Pediatric State of the Art
Prolonged Febrile Seizures and TLE: Hot New Information

December 3, 2012

Shlomo Shinnar, MD, PhD, Co-Chair
Montefiore Medical Center / Albert Einstein College of Medicine
New York, NY

Tallie Z. Baram, MD, PhD, CO-Chair
University of California-Irvine
Irvine, CA

American Epilepsy Society | Annual Meeting
Disclosure – Dr. Baram

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The speaker has no relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients
## Disclosure – Dr. Shinnar

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<td>Cyberonics</td>
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<td>Eisai</td>
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<td>King (now Pfizer)</td>
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<td>Upsher Smith</td>
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Supported by grants NS 43209 NINDS & HD 36867 from NICHD
Learning Objectives

• Manage FS/FSE based on knowledge regarding the relationship of FSE duration and the probability of developing TLE after FSE

• Obtain MRIs on children with FSE that allow evaluation of hippocampal volume and T2 measures (indicators of risk for future TLE).
Agenda

- What FEBSTAT Tells Us About Febrile Status Epilepticus (FSE) and TLE
  Shlomo Shinnar, MD, PhD
- How Might Febrile Status Epilepticus Lead to TLE?
  Tallie Z. Baram, MD, PhD
- Biomarkers for FSE-Induced TLE
  James O. McNamara, MD
- Questions/Discussion
What FEBSTAT tells us about Febrile Status Epilepticus, Hippocampal Sclerosis and Temporal Lobe Epilepsy

December 3, 2012

Shlomo Shinnar, MD, PhD
Montefiore Medical Center / Albert Einstein College of Medicine
New York, NY

American Epilepsy Society  |  Annual Meeting
Learning Objectives

• Review the data on acute findings in children with febrile status epilepticus (FSE)

• Review the data on consequences of FSE

• Discuss how this data informs the controversy on the relationship between FSE and subsequent Hippocampal Sclerosis (HS) and Temporal Lobe Epilepsy (TLE) in humans
Febrile Seizures: ILAE Definition

A seizure occurring in children after age 1 month associated with a febrile illness

Prior neonatal seizures stratified separately

Exclusions:
- Prior unprovoked seizures
- Acute CNS infection
- Electrolyte imbalance
- Other acute symptomatic events

Complex Febrile Seizure

- Prolonged (≥10 or ≥15 min)
- Focal
- Multiple

Duration of First Febrile Seizure
N=154

\[ S(t) = 0.825 \cdot e^{-t/3.87} + (1 - 0.825) \cdot e^{-t/39.33} \]

Hesdorffer et al Ann Neurol 2011;70:93-100
Febrile Seizures in the United States

- Assuming **19 million** children <5 years of age
  - **360,000** (2%) with febrile seizure annually
  - Febrile SE is 5-9% of all febrile seizures
  - **18,000-32,400** with febrile status annually

- **ALTERNATIVE ESTIMATE**
  - Approximately **200,000** cases of SE annually
  - **50%** occur in children under age 16
  - Febrile SE is approx **25%** of all pediatric SE
  - This leads to estimate of **25,000** cases a year
Do Febrile Seizures Cause Hippocampal Sclerosis?

Retrospective studies report that many patients with intractable epilepsy who undergo temporal lobectomy and have MTS give a history of febrile seizures in childhood.

Do Prolonged Febrile Seizures Cause Hippocampal Sclerosis?

Acute and Chronic MRI Changes

Case 7

Case 8

Problems with Studies on Consequences of Very Prolonged Febrile Seizures

1. Small number of cases
   • Injury requires at least 60-90 min febrile seizure
   • Focal
   • At most, 1% of febrile seizures
   • Injury not universal

2. High noise level
   • 10-20% of patients with childhood-onset epilepsy have febrile seizure history
   • Relationship clearly not causal in most cases
   • Difficult to detect therapeutic effect

3. Long latency period
   • While epilepsy can develop within a few years, studies of febrile seizures and MTS suggest latency periods of 8-11 years

Consequences of FSE (FEBSTAT): Goals

Outcomes to be studied include:

- development of Hippocampal Sclerosis (HS)
- development of epilepsy and in particular of Temporal Lobe Epilepsy (TLE)
- occurrence of specific neuropsychological deficits (e.g. memory) in children with and without HS.

