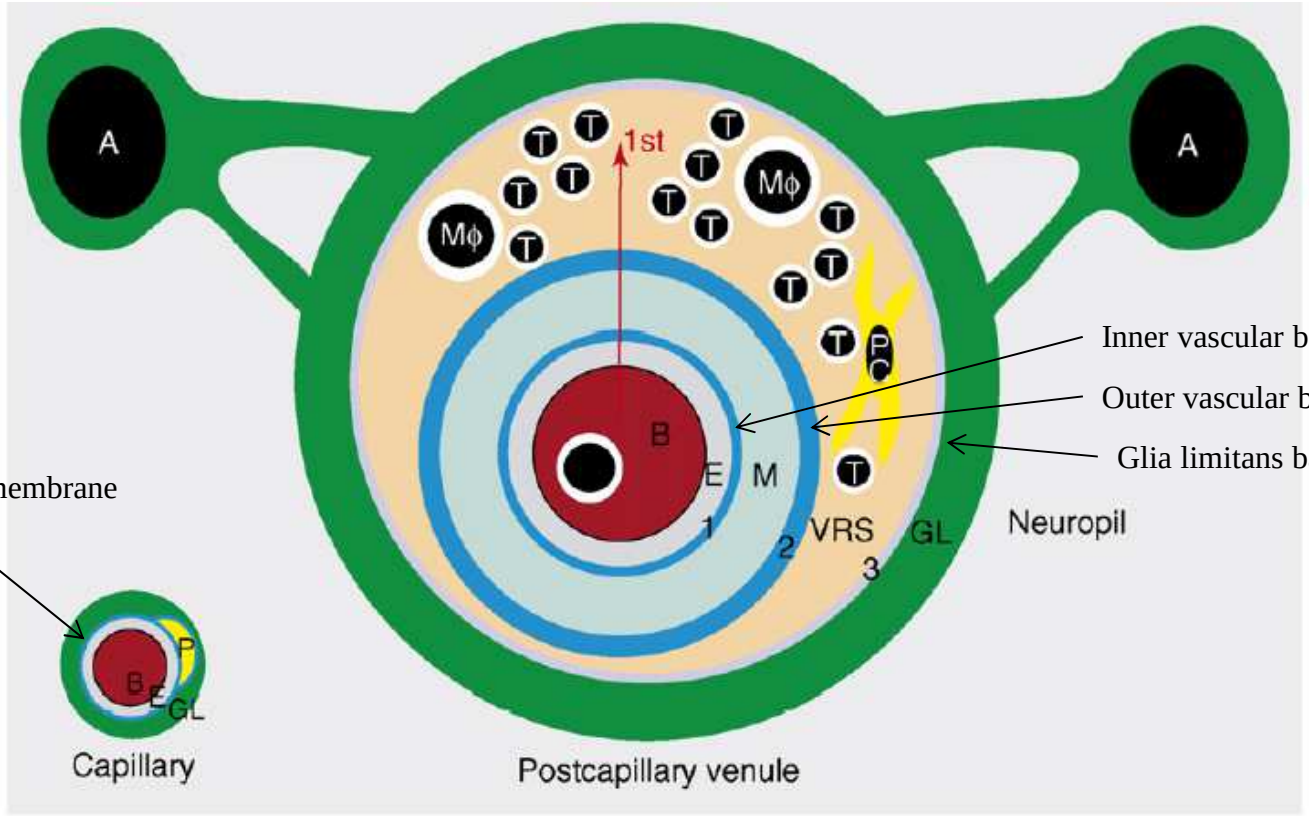
Vessels and Blood-Brain Barrier





Capillary level

The BBB at the postcapillary level



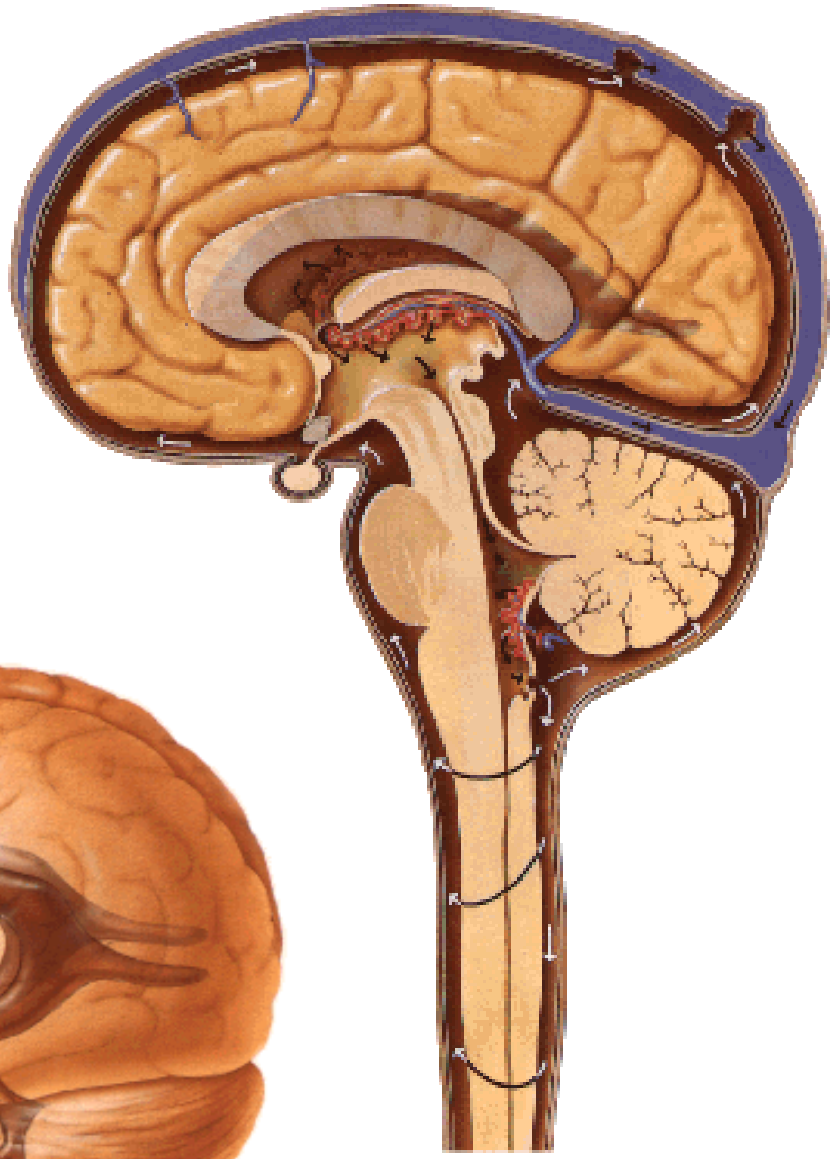
Opinion TRENDS in Immunology Vol.28 No.1
Full text provided by www.sciencedirect.com ScienceDirect

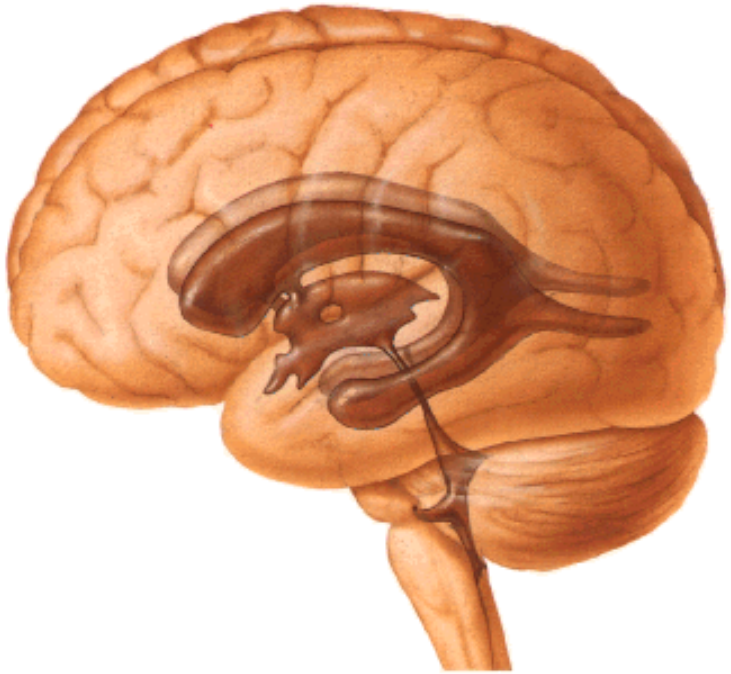
What is the blood–brain barrier (not)?

Ingo Bechmann[1], Ian Galea[2] and V. Hugh Perry[2]

The CSF flow

- From the choroïd plexuses…
- Lateral, 3rd, 4th ventricles
- Posterior fossa cisterns
- Basal cisterns of the skull
- Pericerebral subarachnoïd spaces
- Paccioni granulations
- … to the brain venous sinuses





How the brain defends itself

The immune system of the brain

Immunology of the CNS :

the brain is an immunologically specialized organ

- Foreign organisms have a limited access to the brain
- Immune response must be less noisy than in other organs :
  - Brain poor ability to support swelling
  - Limitation of neuronal destruction
- APC have a limited surface expression of MHC => reduction of the immune response
- There are no resident adaptative immune cells into the CNS

The steps of the CNS innate immune response

(once a microorganism succeed to invade)

1. Recognition of pathogens-associated molecular patterns by the Toll-like Receptors (TLRs) of microglial cells and astrocytes
   - Single and double stranded viral RNA
   - Bacterial lipopolysaccharides, etc.

2. Activation of the TLR-wearing cells, leading to :
   - Production of NO and IFN alpha and beta
   - Expression of MHC on microglia, perivascular macrophages and astrocytes
   - Cytokines & chemokines production by microglia and astrocytes

3. Activation of cerebrovascular endothelial cells

Cytokines and chemokines

- Cytokines : proinflammatory signals (IL-1, IL-6, TNF-alpha) sent to target cells (ie CVE cells)

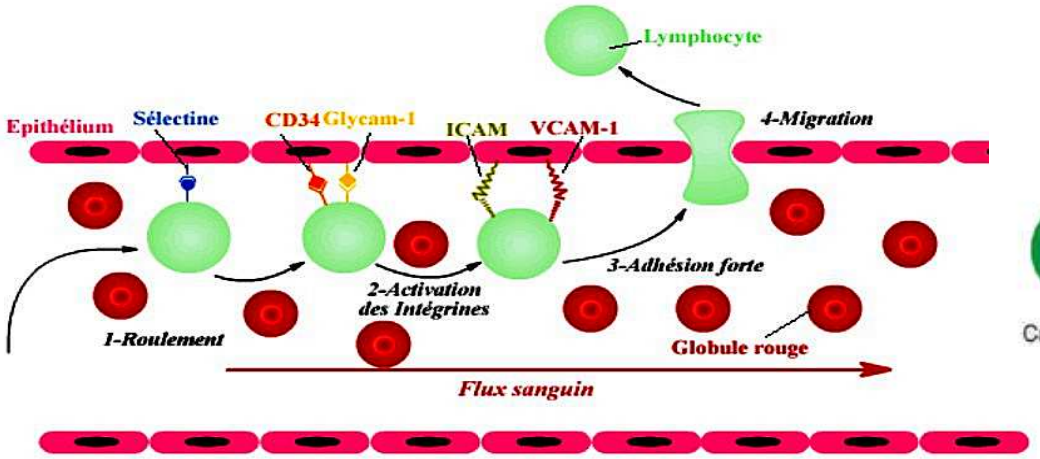
- Chemokines : target migratory cells
  - Mononuclear phagocytes, T lymphocytes
  - CCL2 (MCP-1), CCL3 (MIP-beta), CCL5 (RANTES), CXCL10 (IP10)

