

Hippocampal Sclerosis after Febrile Status Epilepticus: The FEBSTAT Study

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Objective: Whether febrile status epilepticus (FSE) produces hippocampal sclerosis (HS) and temporal lobe epilepsy (TLE) has long been debated. Our objective is to determine whether FSE produces acute hippocampal injury that evolves to HS.

Methods: FEBSTAT and 2 affiliated studies prospectively recruited 226 children aged 1 month to 6 years with FSE and controls with simple febrile seizures. All had acute magnetic resonance imaging (MRI), and follow-up MRI was obtained approximately 1 year later in the majority. Visual interpretation by 2 neuroradiologists informed only of subject age was augmented by hippocampal volumetrics, analysis of the intrahippocampal distribution of T2 signal, and apparent diffusion coefficients.

Results: Hippocampal T2 hyperintensity, maximum in Sommer's sector, occurred acutely after FSE in 22 of 226 children in association with increased volume. Follow-up MRI obtained on 14 of the 22 with acute T2 hyperintensity showed HS in 10 and reduced hippocampal volume in 12. In contrast, follow-up of 116 children without acute hyperintensity showed abnormal T2 signal in only 1 (following another episode of FSE). Furthermore, compared to controls with simple febrile seizures, FSE subjects with normal acute MRI had abnormally low right to left hippocampal volume ratios, smaller hippocampi initially, and reduced hippocampal growth.

Interpretation: Hippocampal T2 hyperintensity after FSE represents acute injury often evolving to a radiological appearance of HS after 1 year. Furthermore, impaired growth of normal-appearing hippocampi after FSE suggests subtle injury even in the absence of T2 hyperintensity. Longer follow-up is needed to determine the relationship of these findings to TLE.

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Febrile seizures (FSs) are common, occurring in 2 to 4% of children.¹ Brief FSs are considered benign,¹ but prolonged FSs are associated with subsequent epi-

lepsy.² Febrile status epilepticus (FSE) occurs in 5 to 9% of children with a first FS,³ accounting for 25% of pediatric status epilepticus,⁴ with 25,000 to 30,000 FSE cases

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Additional Supporting Information can be found in the online version of this article.

annually in the United States. Whether prolonged FSs cause hippocampal sclerosis (HS) and temporal lobe epilepsy (TLE) has been debated for >50 years.⁵

The FEBSTAT study (Consequences of Prolonged Febrile Seizures in Childhood) is prospectively examining outcomes of FSE.⁶ Smaller studies of FSE have reported varied outcomes, from HS to subtle asymmetries.^{7–11} We hypothesized that definite hippocampal T2 hyperintensity immediately following FSE would predict development of HS.⁶ We have reported baseline visual magnetic resonance imaging (MRI) findings, semiology, electroencephalography (EEG), and virology from FEBSTAT.^{6,12–14} Here we analyze acute hippocampal abnormalities and their early evolution on follow-up MRI in children with FSE from FEBSTAT and 2 companion prospective cohorts compared to children with a first simple febrile seizure (SFS) who underwent similar imaging protocols.

Patients and Methods

Subjects

FSE was defined as a FS lasting 30 minutes or longer or repetitive FSs, lasting at least 30 minutes without regaining alertness.¹⁵ Cohort eligibility and procedures have been described.^{6,12} All sites obtained institutional review board approval and informed consent. As initial MRI were obtained after confirming eligibility and obtaining informed consent, children with pre-existing MRI abnormalities were included. The 226 children aged 1 month to 6 years with FSE⁶ were derived from 3 prospective studies (Supplementary Fig 1); 191 were from the FEBSTAT cohort,¹² 23 from the Duke FEBSTAT pilot study,¹¹ and 12 from the Columbia first FS study.¹⁶ Also from the Columbia study, we obtained 38 children with SFSs who had normal initial MRI and 1-year follow-up MRI¹⁶ to serve as controls for FSE children with normal initial MRI. In FSE cases, 67% of acute scans were done within 3 days of FSE and 88% within 7 days. Of 22 children with definite hippocampal T2 hyperintensity on acute MRI, 17 were from FEBSTAT, 4 from Duke, and 1 from Columbia.

