Temporal Lobe Epilepsy: More Than Hippocampal Pathology

Voxel-based Morphometry of the Thalamus in Patients with Refractory Medial Temporal Lobe Epilepsy

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Neuroimage 2005;25:1016–1021

Previous research has suggested that patients with refractory medial temporal lobe epilepsy (MTLE) show gray matter atrophy both within the temporal lobes and in the thalamus. However, these studies have not distinguished between different nuclei within the thalamus. We examined whether thalamic atrophy correlates with the nuclei's connections to other regions in the limbic system. T_1-weighted MRI scans were obtained from 49 neurologically healthy control subjects and 43 patients diagnosed with chronic refractory MTLE that was unilateral in origin (as measured by ictal EEG and hippocampal atrophy observed on MRI). Measurements of gray matter concentration (GMC) were made by using automated segmentation algorithms. GMC was analyzed both voxel by voxel (preserving spatial precision) as well as using predefined regions of interest. Voxel-based morphometry revealed intense GMC reduction in the anterior portion relative to posterior thalami. Furthermore, thalamic atrophy was greater ipsilateral to the MTLE origin than on the contralateral side. Here we demonstrate that the thalamic atrophy is most intense in the thalamic nuclei that have strong connections with the limbic hippocampus. This finding suggests that thalamic atrophy reflects this region's anatomic and functional association with the limbic system rather than a general vulnerability to damage.

Ipsilateral and Contralateral MRI Volumetric Abnormalities in Chronic Unilateral Temporal Lobe Epilepsy and Their Clinical Correlates

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Epilepsia 2005;46:420–430

PURPOSE: To assess the presence, extent, and clinical correlates of quantitative MR volumetric abnormalities in ipsilateral and contralateral hippocampus, and temporal and extratemporal lobe regions in unilateral temporal lobe epilepsy (TLE).

METHODS: In total, 34 subjects with unilateral left (n = 15) or right (n = 19) TLE were compared with 65 healthy controls. Regions of interest included the ipsilateral and contralateral hippocampus as well as temporal, frontal, parietal, and occipital lobe gray and white matter. Clinical markers of neurodevelopmental insult (initial precipitating insult, early age of recurrent seizures) and chronicity of epilepsy (epilepsy duration, estimated number of lifetime generalized seizures) were related to MR volume abnormalities.

RESULTS: Quantitative MR abnormalities extend beyond the ipsilateral hippocampus and temporal lobe with extratemporal (frontal and parietal lobe) reductions in cerebral white matter, especially ipsilateral but also contralateral to the side of seizure onset. Volumetric abnormalities in ipsilateral hippocampus and bilateral cerebral white matter are associated with factors related to both the onset and the chronicity of the patients' epilepsy.

CONCLUSIONS: These cross-sectional findings support the view that volumetric abnormalities in chronic TLE are associated with a combination of neurodevelopmental and progressive effects, characterized by a prominent disruption in ipsilateral hippocampus and neural connectivity (i.e., white matter volume loss) that extends beyond the temporal lobe, affecting both ipsilateral and contralateral hemispheres.

Epilepsy Currents, Vol. 5, No. 5 (September/October) 2005 pp. 187–189
Blackwell Publishing, Inc.

MR Volumetric Analysis of the Piriform Cortex and Cortical Amygdala in Drug-refractory Temporal Lobe Epilepsy

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AJNR Am J Neuroradiol 2005;26:319–332

PURPOSE: The assessment of patients with temporal lobe epilepsy (TLE) traditionally focuses on the hippocampal formation. These patients, however, may have structural abnormalities in other brain areas. Our purpose was to develop a method to measure the combined volume of the human piriform cortex and cortical amygdala (PCA) by using MRI and to investigate PCA atrophy.

METHODS: The definition of anatomic landmarks on MRIs was based on histologic analysis of 23 autopsy control subjects. Thirty-nine adults with chronic TLE and 23 age-matched control subjects were studied. All underwent high-spatial-resolution MRI at 1.5 T, including a tilted T_1-weighted 3D dataset. The PCA volumes were compared with the control values and further correlated with hippocampal, amygdale, and entorhinal cortex volumes.

RESULTS: The normal volume was 530 ± 59 mm^3 (422–644) (mean $\pm$ 1 SD [range]) on the right and 512 ± 60 mm^3 (406–610) on the left PCA (no asymmetry, and no age or sex effect). The intraobserver and interobserver variability were 6% and 8%, respectively. In right TLE patients, the mean right PCA volume was 18% smaller than that in control subjects ($p < 0.001$) and 15% smaller than in left TLE ($p < 0.001$). In left TLE, the mean left PCA volume was 16% smaller than in control subjects ($p < 0.001$) and 19% smaller than in right TLE ($p < 0.001$). Overall, 18 (46%) of the 39 patients had a greater than 20% volume reduction in the ipsilateral PCA. Bilateral atrophy was found in 7 (18%) of 39. Patients with hippocampal volumes of at least 2 SDs below the control mean had an 18% reduction in the mean PCA volume compared with patients without hippocampal atrophy ($p < 0.001$). Ipsilaterally, hippocampal ($r = 0.756$, $p < 0.01$), amygdaloid ($r = 0.548$, $p < 0.01$), and entorhinal ($r = 0.500$, $p < 0.01$) volumes correlated with the PCA volumes.