- CVE cells products
  - Intercellular adhesion molecules
  - Vascular cell adhesion molecules
  - Matrix metalloproteinases

} Entry of systemic immune system cells

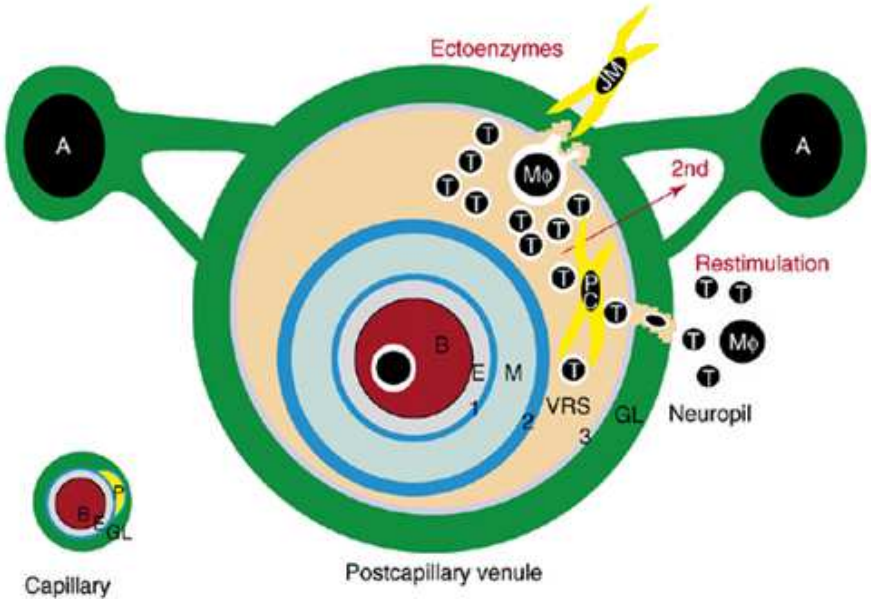
1

Ag detection → cytokines + chemokines
→ increase of the BBB permeability
+ cell rolling, adhesion, migration



2

Matrix metalloproteases + APC
→ parenchymal migration

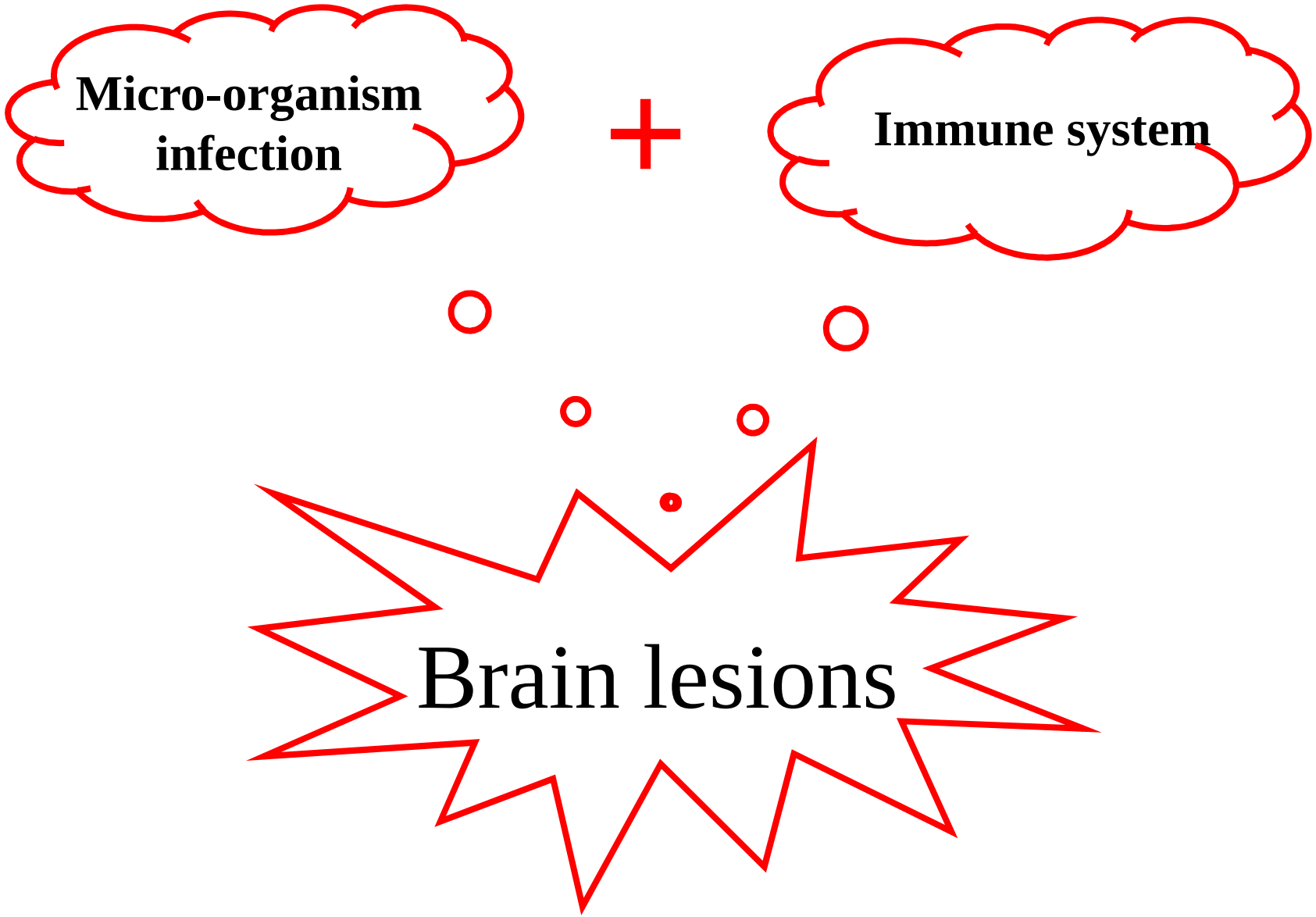


The adaptative immune system

- CNS invasion by immunocompetent cells in response to cytokines and chemokines stimulation

  In order of appearance :

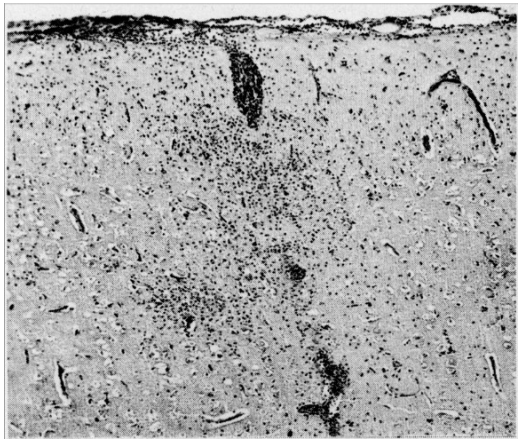
  - NK cells
  - Antigen-specific CD8+ and CD4+ T cells
  - B cells
  - Monocytes and macrophages
- Meningeal & parenchymatous inflammation
- Objective : clearance of the foreign microorganism

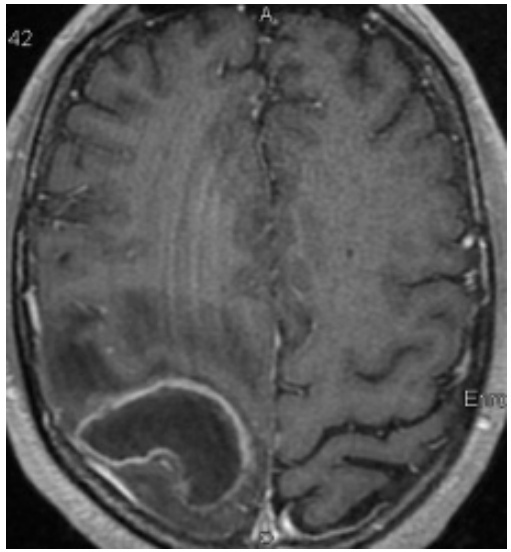

Micro-organism infection
+
Immune system
Brain lesions

Primary lesions due to infection vary

depending on
- the particular/cellular tropism of the microorganism
- the magnitude of the inflammatory response

- Destructive phagedenic process = abscess
- Neuronal dysfunction / death
- Oligodendrocyte dysfunction / destruction
- Astrocyte transformation / destruction / gliosis
- Ependymal necrosis
- Infiltration of inflammatory cells
- Infectious granuloma
- Vasculitis





CNS lesions due to secondary insults

- Brain edema and compression of healthy structures (herniation) and microvasculature
- Hydrodynamic-induced damage (hydrocephalus)
- Infarction (arterial or venous)
- Hypoxic anoxic damage
  - Convulsive status
  - Intracranial hypertension
  - Systemic cardiac/pulmonary deficiency

CNS lesions → clinical manifestations of encephalitis

headache, seizures, focal deficits (motor, sensory, cognitive), consciousness decrease, etc.

2. The micro-organisms

Bacteria
Viruses
Fungi
Parasites

The neurotropism of micro-organisms

- All the foreign micro-organisms do not invade the CNS
- The different routes of neuroinvasion
  - Directly (vicinity)
  - By the blood stream
    - Blood → choroid plexuses → CSF → brain
    - Blood → meninges → CSF → brain
    - Blood → brain
  - By neuronal axonal & trans-synaptic pathway
- Neurotropism and different cell tropisms are organism specific

Different target cells of the CNS

- Neurons : polioencephalitis/myelitis
  - → neuronal death & neuronophagia
    - Cortex
    - Basal ganglia
    - Motor neurons

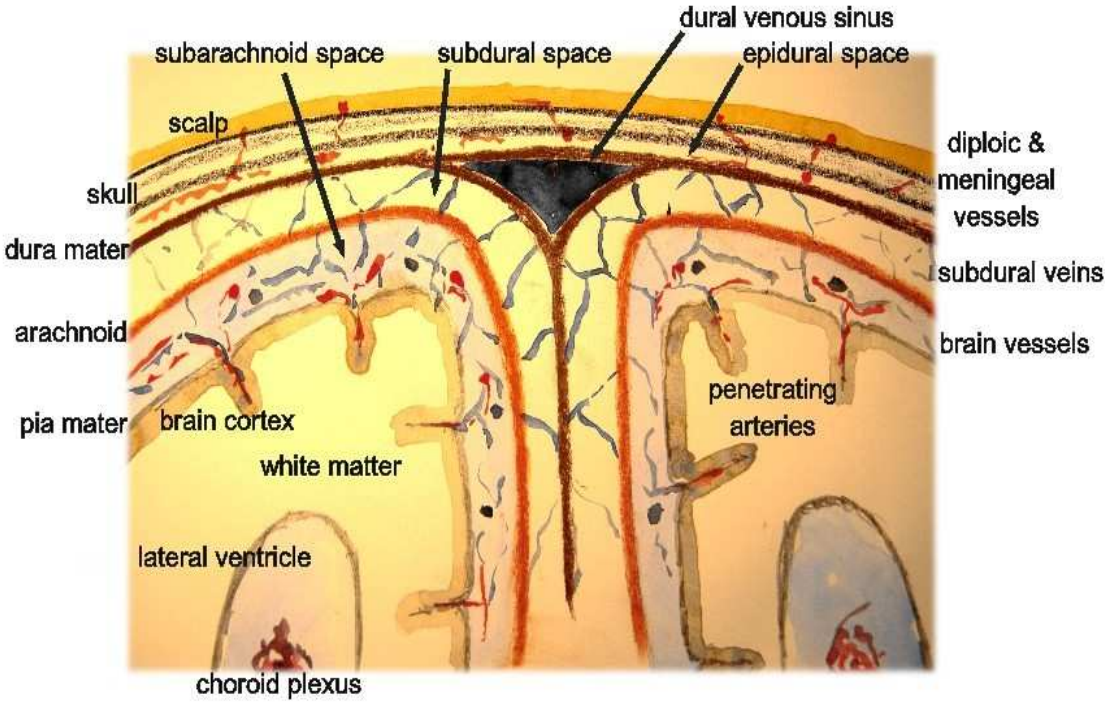
Πολιός = *grey*
λευκός = *white*

- Glial cells : leukoencephalitis
  - Oligodendrocytes → demyelination
  - Astrocytes → BBB dysfunction, astrogliosis
  - Ependymocytes → ventriculitis
  - Microglia → microglial nodules