MRI Sequences

The pulse sequences on GE (Milwaukee, WI) and equivalent on Siemens (Erlangen, Germany) 1.5T MRI systems were: coronal oblique (perpendicular to the hippocampal axis) T2-weighted imaging, fast spin echo sequence, repetition time (TR) = 4,500 milliseconds, echo time (TE) = 96 to 105 milliseconds, echo train length = 7 to 8, field of view (FOV) = 20 × 15cm, slice thickness = 3mm, gap = 0mm, matrix = 256 × 256, and number of excitations (NEX) = 4; coronal oblique diffusion-weighted imaging (DWI), diffusion-weighted echo-planar sequence, TR = 6,000 milliseconds, TE = 76 to 105 milliseconds, partial Fourier, FOV = 22cm, slice thickness = 4mm, gap = 1mm, matrix = 128 (frequency) × 64 (phase), diffusion sensitizing gradients in anterior-posterior, superior-inferior, left-right, b = 1,000; and T1-weighted imaging 3-dimensional coronal fast spoiled gradient-echo sequence, TR = 12 milliseconds, TE = 5 milliseconds, flip

angle = 20 to 30°, full echo, FOV = 20cm, slice thickness = 1.5mm, 124 slices, matrix = 256 × 192, NEX = 2.

Apparent diffusion coefficient (ADC) maps were calculated from DWI using conventional methods.

Visual Analysis of Hippocampal Abnormalities

Hippocampal abnormality was visually assessed by 2 experienced neuroradiologists (J.A.B., S.C.) informed of subject age but blinded to clinical details and type of MRI (acute or follow-up).¹² MRI of SFSs from the Columbia study¹⁶ was interspersed with FSE MRI and identically reviewed by the same central readers. Hippocampal T2 signal (T2Score) was rated from 0 to 4 (0 = normal, 1 = equivocal, 2 = mildly abnormal T2 signal on ≥1 slices, 3 = moderately abnormal, 4 = markedly abnormal throughout hippocampus). For purposes of this analysis, only T2Scores of ≥2 were considered a definite signal abnormality. Six equivocal hippocampi (T2Score = 1) were thereby excluded from the analysis. The radiologic criteria for HS were definite hippocampal atrophy and T2Score of ≥2.^{12,17} Discordant readings were conferenced for consensus. Agreement on hippocampal T2Scores (normal vs equivocal vs abnormal), the primary outcome of visual readings, was excellent (kappa = 0.80; 95% confidence interval = 0.61–0.98).

Volumetric Measurements

Hippocampal regions of interest (ROIs) were traced (SnAP:IRIS¹⁸) using conventional boundaries¹⁹ by a trained observer (Y.X.) blinded to clinical data. Slices posterior to and including the anterior commissure were summed for hippocampal volume. Right to left (Rt/Lt) volume ratios represent the volume of the right divided by that of the left hippocampus. A geometry phantom scanned after FEBSTAT subjects indicated small (median = 2.8%, interquartile range [IQR] = 2.1–3.5) corrections used to adjust volumes in analyses that included only FEBSTAT subjects, as phantoms were not used for the other cohorts. Consistency of volumetric measurements was assessed using the intraclass correlation coefficient (ICC).²⁰ Ten MRI samples randomly selected every 2 months from 33 FEBSTAT subjects across the age range were analyzed independently (Y.X., D.V.L.). ICCs were 0.95 and 0.97 for the left and right hippocampi, respectively.

T2 Signal Intensity and Diffusion Measurements

Analysis of T2 intensity and ADC maps was performed by observers (Y.X., W.A.G.) blinded to clinical data. T2 intensity was measured on coronal sections through the middle of the hippocampal body, where sector boundaries are easily delineated.²¹ Each section was subdivided into 8 equal pie slice-shaped ROIs (Analyze, Mayo Clinic, Rochester, MN), and a circular ROI with a radius one-third of the radius of the pie centered over the hilus was drawn (Fig 2). For all hippocampi, mean T2 signal intensities for each ROI were normalized to ipsilateral thalamic intensity. Control values were then subtracted from the values of hyperintense hippocampi, yielding a number representing the increase over normal T2 signal level for each ROI in affected hippocampi. Two subjects whose initial MRI met the radiological

