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

- Fused gliovascular membrane
- Glia limitans basement membrane
- Outer vascular basement membrane
- Inner vascular basement membrane

What is the blood–brain barrier (not)?
Ingo Bachmann, Ian Galea and V. Hugh Perry
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
Ag detection $\rightarrow$ cytokines + chemokines
$\rightarrow$ increase of the BBB permeability
+ cell rolling, adhesion, migration

Matrix metalloproteases + APC
$\rightarrow$ 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

- Choroid plexus
- Meninges and CSF
  - Leptomeninges
    - Pia mater
    - Arachnoid
  - 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)
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
• Œdema and Necrosis
• Detersion
HSV1 meningoencephalitis
an acute necrotizing panencephalitis
Early phase

Full-blown infection

sequeleae
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

- 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 ophthalmicus & 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
Myelitis
due to Enterovirus
due to Enterovirus

GM involved

WM spared
Exemple of Arbovirus encephalitis: Japanese encephalitis

- Mosquito sting

- Hematogenenous 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

• 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 transynaptic 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

Bacteria
Mycobacterium tuberculosis

- Low-level bacteriemia $\rightarrow$ infection of microvessels endothelial cells $\rightarrow$ caseating vascular focus (Rich focus)
- Meningeal or parenchymatous location
- Release of MT and dissemination $\rightarrow$ 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 → 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., Histoplasma capsulatum, Blastomyces dermatidis, Aspergillus sp.*

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

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<th>Yeast</th>
<th>Branching hyphae</th>
<th>Pseudo hyphae</th>
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<tr>
<td>Leptomeningitis</td>
<td>Large vessels obstruction</td>
<td>Microvasculature obstruction</td>
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<td><em>Blastomyces</em></td>
<td><em>Aspergillosis</em></td>
<td><em>Candida sp.</em></td>
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Aspergillus fumigatus

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