Hesdorffer et al Epilepsia 2012; 53:1471-1480
Consequences of FSE (FEBSTAT): Hypotheses

- Hippocampal volume and T2 signal abnormalities will be seen in MRIs done in children within 72 hours of febrile SE.
- The severity of acute hippocampal abnormalities will predict whether or not HS will be seen on follow up MRIs.
- Children with HS will have memory deficits even prior to development of clinical epilepsy.

Hesdorffer et al Epilepsia 2012; 53:1471-1480
Consequences of FSE (FEBSTAT) Overview

- Recruitment Sites
  - Montefiore Medical Center/Jacobi Medical Center
  - Duke University Medical Center
  - Virginia Commonwealth University
  - Lurie Children’s Hospital (Chicago)
  - East Virginia Medical School

- Data Management Sites
  - International Epilepsy Consortium (VCU)
  - Columbia University
    - Also provide controls

Hesdorffer et al Epilepsia 2012; 53:1471-1480
Consequences of FSE Research Plan: FEBSTAT New Cohort

- Prospectively recruit 200 children presenting with a first episode of febrile SE.
  - Children enrolled within 72 hours of the episode of FSE
    - MRI with thin cuts of the temporal lobe within 72 hours
    - Viral studies
    - EEG
  - At one month baseline neuropsychological testing
  - At one year repeat all of above
  - Also repeat if another episode of status or if develop epilepsy

- These children form a cohort that is being followed long-term in the future. Recruitment completed March 2010. 200 recruited of which 199 eligible.

Hesdorffer et al Epilepsia 2012; 53:1471-1480
Consequences of FSE Research Plan: Duke Existing Cohort

- A cohort of 23 children with FSE prospectively assembled at Duke as part of the pilot data for the FEBSTAT study. Children enrolled within 72 hours of the episode of FSE
  - MRI with thin cuts of the temporal lobe within 72 hours. Protocol very similar to that used in FEBSTAT
  - Majority had EEG

- These children then recruited into FEBSTAT study. Although numbers are small, the follow-up is much longer and they provide a glimpse of what we can expect in the larger FEBSTAT cohort.

Hesdorffer et al Epilepsia 2012; 53:1471-1480
Consequences of FSE Research Plan: Controls

- For comparison with FSE
  - 144 children with first simple FC or first complex FC (not SE)
  - MRI imaging using a similar protocol within 72 hours of the FC.
- This cohort, recruited at Columbia University, serves as controls for:
  - Imaging abnormalities in MRIs done within 72 hours and one year later
  - Behavioral outcomes at baseline and one year later

Hesdorffer et al. Annals of Neurology 2011;70:93-100. DOI: 10.1002/ana.22368
CONSEQUENCES OF FSE (FEBSTAT)
Clinical Characteristics of new Cohort
N=199

◆ Median Seizure duration  70 min (IQR 47-110)
  ■ (Mean Seizure duration  90 min (range 30-702))
  ■ 30-59 min  81 (41%)
  ■ >60 min  118 (59%)

◆ Continuous vs Intermittent
  ■ Continuous  114 (57%)
  ■ Intermittent  85 (43%)

◆ Focal vs Generalized
  ■ Generalized  46 (23%)
  ■ Focal  153 (77%)

◆ >85% did not stop spontaneously but required administration of benzodiazepine to stop it.

Distribution of the duration of febrile SE: FEBSTAT Study (N=119)

\[ S(t) = e^{-\left(\frac{t}{95.9}\right)^{1.68}} \]
Probability that a seizure that has continued to time $t$ will not stop at that point: FEBSTAT Study ($n=119$) (Best fit model from Weibull Distribution)

$[S(t) = e^{-(t/95.9)^{1.68}}]$
FEBSTAT MRI Readings: Acute Post Ictal

- Total acute FSE MRIs reviewed: 191
- Normal 67%
- Abnormal 33%
- Breakdown of abnormalities
  - Increase hippocampal T2 – 11.5%
  - Hippocampal Malrotation or HIMAL – 8%
    - 1 of 15 HIMAL also had hippocampal T2
  - Extrahippocampal abnormality – 16%

Shinnar et al Neurology 2012; 79:871-877
Increased Hippocampal T2 Signal Following FSE

Coronal T2 MRI of 20-month-old with prolonged focal FSE. MRI 1 day after FSE shows increased T2 throughout Right hippocampus which is also slightly larger than Left.