- All types of CNS cells : panencephalitis

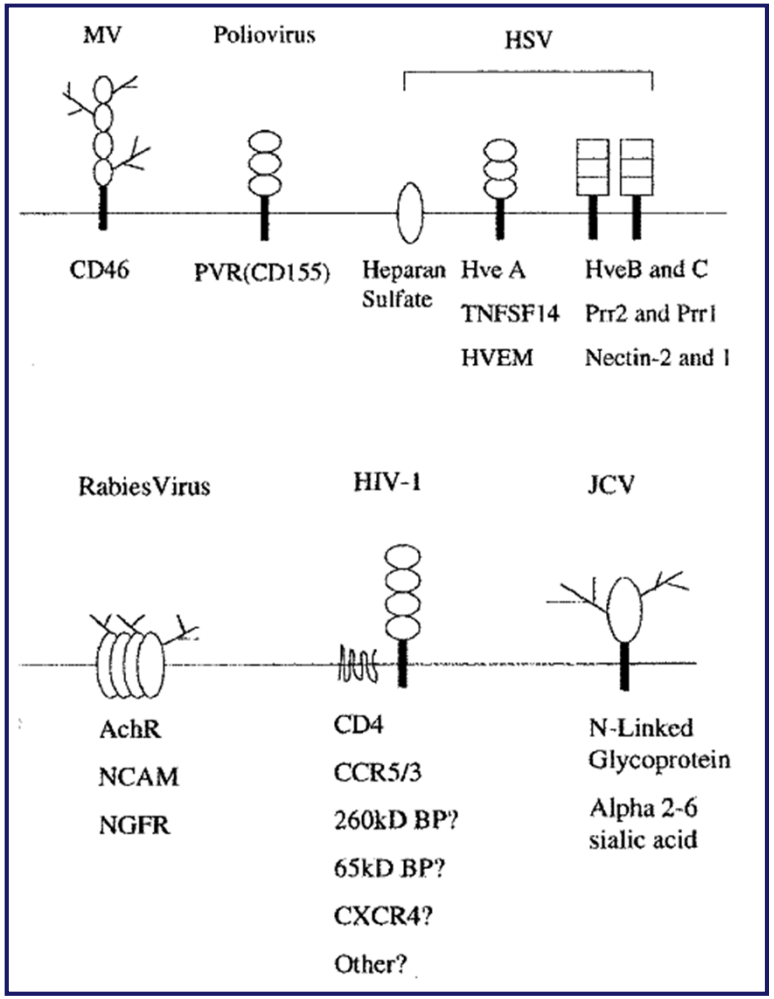
Other targets into the CNS

- Choroïd plexus
- Meninges and CSF
  - Leptomeninges
    - Pia mater
    - Arachnoïd
  - Pachymeninges (dura mater)
- Vessels
  - Vasculitis



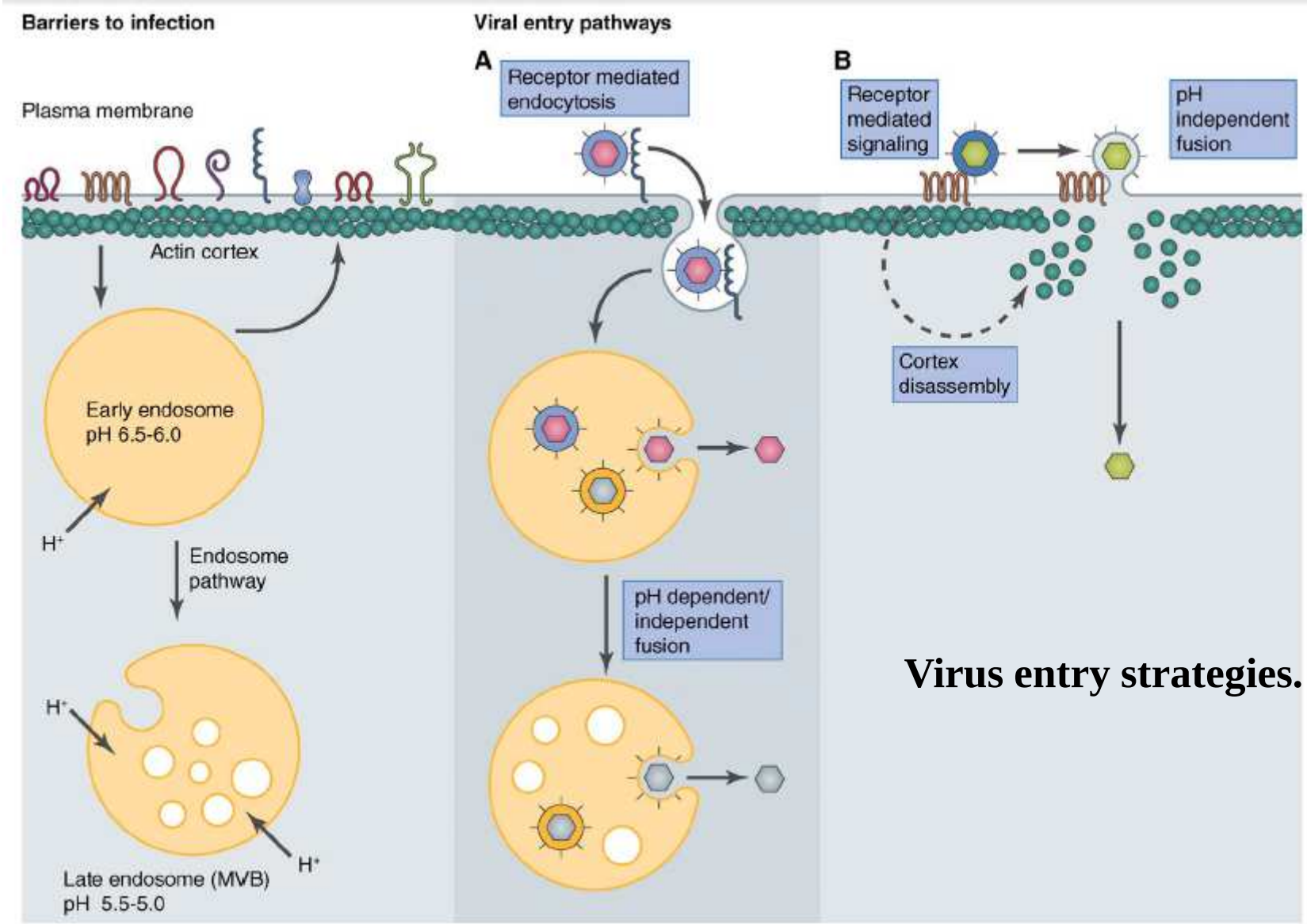
Some examples of encephalitis pathophysiology

- Viruses
  - Herpes simplex 1 panencephalitis
  - Varicella Zoster Virus encephalitis
  - Enterovirus and arbovirus polioencephalitis
  - HIV
  - Rabies
- Bacteria
  - Mycobacterium tuberculosis
  - Listeria monocytogenes
- Parasites
  - Malaria
- Fungi
  - Cryptococcosis
  - Aspergillosis



Schweighardt & Atwood. J Neurovirol;7:187-195

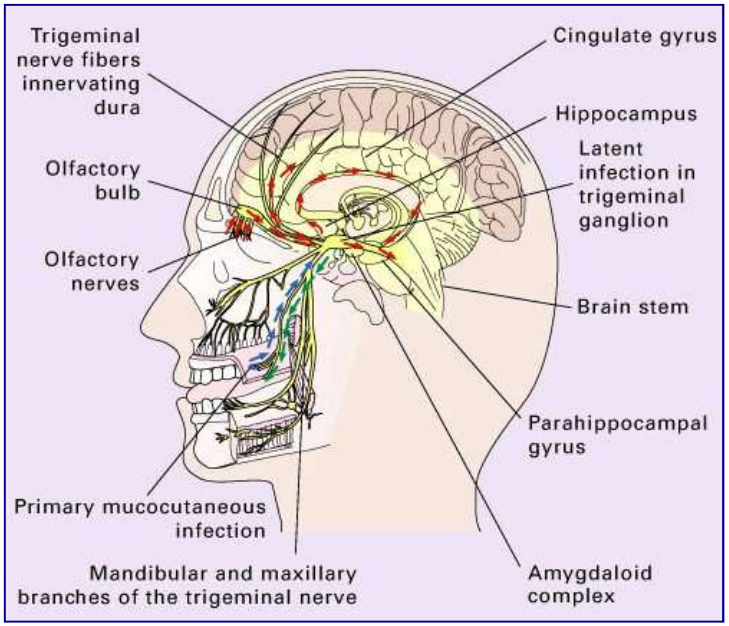
Neurotropic Viruses



Virus entry strategies.

