Febrile seizure;
The role of inflammation in febrile seizure and its relation to epilepsy

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Overview

- Innate and adaptive immunities of the brain
- Evidences of Inflammation in epilepsy
  - Animal models of epilepsy
  - Clinical evidences
  - Febrile seizure and temporal lobe epilepsy
  - Epileptogenic brains and serum in childhood intractable epilepsy
- Roles of inflammation in febrile seizure and relation to epilepsy
- Potential therapeutic applications and future research
Innate and Adaptive Immunity in CNS

- **Innate immune system**
  Immediate action against external agents
  Microglia, Astrocyte, Neuron

- **Adaptive immune system**
  Antigen recognition *via specific Ag-presenting cells & Ag receptors*
  B & T lymphocytes

- Communication between cells of the immune system
  Direct cell-to-cell contact
  Cytokines
Brain; An immune-privileged organ?

- Blood brain barrier
- Graft acceptance
- A lack of a conventional lymphatic drainage
- Low traffic of monocytes & lymphocytes

2010, Neurobiol Dis, Abbott
Inflammatory reaction does occur in the Brain.
Evidences of inflammation in epilepsy

- Human epilepsy
- Febrile seizure
- Epileptogenic brain tissues in intractable childhood epilepsy
- Animal model of epilepsy
Intractable childhood epilepsy improved by immunotherapy

**Rasmussen’s encephalitis**  
45% of patients treated with steroid  
Significant ↑ motor function  
↓ Seizure frequency  
Epilepsia partialis continua (-)

**Infantile spasm**  
ACTH; effective in seizure control, behavior, background EEG  
Oral steroid; 30-40% seizure-free  
Early use; more effective within 1 month of the onset of spasms
Childhood noninfectious neurological diseases associated with the late onset of epilepsy

- **Neonatal Stroke**
  Golomb MR, J of Ped 2007
  75% presented with neonatal seizures
  67 % developed epilepsy after 6 months of age
  The median age at delayed epilepsy onset ; 16 months old

- **Childhood Stroke**
  30% delayed epilepsy ; 4 months ~10 years after unilateral hemispheric stroke

- An important role of *inflammation and breakdown of BBB* as necessary *components in epileptogenesis* following *brain injury*
The late onset of epilepsy in autoimmune diseases

- **Systemic Lupus Erythematosus (SLE)**
  - Prevalence of epilepsy: 10-20% (8 times higher than general)
  - 5-10%: seizures several years before the clinical onset of SLE
  - Epilepsy in SLE: associated with anti-phospholipid Ab

- **Hashimoto thyroiditis**
  - Watemberg, J Child Neurol 2006
  - Hashimoto encephalopathy: high anti-thyroid ab
  - Seizures or agitation or psychiatric illness
  - Unrelated with thyroid functions
  - Respond dramatically with corticosteroid therapy

- **Autoantibodies may trigger seizures and contribute to epileptogenesis**
Increased systemic inflammation in human epilepsy

- **Increased WBC, CRP in blood and CSF**
  
  New onset generalized convulsions without any clinical evidence of CNS or systemic infections than children without seizures
  

- **Polymorphism in the promoter region of IL1-β gene at the -511**
  
  Kanemoto, Epilepsia 2003
  
  Effect to increase production of IL-1β
  
  ↑↑ mTLE with HS than controls or mTLE without HS
Febrile seizure

- The most common form of childhood seizures (Kjeldsen, Epilepsy Res 2002)
  The prevalence; 3~8% in children up to 7 years old
  50% ; between 12 ~ 30 months

- Prolonged febrile seizures (PFS) > 15min
  Ass. with the mesial TLE (2001 Engel)
  30~60% of MTLE have past history of PFS (1999 Theodore)
  8-fold risks of developing epilepsy than simple FS (1976 Nelson)
Epileptogenesis provoked by prolonged experimental febrile seizures

Hippocampal EEG in typical spontaneous electrographic seizures in adult rats (3 months of age) experienced prolonged FS on p10

Long (64 minute) FS > More severe resulting epilepsy

2010 J Neurosci, Baram

2006, Brain, Dube & Baram
Temporal relation between seizures with fever, febrile seizures and epilepsy

Scheffer, BMJ, 2007
Mechanisms of Febrile seizures

1. Fever generates seizures by elevating brain temperature.
2. Hyperthermia-induced hyperventilation and alkalosis
3. Fever mediators contribute to the generation of febrile seizures.
4. Genetic susceptibility to febrile seizure
Immature brain is hyper-excitabile.

