Volumetric MRI, pathological, and neuropsychological progression in hippocampal sclerosis

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CME

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Article abstract—*Objective:* To examine the relationships between age at onset and duration of seizure disorder with severity of hippocampal sclerosis (HS) and cognitive functioning in patients with HS and unilateral temporal lobe epilepsy. *Methods:* Twenty-six subjects had left temporal lobe seizure onset; 20 had right temporal onset. Measures were age at seizure onset, duration of seizure disorder divided by age (seizure duration), history of febrile convulsion (FC), ratio of the smaller hippocampal volume to the larger (HF) as determined by volumetric MRI, and pathologic HS grade. *Results:* Results showed that pathologic HS grade and HF were positively related to seizure duration, and negatively related to seizure onset. When subjects were divided into onset prior to age 10 versus later, subjects with earlier onset had higher mean pathologic HS grade and smaller (more asymmetric) mean HF. When subjects were divided into seizure duration <0.5 (i.e., less than half current lifetime) vs greater, subjects with seizure duration ≥ 0.5 had higher mean pathologic HS grade and lower mean HF. There was also evidence for earlier age at seizure onset and longer seizure duration being associated with worse performance on neuropsychological measures. FC was not related to either seizure duration or age at seizure onset, but patients with a history of FC showed higher pathologic HS grade and lower HF. A history of FC was not related to cognitive functioning.*Conclusions:* Unilateral HS patients with earlier seizure onset and longer duration of epilepsy have more severe HS and greater hippocampal volume asymmetry. This suggests that HS may be a progressive disorder with risk for cognitive dysfunction.

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Temporal lobe epilepsy (TLE) is the most frequent form of partial epilepsy in adults, and hippocampal sclerosis (HS) is the most common neuropathologic finding in patients with medically refractory TLE.[1-3] Approximately 60% to 75% of patients undergoing surgical treatment for TLE are found to have this entity.[1] HS is characterized by neuronal cell loss and gliosis involving hippocampal sectors CA1 and CA3/CA4 with relative sparing of CA2, the subiculum, and the dentate gyrus, although in severe cases pathologic findings may be widespread.[1,3,4] The cause of HS is unknown, although a strong association with childhood febrile convulsions (FC) has been frequently reported.[3,5-11]

The two principal MRI findings of HS are hippocampal atrophy and MRI signal changes indicative of increased tissue free water.[12-15] A routine MRI study can easily miss these findings, but HS is readily detected presurgically by using high-resolution MRI-based hippocampal volume measurements and other appropriate sequences.[12,15-17] Several studies have demonstrated a close correlation between histologically determined cell loss and atrophy determined through hippocampal volumetric measurements.[15,18-21] The presence of unilateral HS, as determined by volumetric MRI, and seizure control after anterior temporal lobectomy (ATL) have also been demonstrated.[22]

Recent studies raise concerns that certain forms of partial epilepsy may be associated with progressive damage to medial temporal lobe structures.[7-11,23-34] These studies, employing a variety of experimental[23-30] and clinical[7-11,30-34] methods, suggest that continuing seizures over time may result in progressive changes in hippocampal structure and function.

In this study we sought to determine if a relationship exists between duration of epilepsy and severity of hippocampal damage and impaired cognitive function in patients with TLE due to HS, controlling for history of FC.

See also pages 169, 315, and 318

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Methods. *Patients.* We studied 46 consecutive patients (24 men) with TLE, age 18 to 68 years (mean 37.4, SD 10.8), who met volumetric MRI criteria for HS. On average, patients had 13 years of education (SD 2.9, range 8 to 25 years) and Wechsler Adult Intelligence Scale–Revised (WAIS-R) full-scale IQ (FSIQ) of 88 (SD 13.6, range 62 to 116). All patients had medically intractable seizures and were being evaluated for possible epilepsy surgery. Seventeen patients had a history of childhood FC. For all patients, video EEG monitoring demonstrated unilateral temporal lobe seizure onset (26 with left temporal onset [LSZ] and 20 with right onset [RSZ]). To date, 28 patients have undergone anterior temporal lobectomy with pathologic grading of hippocampal sclerosis as described below.[18] While awaiting surgery, two patients became seizure-free on medication, and two patients died. The remaining 14 patients are either awaiting operation or have refused surgery.