Shinnar et al Neurology 2012; 79:871-877
Both hippocampi have normal T2 intensity. Left hippocampus slightly increased T2 and reduced anatomical landmarks. Right hippocampus marked increase T2 in lateral inferior aspect, near CA1.
Extrahippocampal temporal lobe abnormality following febrile status epilepticus (FSE)

MRI of 11-month-old child with focal FSE. Seizure was continuous and lasted 120 minutes. MRI 3 days after FSE shows increased T2 signal and enlargement of right hippocampus (arrow in A), accompanied by increased T2 signal in right amygdala (B) and right mesial temporal cortex (C).

Shinnar et al Neurology 2012; 79:871-877
Distribution of Hippocampal T2 Signal Following FSE Has Similarities to Distribution of Pathology in HS

T2 signal intensity usually appears most intense in the region of CA1. Is this a reflection of CA1 selective vulnerability?

With relative sparing of subiculum.

From FEBSTAT: "Consequences of Prolonged Febrile Convulsions in Childhood"

NINDS - R01 NS43209  PI S. Shinnar. Unpublished data

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Measurements Confirm that T2 Signal is Maximal in CA1 After Febrile Status

To measure T2 signal distribution, the hippocampal body cross section was radially partitioned and the relative T2 intensity compared in the sectors.

From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood” NINDS-R01 NS43209 PI S. Shinnar. Unpublished data
Hippocampal ADCs Following FSE

Plot of ADCs (Means and 95% confidence intervals) for Control hippocampi, hippocampi Contralateral to those with increased T2 and Hyperintense hippocampi.

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<th>Hyperintense</th>
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<td>Mean ADC</td>
<td>0.00090</td>
<td>0.00095</td>
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<td>N</td>
<td>31</td>
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From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood”

NINDS-R01 NS43209  PI S. Shinnar. Unpublished data

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Grey matter density differences in FSE versus Simple FC controls

Several areas of significant differences between groups in grey matter density were found in the inferior temporal gyrus bilaterally, the middle temporal gyrus on the right and in the piriform and olfactory cortex.

The areas noted in the figure correspond to the density being higher in FSE cases compared to controls.

From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood”

NINDS - R01 NS43209  PI S. Shinnar.  Unpublished data

Measurements Confirm that T2 Signal is Maximal in CA1 After Febrile SE

To measure T2 signal distribution, the hippocampal body cross section was radially partitioned and the relative T2 intensity compared in the sectors.

Increase of T2 Intensity on Acute (filled squares; N=13).

Inset shows position of ROIs overlying the hippocampal sectors, SS=Sommer Sector, comprising CA1 and Prosubiculum, Sub=subiculum.

Solid and dashed lines represent the means over SS and Non-SS sectors for the Acute and Follow-Up time points, respectively. Bars=95% confidence Intervals.

From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood”

SS-a
SS-b
SS-c
CA2-a
CA2-b
CA3
Sub-a
Sub-b
Hilus

T2 Signal Increase

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# FEBSTAT Acute EEG Findings

- **New Cohort – 199 EEG Readings**
  - **Normal** 109 (55%)
  - **Abnormal** 90 (45%)
    - Focal Slowing 47 (24%)
      - Temporal 45 (23%)
    - Focal Attenuation (12 with slowing) 25 (13%)
      - Temporal 15 (8%)
    - Focal Spikes (8 with slowing) 13 (7%)
      - Temporal 6 (3%)
    - Diffuse slowing 22 (11%)

Nordli et al Neurology 2012 (in press)
EEG of a 12 month old who had one hour of continuous focal status without clear lateralization. The MRI was normal. The EEG was done one day after FSE and shows right temporal slowing. Note that slowing is maximal in the posterior derivation.

