MRI abnormalities following febrile status epilepticus in children

The FEBSTAT study

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ABSTRACT

Objective: The FEBSTAT study is a prospective study that seeks to determine the acute and long-term consequences of febrile status epilepticus (FSE) in childhood.

Methods: From 2003 to 2010, 199 children age 1 month to 5 years presenting with FSE (>30 minutes) were enrolled in FEBSTAT within 72 hours of the FSE episode. Of these, 191 had imaging with emphasis on the hippocampus. All MRIs were reviewed by 2 neuroradiologists blinded to clinical details. A group of 96 children with first simple FS who were imaged using a similar protocol served as controls.

Results: A total of 22 (11.5%) children had definitely abnormal (n = 17) or equivocal (n = 5) increased T2 signal in the hippocampus following FSE compared with none in the control group ($p < 0.0001$). Developmental abnormalities of the hippocampus were more common in the FSE group (n = 20, 10.5%) than in controls (n = 2, 2.1%) ($p = 0.0097$) with hippocampal malrotation being the most common (15 cases and 2 controls). Extrahippocampal imaging abnormalities were present in 15.7% of the FSE group and 15.6% of the controls. However, extrahippocampal imaging abnormalities of the temporal lobe were more common in the FSE group (7.9%) than in controls (1.0%) ($p = 0.015$).

Conclusions: This prospective study demonstrates that children with FSE are at risk for acute hippocampal injury and that a substantial number also have abnormalities in hippocampal development. Follow-up studies are in progress to determine the long-term outcomes in these children. *Neurology*® 2012;79:871–877

GLOSSARY

CI = confidence interval; **DWI** = diffusion-weighted imaging; **ETL** = echo train length; **FOV** = field of view; **FS** = febrile seizures; **FSE** = febrile status epilepticus; **HIMAL** = hippocampal malrotation; **HS** = hippocampal sclerosis; **IQR** = interquartile range; **MTLE** = mesial temporal lobe epilepsy; **TE** = echo time; **TR** = repetition time.

The relationship between prolonged febrile seizures (FS) and subsequent hippocampal sclerosis (HS) and mesial temporal lobe epilepsy (MTLE) remains unclear.[1–8] Retrospective studies of adults with MTLE undergoing evaluation for epilepsy surgery report a strong association,[2–4] but prospective studies of children with FS have failed to confirm this association.[5–8] The prospective studies have been limited by inclusion of all FS resulting in relatively few cases of FSE, lack of sufficient follow-up, and absence of modern imaging techniques. In retrospective studies of MTLE and HS, the mean latency to develop MTLE following FS was 8 to 11 years.[4,9] Recent reports demonstrate that hippocampal injury can occur following prolonged FS, but the frequency and long-term outcome remain unclear.[1,10–13] The Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study is a prospective multicenter study designed to address the relationship between febrile status epilepticus (FSE) and subsequent

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Supplemental data at www.neurology.org

Supplemental Data

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HS and MTLE. The methodology of assembling the cohort and a description of the clinical phenomenology of the first 119 subjects were previously published.[14] In this article, we describe the acute imaging findings in this cohort.

METHODS

FEBSTAT population. Eligible were children, ages 1 month through 5 years, who presented with FSE defined as a single seizure or a series of seizures without full recovery in between lasting ≥30 minutes[15,16] that also met the definition of a FS.[15,17] An FS was defined as a provoked seizure where the sole acute provocation was fever (temperature >38.4°C, 101.0°F) without prior history of afebrile seizures and with no evidence of an acute CNS infection or insult.[15,17] Children with known severe neurologic disability prior to entry were excluded from FEBSTAT. The 5 recruiting sites were Montefiore Medical Center and Jacobi Hospital in the Bronx, New York, New York; Children's Memorial Hospital in Chicago, Illinois; Duke University Medical Center in Durham, North Carolina; Virginia Commonwealth University Hospital in Richmond; and Eastern Virginia Medical School in Norfolk. Details of the recruitment and methodology were previously published.[14]

Standard protocol approvals, registrations, and patient consents. The procedures were approved by the Institutional Review Boards for the Protection of Human Subjects at the participating institutions. Written informed consent was obtained from the parents in all cases.

Procedures. Neurologic examination, EEG, and MRI were performed when possible within 72 hours of the episode of FSE. Virology samples for human herpesvirus 6 and 7 were also obtained and the virology data will be published separately. At 1 month, repeat neurologic examination and virology samples as well as a baseline neuropsychological evaluation were performed. The children are being followed and are being reevaluated at 1 and 5 years after FSE.