MRI methods. MRI studies were performed on a GE 1.5-Tesla, Signa 5.4 unit (GE Medical Systems, Milwaukee, WI). MRI-based volumetric measurements of the hippocampus were performed using a method described previously.[15,35] Volumetric imaging was performed using a 3-D spoiled gradient echo (SPGR) sequence as previously described.[15,16,18] The absolute volumes of the two hippocampi were compared with our normal control population after "normalization" by total intracranial volume.[15] We also analyzed the degree of hippocampal asymmetry between sides by calculating a ratio of the abnormal (i.e., the epileptogenic) side to the normal (nonepileptogenic) side. Patients with TLE were considered to meet volumetric MRI criteria for HS if their absolute volumes were greater than 2 SD below the mean of the control group and/or the hippocampal ratios were less than 0.92.

Additional MRI sequences were obtained to detect the presence of extrahippocampal lesions or other pathology. These included sagittal T1-weighted, horizontal (axial) and coronal T2-weighted, and coronal fluid attenuated inversion recovery (FLAIR) sequences.

Surgical methods. Hippocampal specimens were obtained by techniques similar to those described in a recent study.[36]

Neuropathologic methods. The fresh temporal lobe tissue blocks were received in the operating room, oriented, and allowed to fix by immersion in 10% buffered formalin for 24 to 48 hours. In most cases, three separate blocks of tissue were obtained and examined: a lateral temporal block, an anterior amygdaloid block, and a hippocampal block. After fixation, the hippocampal segments were sectioned in serial fashion progressing from anterior to posterior and were stained with hematoxylin and eosin and Luxol fast-blue/cresyl violet. Astrocytosis was detected by the immunohistochemical method for detection of glial fibrillary acidic protein (GFAP) antigen (Dako, Carpinteria, CA, avidin-biotin method). Microscopic grading of the severity of HS was accomplished by one of the authors (W.J.K.) without knowledge of the volumetric MRI data, using the schema outlined in table 1 and described previously.[18]

Neuropsychological methods. All patients received presurgical neuropsychological testing. Measures used in this study included the following: WAIS-R FSIQ, Verbal IQ (VIQ), and Performance IQ (PIQ) scores and age-scaled subtest scores; Wechsler Memory Scale–Revised Logical Memory immediate and delayed percentile ranks (WMLI and WMLD) and Visual Reproduction immediate and delayed percentile ranks (WMVRI and WMVRD); Benton Multilingual Aphasia Examination percentile ranks (MAE); and California Verbal Learning Test (CVLT) z-scores.

Table 1 *Hippocampal sclerosis: pathologic grading schema (adapted from Watson et al[18])*

Grade	Description
0	Normal
I	Gliosis with slight (<10%) or no neuronal cell loss in CA1, CA3, and/or CA4
II	Gliosis with 10–50% neuronal cell loss in CA1 and/or CA3/CA4
III	Gliosis with >50% neuronal cell loss in CA1 and 10–50% cell loss in CA3/CA4; sparing of CA2
IV	Gliosis with >50% neuronal cell loss in CA1 and CA3/CA4; sparing of CA2
V	Gliosis with >50% neuronal cell loss in CA1–CA4; dentate gyrus, subiculum, and parahippocampal gyrus may be involved

Data analysis. Two continuous and three nominal independent measures were used in this study. The two continuous measures were age at onset of afebrile seizures (in years; age at seizure onset) and duration of seizure disorder as a proportion of total life span (seizure duration; duration of seizure disorder divided by age). The latter measure was used instead of simple duration of seizure disorder given the relatively large age range of our subjects (18 to 68 years) and the correlation between age and duration of seizure disorder (age obviously sets the upper limit of possible duration of seizure disorder). There is likely a difference between a 20-year-old subject experiencing seizures for 10 years versus a 50-year-old subject experiencing seizures for 10 years, and providing some correction for age was deemed prudent.