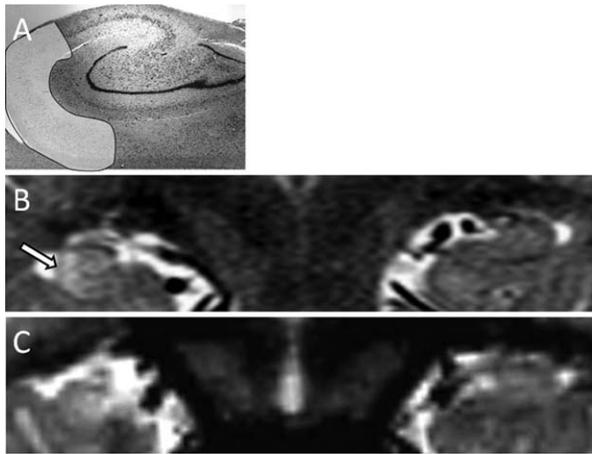


FIGURE 1: Increased hippocampal T2 signal following febrile status epilepticus (FSE). (A) Nissl stain of hippocampal body outlining area of Sommer's sector (courtesy G. Mathern). (B) Acutely swollen and hyperintense right hippocampus of a 13-month-old male 3 days after a 120-minute-long episode of FSE. Note that the right hippocampus is larger and has increased T2 signal most prominent in Sommer's sector (arrow). (C) Follow-up magnetic resonance imaging 6 months later of the same child showing the right hippocampus to be smaller; the T2 signal increase is persistent but no longer maximum in Sommer's sector.

criteria for HS were excluded to limit the analysis to acutely injured hippocampi. Hippocampal ADCs were obtained by averaging ADCs of ROIs drawn on coronal ADC maps excluding all nonhippocampal voxels. Not all hippocampi had usable DWIs due to technical issues or subjects being imaged prior to routine use of DWI.

Controls for Analyses

We selected controls appropriate for each analysis (Supplementary Table 1). Controls for growth of hyperintense hippocampi had FSE and normal baseline MRI. For analysis of Rt/Lt volume ratios and hippocampal growth in FSE subjects with normal baseline MRI, controls were 38 children with SFSs and normal MRI from the Columbia study. For ADC evolution after FSE and for T2 signal distribution in hyperintense hippocampi, controls with FSE and normal hippocampal signal were used. For each analysis, controls were matched by age, gender, hippocampal lateralization, and latency from FSE to baseline MRI.

Other Studies

The FEBSTAT cohort had EEG and virology studies done for human herpesvirus 6 (HHV6) and HHV7 at baseline. DNA was also banked at Coriell.⁶ Details are in the online files (Supplementary Results).

Statistics

Results of statistical analysis (D.C.H., E.B., C.L.) are presented as mean and standard deviation. A mixed effect model with subject-specific random intercept was used to analyze hippocampal growth, adjusting for age and gender.²² All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC). Tests of the fixed effects were performed when the mixed model

indicated a difference between the 2 groups or between the acute and follow-up time points. A Bonferroni approach was used to correct for the multiplicity of tests. Multivariate regression models examined effects of other risk factors on hippocampal volume (see Supplementary Results).

Results

Hippocampal T2 Signal in Acute MRI

Definite abnormal hippocampal signal occurred in 22 (9.7%) of 226 FSE children. Fifteen were right-sided, 6 were left-sided, and 1 was bilateral. On visual inspection, the most intense T2 signal appeared in CA1 and the pro-subiculum coinciding with Sommer's sector,^{23,24} located in the lateral inferior aspect of the hippocampal body (Fig 1). This was confirmed by measurement of T2 signal intensity in all acutely hyperintense hippocampi (Fig 2). Contralateral hippocampal T2 intensity was not increased.

Nine subjects with hippocampal hyperintensity also had other MRI abnormalities described previously¹²; 4 had hippocampal malrotation (HIMAL), and 5 had extra-hippocampal abnormalities (see Supplementary Results: Additional Abnormalities and Supplementary Table 2).

Quantitative Acute Hippocampal Volumes and ADCs

Of the 21 cases with unilateral abnormal hippocampal signal, hyperintense hippocampi were larger than contralateral hippocampi in 13 (61.9%). Excluding 3 subjects with

