Epilepsy and Brain Inflammation
- Introduction -

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I. Experimental Evidence (Vezzani et al., Nat Rev Neurol 2011;7:31-40)

1. Seizures cause inflammation
2. Inflammation causes seizures
3. Inflammation during early developmental stage (in P7 to P14 in rats) results in enduring changes in neural hyperexcitability
4. Inflammation causes cell loss and synaptic reorganization

Inflammation is an important mechanism of “Epileptogenesis” and “Disease Progression”
Epilepsy and Brain Inflammation

I. Experimental Evidence

- Investigations of the IL-IB system and markers of adaptive immunity in pilocarpine SE-model of Rats

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Ravizza et al., Neurobiol Disease 2008;29:142-160
Epilepsy and Brain Inflammation

II. Clinical Evidence

• Development of epilepsy via immunological and/or inflammatory mechanisms
• Pathology of inflammation from patients with refractory epilepsies
• Demonstration of Inflammatory Markers in patients with epilepsy
Epilepsy and Brain Inflammation
II. Clinical Evidence

I. Development of epilepsy via immunological and/or inflammatory mechanisms

(1) In SLE,
   (a) 10-20% develop epilepsy (8 times of control)
   (b) presence of anti-phospholipid (aPLs) or anti-cardiolipin antibodies is associated with higher incidence of epilepsy (RR: 3.7)

(2) In Landau-Kleffner syndrome (acquired epileptic aphasia), antibodies reacting with brain endothelial cells were demonstrated and anti-immune therapy is often effective

(3) In Rasmussen Encephalitis, GluR3Ab and other Ab were demonstrated and anti-immune therapy is one of standard treatment

(4) In Limbic encephalitis and other multifocal paraneoplastic encephalitis
Limbic Encephalitis

• Clinical features: rapidly progressive memory deficits, psychiatric Sx, and recurrent seizures

• LAB features: inflammatory findings in CSF, EEG of TLE, MRI abnormalities, and Anti-neuronal antibodies

Limbic Encephalitis

• Anti-neuronal antibodies
  (i) intracellular Ags: Hu, Ma2, CV2/CRMP5, and amphyphysin
    - associated with cancer, prominent infiltration of cytotoxic T cells, and limited response to treatment
  (ii) Cell membrane Ags: VGKC, NMDAR, ganglionic Ach R
    - less frequently associated with cancer, antibody related damages, and better response to immunotherapy

2. Pathology of Inflammation in patients with Refractory Epilepsy

a. microglial activation and proliferation were seen in 50% of 92 cases with cryptogenic RE by H&E stain  
   ([Najjar et al., neurologist 2011;17-249-254])

b. in patients with MTLE with HS
   ◊ Over-expression of NFκB in reactive astrocytes, surviving pyramidal cells, and hilar neurons  
     ([Crespel et al., Brain Res 2002;952:159-169])

   ◊ Microglial and marcophage activation, increased reactivity of IL-1β and IL-1RI, and albumin reactivity around blood vessels were seen the hippocampus  
     ([Ravizza et al., Neurobiol Dis 2008;29:142-160])

c. in patients with Tuberous Sclerosis
   ◊ Activation of complement cascades, IL-1β signaling infiltration of lymphocytes in the perivascular zones, and perivascular leakage of albumin in the epileptogenic tubers  
     ([Boer et al., Epilepsy Res 2008;78:7-21])

d. in patients with focal cortical dysplasia (FCDs)
   ◊ Activation of astrocytes and microgyria/macrophages, T-lymphocytes in FCD  
     ([Iyer et al., Epilepsia 2010;51:1763-1773])
3. Demonstration of Inflammatory markers

(1) Neuroimaging

a. MRI using iron oxide contrast conjugated to the vascular cell adhesion molecule 1 (VCAM-1)

b. PET using a radiolabeled ligand of translocator protein (TSPO), a marker of inflammation; “$^{11}$C-(R)-PK11195”, and “$^{11}$C-PBR28”

  n = 16 pts with TLE, PET using “C-PBR28”
  Asymmetric overexpression of TSPO in the ipsilateral hippocampus in 12 pts (all 9 pts with HS, 3 of 7 pts without HS)
Coronal sections of MR, PET, and fused PET/MR images demonstrate distribution of radioactivity in brain after injection of $^{11}$C-PBR28 in patient with left-sided temporal lobe epilepsy. PET image is summed from 0 to 120 min. Right side of brain appears on left side of image. Area within red rectangles appears magnified in bottom row. There is higher uptake in ipsilateral than in contralateral side in choroid plexus (red arrow) and hippocampus (black arrow).
3. Demonstration of Inflammatory Markers

(2) Inflammatory cytokines in CSF and serum

- **Lehtimäki et al.** (*J Neuroimmunol* 2004;152:121-125)
  - n=33; single GTCS (n=16), repetitive GTCS (n=10), prolonged PS (n=7)
  - Serum (n=33) & CSF (n=25) ≤ 24 hrs after Sz
  - IL-6 and its soluble receptors (sIL-6R, sGp130)
    - Increased IL-6 in CSF and serum
    - Decreased sIL-6R in CSF and serum
    - Largest changes in patients with repetitive GTCS, suggesting Sz may induce the release of inflammatory cytokines
3. Demonstration of Inflammatory Markers

c. Genetic predisposition for exaggerated inflammation

- Meta-analysis of association studies of SNP at the promoter region of IL-1β (IL-1β-511T) with temporal lobe epilepsy and febrile seizure susceptibility
- A modest association (OR 1.48:1.09-2.00;p=0.01) between IL-1β-511T polymorphism and TLE with HS
Epilepsy and Brain Inflammation: II. Clinical Evidence

- Summary -

• Significant accumulation of clinical evidence linking epilepsy and brain inflammation, which are largely consistent with Experimental Data

• Clinical evidence provide plausible “Research Hypothesis”
  
  (1) “Role of Inflammation” in
  - (a) Epileptogenesis
  - (b) Drug Resistant Epilepsies
  - (c) Progressive cognitive deterioration

  (2) “Identification of Inflammatory Markers” for diagnostic and therapeutic interventions
  - (a) prediction of progressive deterioration
  - (b) anti-inflammatory therapy
  - (c) specific targets of drug development
Thanks for Your Attention!