Epileptogenesis and Seizures in the Developing Brain

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What is the Diagnosis?

Child presents with seizures, hypotonia, hepatomegaly and craniofacial abnormalities

A. Pompe’s Disease
B. Gaucher Disease
C. Hydrocephalus
D. Zellweger syndrome

What is the Diagnostic Test?

A. Measurement of plasma very-long-chain fatty acid (VLCFA)
B. Peroxisome level
C. Blood ammonia (NH3) level
D. Serum Uric acid
Epileptogenesis is a process by which a normal brain develops epilepsy, a chronic condition in which seizures occur.
Initiation, Maintenance, and Progression of Chronic Epilepsy

Initiating Event

Genetics

Critical modulators

Structural / Functional changes

Seizures

Refractory Epilepsy?

Age

Neurobehavioral changes, Cognitive impairment?

Days, Months, Years

HS White
Acquired Epileptogenesis

- Epileptogenic brain insult
- Genetic background
- SE, TBI, stroke
- Latency
- Epileptogenesis
- Spontaneous seizures (epilepsy)

Parallel and sequential neurobiological processes:
- Neuronal death
- Neurogenesis
- Gliosis
- Sprouting
- Extracellular matrix
Ion-channel activation
Post-translational changes
Immediate early genes

Transcriptional events
Neuronal death
Inflammation

Sprouting
Network reorganization
Neurogenesis
Gliosis

Cascade of events?
Biomarkers?
Therapeutic targets?

Epilepsy
Emergence of spontaneous seizures

Level of activity

Initial insult
Minutes
Days

Time
Weeks
Neuronal Circuitry Between Entorhinal Cortex And Hippocampus
Cell Loss Following Status Epilepticus

Control

Post SE

CA3
Sprouting
Dendrites
Cell Body
Axons
Targets

Normal

Sprouting
Aberrant Neurogenesis and Connections
Mossy Fiber Sprouting Following Status Epilepticus

Control

Post SE
Hippocampal Anatomy: Normal And Hippocampal Sclerosis

- Pes
- Body
- Tail

Hipp. Sclerosis

- CA2
- Sommer’s Sector
- End-folium
Seizure-Induced Cell Loss
Serpent River
WEATHER STATION

IF THE ROCK IS WET... It's Raining
IF THE ROCK IS SWAYING... It's Windy
IF THE ROCK IS HOT... It's Sunny
IF THE ROCK IS COOL... It's Overcast
IF THE ROCK IS WHITE... It's Snowing
IF THE ROCK IS BLUE... It's Cold
IF THE ROCK IS GONE... TORNADO
Initiation, Maintenance, and Progression of Chronic Epilepsy

- Genetics
- Initiating Event
- Critical modulators
- Age
- Refractory Epilepsy?
- Seizures
- Structural / Functional changes
- Neurobehavioral changes, Cognitive impairment?

Days, Months, Years
(a) Avant apprentissage

(b) Après apprentissage

Plate-forme immergée (invisible)
Piscine d'eau laiteuse (opaque)
Water Maze Performance: Hidden platform

Early Trial

Late Trial

Normal Rat

Hippocampal Lesioned Rat
Water Maze Performance: Visible Platform

Late Trial

Normal Rat

Hippocampal Lesioned Rat
Water Maze Performance Following Neonatal Seizures

de Rogalski Landrot, 2001
Mossy Fiber Sprouting Following Neonatal Seizures
Mossy Fiber Sprouting Following Neonatal Seizures
Effects Of Status Epilepticus In Adult Rats

A and B: Synaptic reorganization
C and D: CA3 neuronal loss

Parent et al., 1997

Neoneurogenesis
Neurogenesis
Reduced Neurogenesis Following Neonatal Seizures

McCabe et al. 2000
Neonatal Seizures Reduce Neurogenesis

Decreased neurogenesis following status epilepticus or recurrent seizures in the immature brain.

McCabe et al, 2000
BrdU-Labeled Cells in Adult Animals

McCabe et al, 2000
Developmental Changes in GABA\textsubscript{A} Receptor Expression and Function

Seizures at Different Ages Cause Distinct Patterns of Inhibitory Changes

Example of GABA<sub>A</sub> receptor subunit composition

Zhang et al., *Neuroscience* 2004
A Single Episode of Neonatal Seizures Permanently Alters Glutamatergic Synapses

Brandon J. Cornejo, BS, 1,2 Michael H. Mesches, PhD, 1,3,4 Steven Coultrap, PhD, 1 Michael D. Browning, PhD, 1,5 and Timothy A. Benke, PhD, MD1,5,5,6


![Diagram showing synaptic changes before and after neonatal seizures, with labels for LTP, LTD, NR2A, NR2B, GluR1, and GluR2.](image-url)
Immature Rat Model of Prolonged Febrile Seizure

- Age appropriate
- Physiological temps
- >98% seizure induction
- EEG validated
- Controlled seizure duration
- Fever mediators involved
- No mortality, morbidity

Courtesy of Tallie Z. Baram
Prolonged Febrile Seizures May Be Epileptogenic

- Epilepsy in 35%
- EEG abnormalities in many
- High sensitivity to convulsants
- Hyper-excitable hippocampus

Dube et al., 2006
Epileptogenesis in Prolonged Febrile Seizures

Cell Death - No

Transient injury - Yes

Toth et al., 1998

Epileptogenesis in Prolonged Febrile Seizures
Molecular Basis for Febrile Seizure-Induced Changes

Channel consists of 4 (homomeric) subunits

Hyperpolarization activated cyclic-nucleotide gated

<table>
<thead>
<tr>
<th>Major Location</th>
<th>HCN1</th>
<th>HCN2</th>
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<tbody>
<tr>
<td>Hippocampus</td>
<td></td>
<td>Thalamus</td>
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<tr>
<td>Brainstem</td>
<td></td>
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<th>Location</th>
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<tr>
<td>Fast kinetics</td>
<td>Modest cAMP gating</td>
<td>Slow kinetics</td>
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<td></td>
<td>Robust cAMP</td>
</tr>
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Seizures Reduce HCN1 Resulting in Increased Excitability
Development of epilepsy

Normal: Migration of newly born GC from SGZ to GCL

Febrile seizure: Reversal migration

Epilepsy: Aberrant excitatory connections

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Normal EEG: Normal

Seizure: Seizure

Ectopic GC → Sprouting

↑GABA_A-R
↑Excitation
↑Ca^{2+} influx
Electrode Implantation
Place Cells Form Spatial Map
Spontaneous Seizure

Mild Change

Silent to Active

Unstable

Active to Silent

Interneuron

Zhou et al., 2007
Cont.  Cont.  RS  RS
PC
PC
PC
INT

Mean = 0.528
Mean = 0.824

Number of Cells

Coherences

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
0
10
20
30
40
Cont.
RSRS
Neonatal Seizures: Stability of Cells
Seizures in the Developing Brain

- Seizures can cause “damage” without cell loss
- Recurrent seizures result in:
  - Altered synaptogenesis (sprouting)
  - Decreased in dendritic spines
  - Reduced neurogenesis
  - Changes in receptor subunit configuration/physiology/distribution
  - Cognitive impaired
  - Impaired synaptic function
  - Aberrant single cell
Thank You!