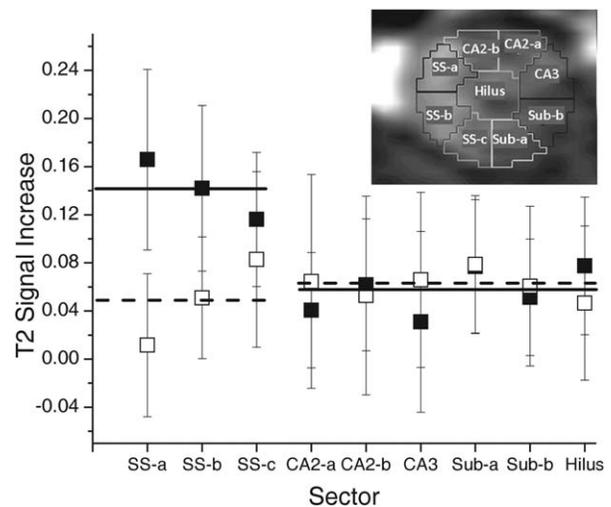


FIGURE 2: Increased T2 on acute and follow-up magnetic resonance imaging (MRI). Inset shows regions of interest (ROIs) overlying hippocampal sectors. SS = Sommer's sector; Sub = subiculum. Plot shows increase in T2 intensity by hippocampal sector in the acute (filled squares; $n = 21$) and follow-up (open squares; $n = 13$) MRI. On acute scans, the mean (\pm standard deviation) increase in T2 signal across all 3 Sommer's sector ROIs was $0.141 (\pm 0.136)$ versus $0.057 (\pm 0.099)$ for all other sectors (t test; $p < 0.001$). Solid and dashed lines indicate means over SS and non-SS sectors at acute and follow-up MRI, respectively. Bars = 95% confidence intervals.

pre-existing small hippocampi described below, mean volume of hyperintense hippocampi was greater than that of contralateral hippocampi ($2,273 \pm 600.7$ vs $2,111 \pm 533.6$ mm³; paired *t* test; *p* = 0.02; *n* = 18).

Two subjects had visually small and hyperintense hippocampi meeting our radiologic criteria of HS.¹² These hippocampi, imaged 2 days following FSE, were also small by volumetric measurement. Another child had a small schizencephalic hemisphere and a small hyperintense ipsilateral hippocampus.

ADC maps were available for 13 of 22 subjects with hyperintense hippocampi after excluding the 2 subjects with HS and the 1 subject with bilateral hyperintensity. The mean ADC of the hyperintense hippocampi (1.01×10^{-3} mm²/s $\pm 8.35 \times 10^{-5}$; *n* = 13) was lower than that of the matching contralateral hippocampi (1.05×10^{-3} mm²/s $\pm 9.90 \times 10^{-5}$; *n* = 13), but this difference was not statistically significant (paired *t* test; *p* = 0.06).

Follow-up MRI

Follow-up MRI were available for 139 FSE subjects. Of these, 130 were technically adequate for evaluation of initial and final T2 signal, with follow-up intervals between 1 month and 2.5 years (median = 1.07 years, IQR = 1.00–1.25). Among the 130 subjects, 116 had initially normal hippocampal signal, and only 1 developed abnormal signal on follow-up after a second episode of FSE; none had radiologic evidence of HS.

Of the 22 with abnormal hippocampal signal, 14 returned for follow-up MRI, some of whom had additional abnormalities (see Supplementary Results: Additional Abnormalities and Supplementary Table 2). Ten of the 14 (71.4%) met visual criteria for HS on follow-up, including 1 who had HS on the initial MRI. Volumetric measurement indicated that volume loss was more frequent than HS, with 13 of 15 (87%) hyperintense hippocampi in 12 of 14 (85.7%) subjects showing decreased volume, including both hippocampi of the subject with bilateral hyperintensity (Fig 3A). Although 4 subjects with follow-up MRI had HIMAL in addition to hyperintensity, HIMAL alone does not produce hippocampal shrinkage (see Supplementary Results).

It was unlikely that the severity of the initial insult differed in those with and without follow-up, because there were no significant differences between these groups for febrile status duration and hippocampal T2Scores, or in the incidence of focal status and EEG abnormalities. However, in the 22 with hippocampal hyperintensity, the presence of multiple conditions affecting well-being, such as developmental delay, epilepsy, or recurrent status, seemed to increase the likelihood of follow-up (see Supplementary Results: Proportion with Follow-up). For instance, of the

22 with hippocampal hyperintensity, 5 developed epilepsy early, mostly not TLE, and all returned for follow-up.

T2 signal intensity no longer appeared greatest in Sommer's sector on follow-up MRI (see Fig 1C). Measurements (see Fig 2) confirmed this visual impression, with mean signal increase in Sommer's sector of 0.048 (± 0.088) compared to 0.062 (± 0.095) in the remaining sectors (*t* test; *p* = 0.5).