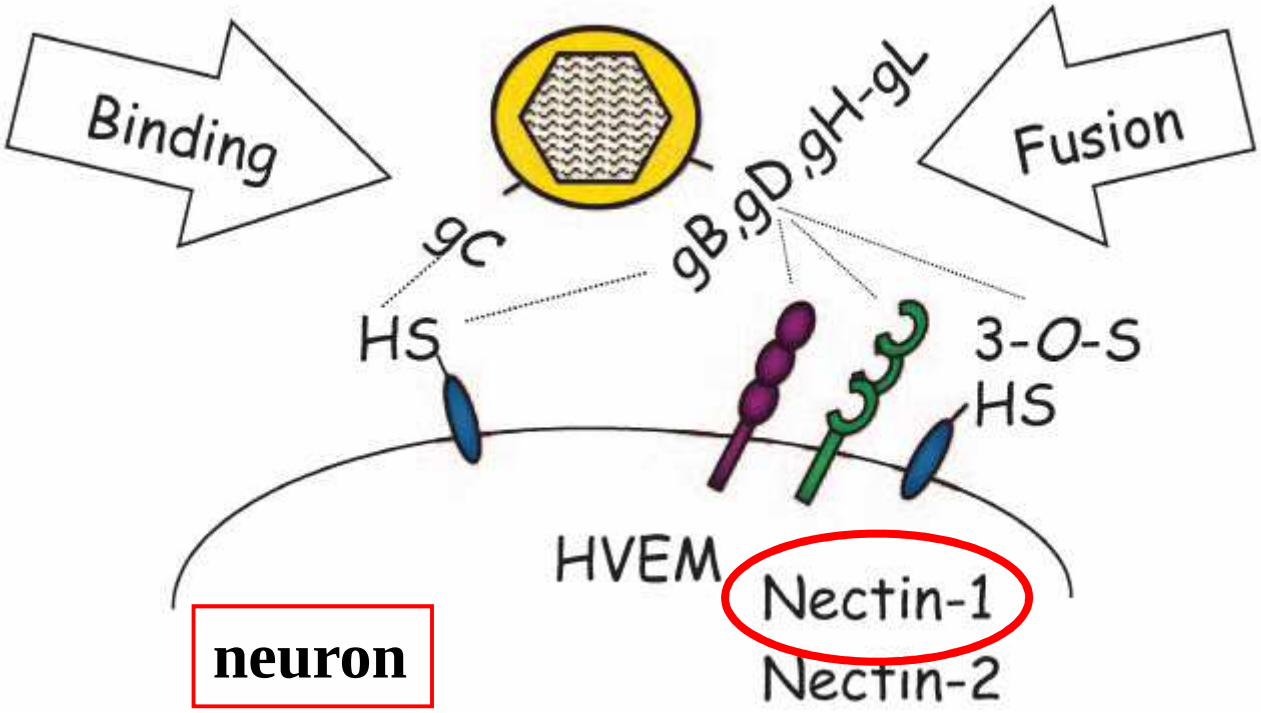
J Cell Biol.2011;195:1071-1082

HSV-1

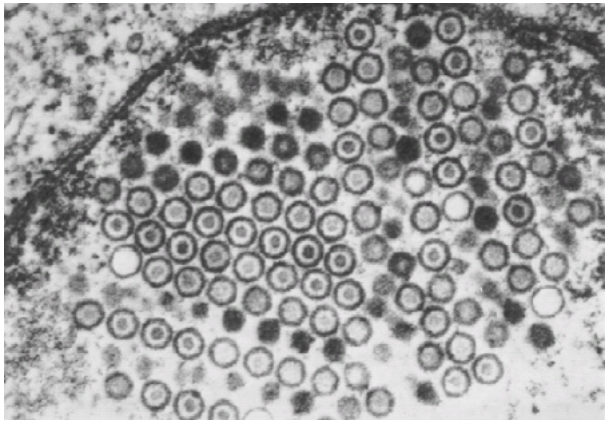


- Route of entry
  - Reactivation of latent infection
    - Trigeminal ganglion
    - Other sites of latent CNS virus (olfactory bulb, pons, medulla)
  - Direct neuroinvasion (olfactory sensory cells)
  - Hematogenous spread during viraemia (prodromal phase)

- Cell infection involves
  - Viral glycoproteins (gB, gC, gD, gH, GL)
  - Neuronal surface molecules (heparan sulfate, HVEM, nectin 1 & 2)


Binding
gC
gB,gD,gH-gL
Fusion
HS
3-O-S
HS
HVEM
Nectin-1
Nectin-2
neuron

After cell entry



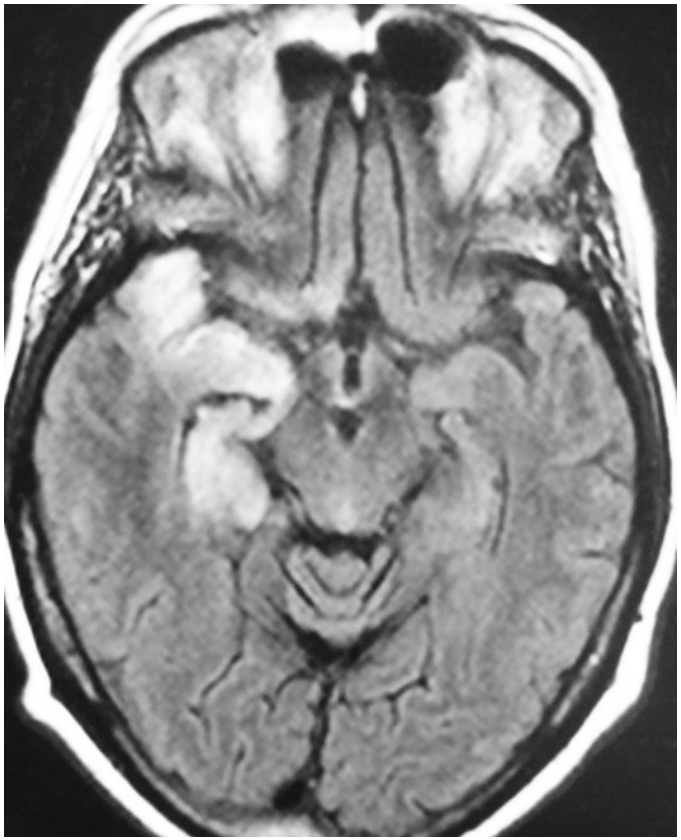
- HSV is a DNA virus :
  - nuclear invasion
  - DNA replication
  - DNA expression & protein production

- Host cell lysis
- Virus spread & mutiple cell type infection (panencephalitis)
- MHC expression and immune system recruitment

- Massive inflammatory response
- Œdema and Necrosis
- Detersion

HSV1 meningoencephalitis

an acute necrotizing panencephalitis



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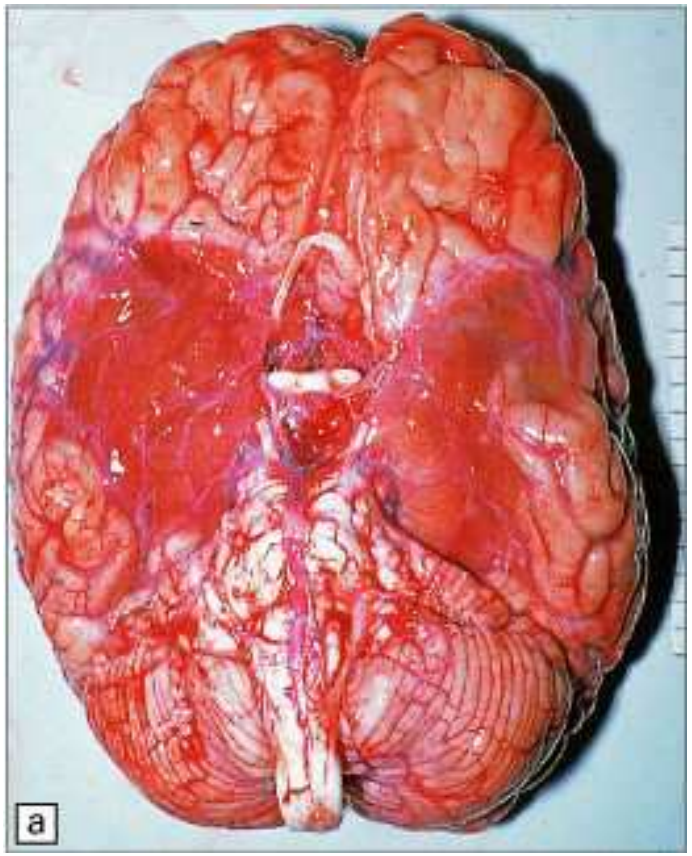
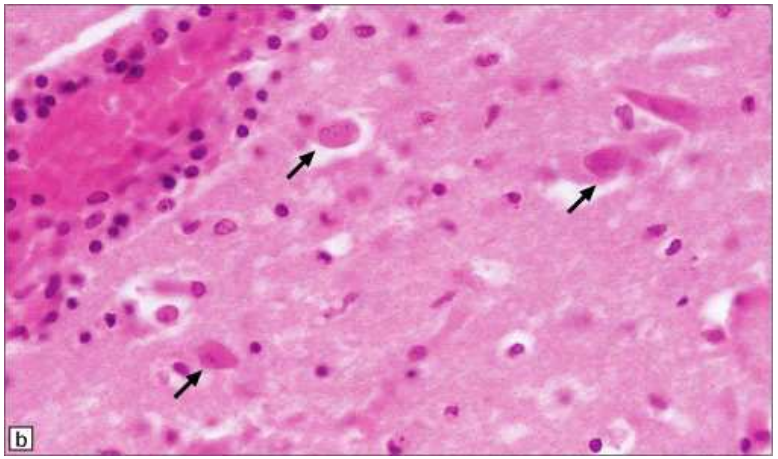
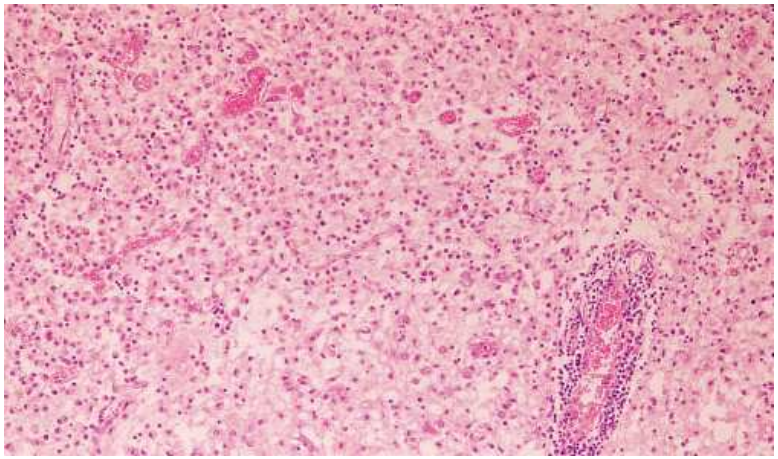
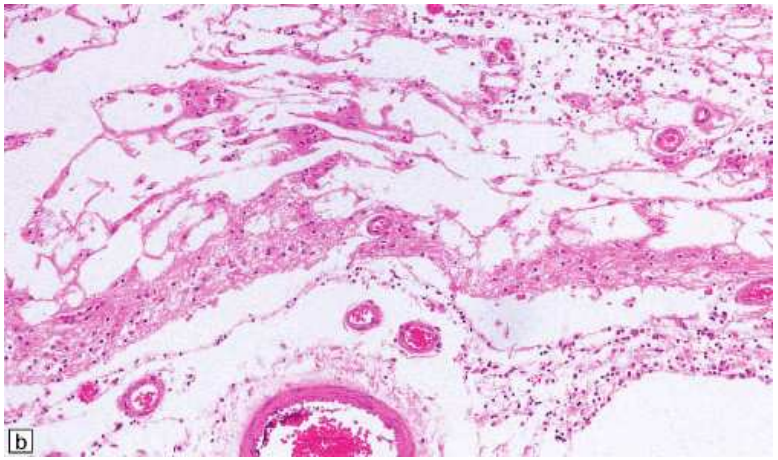


Early phase



Full-blown infection

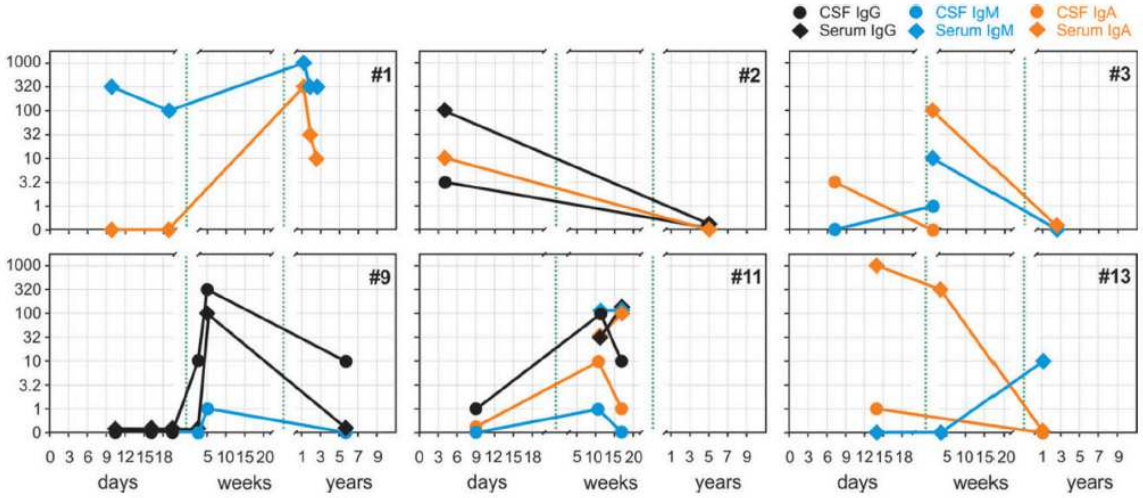




sequelae

HSV encephalitis and auto-immunity

- Anti-NMDAR antibodies are observed in the blood, CSF or both during the acute-subacute phase of the encephalitis in 30% of the cases, *but not during EV and VZV encephalitis*