Source documents were reviewed by a central phenomenology core (S. Shinnar, J.M.P., D.R.N.), which was blinded to the EEG and MRI findings when classifying the seizures. EEGs were reviewed by 2 central EEG readers (D.R.N., S.L.M.) and MRIs by 2 central neuroradiology readers (J.A.B., S.C.). All central reviewers were blinded to all the clinical details of the subject as well as the nature of the scan (acute vs 1 year follow-up or other) but were provided the age of the subject at the time of the examination. Any discrepancies were then discussed and a consensus reached. While it was not possible to completely blind to the Columbia cohort, it included both complex FS and 12 cases of FSE so readers were blinded to whether FSE or not and whether scan was baseline or not.

MRI studies were coded as normal, suspect, or abnormal. Abnormal was coded when an abnormality of clear pathologic significance was found. Suspect was coded when the abnormality was equivocal (e.g., increased T2 signal seen on only 1 slice and felt to be uncertain) or of unclear pathologic significance (e.g., developmental abnormalities of the hippocampus other than hippocampal malrotation [HIMAL], an isolated unidentified bright object, an arachnoid cyst without mass effect). HIMAL was defined as incomplete rotation of the hippocampus with normal size and signal intensity but abnormally rounded shape and blurred internal structure.[18,19] Additional findings often noted were an atypical collateral sulcus angle and atypical position and size of the fornix.[18] Radiologic criteria for HS were decreased hippocampal volume and presence of increased hippocampal T2 signal.

Imaging. MRIs were performed on GE and Siemens 1.5 T MRI systems using the following imaging pulse sequences: GE Systems: coronal oblique (slices perpendicular to the temporal lobe axis) T2-weighted fast spin echo, repetition time (TR)/echo time (TE) = 4,500/96, echo train length (ETL) = 8, 20 × 15 cm field of view (FOV), 3 mm slice, 0 mm gap, 256 × 256 matrix, and 4 NEX. Diffusion-weighted imaging (DWI) pulse sequence parameters were 2D, coronal, DW-EPI, TR/TE = 6,000/76–105, partial Fourier, 22 cm FOV, 4 mm slice, 1 mm gap, 128 (frequency) × 64 (phase) matrix, diffusion sensitizing gradients in anterior-posterior (AP), superior-inferior (SI), and left-right (LR) directions, b = 1,000; Siemens Systems: coronal oblique (slices perpendicular to the temporal lobe axis) T2-weighted turbo spin echo with pulse sequence parameters: TR/TE = 4,500/101, turbo factor 7, 20 × 15 cm FOV, 3 mm slice, distance factor = 0% (no gaps), 256 × 256 matrix (3/4 FOV), and 4 NEX. DWI sequence parameters were 2D, coronal, DW-EPI, TR/TE = 190/76–105, 22 cm FOV, 4 mm slice, 20% distance factor (1 mm gap), 5/8 phase partial Fourier, 128 (frequency) × 64 (phase) matrix.

For both systems the final diffusion image was the 3 direction trace mode (gradients in AP, SI, LR), b = 1,000, and bandwidth = 1,345 Hz/pixel. T1-weighted images were used to measure hippocampal volumes. GE Systems used a 3D coronal fast spoiled gradient recalled of the whole head TR/TE/flip = 2/5/30° (full echo), 20 cm FOV, 1.5 mm slice, 124 slices, 256 × 192 matrix, 2 NEX. Siemens Systems used a T1-weighted 3D coronal spoiled Turboflash of the whole head, 3D, TR/TE/flip = 12/5/20° (full echo), 20 cm FOV, 1.5 mm slice, 124 slices, 256 × 192 matrix, 2 NEX protocol.

Controls. We used a group of 96 children age 6 months to 5 years who presented with a first FS between March 1999 and April 2004 to The Morgan Stanley Children's Hospital Pediatric Emergency Department, New York, and were recruited to a prospective study of children with a first FS (the Columbia Febrile Seizure Study[20]). Of the 159 children enrolled in that study, 145 had MRIs that were available to the FEBSTAT team for review. Of these, 96 (66%) were classified as having simple FS and serve as the imaging controls for the FEBSTAT study. An additional 37 (25.5%) had complex febrile seizures (not FSE) of whom 20 (53.1%) were focal.