Both acute and follow-up ADCs were available for 7 subjects with hyperintense hippocampal signal. The mean ADC had increased by 3.7% (± 12.8), whereas over the same interval, the mean hippocampal ADC had decreased by 11% (± 12.4) in 14 matched FSE controls (*t* test; *p* = 0.02), as expected in normally maturing brain.²⁵

Previous studies of FSE report that hippocampi appearing normal acutely become increasingly asymmetric on follow-up, suggesting subtle injury.^{8,9} To detect subtle effects in our cohort, we selected from our FSE and SFS subjects only those with completely normal acute MRI and available follow-up MRI obtained between 6 and 24 months after the initial seizures, yielding 59 FSE and 38 SFS cases. We analyzed hippocampal volumes and volume ratios in these cases using a linear mixed model, controlling for age and gender. Subsequent *t* tests were performed on the fixed effects to compare the simple main effects for SFS and FSE subjects at acute and follow-up MRI. The mean Rt/Lt volume ratio estimated from the model was significantly less in FSE subjects than in SFS subjects (see Fig 3B). Mean right and left hippocampal volumes of the FSE group were less than those of the SFS group on acute and follow-up MRI, and FSE hippocampi appeared to grow more slowly (see Fig 3C, D).

Although it is too early to determine the ultimate incidence and types of epilepsy in this cohort, at the time of this follow-up MRI, only 16 of 226 children had developed epilepsy (7.1%). Three had clinical Dravet syndrome and normal MRI. The great majority of the epilepsy was not TLE, which is not surprising given the prolonged latency of TLE following FSE.^{26,27} Developmental delay, determined on enrollment using the Bayley Scales of Infant Development, was also uncommon and found in only 31 of 226 with FSE (13.7%) and in 4 of 22 with hippocampal hyperintensity (18.2%).

Other Risk Factors Influencing Hippocampal Volume Change after FSE

In the 59 FSE cases with visually normal baseline MRI, we examined the effect of age at FSE, duration, focality, focal slowing or attenuation on baseline EEG, and

