

NEW EVIDENCE SUPPORTS COGNITIVE DECLINE IN TEMPORAL LOBE EPILEPSY

Cognitive Prognosis in Chronic Temporal Lobe Epilepsy. Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, Bell B. *Ann Neurol* 2006;60:80–87. **OBJECTIVE:** First, to determine whether patients with chronic temporal lobe epilepsy have a different cognitive trajectory compared to control subjects over a prospective 4-year interval; second, to determine the proportion of patients who exhibit abnormal cognitive change and their profile of demographic, clinical epilepsy, and baseline quantitative magnetic resonance imaging characteristics; and third, to determine the most vulnerable cognitive domains. **METHODS:** Participants with chronic temporal lobe epilepsy ($N = 46$) attending a tertiary referral clinic and healthy control subjects ($N = 65$) underwent neuropsychological assessment and reevaluation 4 years later. Analysis of test–retest patterns identified individual patients with adverse cognition outcomes. **RESULTS:** The prospective cognitive trajectory of patients with chronic temporal lobe epilepsy differs from age- and sex-matched healthy control subjects. Lack of practice effects is common, but frank adverse cognitive outcomes are observed in a subset of patients (20%–25%), particularly in vulnerable cognitive domains that include memory. Cognitive declines are associated with a profile of abnormalities in baseline quantitative magnetic resonance volumetrics, lower baseline intellectual capacity, as well as longer duration of epilepsy and older chronological age. **INTERPRETATION:** Cognitive prognosis is poor for a subset of patients characterized by chronicity of epilepsy, older age, lower intellectual ability, and more baseline abnormalities in quantitative magnetic resonance volumetrics.

COMMENTARY

This recent report by Hermann et al. provides the most systematic evidence to date for the presence of evolving cognitive deficits in persons with epilepsy. Unlike previous investigations of cognitive change in patients with epilepsy,

subjects in this study were evaluated prospectively during an interval of 4 years. The study provided thorough documentation of seizure history and antiepileptic drug (AED) use in the epilepsy group as well as careful matching of demographic characteristics between the control and epilepsy groups. Some of the findings are subtle yet clearly supportive of previous cross-sectional results on cognition in epilepsy. The subtlest finding involves the fact that the epilepsy group fell short of predicted cognitive test scores upon retesting; the predicted scores were statistically derived from test–retest scores in the control group. That is, the practice effect, which typically results in an improved score when repeating a cognitive test (even over a 4-year span), was not found in the epilepsy group. Therefore, although the test scores for the epilepsy group generally demonstrated little cognitive decline over the study interval, retesting of normal controls revealed significantly improved scores. Overall, 57% of the control group's test results improved upon retest, while only 6% of the temporal lobe epilepsy group improved.

Using z-scores more than 2.0 standard deviations below expected, Hermann and colleagues identified a subset of patients with chronic temporal lobe epilepsy who had cognitive decline over time (approximately 25%–40% of the epilepsy group). The cognitive decline occurred most frequently in the domains of confrontational naming, delayed visual memory, delayed verbal memory, and motor speed. Within the epilepsy group, predictors of decline in performance on specific cognitive tests included lower IQ at baseline, longer duration of epilepsy, smaller baseline left hippocampus, decreased volume in other brain compartments on volumetric MRI, and older age at the time of the study. These factors are not unexpected, based on reports from cross-sectional studies of intellect and neuropsychological testing in adults with epilepsy.

The authors previously have reported on cross-sectional cohorts that demonstrated that longer duration of epilepsy is associated with cognitive deficits (1); they also have reported an association of cognitive deficits with smaller hippocampal volume as well as with reduced total brain volume (2,3). Multiple, previous investigators have validated these findings with reports of memory impairment associated with hippocampal atrophy (2–7). Another report links decreasing hippocampal volume with longer duration of epilepsy (8). Therefore, hippocampal atrophy may be a marker for cognitive impairment as well as a predictor of cognitive decline. Although the earlier cross-sectional study indicated that fewer years of formal education was a risk factor for cognitive decline within the epilepsy group, this prospective study did not corroborate that finding (1). The earlier study also reported that seizure onset before the age of 14 years was a risk factor for cognitive decline (2)—again, a factor that was not found in the current study; however, most of the subjects did have an early onset of epilepsy (mean age of onset 11.1 years, SD 7.3). Therefore, the investigators simply

may not have had enough subjects with an age of onset above 14 years to make a meaningful comparison, using age 14 years as a cutoff point.

Antiepileptic drugs (AEDs) and recurrent seizures—the factors usually considered to be either confounders and/or contributors to cognitive dysfunction in epilepsy—are well accounted for in this study and did not emerge as risk factors. The only exception to this finding was AED polytherapy, which was associated with adverse change in confrontational naming and speeded fine motor dexterity. The mean number of secondary generalized seizures during the entire 4-year study was low, at 2.8. If AEDs and seizures are not predictors of cognitive decline, the epileptic process itself emerges as a major factor in producing cognitive decline. The fact that smaller brain compartments, particularly the hippocampi, are predictors of progressive cognitive dysfunction supports the hypothesis that brain injury and degeneration are aspects of the epileptic process. Further, if recurrent seizures are reasonably considered to be part of an epileptic process, hippocampal atrophy and T2 signal abnormalities may predict seizure recurrence over the long term, even among patients who have prolonged seizure-free periods off AEDs (9). In other words, this finding supports numerous previously published studies that mesial temporal sclerosis is a predictor of medical intractability.

The findings by Hermann et al. pull together several spheres of information to support the concept that epilepsy is an entity characterized by more than recurrent seizures and their sequelae. Therefore, when patients complain of cognitive difficulties and memory problems, it should be kept in mind that it is not always the AEDs, depressed mood, or even the seizures causing their complaints—it could be that they are experiencing progressive cognitive impairment that is an inherent part of the epileptic process.

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References

1. Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, Seidenberg M, Hermann BP. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology* 2004;62:1736–1742.
2. Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Prog Brain Res* 2002;135:429–438.
3. Oyegbile TO, Bhattacharya A, Seidenberg M, Hermann BP. Quantitative MRI biomarkers of cognitive morbidity in temporal lobe epilepsy. *Epilepsia* 2006;47:143–152.
4. Griffith HR, Pyzalski RW, O'Leary D, Magnotta V, Bell B, Dow C, Hermann B, Seidenberg M. A controlled quantitative MRI volumetric investigation of hippocampal contributions to immediate and delayed memory performance. *J Clin Exp Neuropsychol* 2003;25:1117–1127.

5. Martin RC, Sawrie SM, Knowlton RC, Bilir E, Gilliam FG, Faught E, Morawetz RB, Kuzniecky R. Bilateral hippocampal atrophy: consequences to verbal memory following temporal lobectomy. *Neurology* 2001;57:597–604.
6. Baxendale SA, van Paesschen W, Thompson PJ, Connelly A, Duncan JS, Harkness WF, Shorvon SD. The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia* 1998;39:158–166.
7. Reminger SL, Kaszniak AW, Labiner DM, Littrell LD, David BT, Ryan L, Herring AM, Kaemingk KL. Bilateral hippocampal volume predicts verbal memory function in temporal lobe epilepsy. *Epilepsy Behav* 2004;5:687–695.
8. Theodore WH, Bhatia S, Hatta J, Fazilat S, De Carli C, Bookheimer SY, Gaillard WD. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. *Neurology* 1999;52:32–36.
9. Cardoso TAM, Coan AC, Kobayashi E, Guerreiro CAM, LI LM, Cendes F. Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal. *Neurology* 2006;67:134–136.