44 cases

IgG, IgA and IgM
Variable kinetics

No clinical difference between Ab+ and Ab- groups

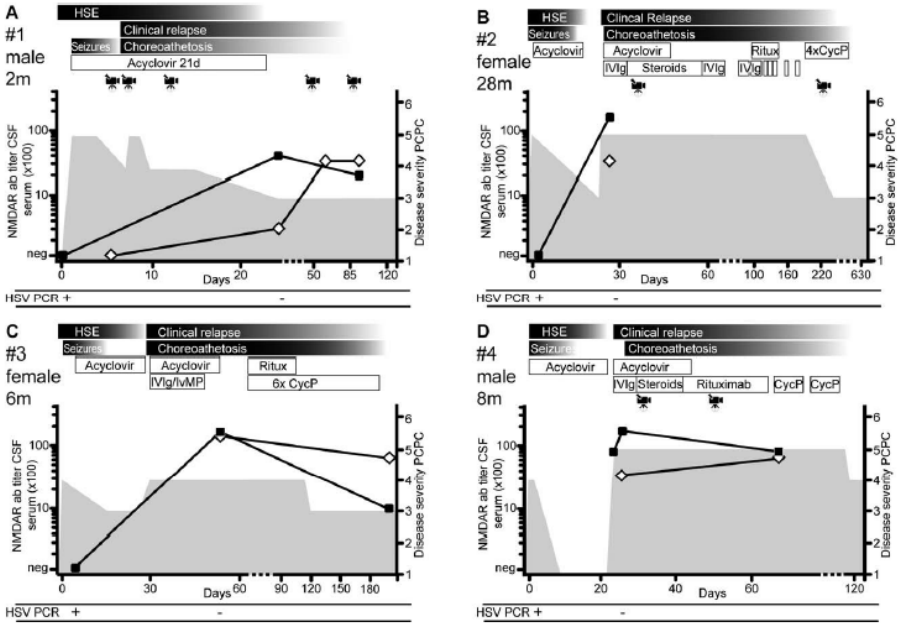
Prüss et al. Ann Neurol.2012;72:903-911

- Relapses are frequently linked to the occurrence of anti-NMDAR Ab
  - Mainly described in children
  - Could account for half of the cases

Hacohen et al. Mov Dis.2013;20:90-96

‘Herpes virus encephalitis is a trigger of autoimmunity’ Armangue et al. Ann Neurol 2014;75:317–323

- 4 children (+1 adult) having a HSVE relapse (delay 7-41 days)



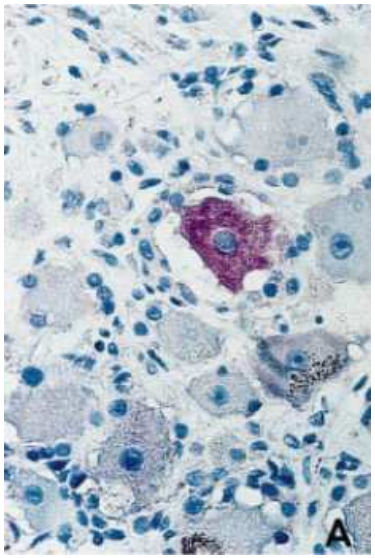
- 34 retrospective cases of HSVE tested after 1week
  - 3 : anti NMDAR positive, all relapsing
  - 10 : other unknown neuronal surface antibody

Mechanism of antibody production :

- Molecular mimicry ?
- Antibody production secondary to neuronal lysis and antigen release ?

VZV meningoencephalitis pathophysiology

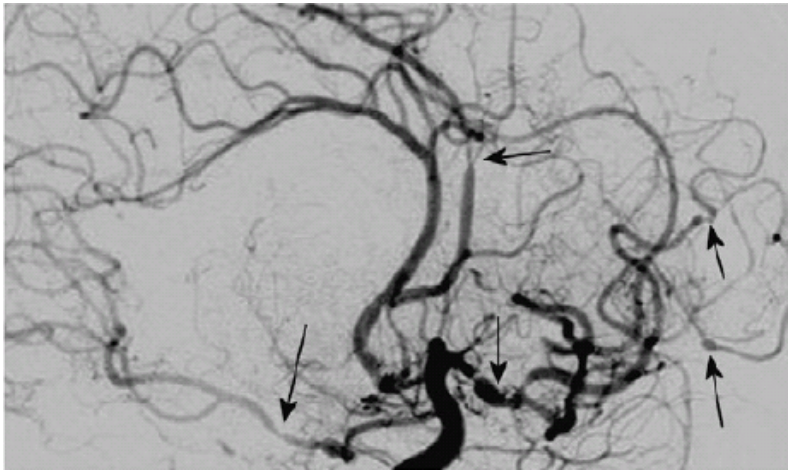
- Context : VZV primary infection or reactivation
- Meningeal inflammation
- Brain swelling
- Parenchymal VZV infection
  - Present in varicella encephalitis
  - Uncertain in VZV reactivation encephalitis
- Focal vasculitis of different vessel sizes with endothelial and smooth muscle in vessel walls infection

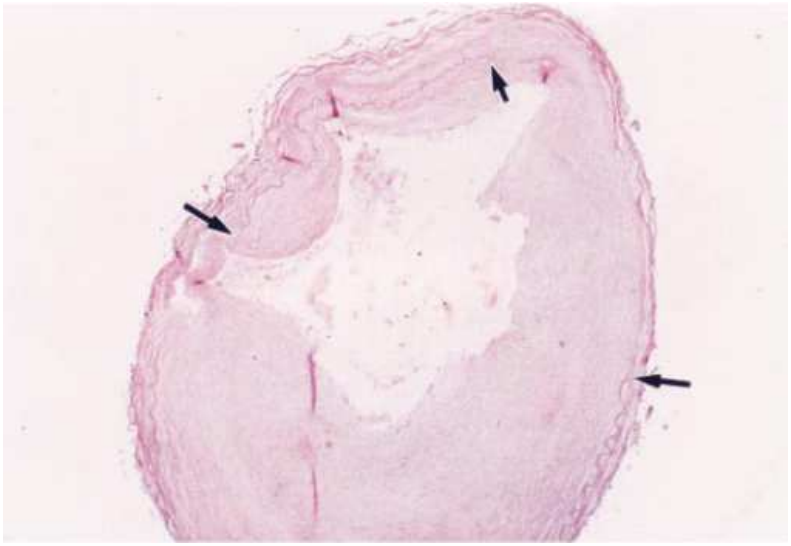


Role of immunocompromission
•Elderlies
•Lymphoma & cancer
•Immunosuppressant drugs
•AIDS

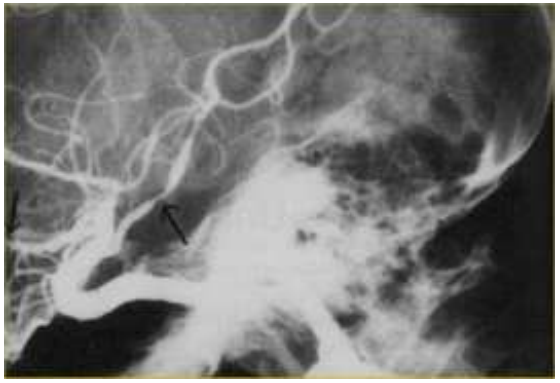
VZV vasculopathies

Multifocal (AIDS)

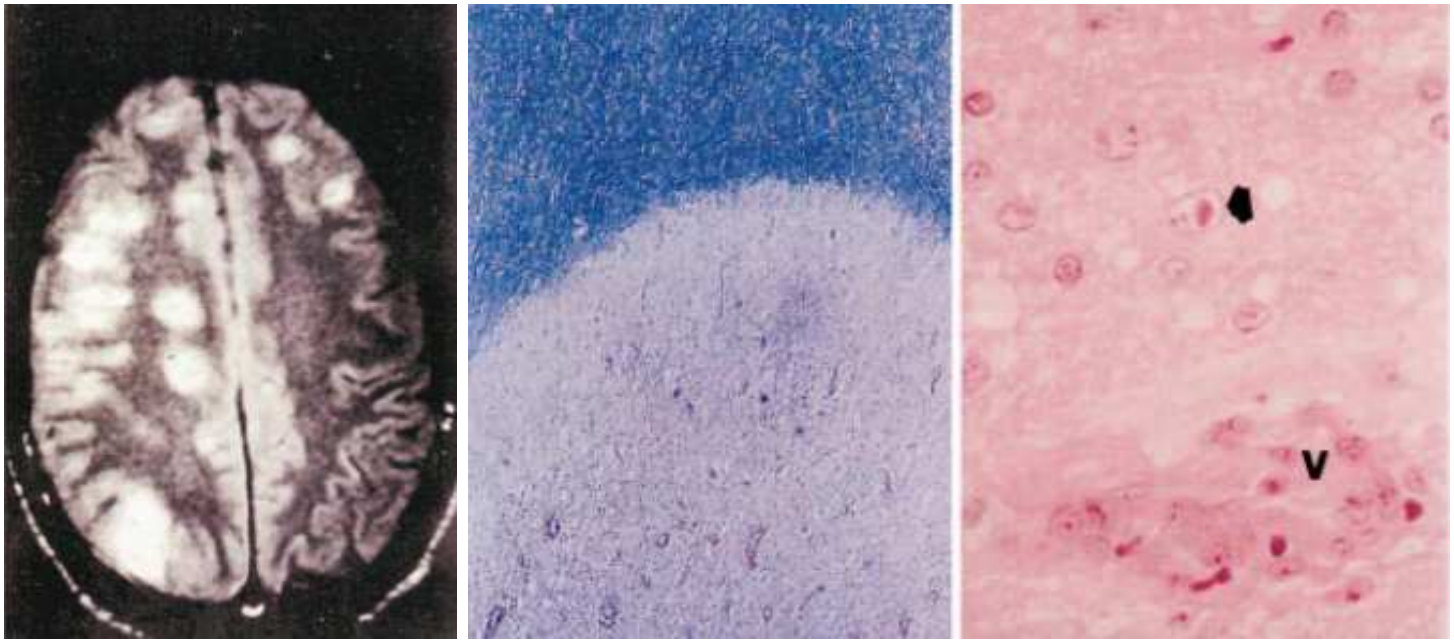




Zoster ophtalmicus & contralateral hemiplegia



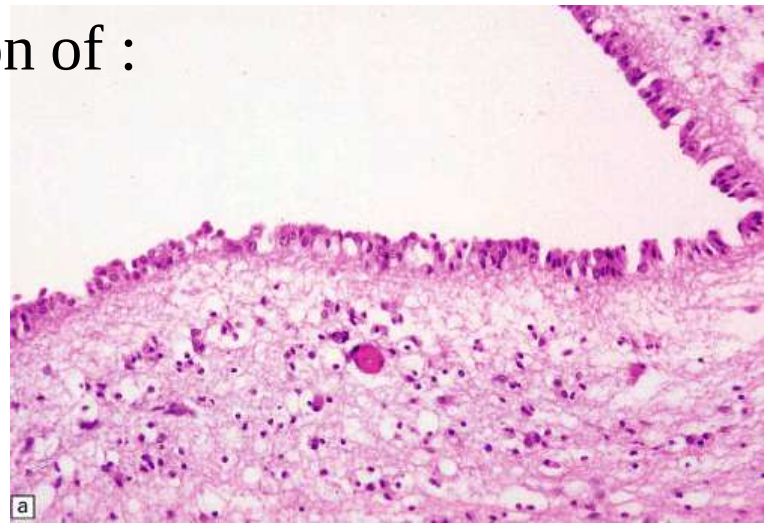
Demyelinating meningoencephalitis



A I D S

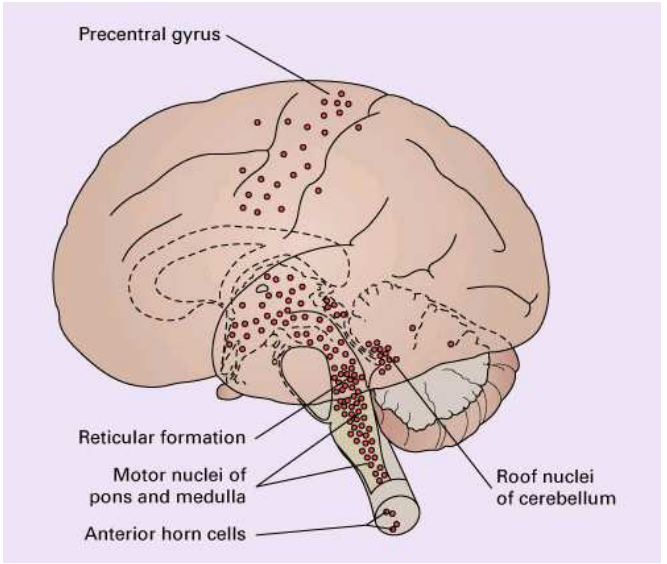
VZ reactivation & infection of :
Astrocytes
Oligodendrocytes
Ependymocytes
Endothelial cells