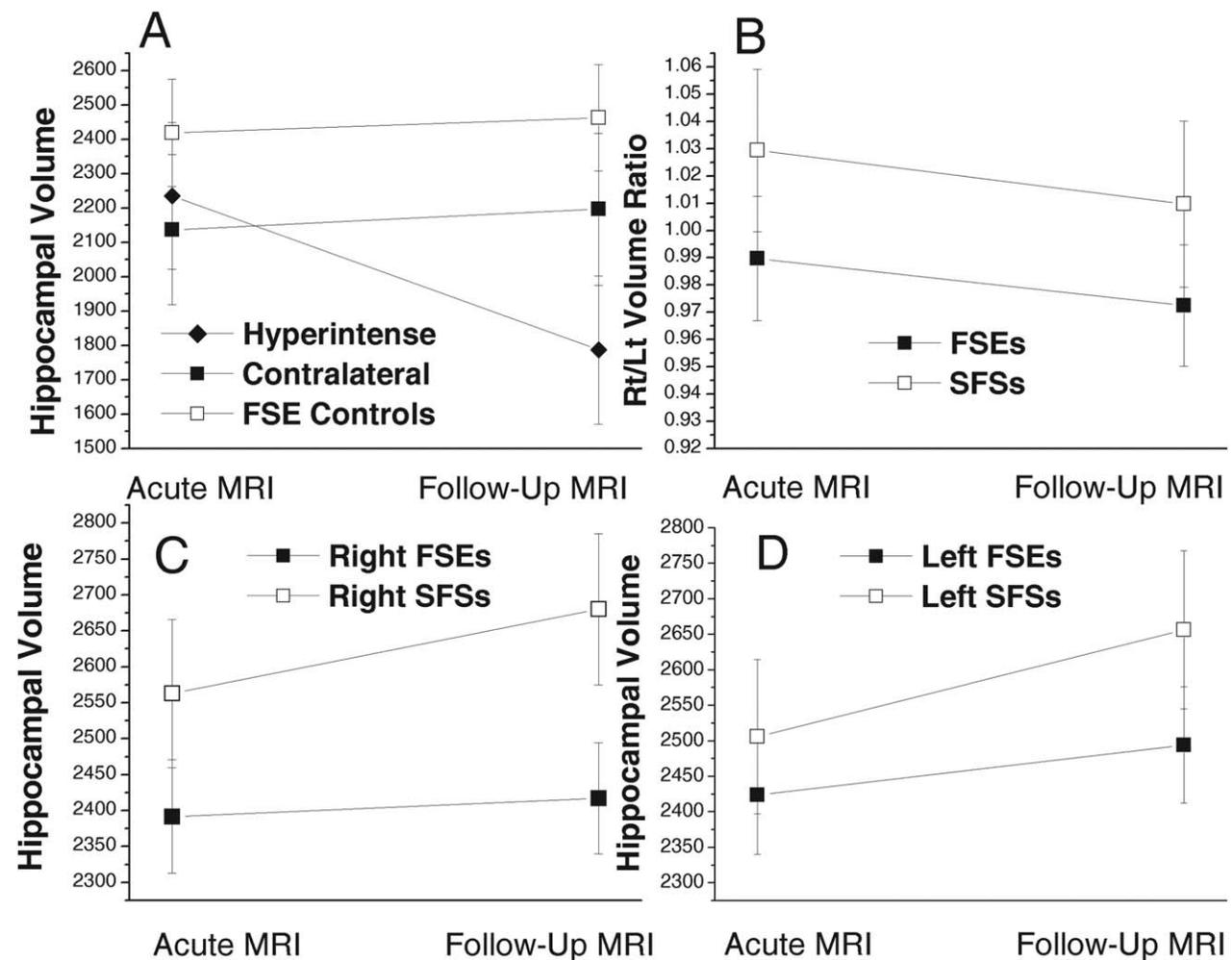


FIGURE 3: Hippocampal volumes from acute and follow-up magnetic resonance imaging (MRI). (A) Hyperintense hippocampi (Hyperintense; $n = 15$) versus hippocampi contralateral to them (Contralateral; $n = 13$) and control hippocampi from febrile status epilepticus (FSE) subjects with normal acute MRI (FSE Controls; $n = 30$). The number of hyperintense hippocampi is greater than the number of contralateral hippocampi because 1 subject had bilateral hyperintensity. Note that the hyperintense hippocampi lost approximately 20% of volume between the initial and follow-up MRI, whereas the contralateral and FSE control hippocampal volumes increased. The mixed linear model indicated that, at follow-up MRI, the mean volume of hyperintense hippocampi was less than that of the controls ($p < 0.0001$) and the contralateral hippocampi ($p = 0.0001$). At the baseline MRI, the mean volumes of the groups were not significantly different. (B) Right to left (Rt/Lt) volume ratios of FSE subjects with normal acute MRI were less than those of simple febrile seizure (SFS) subjects with normal acute MRI (mean estimated Rt/Lt volume ratios of 0.98 vs 1.03, respectively; F test $p = 0.02$). Rt/Lt ratios did not change significantly from baseline to follow-up MRI (F test $p = 0.10$). (C) Right hippocampal volumes of FSE were less than those of the SFS group by 171 and 262mm³ at the acute and follow-up MRI, respectively (Bonferroni adjusted $p = 0.03$ for acute and $p < 0.001$ for follow-up). (D) Left hippocampal volumes of FSE were less than those of SFS subjects by 82 and 162mm³ at the acute and follow-up MRI, although these differences did not attain significance (Bonferroni adjusted $p = 0.90$ for acute and $p = 0.07$ for follow-up). From the acute to follow-up MRI, the volumes of both sides increased for SFS subjects (Bonferroni adjusted left side: $p = 0.03$; right side: $p = 0.11$). For FSE subjects, the slope of growth was flatter and volume change was not significant on either side (left side: $p = 0.74$; right side: $p = 1.00$). Bars are 95% confidence intervals. For B, C, and D, the groups were identical to FSEs ($n = 59$) and SFS controls ($n = 38$).

presence of HHV6 or HHV7 viremia on change in hippocampal volume (see Supplementary Results). On multivariate analysis, hippocampal volume change was affected by age, with younger age showing more growth, but only in the left hippocampus, and HHV6/HHV7 viremia, with those with viremia showing more growth on both sides, even after adjusting for age. We were unable to assess these factors in hippocampi with

abnormal signal because essentially all these cases had volume loss.

Discussion

It is clear from FEBSTAT¹² and other studies^{7,28–30} that FSE can result in acute hippocampal injury visible on MRI. This report demonstrates, furthermore, that the increased hippocampal signal is maximal in Sommer's

sector acutely and that many of the affected hippocampi lose volume, meeting radiologic criteria for HS.¹⁷ Additionally, even in our subjects with normal acute MRI, subsequent decreased hippocampal growth suggests a subtle acute hippocampal injury.

