

PROGRESSIVE DAMAGE IN EPILEPSY

Hippocampal Sclerosis Is a Progressive Disorder: A Longitudinal Volumetric MRI Study

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Twelve patients with refractory temporal lobe epilepsy and unilateral hippocampal sclerosis had repeated volumetric magnetic resonance imaging scans after a mean of 3.4 years to determine whether progressive hippocampal volume loss occurred. Seizure-free patients showed no change in hippocampal volume. Patients with continuing seizures had a decline in ipsilateral hippocampal volume that correlated with seizure frequency. Patients with medically refractory temporal lobe epilepsy and unilateral hippocampal sclerosis have progressive hippocampal atrophy.

Progressive Neocortical Damage in Epilepsy

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Our objective was to determine the pattern and extent of generalized and focal neocortical atrophy that develops in patients with epilepsy and the factors associated with such changes. As part of a prospective, longitudinal follow-up study of 122 patients with chronic epilepsy, 68 newly diagnosed patients, and 90 controls, serial magnetic resonance imaging scans were obtained 3.5 years apart. Image subtraction was used to identify diffuse and focal neocortical change that was quantified with a regional brain atlas and a fully automated segmentation algorithm. New focal or generalized neocortical volume losses were identified in 54% of patients with chronic epilepsy, 39% of newly diagnosed patients, and 24% of controls. Patients with chronic epilepsy were significantly more likely to develop neocortical atrophy than were control subjects. The increased risk of cerebral atrophy in epilepsy was not related to a history of doc-

umented seizures. Risk factors for neocortical atrophy were age and multiple antiepileptic drug exposure. Focal and generalized neocortical atrophy commonly develops in chronic epilepsy. Neocortical changes seen in a fourth of our control group over 3.5 years were likely to reflect physiological changes. Our results show that ongoing cerebral atrophy may be widespread and remote from the putative epileptic focus, possibly reflecting extensive networks and interconnections between cortical regions.

COMMENTARY

Progressive neuronal loss may be an important factor in understanding epileptogenesis, neurocognitive impairment, adverse antiepileptic drug (AED) effects, and psychopathology in patients with seizure disorders. Two recent studies used quantitative magnetic resonance imaging (MRI) techniques to evaluate the presence of progressive neocortical or hippocampal damage in individuals with epilepsy.

Fuerst et al. evaluated repeated MRI-based hippocampal volumetric studies in 12 patients with medically refractory temporal lobe epilepsy. All patients had unilateral hippocampal sclerosis and unilateral temporal lobe epilepsy. The lateralization of the hippocampal volume loss was concordant with the temporal lobe of seizure origin in all patients. The 12 patients did not undergo surgical treatment for partial epilepsy (nine refused operation, and three became seizure free with AED medication). The mean duration between two MRI studies was 3.4 years. Three of the 12 patients were seizure free, and nine experienced recurrent partial seizures. The patients with seizure activity had a significant volume loss in the ipsilateral hippocampal formation, which correlated with seizure frequency. There was no interval reduction in the mean contralateral hippocampal volume and no change in the hippocampal volumetric analysis in the three patients rendered seizure free.

The study by Liu et al. evaluated serial MRI scans in three groups: group I, 122 patients with chronic epilepsy; group II, 68 patients with newly diagnosed seizures; and group III, 90 controls. Image subtraction was used to assess any regional or diffuse neocortical progressive damage in these individuals. The change was quantified with a regional brain atlas and an automated

segmentation algorithm described in detail by the investigators. The mean duration between serial MRI scans was 3.5 years. Twenty-three patients were excluded because of possible significant comorbid conditions (e.g., alcohol abuse) or recognition of clinical factors that might alter the imaging study (e.g., surgical treatment). The 114 patients with chronic epilepsy in this series included: temporal lobe epilepsy ($n = 45$), generalized epilepsy ($n = 35$), and frontal lobe epilepsy ($n = 21$). Thirty-three of the 53 patients included in the study group who were newly diagnosed with epilepsy had partial seizure disorders. Focal or generalized volume loss (i.e., progressive neocortical damage) occurred in 54% of patients with chronic epilepsy, 39% of newly diagnosed patients, and 24% of controls. A significant difference was found between groups I and III. The most common change in the patients with epilepsy was generalized volume loss. The factors predictive of neocortical volume loss included age and use of multiple AED medications. Seizure frequency was not an important predictor of atrophy. The progressive neocortical damage was not limited to the region or lobe associated with seizure activity or the specific seizure type.

These studies indicate that quantitative structural neuroimaging techniques may prove more useful than “simply” identifying pathological findings underlying the epileptogenic zone. Serial or longitudinal MRI studies may be used to evaluate the presence of progressive damage intimately related to

the seizure disorder. The protocols discussed by the investigators in these two series lend themselves to research applications. Hippocampal volume loss in the first study occurred in patients with medial temporal lobe epilepsy related to hippocampal sclerosis. The volume reduction has been demonstrated to correlate with the presence of hippocampal cell loss. Fuerst et al. showed that all nine patients with continued seizures had a significant volume reduction in the ipsilateral temporal lobe. The neuronal loss may reflect the presence of recurrent seizure activity. These patients may be appropriate candidates for early surgical treatment of their seizure disorder. Potentially, the consequences of the progressive hippocampal cell loss include cognitive decline and psychiatric comorbidity. The study of Liu and colleagues revealed that diffuse neocortical changes were a prominent feature even in patients with a localization-related seizure disorder. The potential reasons for this generalized change include subclinical seizure activity, AED therapy, underlying neurological disorder, or a genetic predisposition. A combination of factors, including age, also must be considered. Importantly, the occurrence of seizures was not of prognostic importance with regard to the morphologic alterations. In conclusion, epilepsy may be associated with a progressive disorder. The use of quantitative neuroimaging may play a pivotal role in our understanding of the illness and in selecting appropriate treatment.

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