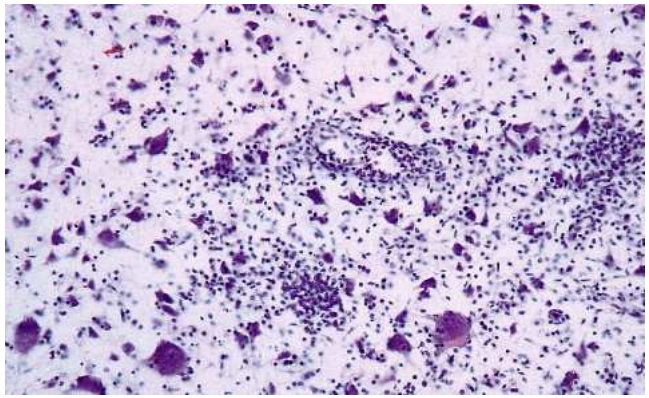
Ventriculitis

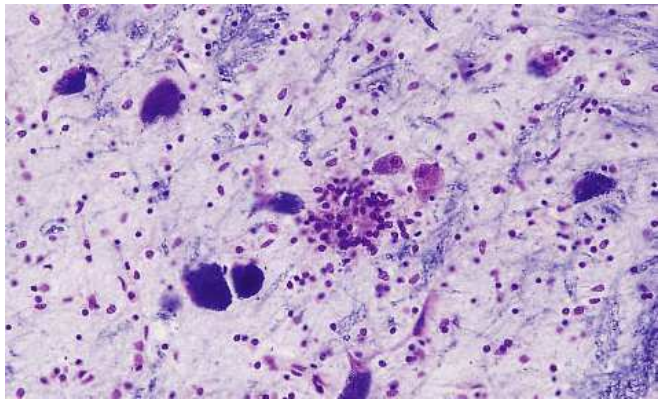


Enterovirus polioencephalitis

- RNA viruses
  - Enterovirus (70,71)
  - Poliovirus (1, 2, 3)
  - Cocksackie (A4, A7, B3)
  - Echovirus (2, 9, 30)



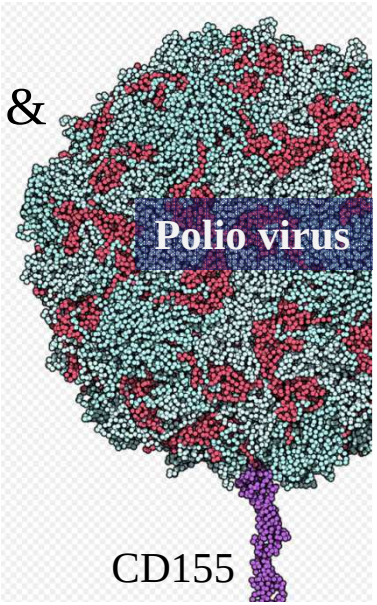




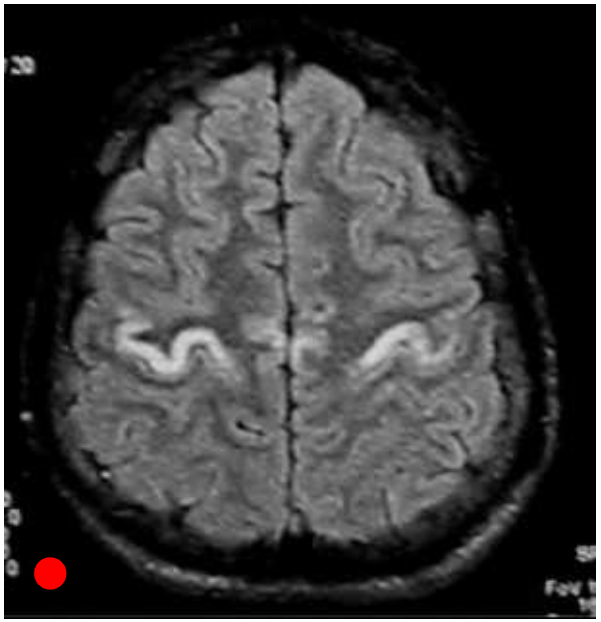
Poliovirus Inflammation, microglial nodules, neuronophagia Cocksakie

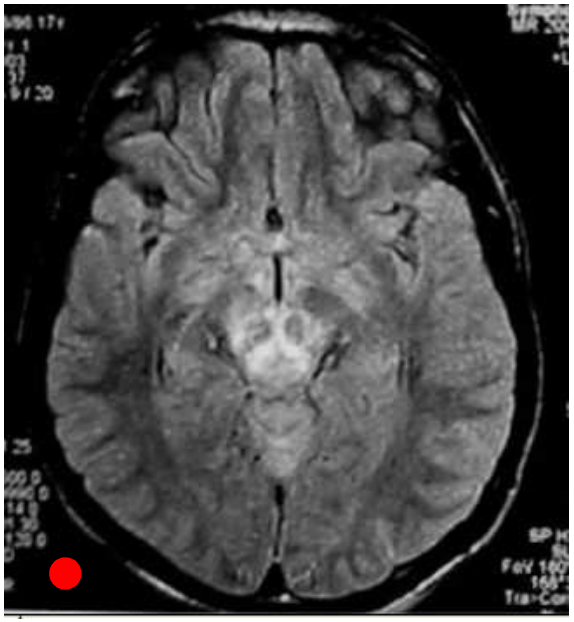
- Multiple routes of CNS invasion (after fecal-oral transmission)
  - BBB crossing during viremia
  - BBB crossing by EV-infected immune cells : (Trojan horse)
  - Neuronal centripetal spreading from damaged muscle nerve terminals

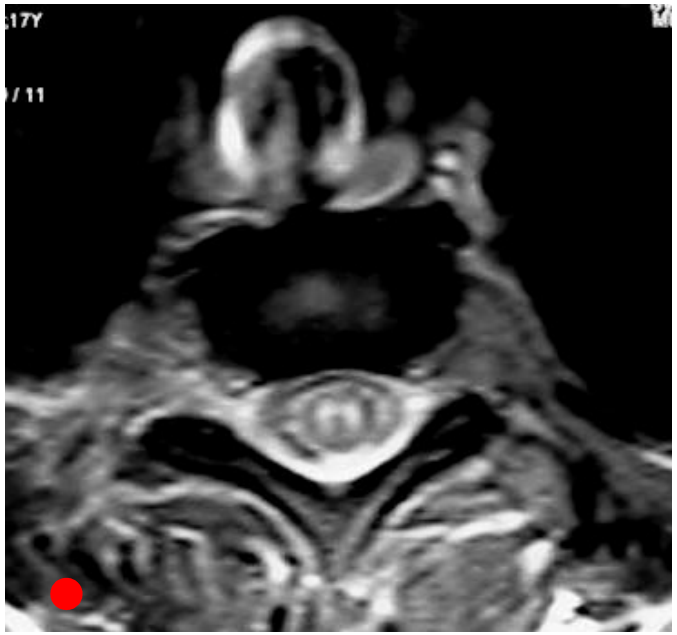
- Specific CNS neurotropism (neuronal, glial & meningeal)
  - Poliovirus binds to cell receptor CD155 of :
    - All neurons including ganglionic sensory cells ; astrocytes & oligodendrocytes
    - pyramidal tract and spinal cord anterior horn
  - EV 71 (cell receptor SCARB2) :
    - Neurons & astrocytes
    - Basal ganglia and pyramidal systems, reticular formation
  - Coxsackie (cell receptor CAR) :
    - Neuronal progenitor cells and neurons
    - Choroid plexus, neurogenic regions, hippocampus, cortex



- Role of humoral immunity defect in Echovirus encephalitis







Meningo
Polio
Encephalo
Myelitis
due to Enterovirus

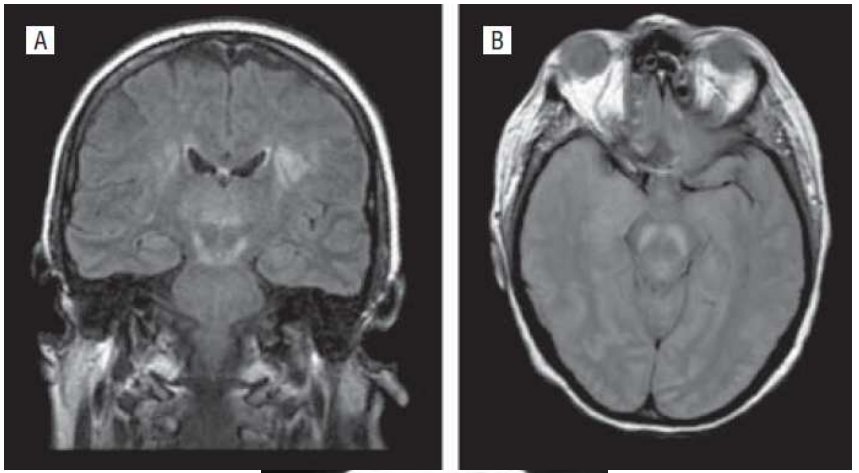
GM involved

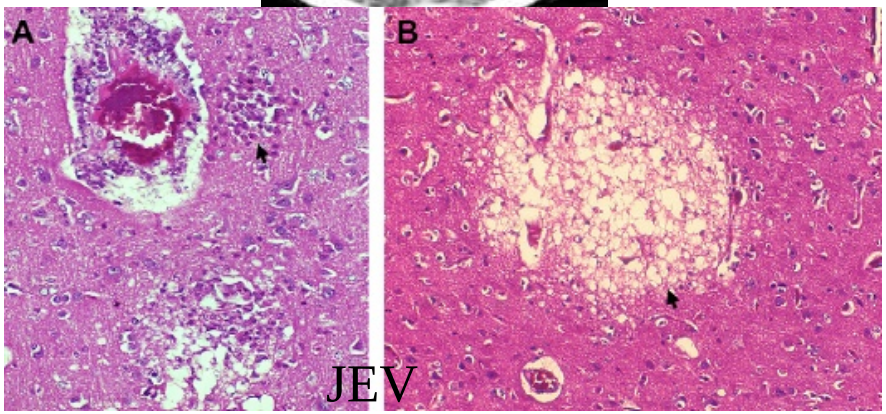
WM spared

Exemple of Arbovirus encephalitis : Japanese encephalitis

NEURO & NEURONOTROPISM

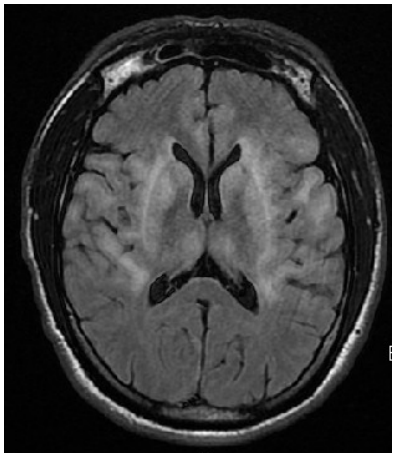
- Mosquito sting
- Hematogenous invasion
- Infection of
  - Meningeal,
  - Neuronal
  - Endothelial cells
- Polio-encephalitis
  - Brain & cerebellar cortex,
  - basal ganglia,
  - substantia nigra,
  - thalamus,
  - hippocampus,
  - pons, medulla oblongata
  - spinal cord anterior horn