Evidence for cytotoxic edema was found in the combination of abnormal signal in Sommer's sector, reflecting the known vulnerability of that sector to seizures,^{23,31} increased hippocampal volume, and a trend for reduced ADCs. Although acutely increased ADCs were found in 1 study of FSE, those hippocampi did not have visibly increased T2 signal³² as our subjects did. On follow-up, T2 hyperintensity was no longer maximal in Sommer's sector and this change in distribution, along with reduced volume and increasing ADCs may reflect chronic changes of neuronal loss and gliosis in Sommer's sector as described by others.^{23,24,33} The combined MRI findings of increased hippocampal signal and atrophy seen here are reliable indicators of HS.¹⁷

The appearance consistent with HS on initial MRI of 2 of our subjects was unexpected and supports the suggestion that HS might occasionally precede FSE made by others using retrospective analysis.^{34,35}

Reliable biomarkers for TLE following FSE will be essential to identify children at risk once antiepileptogenic intervention becomes available.^{36,37} Few data are available for evaluation of such markers in humans, although important biomarker studies in animal models of FSE³⁸ exist. Presently, we can assess biomarkers for HS only, as latency from FSE to the appearance of TLE can be ≥ 10 years.^{26,27} However, in the setting of FSE, it seems that T2 hyperintensity at baseline both greatly increases the risk for developing HS and is a prerequisite for appearance of HS 1 year after FSE. Finally, our estimate of the proportion with HS must be tempered by consideration of the limited sample size.

Abnormal hippocampal growth has been reported after FSE even in hippocampi with an initially normal-appearing MRI.^{8,9} Therefore, we analyzed the growth of hippocampi appearing normal at baseline. The Rt/Lt volume ratios of our FSE subjects with normal MRI were abnormally low, but did not change from the baseline to follow-up, whereas SFS controls had a mean Rt/Lt ratio > 1 as expected.³⁹ In addition, hippocampal volumes and growth were greater in subjects with SFS compared to those with FSE. The decreased right hippocampal volume of the FSE hippocampi and the predominance of hyperintensity on the right suggest asymmetric hippocampal vulnerability present before FSE, as has been suggested previously.⁴⁰ Finally, we looked for predictors of slowed growth in hippocampi appearing normal at baseline. Although baseline EEGs correlate with baseline imaging

abnormalities,¹³ they did not predict hippocampal volume change over the first year. FS duration is clearly an important predictor of T2 signal abnormalities, as our SFS controls had no signal abnormalities.¹² However, among our FSE cases differences in duration did not seem to affect baseline or 1-year hippocampal findings.¹² We cannot explain why HHV6/HHV7 viremia cases showed more growth. It remains to be seen whether slowed hippocampal growth alone predicts HS.

Our study has limitations. Without MRI prior to FSE, ADCs and volumetrics must provide evidence that the hippocampal abnormalities that are seen are acute. Although abnormal hippocampal signal following FSE evolved to radiological HS over a year, there is no pathological confirmation. Follow-up MRI are not available on all subjects for a variety of reasons, chief among them being parental concern about sedated MRI of a child who, although at risk, was perceived to be doing well at the time. This problem was expected, and the study was powered based on a 70% follow-up rate at 1 year. In the group with abnormal hippocampal signal, multiple additional abnormalities were more likely to be associated with follow-up. Whether these abnormalities, such as developmental delay or epilepsy, increased the likelihood of HS cannot be determined from our limited sample. However, children with known severe prior abnormalities were excluded from FEBSTAT.⁶ Finally, given the limitations inherent in imaging of children requiring sedation, full MRI protocols were not always obtainable.

In conclusion, T2 hyperintensity following FSE often evolved to visual appearance of HS on MRI.^{10,11,17} Even children with FSE and normal MRI had smaller hippocampi and reversed Rt/Lt hippocampal volume ratios compared to the SFS group. This may reflect subtle abnormalities in hippocampal development that predispose to FSE. Furthermore, compared to SFS controls, visually normal hippocampi of FSE subjects grew more slowly, suggesting that they sustained an insult. As the latency of TLE following FSE is usually prolonged,^{26,27} longer follow-up, now in progress, is needed to determine the final clinical outcomes in this cohort.

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Potential Conflicts of Interest

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