The children had MRI at baseline and at 1 year on a 1.5 T GE scanner using an imaging protocol similar to the FEBSTAT 1. The clinical features and the semiology of all these cases were rereviewed by the FEBSTAT phenomenology team[18] and MRIs were reread by the FEBSTAT imaging core (J.A.B., S.C.) intermixed with MRI studies of the FEBSTAT cohort.

Statistics. Data were summarized as frequency and percent for the different abnormalities. Comparison of the frequencies was done using the χ^2 test and Fisher exact test.[21] For analysis of risk factors, a logistic regression model was used for those with increased hippocampal T2 signal.[22] An α level of 0.05 was used for all analyses.

For comparison of each rater to the consensus determination, inter-rater reliability was calculated using the κ statistic, and a 95% confidence interval (CI) was constructed.[22] A κ of >0.75 was considered to be excellent agreement beyond chance, a κ of 0.41 to 0.74 was considered to be good agreement, and κ

≤0.40 was considered to be poor agreement. Statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS **Population.** During the recruitment between June 1, 2003, and January 12, 2010, 199 children were enrolled in FEBSTAT. For the 191 cases with baseline MRI, the median age at time of FSE was 15.7 months (interquartile range [IQR] = 12.0–24.3), and the youngest child was 4.3 months old. In the control group of children with simple FS, the median age at time of FS was 19.7 months (IQR = 16.5–25.2) and the youngest child was 7.7 months old. In the FSE group, 37 (19%) had prior FS whereas the control group was limited to children with a first FS. While most children in the FEBSTAT and control cohorts had normal development prior to their presenting seizure, a higher proportion of children with FSE had abnormal development than did controls (6.8% vs 0%). The median duration of FSE was 71.7 (IQR = 48–120) minutes. Of the 191 cases, 129 (68%) were considered to be definitely (n = 95) or probably (n = 34) focal. Cerebral lateralization was definite in 57 (60%) of the 95 cases considered definitely focal. The majority of FSE cases were classified as continuous (n = 107; 56%), with the remainder being intermittent without full recovery in between.[14–17]

Of 199 children in the FSE group, 191 (96%) had an initial MRI performed. The MRI was performed within 3 days of FSE in 129 (67.5%) cases, within 1 week in 165 (86%) cases, and more than 1 week after FSE in 26 (13.6%). The delay or lack of acute imaging was most often due to concern about safety of sedation due to the child's acute febrile illness. In the controls, MRI was performed within 3 days of FS in 49 (51%) cases, within 1 week in 88 (91.7%) cases, and more than 1 week after FS in 8 (8.3%).

Imaging results. The baseline imaging data are summarized in the table. Overall, there is a much higher proportion with imaging abnormalities in children with FSE compared with simple FS controls. The differences, however, are essentially limited to hippocampal abnormalities ($p < 0.001$) and to abnormalities of the adjacent temporal lobe ($p = 0.015$).

Hippocampal abnormalities. Twenty-two (11.5%) children with FSE had definite or equivocal abnormal hippocampal T2 signal. An example is shown in figure 1. In the 17 children with definitely abnormal hippocampal T2 signal, the T2 signal was exclusively right-sided in 13 cases, left-sided in 3 cases, 2 of which had other developmental abnormalities, and bilateral in only 1 case. Abnormal hippocampal T2 signal was not seen in any of the controls with simple FS. Interrater reliability on the presence of increased hippocampal T2 was excellent at 0.87 (95% CI 0.74–0.996) and consensus was achieved after review in all cases.

Of the 17 cases with definitely increased hippocampal T2, 6 (35%) were also believed to have an enlarged hippocampus on the ipsilateral side on visual reading, 9 (53%) did not have any visually detectable definite volume abnormalities, and 2 cases had small hippocampi on the side of the T2 signal and met the radiologic criteria for HS. Of the 2 children with HS at the time of the initial scan, 1 was a 5-year-old with no prior history of seizures but who was known to be autistic. The other was an 18-month-old developmentally normal child with a history of a prior simple febrile convulsion at age 9 months.

Abnormal T2 signal was present in the adjacent temporal lobe, amygdala, or insula in 6 (27%) of the 22 cases with abnormal hippocampal T2 signal (4 with definite and 2 with equivocal signal abnormality) and in none of the controls. An example is shown in figure 2. In all cases, the signal abnormality was on the same side as the hippocampal T2 abnormality.