Nordli et al Neurology 2012 (in press)
EEG of a 38 month old who had one hour of continuous status with definite clinical lateralization to the left. There was equivocal hippocampal T2 abnormality. The EEG was done two days after FSE and shows left temporal attenuation of faster frequencies.

Nordli et al Neurology 2012 (in press)
Risk factors for significant focal slowing on baseline EEG in 199 children with FSE

<table>
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<tr>
<th>Factor</th>
<th>N with focal slowing (%)</th>
<th>N without focal slowing (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
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<td><strong>Peak Temperature</strong></td>
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<tr>
<td>≥104 F</td>
<td>4 (8.5%)</td>
<td>51 (33.6%)</td>
<td>0.18 (0.06, 0.5)</td>
<td>0.2 (0.06, 0.69)</td>
</tr>
<tr>
<td>&lt;104 F</td>
<td>43 (91.5%)</td>
<td>101 (66.5%)</td>
<td>1.00 (Referent)</td>
<td>1.00</td>
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<tr>
<td><strong>Focal Seizure</strong></td>
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<tr>
<td>Focal</td>
<td>42 (89.4%)</td>
<td>93 (61.2%)</td>
<td>5.3 (2.0, 14.2%)</td>
<td>4.5 (1.6, 12.6)</td>
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<tr>
<td>Not Focal</td>
<td>5 (10.6%)</td>
<td>59 (38.8%)</td>
<td>1.00</td>
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<td><strong>Hippocampal Abnormality</strong></td>
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<tr>
<td>Present</td>
<td>11 (25.6%)</td>
<td>19 (13.1%)</td>
<td>2.3 (0.99, 5.3)</td>
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<tr>
<td>Absent</td>
<td>32 (74.4%)</td>
<td>126 (86.9%)</td>
<td>1.00</td>
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<tr>
<td><strong>Hippocampal T2 signal abnormality</strong></td>
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<tr>
<td>Present</td>
<td>10 (23.3%)</td>
<td>7 (4.8%)</td>
<td>6.0 (2.1, 16.9)</td>
<td>4.8 (1.6, 14.7)</td>
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<tr>
<td>Absent</td>
<td>33 (76.7%)</td>
<td>138 (95.2%)</td>
<td>1.00</td>
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</tr>
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</table>

FSE duration, Age, and Gender were not associated with focal slowing

Nordli et al Neurology 2012 (in press)
Data Available on 169 of 199 (84.9%) children with FSE

HHV-6B viremia was found in 54 (32.0%)
- 38 (22.5%) with primary and 16 (9.5%) with reactivated infection.

HHV-7 viremia was found in 12 (7.1%).
- (8 with primary and 4 with secondary infection)

No HHV-6B or HHV-7 viremia in 111 (65.7%)

HHV-6B/HHV-7 are most common cause of febrile illness associated with FSE.

No differences in clinical semiology or acute imaging or EEG abnormalities between HHV+ and – cases.

Long term follow-up needed to determine whether FSE associated with HHV-6B or HHV-7 infection are associated with a differential rate of developing HS/TLE following FSE.

Epstein et al Epilepsia 2012;53:1481-1488
Number of CSF WBCs/mm³ in 136 children with FSE who underwent a non-traumatic LP (<1000 red blood cells/mm³)

Consequences of Prolonged Febrile Seizures (FEBSTAT): Genetics and Genomics

- NINDS Genetics Repository
  - Processing samples and create cell lines
  - Pilot grant obtained from ICE to look at ion channel mutations in this cohort
- Cincinnati Genomics Repository at 5 year visits
  - Specimens being collected to examine gene expression changes that may occur PRIOR to development of epilepsy.
Febrile Status Epilepticus
Consequences
Representative Coronal sections showing increased T2 signal following FSE.