HIV

- Route of entry
  - early contamination of CNS : primary encephalitis → resting virus
  - during AIDS : Trojan horse (mononuclear phagocytes) + direct invasion
  - CNS cells targets = microglial cells & astrocytes



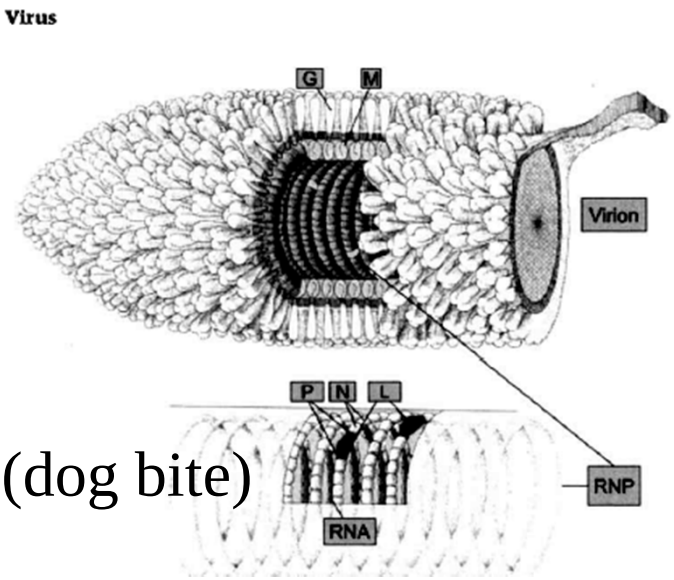
During the primary infection

During full-blown AIDS

During controlled systemic but not CNS HIV infection

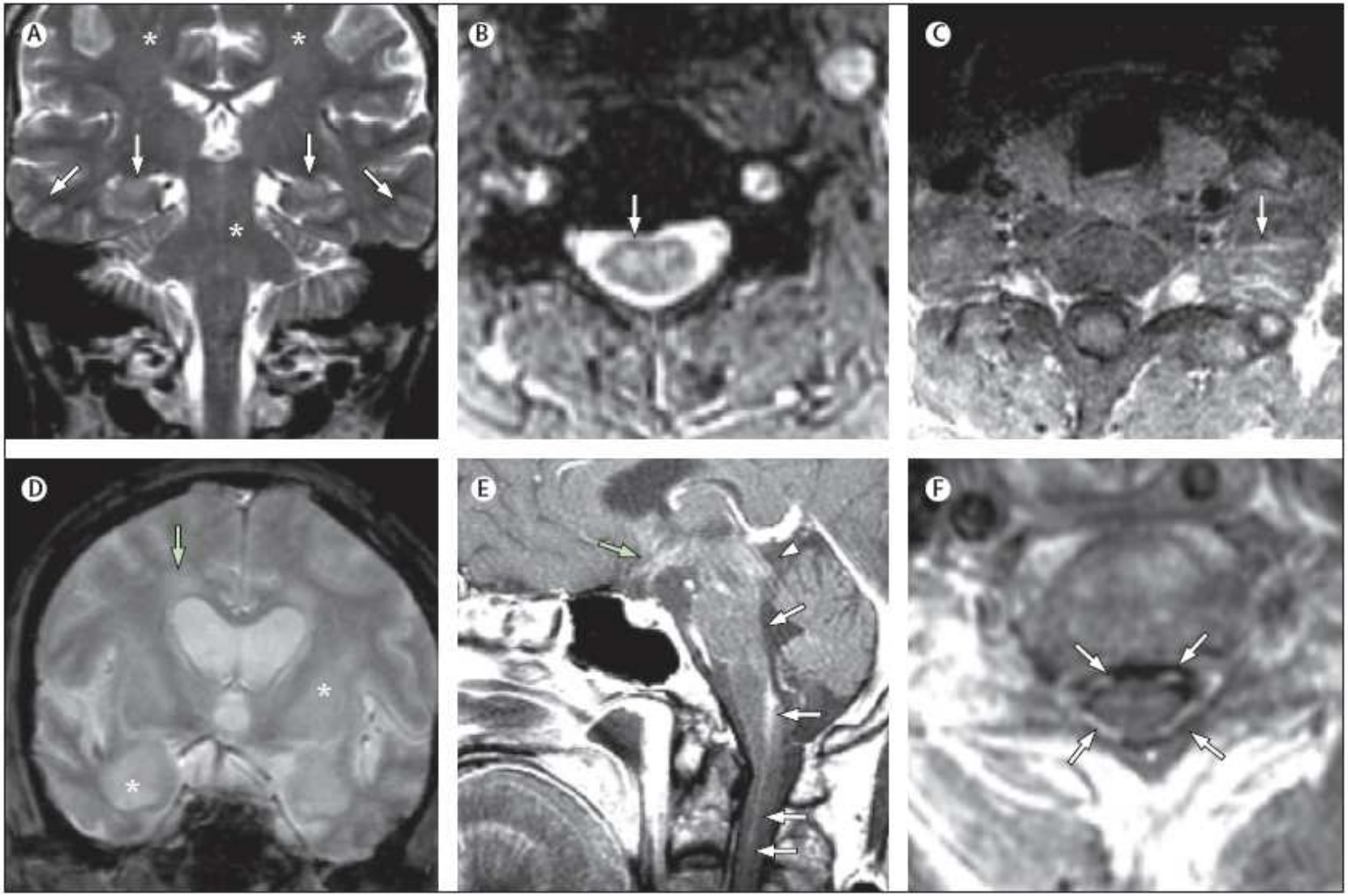
- Different forms of neuropathology :
  - Leukoencephalitis
  - Poliodystrophy due to host & viral toxic factors
  - IRIS (CD8 massive infiltration)

Rabies



- Infection through a skin/muscle wound (dog bite)
- Neurotropism
  - Slow rate replication in muscle fibers
  - Entry through nicotinic receptor of motor endplate
  - Sensory/autonomic skin innervation (?)
- Retrograde axonal transport to the spinal cord
- Cell to cell and transsynaptic ascending spreading
- Brain neuronal infection (caudal-rostral polio-encephalitis)
- Centrifugal dissemination from the brain to the innervated organs (skin, salivary glands, myocardium,…)

Furious rabies



Paralytic rabies

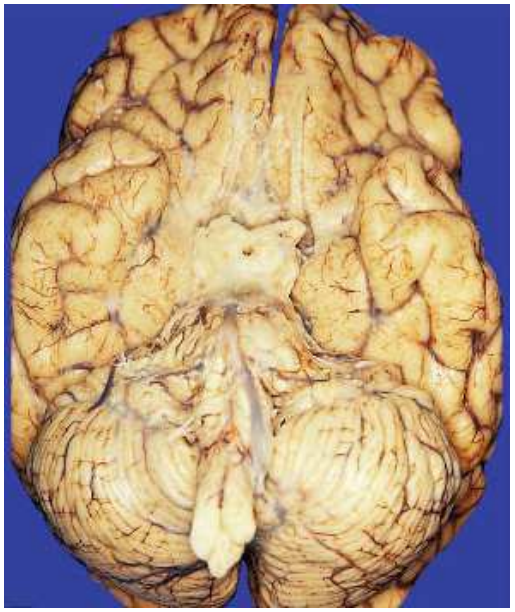
Lancet Neurol 2013; 12: 498–513

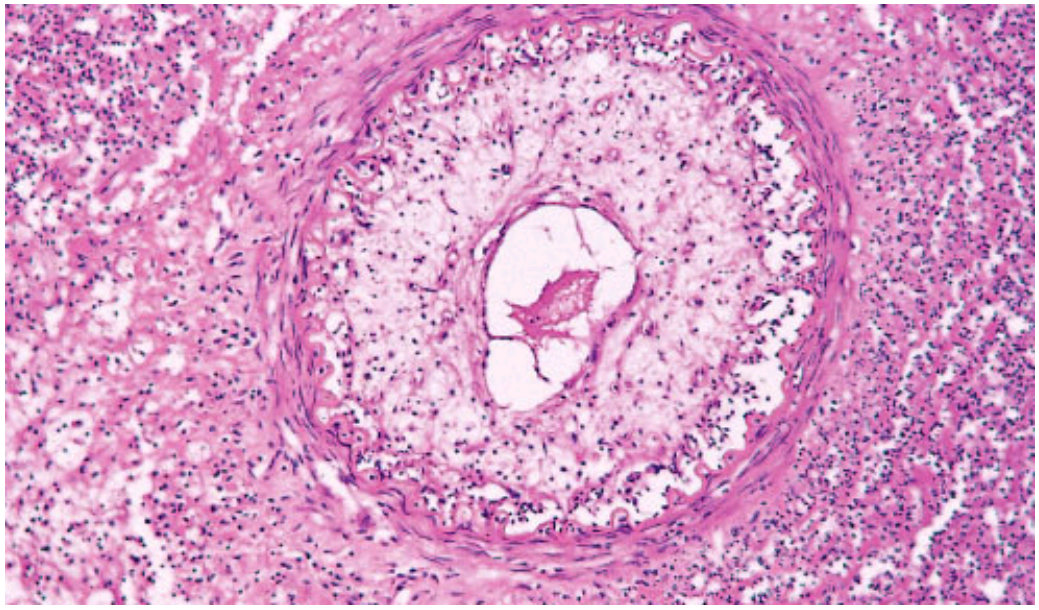
Bacteria

Mycobacterium tuberculosis

- Low-level bacteriemia → infection of microvessels endothelial cells → caseating vascular focus (Rich focus)
- Meningeal or parenchymatous location
- Release of MT and dissemination → meningitis, encephalitis, tuberculoma, abscess

- Tuberculous meningoencephalitis
  - Dense gelatinous inflammatory exsudate
    - Most florid in the basal cisterns (as a result of the flow pattern of CSF)
    - Prepontine and around the spinal cord
    - Surrounding nerves and arteries (vasculitis)
    - Impairment of CSF flow