A developmental abnormality of the hippocampus was present in 20 FSE cases and in 2 controls ($p = 0.0097$). Of these, HIMAL (figure 3) was most common and was present in 15 (7.9%) FSE cases and in 2 controls ($p = 0.06$). HIMAL was left-sided in 13 (87%) of the 15 cases in FSE group and in 1 of the 2 control cases. The remaining cases were bilateral. There were no cases of exclusively right-sided HIMAL. Increased T2 signal in the left hippocampus was present on 1 of the left-sided HIMAL FSE cases.

Clinical correlation. While the majority of seizures were of partial onset, definite lateralization based on clinical criteria was only possible in 60 cases. In the 27 cases of unilateral increased T2 signal or abnormal hippocampal development, semiology of seizures was lateralizable in 8 cases and lateralized to the same side in 6.

Extrahippocampal abnormalities. There were a variety of extrahippocampal abnormalities (table). Overall, these did not appear to be different in the FSE group than in the simple FS controls. However, temporal lobe abnormalities (temporal lobe, amygdala, and insula) were more common in FSE cases than controls ($p = 0.015$). In particular, T2 signal abnormalities were only present in FSE cases and then only in those who also had abnormal hippocampal T2 signal, indicating a more extensive area of acute injury (table).

Risk factors. Within the FSE group, age, duration of seizure, total convulsive time, focality, and peak tem-

Table Type of MRI abnormalities at baseline in 191 children with febrile status epilepticus and 96 children with first simple febrile seizure

	FSE (n = 191), n (%)			Simple FS, n (%)			
MRI finding	All	Definite	Suspect	All	Definite	Suspect	*p* Value
Any abnormality	63 (33.0)	46 (24.1)	17 (8.9)	17 (17.7)	9 (9.4)	8 (8.3)	0.0008
Hippocampal abnormality	40 (20.9)	30 (15.7)	10 (5.2)	2 (2.1)	2 (2.1)	0	<0.0001
Abnormal T2 signal	22 (11.5)	17 (8.9)	5 (2.6)	0	0	0	<0.0001
Developmental abnormality	20 (10.5)	16 (8.4)	4 (2.1)	2 (2.1)	2 (2.1)	0	0.0097
HIMAL	15 (7.9)	15 (7.9)	0	2 (2.1)	2 (2.1)	0	0.06
Other	5 (2.6)	0	4 (2.6)	0	0	0	0.17
Nonhippocampal abnormality	30 (15.7)	22 (11.5)	8 (4.2)	15 (15.6)	7 (7.3)	8 (8.3)	1
Temporal lobe/amygdala	15 (7.9)	8 (4.2)	7 (3.7)	1 (1.0)	1 (1.0)	0	0.015
Abnormal T2 signal	6 (3.1)	4 (2.1)	2 (1.0)	0	0	0	0.18
Arachnoid cyst	2 (1.0)	1 (0.5)	1 (0.5)	0	0	0	0.55
Gliosis	1 (0.5)	1 (0.5)	0	0	0	0	1
Unidentified bright object	2 (1.0)	0	2 (1.0)	0	0	0	0.55
Other	1 (0.5)	1 (0.5)	0	1 (1.0)	1 (1.0)	0	1
Delayed myelination	4 (2.1)	2 (1.0)	2 (1.0)	0	0	0	0.30
Extratemporal	20 (10.5)	16 (8.4)	4 (2.1)	14 (14.6)	6 (6.3)	8 (8.3)	0.34
Abnormal T2 signal	0	0	0	1 (1.0)	0	1 (1.0)	0.33
Error in brain development	5 (2.6)	5 (2.6)	0	1 (1.0)	1 (1.0)	0	0.68
Tumor	1 (0.5)	1 (0.5)	0	0	0	0	1
Infarct	1 (0.5)	1 (0.5)	0	1 (1.0)	1 (1.0)	0	1
Atrophy	3 (1.6)	3 (1.6)	0	5 (5.2)	2 (2.1)	3 (3.1)	0.12
Diffuse	3 (1.6)	3 (1.6)	0	1 (1.0)	1 (1.0)	0	1
Focal	0	0	0	4 (4.2)	1 (1.0)	3 (3.1)	0.012
Unidentified bright object	2 (1.0)	0	2 (1.0)	3 (3.1)	1 (1.0)	2 (2.1)	0.34
Chiari I	1 (0.5)	1 (0.5)	0	1 (1.0)	1 (1.0)	0	1
Gliosis	2 (1.0)	2 (1.0)	0	0	0	0	0.55
Arachnoid cyst	1 (0.5)	0	1 (0.5)	1 (1.0)	0	1 (1.0)	1
External hydrocephalus	3 (1.6)	3 (1.6)	0	1 (1.0)	1 (1.0)	0	1
Other	3 (1.6)	2 (1.02)	1 (0.5)	2 (2.1)	0	2 (2.1)	1

