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?
CNS manifestations

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

What is the blood–brain barrier (not)?

Ingo Bechmann¹, Ian Galea² and V. Hugh Perry²
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 $\rightarrow$ choroid plexuses $\rightarrow$ CSF $\rightarrow$ brain
    • Blood $\rightarrow$ meninges $\rightarrow$ CSF $\rightarrow$ brain
    • Blood $\rightarrow$ 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

- 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
Neurotropic Viruses

Virus entry strategies.
**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)
neuron

Binding

Fusion

gB, gD, gH, gL

HVE M

Nectin-1

Nectin-2

HS

3-O-S

neuron
After cell entry

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

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

- Massive inflammatory response
- ÙEdema and Necrosis
- Detersion
HSV1 meningoencephalitis
an acute necrotizing panencephalitis
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*

  ![Graphs showing IgG, IgA, and IgM kinetics](image)

  **44 cases**
  
  IgG, IgA and IgM
  
  Variable kinetics

  No clinical difference between Ab+ and Ab- groups
  

- 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 1 week
  - 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 immunocompromise
- Elderlies
- Lymphoma & cancer
- Immunosuppressant drugs
- AIDS
VZV vasculopathies

Multifocal (AIDS)

Zoster ophtalmicus & contralateral hemiplegia
Demyelinating meningoencephalitis

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)
• 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 Encephalo Myelitis due to Enterovirus

GM involved ●
WM spared ●
Exemple of Arbovirus encephalitis: Japanese encephalitis

- 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 $\rightarrow$ resting virus
  - during AIDS: Trojan horse (mononuclear phagocytes) + direct invasion
  - CNS cells targets = microglial cells & astrocytes

  ![During the primary infection](image1)
  ![During full-blown AIDS](image2)
  ![During controlled systemic but not CNS HIV infection](image3)

- **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 exudate
    • 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 $\rightarrow$ meningitis
  – Neuronal spread: rhombencephalitis
    • Haematogenous dissemination $\rightarrow$ neuronal infection (cranial nerves) $\rightarrow$ cell-cell and axonal CNS spreading
    • oral mucosa $\rightarrow$ trigeminal nerve $\rightarrow$ 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.*, *Histoplasma capsulatum*, *Blastomyces dermatidis*, *Aspergillus sp.*

• Lesions: basal meningitis, parenchymal granulomas and abscesses, vascular infiltration / obstruction
# LESIONS

<table>
<thead>
<tr>
<th>Yeast</th>
<th>Branching hyphae</th>
<th>Pseudo hyphae</th>
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</thead>
<tbody>
<tr>
<td>Leptomeningitis</td>
<td>Large vessels obstruction</td>
<td>Microvasculature obstruction</td>
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<tr>
<td><em>Blastomyces</em></td>
<td><em>Aspergillosis</em></td>
<td><em>Candida sp.</em></td>
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<tr>
<td><em>Candida</em></td>
<td><em>Cladosporium</em></td>
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<td><em>Coccidioides</em></td>
<td><em>Fusarium</em></td>
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<td><em>Cryptococcus</em></td>
<td><em>Mucormycosis</em></td>
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<td><em>Histoplasma</em></td>
<td><em>Allescheria boydii</em></td>
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<td><em>Paracoccidioides</em></td>
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<td><em>Sporotrichum</em></td>
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<td><em>Torulopsis</em></td>
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Aspergillus fumigatus  

Exserohilum rostratum
### As many microorganisms, as many pathophysiologies of the encephalitis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Bactéria</th>
<th>Parasite</th>
<th>Fungus</th>
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<tbody>
<tr>
<td>Herpes viruses (HSV1&amp;2, VZV, EBV, CMV, HHV6B)</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Toxoplasmosis</td>
<td>Cryptococcosis</td>
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<tr>
<td>VIH</td>
<td><em>Listeria monocytogenes</em></td>
<td>Malaria (falciparum)</td>
<td>Coccidioidomyces</td>
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<td>Measles</td>
<td><em>Streptococcus</em></td>
<td>Trypanosomiasis</td>
<td>Histoplasmosis</td>
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<td>Mumps</td>
<td><em>Neisseria meningitidis</em></td>
<td>Cysticercosis</td>
<td>Aspergillus fumigatus</td>
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<tr>
<td>Enterovirus, Parechovirus</td>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Toxocaris</td>
<td>Blastomycosis</td>
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<td>Lymphocytic choriomeningitis</td>
<td><em>Legionella pneumophila</em></td>
<td>Sparganosis</td>
<td><em>Mucor circelloides</em></td>
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<td>West Nile virus</td>
<td><em>Borrelia burgdorferi</em></td>
<td>Paragonimosis</td>
<td><em>Scedosporium prolificans</em></td>
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<td>Japanese encephalitis</td>
<td><em>Bartonella henselae</em></td>
<td>Gnathostomiasis</td>
<td><em>Scedosporium apiospermum</em></td>
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<td>Tick-borne encephalitis</td>
<td><em>Brucella melitensis</em></td>
<td>Schistosomiasis</td>
<td><em>Fusarium species</em></td>
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<td>Dengue</td>
<td><em>Rickettsia conorii</em></td>
<td>Multilocular echinococcosis</td>
<td><em>Cladophialaphora bantiana</em></td>
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<td>Chickungunya</td>
<td><em>Coxiella burnetii</em></td>
<td>Naegleria fowleri</td>
<td><em>Ochroconis gallopava</em></td>
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<td>Toscana virus</td>
<td><em>Francisella tularensis</em></td>
<td><em>Acanthamoeba spp</em></td>
<td><em>Exophillum rostratum</em></td>
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<tr>
<td>American arboviroses (Eastern equine, Western equine, Colorado, California (LaCrosse), Saint-Louis, Powassan, Deer tick virus, Venezuela equine)</td>
<td><em>Ehrlichia chaffeensis</em></td>
<td><em>Balamuthia mandrilaris</em></td>
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<td>Australian arboviroses (Murray valley)</td>
<td><em>Treponema pallidum</em></td>
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<td>Rift Valley fever</td>
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<td>Hanta virus</td>
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<td>Hendra virus</td>
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<td>Nipah virus</td>
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<td>Rhabdovirus</td>
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<td>Respiratory viruses : influenza, parainfluenza, adenovirus, respiratoire syncitial</td>
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