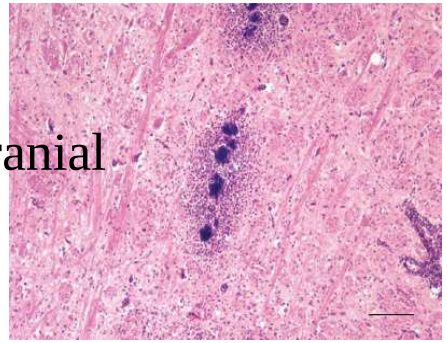




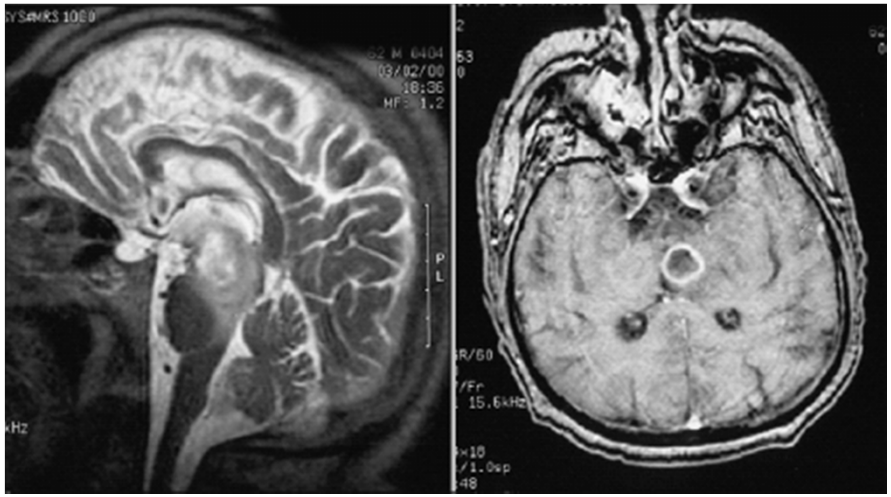
meningeal exudate of macrophages, lymphocytes, plasma cells, and fibrin

Listeria monocytogenes

- Route to brain/meningeal infection
  - Haematogenous spread from gut → meningitis
  - Neuronal spread : rhombencephalitis
    - Haematogenous dissemination → neuronal infection (cranial nerves) → cell-cell and axonal CNS spreading
    - oral mucosa → trigeminal nerve → brainstem



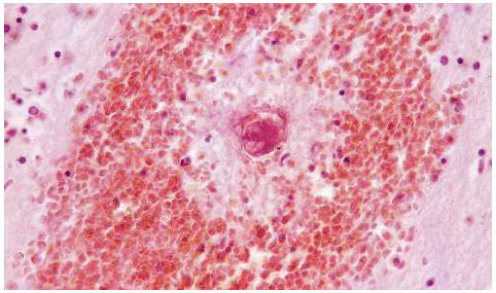
Role of immunosuppression
in the initial phase of infection



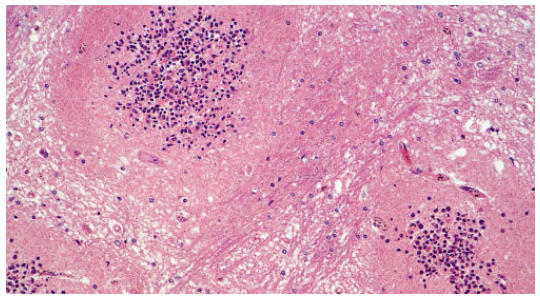
Parasites

Cerebral malaria

- Plasmodium falciparum infection causing a global CNS dysfunction
- Sequestration of parasitized red blood cells in the brain microvasculature : engorgement of small vessels
- Deposition of Ag-Ab complexes, endothelial damage and platelet aggregation : edema, capillary necrosis, perivascular haemorrhages



Haemorrhage centered by a necrotic blood vessel



Dürck granuloma

- Cell-mediated immune inflammatory response : parenchymal and meningeal inflammation

Fungi

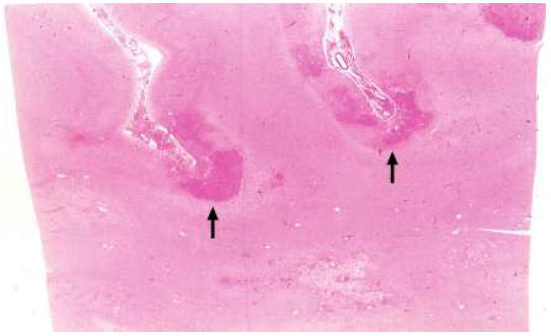
- Route of infection
  - Inhalation, skin wound or gut translocation
  - Brain invasion : haematogenous route or direct from infected sinus air or bone

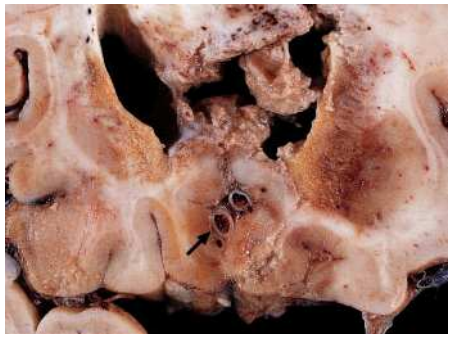
- Immunocompromission is frequent
  - *Cryptococcus neoformans*, *Candida sp.*, H*istoplasma capsulatum*, *Blastomyces dermatidis*, *Aspergillus sp.*

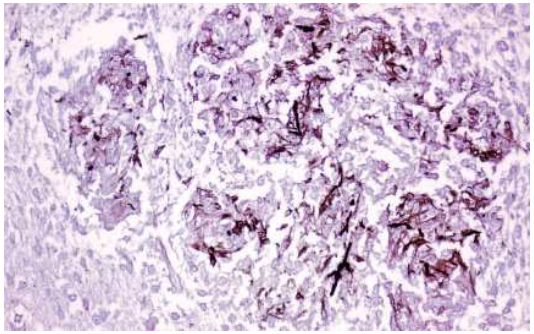
- Lesions : basal meningitis, parenchymal granulomas and abscesses, vascular infiltration / obstruction

LESIONS

Yeast	Branching hyphae	Pseudo hyphae
Leptomeningitis	Large vessels obstruction	Microvasculature obstruction
Blastomyces *Candida* *Coccidioides* *Cryptococcus* *Histoplasma* *Paracoccidioides* *Sporotrichum* *Torulopsis*	*Aspergillosis* *Cladosporium* *Fusarium* *Mucormycosis* *Allescheria boydii*	*Candida sp.*





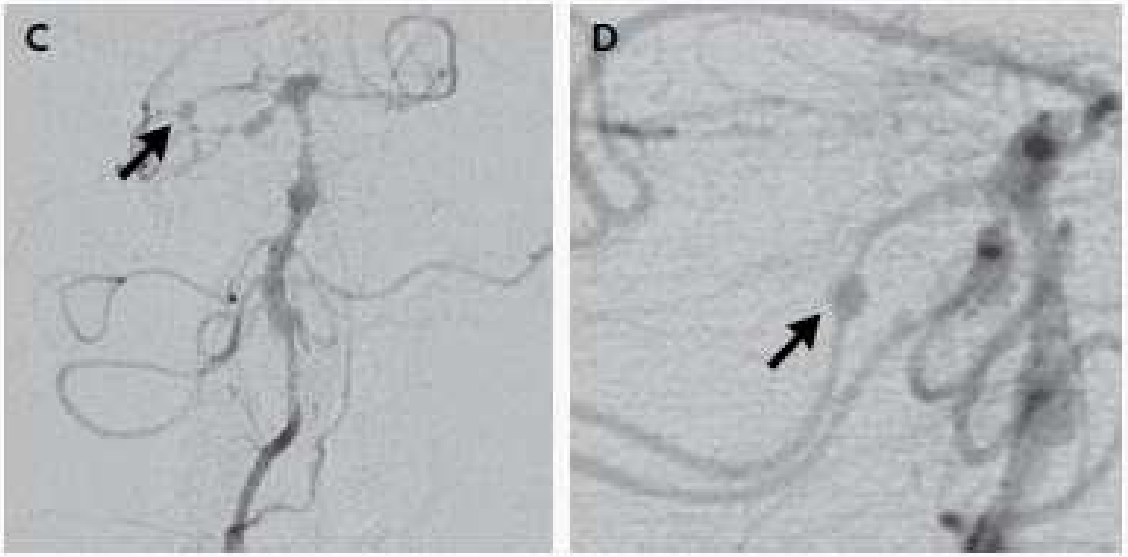


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

The Index Case for the Fungal Meningitis Outbreak in the United States

April C. Pettit, M.D., M.P.H., Jonathan A. Kropski, M.D., Jessica L. Castilho, M.D., M.P.H., Jonathan E. Schmitz, M.D., Ph.D., Carol A. Rauch, M.D., Ph.D., Bret C. Mobley, M.D., Xuan J. Wang, M.D., Steven S. Spires, M.D., and Meredith E. Pugh, M.D., M.S.C.I.



Aspergillus fumigatus

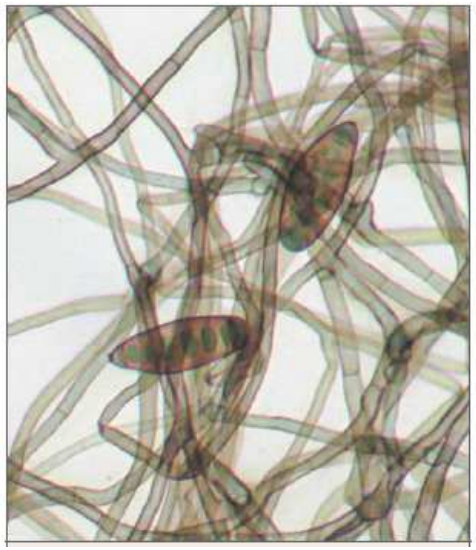
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Fungal Infections Associated with Contaminated Methylprednisolone Injections — Preliminary Report

Carol A. Kauffman, M.D., Peter G. Pappas, M.D., and Thomas F. Patterson, M.D.



Exserohilum rostratum

Virus	***Bactéria***	***Parasite***	***Fungus***
Herpès viruses (HSV1&2, VZV, EBV, CMV, HHV6B)	*Mycobacterium tuberculosis*	Toxoplasmosis	Cryptococcosis
VIH	*Listeria monocytogenes*	Malaria (falciparum)	Coccidioidomycosis
Measles	*Streptococcus*	Trypanosomiasis	Histoplasmosis
Mumps	*Neisseria meningitidis*	Cysticercosis	Aspergillus fumigatus
Enterovirus, Parechovirus	*Mycoplasma pneumoniae*	Toxocarosis	Blastomycosis
Lymphocytic choriomeningitis	*Legionella pneumophila**	Sparganosis	*Mucor circinelloides*
West Nile virus	*Borrelia burgdorferi*	Paragonimosis	*Scedosporium proloficans*
Japanes encephalitis	*Bartonella henselae*	Gnathostomosis	*Scedosporium apiospermum*
Tick-borne encephalitis	*Brucella melitensis*	Schistosomiasis	*Fusarium species*
Dengue	*Rickettsia conorii*	Multilocular echinococcosis	*Cladophialophora bantiana*
Chickungunya	*Coxiella burnetti*	*Naegleria fowleri*	*Ochronconis gallopava*
Toscana virus	*Francisella tularensis*	*Acanthamoeba spp*	*Exerophillum rostratum*
American arboviroses (Eastern equine, Western equine, Colorado, California (LaCrosse), Saint-Louis, Powassan, Deer tick virus, Venezuela equine)	*Ehrlichia chaffeensis*	*Balamuthia mandrilaris*	
Australian arboviroses (Murray valley)	*Treponema pallidum*		
Rift Valley fever			
Hanta virus (Puumala)			
Hendra virus			
Nipah virus			
Rhabdovirus			
Respiratory viruses : influenza, parainfluenza, adénovirus, respiratoire syncitial			

conclusion

As many microorganisms, as many pathophysiologies of the encephalitis