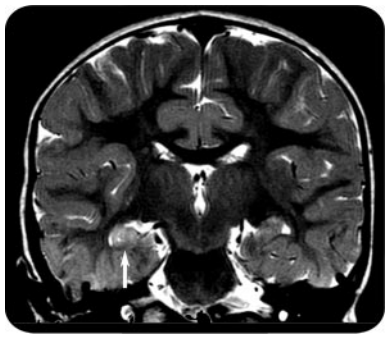
Abbreviations: FS = febrile seizures; FSE = febrile status epilepticus; HIMAL = hippocampal malrotation.

peratures were not predictors of abnormal hippocampal T2 signal. In addition, timing of MRI, occurrence of prior FS, and developmental status were not associated with a differential rate of abnormalities including abnormal hippocampal T2 signal.

DISCUSSION The baseline data from the FEBSTAT study indicate that approximately 11% of children who experience an episode of FSE have MRI evidence of an acute injury to one hippocampus. We have previously reported that these prolonged FS rarely stopped spontaneously and that administration of an abortive agent was needed in approximately 85% of the cohort.[14] This would imply that in the era prior to the widespread use of benzodiazepines, FSE may have lasted even longer and may have been associated with a higher rate of hippocampal injury and a greater risk for subsequent morbidity.

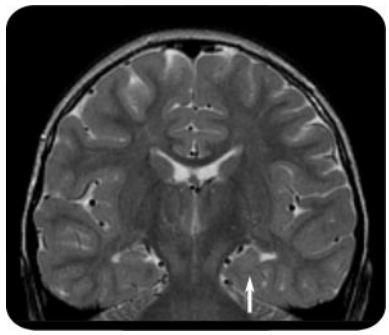
When T2 signal intensity was increased it was unilateral, most commonly the right hippocampus. One prior report suggested that right-sided HS is more common following febrile seizures,[23] but this study did not have acute imaging. Interestingly, a widely studied animal model of febrile seizures in rats also produces asymmetric hippocampal hyperintensity, right greater than left.[24] In the rat model, however, the increased hippocampal T2 signal is bilateral though asymmetric. In our human data, with the exception of 1 case which demonstrated bilateral increased T2 signal, the visually recognized T2 signal abnormality was always unilateral. This lateralization remains unexplained as does the almost exclusively left-sided appearance of HIMAL. While visual analy-

Figure 1 Hippocampal abnormality following febrile status epilepticus (FSE)



Coronal T2 MRI of 20-month-old child with focal FSE. Seizure was intermittent with total duration of 360 minutes, total convulsive time of 81 minutes, and duration of longest convulsion of 60 minutes. MRI performed 1 day after the episode of status demonstrates increased T2 signal throughout the right hippocampus (arrow) which is also slightly larger than the left side. No other abnormalities are noted.

Figure 3 Hippocampal malrotation (HIMAL) in child with febrile status epilepticus (FSE)



MRI of 40-month-old child with generalized FSE. Seizure was intermittent with total duration of 120 minutes, longest convulsion of 25 minutes, and total convulsive time of 50 minutes. Child had a prior complex febrile seizure (not status) at 24 months. MRI performed 4 days after the episode of status demonstrates the HIMAL abnormality. There is incomplete rotation of the left hippocampus (arrow) with normal size and signal intensity but abnormally rounded shape and blurred internal architecture.

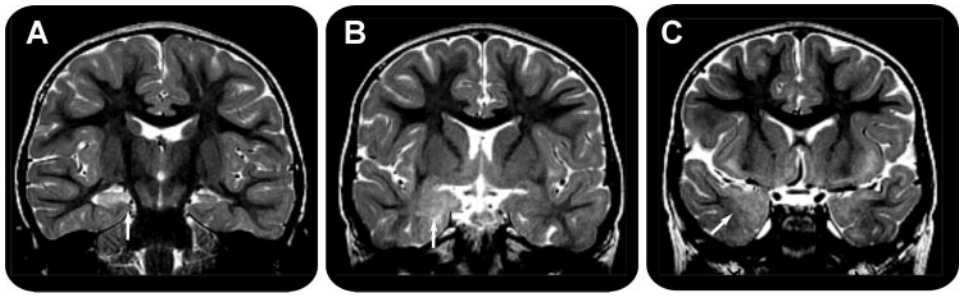
sis, which was the primary analysis, may be more sensitive to asymmetry, quantitative analysis of T2 signal did not demonstrate any bilateral abnormalities that were missed on visual inspection.

