

## DO SEIZURES HARM THE BRAIN?

### Cognitive Decline in Severe Intractable Epilepsy

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**PURPOSE:** To explore the relation between seizure-related variables and cognitive change in patients with severe intractable epilepsy.

**METHODS:** A retrospective analysis of data from 136 patients who had undergone a cognitive assessment on two occasions at an interval of  $\geq 10$  years. Cognitive measures included tests of memory and executive skills in addition to intelligence quotients (IQ). Details were available regarding seizure type and frequency in the intertest interval.

**RESULTS:** Cognitive decline was severe and occurred across a wide range of cognitive functions. The frequency of generalized tonic–clonic seizures was the strongest predictor of decline. Complex partial seizure frequency was associated with a decline in memory and executive skills but not in IQ. Seizure-related head injuries and advancing age carried a poor cognitive prognosis, whereas periods

of remission were associated with a better cognitive outcome. Early age at onset was not implicated, and duration of epilepsy was a much less potent predictor of cognitive decline than has been reported in cross-sectional studies. No evidence indicated that a higher level of cognitive function protected against cognitive decline.

**CONCLUSIONS:** Our findings, together with those from animal studies and surgically treated patients, suggest that seizures can have a direct adverse effect on cognition and that good seizure control even after years of intractability can have a beneficial impact on cognitive prognosis. This study was based on individuals who merited two cognitive assessments  $\geq 10$  years apart and hence is biased in favor of those with the most severe forms of refractory epilepsy and those with decline.

### COMMENTARY

The association between epilepsy and an increased risk of cognitive deficit has long been recognized, and it is part of the definition of some types of epilepsies, such as Lennox–Gastaut syndrome. Subtle alterations in cerebral function even have been detected in patients with what are generally considered benign forms of epilepsy, such as childhood epilepsy with centrotemporal spikes. The issue of whether some or all epilepsies in effect are progressive brain diseases, however, is a more complex problem and of concern both to patients, who anxiously ask, “Will my seizures cause brain damage?” and to veteran clinicians, who have observed long-term cognitive decline in some of their patients with intractable, frequent seizures. The study by Thompson and Duncan adds to debate on the subject, but provides no definitive answers.

Pertinent questions in the debate on whether epilepsy is a progressive brain disease include: Do any patients with epilepsy suffer cognitive decline? If so, patients with which types of epilepsy? What sort of cognitive functions are at risk? What is the time course of the changes? Is there a way to prevent or

minimize the deterioration? The literature on the subject is vast, with conflicting results that probably reflect variations in study design (retrospective or prospective), population studied (well-controlled epilepsy or intractable disorders), length of intertest interval, age of the patients, and perhaps, duration of epilepsy before the first testing. The most convincing studies on cognitive function are prospective, include a control population, and/or have a long intertest interval.

A prospective study similar to that of Thompson and Duncan, but with intertest intervals of less than 5 years, was carried out on an intractable Swedish population (1). Compared to healthy controls, the patient group demonstrated a significant decline in retention of new verbal and visual-spatial information as well as in performance aspects of general cognition. This finding is similar to the findings of Thompson and Duncan, whose patients showed mean declines in verbal learning and recall from the 10th percentile to less than the 1st percentile and drops in performance IQ from the 25th percentile to the 9th percentile. In contrast, a study by Holmes et al. emphasized the lack of overall cognitive decline in a 35-patient cohort of adults with intractable complex partial and tonic–clonic seizures, who were followed for 10 years (2). Within the cohort, however, reductions in some subtest scores were found, especially those emphasizing speed of responses or use of visual-spatial skills.

In a relatively small Norwegian study, adults and children with refractory epilepsy were tested at the time of enrollment and then again at the intervals of 6.0 years and 3.5 years, respectively, using only the Wechsler's Intelligence Scales (3). Although the course of the epilepsy was the same and the number of antiepileptic drugs (AEDs) was similar in the two groups, mean Wechsler scores declined in the children and actually increased in the adult group. Studies of patients with well-controlled epilepsy have generally failed to detect cognitive decline over time (4). A controlled, prospective study was carried out on 42 Dutch children with newly diagnosed idiopathic or cryptogenic epilepsy. This study was unusual in that initial testing which was performed before administration of any AED. In the patient population, significant initial reductions were found for measures of learning, memory span for words, attention, and behavior. Over the course of 3.5 years, however, no significant group changes were detected in either cohort (5). Some indirect measures of cortical integrity also suggest that uncontrolled epilepsies may cause progressive brain injury. A cross-sectional study of patients with medically intractable temporal lobe epilepsy demonstrated a correlation between reduction of ipsilateral hippocampal volume on MRI and duration of epilepsy (6). Using MR spectroscopy, the same study found that patients with more frequent tonic-clonic seizures also had bilateral reductions of the neuronal marker *N*-acetylaspartate.

In everyday practice among the intractable epilepsy population, the toll on cognition taken by some AEDs or by the use of polytherapy is obvious and widespread. Yet, the possible influence of long-term drug use on serial cognitive testing, especially in patients whose AEDs may well have changed in systematic ways, are generally ignored in longitudinal studies. Possible permanent effects of AEDs on learning or development in children are suspected by some clinicians and may explain disparate findings in adults and children in studies, such as the Norwegian study.

The study by Thompson and Duncan clearly demonstrates the difficulties inherent in performing clinical studies that produce results that are unambiguous and generalizable. Strengths of the study include the large size of the study cohort (136 patients) as well as the long intertest interval. The psychometric test battery was unusually detailed, allowing precise detection of decline in specific types of function. However, the study also included serious design weaknesses, some of which bias the results in favor of finding intellectual decline. Most important, study patients were selected on the basis of having received repeated cognitive testing, all but 51 of them because of "concern over cognitive decline." Patients were enrolled either from a long-term inpatient facility for individuals with difficult epilepsies or from a tertiary outpatient epilepsy center. The median duration of epilepsy was very long, 35 years. Head injuries (undefined) were frequent enough in the patients (37%) to contribute sta-

tistically to the risk of cognitive decline. Finally, the biggest confounder in the interpretation of their data is the systematic difference in AED use between the first and the second testing sessions. The number of patients taking three or four AEDs, for example, jumped from 33% to 48%. In addition, at the time of the first tests, no patients were on topiramate or tiagabine; at the second testing session, 14% were on these drugs—both of which can cause cognitive abnormalities, especially when used in polytherapy or in high doses (7). In contrast, the number of patients on barbiturates shrank from 32% to 11%, a change that might be expected to improve test scores in some patients. Potential effects on cognition of these changes in AEDs are impossible to evaluate from the data given.

Thompson and Duncan found a particularly strong relationship between cognitive decline and the frequency of generalized tonic-clonic seizure. Even frequent complex partial seizures, however, were associated with worsening scores in tests of verbal learning, delayed recall, and semantic fluency, suggesting site-specific cerebral effects of seizures or of epileptogenic pathology, which may not be wholly explained by the systemic effects of major convulsions or falls. All in all, the study adds to the evidence that in patients with intractable epilepsy, repeated seizures of any type—and not only tonic-clonic ones—may pose a serious risk to quality of life and also may take a long-term toll on intellectual function.

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