Right side of the brain is on the left side of the figure.  A) Nissl stain of cross section of hippocampal body with shaded insert outlining area of Sommer’s sector (Courtesy G. Mathern).  B) Acute T2 weighted MRI 3 days after a 120 min duration episode of status epilepticus in a 13 month old male.  C) Follow up MRI of same subject 6 months later.  Note in (B) the increased size and signal of the right hippocampus with maximum signal in the lateral margin of the hippocampus (Arrow) in the location of Sommer’s sector.  At follow up (C), the hippocampus is small and the signal distribution is no longer most intense in Sommer’s sector.

From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood” NINDS-RO1 NS43209 PI S. Shinnar. Unpublished data
Measurements Confirm that T2 Signal is Maximal in CA1 After Febrile SE

To measure T2 signal distribution, the hippocampal body cross section was radially partitioned and the relative T2 intensity compared in the sectors. Increase of T2 Intensity on Acute (filled squares; N=13).

Inset shows position of ROIs overlying the hippocampal sectors, SS=Sommer Sector, comprising CA1 and Prosubiculum, Sub=subiculum. Solid and dashed lines represent the means over SS and Non-SS sectors for the Acute and Follow-Up time points, respectively. Bars=95% confidence intervals.

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Examples of Hippocampal Volume Changes

After FSE: Is this pattern a biomarker for TLE?

HV in FU MRIs

Onset TLE

Vol Loss
(Bilateral)
Asymmetric Growth

Late Atrophy?

From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood”

NINDS - R01 NS43209  PI S. Shinnar.  Unpublished data
FEBSTAT – Early Clinical Outcomes

- Mortality to date in FEBSTAT: 3 deaths, 2 due to SUDEP and 1 due to the underlying illness.

- 23 children have experienced recurrent SE: 21 with FSE, 5 with afebrile SE, and 3 with both.

- Among new cohort, 27 (13%) have developed epilepsy. As expected, most of these cases are not TLE which has a longer latency.
  - 3 have Dravet syndrome.

- In the Duke pilot cohort (n=23), 7 (30%) have developed epilepsy, including 2 cases with medically refractory TLE who have undergone temporal lobectomy.

From FEBSTAT: “Consequences of Prolonged Febrile Convulsions in Childhood”

NINDS - R01 NS43209  PI S. Shinnar.   Unpublished data
Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT): Conclusions

- Hippocampal injury following FSE is not universal.
- When it does occur, it is maximal in CA1 and relatively spared other hippocampal regions. This is similar to the pattern seen in Human TLE with HS.
- While FSE can occur in children with normal hippocampi, as a group, children with FSE have smaller hippocampi than those with simple FS.
- Following FSE, hippocampi demonstrating increased T2 signal acutely shrink.
- Following FSE, even those hippocampi that appear normal following FSE, fail to grow compared with hippocampi in children with simple FS suggesting injury.
Biomarkers for Epileptogenesis, HS or TLE following FSE?

What we need to do now

- Complete long term follow up of the FEBSTAT study cohort to determine
  - Is a "hot hippocampus" following FSE sufficient for prediction of subsequent HS? – Preliminary data suggests yes
  - Is a "hot hippocampus" following FSE sufficient for prediction of subsequent TLE? – Unknown
  - Is a "hot hippocampus" following FSE necessary for prediction of subsequent HS or TLE? – Unknown

- Memory deficits in children with hippocampal injury – in progress. As median age 15 months, reliable memory testing being done at 5 year visit.
- Comorbidity - DISC being given at 5 year visit.

- Can the EEG be used as a surrogate marker?
- Is HHV6 associated with a higher rate of developing TLE/HS

Role of genetics and genomics

From FEBSTAT: "Consequences of Prolonged Febrile Convulsions in Childhood"
NINDS - R01 NS43209 PI S. Shinnar. Unpublished data

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FEBSTAT: Conclusions

- The results of this longitudinal study will ultimately resolve the controversy on the relationship between prolonged febrile seizures in childhood and HS and TLE.
- As latency to clinical epilepsy is 8-11 years, we need time to get final answer.
- In the meantime, preventing hippocampal volume loss at one year is an attractive target for antiepileptogenesis trials.

- Occurs in a substantial portion of cases
- Can be readily measured
- Biological plausibility

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