Hippocampal abnormalities following FSE were observed in a small cohort of 21 cases.[12] However, that report noted increased T2 relaxation times and some volume asymmetry, while we are reporting visually evident increased T2 signal in the hippocampus, a more striking abnormality. Therefore, our results are not directly comparable, though both are presumed evidence of acute hippocampal injury. A significant rate of hippocampal volume asymmetry with no evidence of T2 abnormalities was also reported in a small sample of 18 children with prolonged FS.[13]

Analysis of risk factors for hippocampal T2 hyperintensity after FSE failed to find any significant predictors in children with FSE. Note that our cohort is young with 89% under 3 years of age, the median seizure duration is >70 minutes, and 3/4 are focal in nature.

Based on prior studies, we expected that increased seizure duration would be associated with an increased risk for hippocampal injury.[5,10,24,25] However, since the FEBSTAT study was restricted to FSE and seizures were long with median duration of 71 minutes, this may have obscured the relationship between duration and abnormal T2 signal. However, there were no cases of hippocampal or temporal lobe T2 signal abnormalities in the simple FS controls. T2 signal abnormalities were also not seen in the 37 children in the Columbia cohort with complex FS that were not FSE.[20] This is not simply a matter of technique specific to FEBSTAT, as 1 of the 12 children in the Columbia cohort classified as FSE[20] had abnormal hippocampal T2 signal. Similarly, while focality defined based on purely clinical semiology

Figure 2 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 performed 3 days after the episode of FSE. Note increased T2 signal and enlargement of the right hippocampus (arrow in A), accompanied by increased T2 signal in the right amygdala (B) and right mesial temporal cortex (C).

failed to reach significance as a risk factor for abnormal T2 signal, focality is strongly associated with duration in both febrile and afebrile seizures.[20,26,27] Most likely, restriction of our FEBSTAT cohort to those with FSE, felt to be at highest risk for hippocampal injury, may have obscured associations with duration and focality.

In addition to T2 signal abnormalities, developmental abnormalities of the hippocampus and temporal lobe were more common in children with FSE. In particular, HIMAL, which has until recently been felt to be of unclear clinical significance,[18,19,28] was more common in the FSE group than in controls. HIMAL is a rare incidental finding in patients without seizures.[19] More recently, in children with epilepsy, it has been associated with cognitive deficits perhaps involving prefrontal mechanisms.[29]

The occurrence of HIMAL in this population is consistent with the hypothesis that prolonged FS are more likely to occur in brains with a predisposition to seizures. In a study of children with a first FS, those with a prolonged FS (>10 minutes) were more likely to have abnormal development than those with a brief simple FS.[20] In a prior MRI study of FSE, increased hippocampal T2 signal was more likely to be present in those with coexisting imaging abnormalities.[10,11] Other studies have reported subtle hippocampal malformations as predisposing to prolonged FS and subsequent HS.[30–33] Furthermore, studies of patients undergoing temporal lobectomy for refractory TLE report a high rate of microdysplasia.[34] Animal data also support the concept that brains with a preexisting abnormality may be more susceptible to injury.[35,36]

The data from the FEBSTAT study demonstrate that there is MRI evidence of acute hippocampal injury following FSE in a substantial minority of children. This does not imply that the other children have not sustained a more subtle injury. Ongoing follow-up of the FEBSTAT cohort is in progress and will ultimately address the following questions. Is presence of acute abnormal T2 signal an accurate predictor of subsequent anatomic HS and ultimately of MTLE? In the absence of visually apparent MRI evidence of acute injury, what is the risk of subsequent HS and MTLE? Does the presence of a developmental anomaly of the hippocampus increase the risk of developing HS following FSE? Given the long latency between FSE and the onset of MTLE,[1,4,9] it will be some time before all the questions are addressed but we hope that the FEBSTAT cohort will ultimately answer these questions.

AUTHOR CONTRIBUTIONS

All authors participated in the design and execution of the overall FEBSTAT project. Drs. Shinnar, Bello, Chan, Hesdorffer, Lewis, and MacFall designed the specific imaging project reported in this manuscript. All authors participated in the execution of the work reported in this manuscript. The data analysis and statistics were performed by Drs. Hesdorffer and Sun. All authors participated in writing and editing the manuscript.

DISCLOSURE

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