2010. Jensen, Nat Rev Neurol

2007, Physiol. Rev, Ben-Ari, Y.
Hyperthermia

in immature CA1 neurons of the rat hippocampus

Qu, Neurobiol Dis, 2007
Hyperthermia-induced respiratory alkalosis in the immature brain

Cerebral alkalosis enhances neuronal excitability.
Hyperthermia-induced seizures are associated with brain alkalosis

Aram, Neurosci Lett, 1987

Schuchmann, Nat Med 2006
Febrile seizures by a hyperthermia-induced respiratory alkalosis

Hippocampal recording in P 9 rats

Schuchmann, Nat Med 2006
Inflammatory mediators

IL-1 production from dsRNA–stimulated leukocytes
In febrile seizure patients

Increased proinflammatory Cytokine IL-6 and IL-1β in febrile seizure patients

2006, Matsu, Ped Neurol

2011, Choi, J Neuroinflamm
Genetic susceptibility to Inflammation in FS

- **Genetic susceptibility to inflammation**  
  Virta, Ped Neurol 2002, Kanemoto, Epilepsia 2003  
  Family history of febrile seizure; 17-30%  
  Biallelic polymorphism in the promotor region of IL-1β -511;  
  Increase IL-1β production

- **Human Herpesvirus-6 infection**  
  Kondo, J Infect Dis 1993, Asano, Pediatrics 1994  
  Exanthem subitum; 90%- children < 2 years old,  
  the period of greatest susceptibility to febrile seizures.  
  HHV-6 DNA (+) more frequently in CSF of patients with 3 or  
  more seizures than those with a single febrile seizure.
IL-6 (-174) G>C polymorphism in FS

- Genotypic frequency (%)
  - Korean children
    - Chi-square
    - $P = 0.05$
  - Turkish children
    - Chi-square
    - $P < 0.05$

IL-6 (pg/dl)
- Mann Whitney test
  - $p = 0.2$

2011, Choi & Hwang, IEC in Rome
2012, Haspolat, Ped Neurol
Seizures cause acute and chronic brain inflammation
Animal models of KA-induced seizures (Two hit P15- P45, sacrifice P55)

2007, Epilepsia, Koh & Wainwright
Activation of TLR4 and HMGB1 in human hippocampal sclerosis

TLR4; a key receptor of innate immunity can be activated by molecules released by injured tissues
HMGB1; released by necrotic cells, binds to TLR4

2010, Maroso & Verzzani, Nat Med
Activation of Plasminogen system in human HS & malformation of cortical developments

Plasminogen system affect the permeability property of the BBB.
Inflammation induced by LPS enhances epileptogenesis in immature rats and partially reversed by IL1RA

Animal models of kindling starting postnatal day 14

2010, Epilepsia, Auvin & Sankar
Dose-dependent anticonvulsant effects of HMGB1-TLR4 antagonists in KA-induced seizures model

- Vehicle + KA
- Lps-Rs + KA
- BoxA + KA
- Cyp + KA

BoxA; a fragment of HMGB1 with antagonistic activity

*Rhodobacter sphaeroides* LPS(Lps-Rs) and cyanobacterial LPS(Cyp); TLR4 antagonists

![Graph showing the number of seizures and ictal activity](image-url)
Dexamethasone treatment in pediatric drug-resistance epilepsy; reduction of seizure & hyperintensity of FLAIR
Increased serum cytokines in febrile seizure or afebrile status epilepticus; *IL-1β, IL-6, TNFα, HMGB1*

2011, Choi & Shin, J Neuroinflammation
Increased cytokines in epileptogenic brain lesions of intractable childhood epilepsy; *IL-1β, IL-8, IL-12p70, MIP-1β*
Chronic brain inflammation in epileptogenic lesions of intractable childhood epilepsy

Diffuse microglial activation; 73%

Panlaminar astrocyte activation; 100%

2009, Choi, Neuroinflammation
Diffusely increased DNA fragmentation in epileptogenic lesions of intractable childhood epilepsy

2009, Choi & Koh, J Neuroinflammation
Inflammation imaging in epilepsy patient with MCD
- [C11]PK11195, a marker of activated microglia

**Ictal** FDG-PET
Hypermetabolism

**Interictal** FDG-PET
Hypometabolism

**PK11195-PET** on CT
Increased Uptake

**OP; FCD**
CD68(+) activated microglia

2011, Butler, J Neuroimaging
Interplay between inflammation & epilepsy

Initial precipitating event

Periphery (Infection, Autoimmunity)
- Leukocytes
  - BBB breakdown (Albumin, IgG)
  - Astrocytes: Ionic imbalance, Glutamate uptake

Inflammation (Interleukins, TNF-α, Complement, COX, Chemokines, Cell adhesion molecules, Danger signal)

CNS (Infection, Trauma, Stroke, Seizures)
- Glia/Neurons
  - Neurons: Ion channels (glutamate/GABA receptors)
  - Astrocytes: Glutamate release
  - Neurons/Glia: Neurogenesis, Sprouting, Angiogenesis

non transcriptional

transcriptional

Increased excitability

Seizures ± Cell death

Epilepsy

Inflammation

2011, Verzzani, Epilepsia
New Anti-inflammatory treatments for refractory epilepsies?

- Anti-cytokines
  - Receptor blockers
  - Synthesis inhibitors
  - Neutralizing monoclonal antibodies

- Anti-PGE2 receptors
- Anti–cell adhesion molecules
- Resealing of the BBB
- Anti-mTOR (rapamycin for TS)

2011, Verzzani, Epilepsia
Brain inflammation is one of key factors contributing to the epileptic process, promoting increased neuronal excitability, decreased seizure threshold.

Prolonged febrile seizure in hyperexcitable immature brain may cause ongoing inflammation and intractable seizures afterwards.

Cortical dysplasia; a critical role to both the initial and subsequent clinical course after a prolonged febrile seizures.
THANK YOU!