It should be noted that although the variables age at seizure onset and seizure duration were considered separately in this study, in this context they are not statistically independent from one another (orthogonal). Deleterious effects of intractable seizures or underlying neuropathology on brain and cognitive functioning are likely to be a function of both age at onset and duration of seizure disorder (as well as other factors not considered in this study, such as frequency of seizures). The two factors could be independently tested in animal models of seizure disorders, where direct manipulation of both is possible. However, in naturally occurring human epileptic populations, age at seizure disorder onset, age at evaluation, and thus duration of seizure disorder tend to be strongly related. Using a cross-sectional design, it is not feasible to test the unique influence of each factor with satisfactory power given the typical sample size encountered in clinically based research. Some combinations of age at onset and duration of seizure disorder are simply too rare in clinical samples (e.g., onset in later life with long duration of the disorder).

To form two of the nominal variables, patients were subdivided into earlier (EOS) or later (LOS) age at seizure

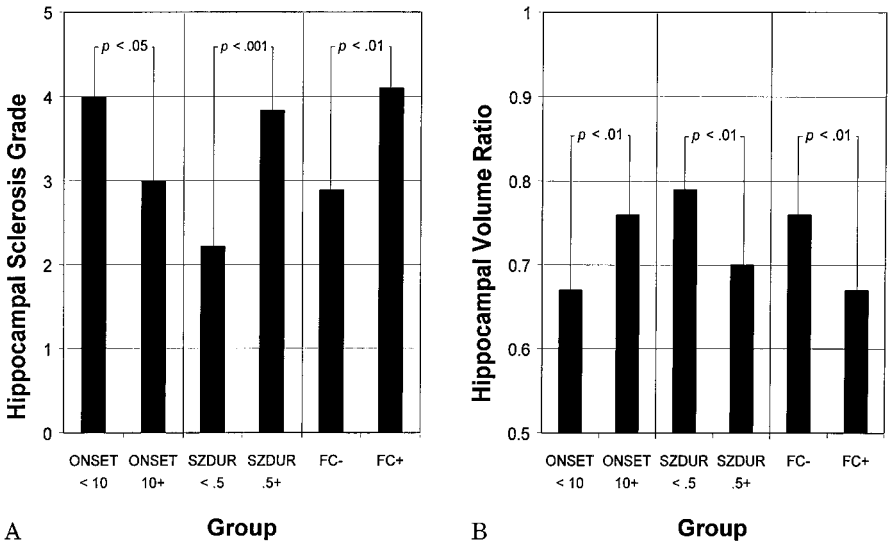

Figure. A) Mean hippocampal sclerosis grade for patients with seizure onset before vs after 10 years of age, patients with seizure duration of less than vs greater than half of lifespan, and patients with (FC+) and without (FC−) a history of febrile convulsions. B) Mean hippocampal volume ratios.

onset (<10 years vs 10+ years), and by shorter (SD) or longer (LD) seizure duration (<0.5 vs 0.5+). The former cutpoint was selected to distinguish between patients with onset of seizures in childhood (i.e., prepubertal onset) versus patients with onset in adolescence and adulthood. The latter cutpoint (seizures for less than half of life span versus greater) was arbitrary, but logical given the exploratory nature of this study, and resulted in a reasonably uniform division of subjects. The third nominal variable was history of childhood FC, dummy coded as present (1) or absent (0). Further subdivision of FC into complex (prolonged) or simple types was not attempted, as reliable historic data for making this determination were not available for many patients.

The relationships between age at seizure onset, seizure duration, and FC with severity of HS (pathologic HS grade) and hippocampal volume asymmetry (HF) were evaluated by three methods. First, correlation coefficients were calculated between the two sets of variables. Second, four multiple regression analysis models were tested, using FC and age at seizure onset, and FC and seizure duration, to predict pathologic HS grade and HF. Third, differences between the subgroups (EOS vs LOS; SD vs LD; FC present or absent) on mean pathologic HS grade and HF were tested using one-way ANOVA.

Relationships between age at seizure onset, seizure duration, and FC with neuropsychological measures were evaluated with correlations calculated between the two sets of variables. These analyses were conducted separately for LSZ and RSZ patients, as the side of onset should have differential effects on neuropsychological measures.