CONCLUSIONS: The quantification of PCA volume with MRI showed that the PCA is extensively damaged in chronic TLE patients, particularly in those with hippocampal atrophy.

COMMENTARY

Temporal lobe epilepsy (TLE) is the most common symptomatic partial seizure disorder in adult patients and a frequent indication for surgical treatment of intractable epilepsy. Patients with TLE may have a surgically remediable epileptic syndrome and may be favorable candidates for operative intervention. The region of seizure onset often involves the amygdalohippocampal complex in the mesial temporal lobe, that is, medial TLE. Less commonly, the ictal-onset zone is limited to the temporal neocortex. The hallmark pathology of medial TLE is hippocampal sclerosis with neuronal loss in the CA1, CA3, and CA4 hippocampal subfields, as well as tissue damage and gliosis extending into other mesial temporal structures. Individuals with extrahippocampal, neocortical TLE may have other types of pathologic substrates, such as foreign-tissue lesions.

The introduction of MRI permitted identification of hippocampal atrophy and signal-intensity change in patients with TLE who were being considered for epilepsy surgery (1,2). The anatomic structure of the hippocampal formation in the temporal horn of the lateral ventricle facilitated detection of volume loss associated with hippocampal sclerosis (2,3). The MRI-identified hippocampal structural changes were shown to be a surrogate for focal cell loss and proved to be a reliable indicator of the temporal lobe of seizure origin (3). Hippocampal morphologic changes associated with hippocampal sclerosis have correlated with a favorable operative outcome in patients with medial TLE undergoing surgical treatment. Visual inspection alone is usually sufficient to identify unilateral or asymmetric hippocampal formation atrophy. Quantitative volumetric studies permitted an objective assessment of unilateral or bilateral hippocampal atrophy associated with neuronal loss and were useful for research applications (1–4).

Previous studies using morphometric measurements have provided additional compelling evidence that extrahippocampal volume loss may occur in patients with medial TLE (2–7). The volume diminution occurred predominantly in gray matter structures directly connected to the epileptogenic hippocampal formation, such as the amygdala and entorhinal cortex, and may represent neuronal cell loss (3,7). The maximal region of atrophy is usually ipsilateral to the epileptic temporal lobe (2,3,7). Volumetric abnormalities also have been identified in the basal ganglia and cerebellum (4–6). The structural neuroimaging alterations have been most prominent in patients with hippocampal atrophy (2,6). Long-term intracranial EEG

recordings in one series demonstrated that the localization of the ictal-onset zone was concordant with the entorhinal cortical atrophy in 63% of patients with medial TLE (7).

A potential mechanism for these structural changes includes the anatomic and functional connections to the hippocampus in patients with medial TLE (2–8). The studies by Bonilha et al. and Gonçalves Pereira et al. support the hypothesis that direct connections between neuronal structures and the mesial temporal lobe account for the temporal lobe and thalamic structural alterations. Previous reports also suggested that the relation between the hippocampus and amygdala as well as between the entorhinal and perirhinal areas may explain the volume diminution ipsilateral to the epileptic temporal lobe. Another pathogenesis to be considered for the widespread morphologic alterations may be the recurrent seizures or the underlying symptomatic proconvulsant etiology (9). Conflicting evidence concerns the effect of repetitive seizure activity on neuronal function and structure (9,10). Recurrent seizures induce brain plasticity that may result in either neuronal cell loss or neuroprotection (9). Intractable epilepsy or generalized convulsive status epilepticus may induce progressive neuronal loss, hippocampal atrophy, and increase in susceptibility to network synchronization (6,9). The presence of generalized tonic–clonic seizures in one study did not correlate with hippocampal formation atrophy (10). Variably, sequential MRI studies in patients with intractable partial epilepsy show progressive hippocampal and extrahippocampal volume loss related to the repetitive seizures (6,9).

Potentially, seizure propagation to gray matter structures and the subcortical white matter connected to the medial temporal lobe may be the basis for the more extensive morphologic alterations (4–6). The study of Seidenberg et al. indicated that the white matter and gray matter changes may occur ipsilateral and contralateral to the epileptic brain tissue. The factors that correlated with the morphologic changes include the presence of a remote symptomatic etiology, early age at seizure onset, long duration of epilepsy, and an increase in seizure frequency. This outcome would suggest that the etiologic insult, combined with the progressive effects of seizures, may contribute to the structural changes. The findings in these investigations also may have important implications in understanding comorbid conditions that occur in individuals with TLE, including depression, cognitive impairment, and focal neurologic deficits.

Several pivotal questions remain to be answered regarding the implications and significance of these interesting neuroimaging observations. Ultimately, longitudinal studies using MRI will be necessary to see whether progressive morphologic abnormalities occur in patients with TLE (10). These three current investigations do not permit the identification of any one causative factor, such as neurodevelopment or repetitive seizures, as the etiology of the morphologic abnormalities involving white matter and gray matter. The importance of the neuroimaging findings with regard to seizure type, propensity to secondarily generalized tonic–clonic seizures, and status epilepticus should be elucidated. It is not known whether mesial temporal or more widespread anatomic changes are of prognostic importance in patients undergoing surgical treatment for TLE. The effect of contralateral or extratemporal volume loss on surgical outcome also is unknown. Determining the mechanism(s) for the morphologic alterations in TLE may have important implications in understanding epileptogenesis, the neural network in epilepsy, and potentially, neuroprotection.

by Gregory D. Cascino, MD

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