Results. Zero-order correlations showed no relationship between FC and seizure duration ($r = 0.18$, NS) or FC and age at seizure onset ($r = -0.22$, NS) Subjects with FC had an average seizure duration of 0.66, versus 0.55 for subjects without FC ($F(1,42) = 1.46$, NS) Subjects with FC had an average age at seizure onset of 11.60, versus 17.19 for subjects without FC ($F(1,42) = 2.12$, NS). FC was related to both pathologic HS grade ($r = 0.50$, $p < 0.01$) and HF ($r = -0.45$, $p < 0.01$). Mean pathologic HS grade for patients with vs without FC is presented in the figure, A; mean HF is presented in the figure, B. Patients with FC had higher pathologic HS grade (4.1 vs 2.9; $F(1,26) = 8.55$, $p < 0.01$) and lower HF (0.67 vs 0.76; $F(1,42) = 10.88$, $p < 0.01$) as compared to patients without FC.

There was a negative correlation between seizure duration and HF ($r = -0.42$, $p < 0.01$), with patients having longer duration of epilepsy showing greater hippocampal volume asymmetry. Seizure duration was positively related to pathologic HS grade ($r = 0.58$, $p < 0.01$), with longer duration of seizure disorder being associated with higher-grade hippocampal sclerosis. Age at seizure onset had a negative relationship with pathologic HS grade ($r = -0.51$, $p < 0.01$); patients with earlier onset of seizures had higher-grade HS. Age at seizure onset was positively correlated with HF ($r = 0.36$, $p < 0.05$); patients with earlier onset of seizures had greater hippocampal volume asymmetry.

Multiple regression analysis showed that FC and seizure duration predicted pathologic HS grade ($F(2,24) = 12.91$, $p < 0.01$), with $R^2 = 0.52$. Both FC and seizure duration contributed to the regression model ($r_{\text{pathologic HS grade(FC.seizure duration)}} = 0.43$, $r_{\text{pathologic HS grade(seizure duration.FC)}} = 0.53$, $ps < 0.01$). Similarly, multiple regression analysis showed that FC and seizure duration predicted HF ($F(2,24) = 10.66$, $p < 0.01$), with $R^2 = 0.47$. Both FC and seizure duration contributed to the regression model ($r_{\text{HF(FC.seizure duration)}} = -0.46$, $r_{\text{HF(seizure duration.FC)}} = -0.47$, $ps < 0.01$).

Multiple regression analysis showed that FC and age at seizure onset predicted pathologic HS grade ($F(2,24) = 10.82$, $p < 0.01$), with $R^2 = 0.47$. Both FC and age at seizure onset contributed to the regression model ($r_{\text{pathologic HS grade (FC.age at seizure onset)}} = 0.42$, $r_{\text{pathologic HS grade(age at seizure onset.FC)}} = -0.49$, $ps < 0.01$). Similarly, multiple regression analysis showed that FC and age at seizure onset predicted HF ($F(2,24) = 8.35$, $p < 0.01$), with $R_2 = 0.41$. Both FC and seizure duration contributed to the regression model ($r_{\text{HF(F-C.age at seizure onset)}} = -0.45$, $p < 0.01$, $r_{\text{HF(age at seizure onset.FC)}} = 0.40$, $p < 0.05$).

Mean pathologic HS grade for patients with EOS (4.0) vs patients with LOS (3.0) are presented in the figure, A. EOS patients had higher pathologic HS grade than patients with LOS ($F(1,26) = 4.96$, $p < 0.05$). Panel A of the figure also depicts mean pathologic HS grade for patients

Table 2 *Correlations between age at seizure onset and seizure duration with neuropsychological measures*

Measure	Age at seizure onset	Seizure duration
Left onset		
Full-Scale IQ (WAIS-R)	0.39*	NS
Verbal IQ	0.41*	NS
Vocabulary	0.50†	NS
Comprehension	0.47*	−0.41*
Similarities	0.53†	−0.40*
Picture Arrangement	0.57†	−0.57†
Benton Tokens	0.48*	−0.44*
WMS-R Logical Immediate	0.48*	−0.40*
WMS-R Logical Delayed	0.47*	−0.41*
WMS-R Visual Delayed	0.54†	−0.57†
Right onset		
CVLT Delayed Free Recall	0.51*	−0.48*
CVLT Delayed Cued Recall	0.59†	−0.56*
CVLT Recognition	0.59†	−0.50*
CVLT Discriminability	0.48*	−0.54*
WMS-R Visual Immediate	0.54*	−0.62†

* $p < 0.05$.
† $p < 0.01$.

WAIS-R = Wechsler Adult Intelligence Scale–Revised; WMS-R = Wechsler Memory Scale–Revised; CVLT = California Verbal Learning Test.

with SD (2.2) vs patients with LD of seizures (3.8). The LD patients had higher pathologic HS grade ($F(1,26) = 18.87$, $p < 0.001$).

Mean HF for patients with EOS (0.67) vs LOS (0.76) are shown in the figure, B. Patients with earlier seizure onset had greater hippocampal volume asymmetry than patients with later seizure onset ($F(1,44) = 12.40$, $p < 0.01$). Panel B of the figure also shows mean HF values for SD (0.79) vs LD of seizures (0.70). Patients having seizures more than half their life had more asymmetric mean HF values ($F(1,44) = 8.29$, $p < 0.01$).

Significant correlations between age at seizure onset and seizure duration with neuropsychological measures for LSZ patients are shown in table 2. Earlier onset of seizures was associated with lower WAIS-R FSIQ and VIQ, and lower age scaled scores on the Vocabulary, Comprehension, Similarities, and Picture Arrangement subtests. Earlier onset was also correlated with lower scores on the MAE Token Test, Wechsler Memory Scale–Revised (WMS-R) Logical Memory immediate and delayed percentile ranks, and WMS-R delayed Visual Reproduction percentile ranks. Patients with longer duration of seizure disorder showed a similar pattern of associations, although the correlations of seizure duration with WAIS-R FSIQ, VIQ, and Vocabulary were not significant. FC did not correlate with any neuropsychological measure.

Significant correlations between age at seizure onset and seizure duration with neuropsychological measures for RSZ patients are also shown in table 2. Worse immediate nonverbal memory performance (WMVRI) was associated with both earlier onset of seizures and longer duration of seizure disorder. Longer seizure duration and earlier age at seizure onset were also associated with worse CVLT delayed free and cued recall, recognition, and discriminability scores. FC did not correlate with any neuropsychological measure used in this study.

Discussion. Our results suggest that HS may be a progressive condition. Patients with earlier onset of seizures, and who have seizures for a greater proportion of their life, demonstrate higher-grade HS and greater hippocampal volume asymmetry on MRI.

These findings agree wholly[7] or in part[8,9,11,31-34] with prior studies. Several authors have found longer duration of epilepsy,[8,31-34] earlier age at onset,[9,11] or both[7] to be related to diminished hippocampal volumes, reduced NAA/Cr, prolonged T2 relaxation times, or increased severity of HS on pathologic evaluation. One study[10] failed to demonstrate such a relationship, but possible reasons for this are presented by Tasch et al.[7] Many animal studies have demonstrated that seizures can produce progressive neuronal loss in the hippocampus.[23-30] Taken together, these studies suggest that HS is caused by an early insult followed by gradual progressive damage over time.[7,37]

This progression may have significant functional consequences. Earlier onset of seizures and longer duration of seizure disorder are associated with worse performance on neuropsychological tests. Affected areas of cognition include IQ, language, and memory, depending on the side of seizure onset.

One recent study[31] also noted a "moderate decline in verbal learning and memory functions and mild decline in visuospatial memory functions" in a patient with progressive hippocampal atrophy over 4 years.

Consistent with previous studies,[3,5-11] FC were associated with higher-grade HS and volumetric asymmetry. However, a history of FC was not associated with age at onset or duration of epilepsy, and the effect of FC on HS was independent of these variables. Similar findings have been reported recently.[8]

As other investigators have reported, a history of FC was also not associated with lower cognitive functioning.[38,39] These results suggest that in our patients worse cognitive performance was not due to the potentially more severe effects of early CNS insult (FC) on general cognitive development, but was rather due to earlier onset and longer duration of intractable seizures.

The cross-sectional design of this study necessarily limits the robustness of our findings. Longitudinal monitoring of patients with intractable TLE due to HS who do not undergo surgical treatment and examination of other factors that may contribute to deterioration of neurologic and neuropsychological functioning are needed. However, in the meantime, the findings of this, and other, studies support the concept of HS as a progressive epileptic disorder that should be managed aggressively.

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