Significance of Fornix Atrophy in Temporal Lobe Epilepsy Surgery Outcome

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Background: Previous magnetic resonance imaging (MRI) studies have shown concurrent fornix atrophy in a large proportion of patients with hippocampal atrophy. The contribution of the fornix as an independent preoperative determinant of surgical outcome is unknown.

Objective: To evaluate the contribution of the fornix as a determinant of surgical outcome in patients with preoperatively determined temporal lobe epilepsy.

Methods: We selected 78 patients who had undergone anterior temporal lobectomy for intractable temporal lobe epilepsy at the University of Alabama at Birmingham Epilepsy Center during a 24-month period. All patients underwent standard presurgical investigations and intracranial investigations when needed. Magnetic resonance imaging volumetric studies were performed prior to surgery using previously published techniques. Patients were assessed regularly for postoperative seizure control. Outcome after at least 3 years was evaluated using Engel's classification for epilepsy. The χ² test was used to compare categorical data.

Results: Seventy-eight patients were included in this study. Eight patients were excluded because of inadequate follow-up. Thirty-five patients (44.9%) had unilateral isolated hippocampal atrophy exclusively on MRI volumetry, 29 (37.2%) had unilateral hippocampal atrophy with ipsilateral fornix atrophy, and 6 (7.7%) had isolated fornix atrophy without hippocampal atrophy. Twenty-eight patients (80%) in the unilateral hippocampal atrophy group were seizure free (ie, Engel class 1: patients who are completely seizure free with no aura and who do not receive antiepileptic drugs) compared with 21 patients (73%) in the fornix and hippocampal atrophy group (P = .57). All 6 patients with isolated fornix atrophy achieved an Engel's class 1 outcome.

Conclusions: These findings suggest that identification of fornix atrophy with or without associated hippocampal atrophy is not an important preoperative determinant of surgical outcome. However, in the presence of a normal hippocampus, fornix atrophy may be valuable in predicting seizure-free outcome.

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Temporal lobe epilepsy is associated with a relatively well-defined clinico-electrographic epileptic syndrome of localized anterior temporal lobe electroencephalographic abnormalities, memory dysfunction, and hippocampal atrophy or sclerosis on magnetic resonance imaging (MRI).1,2

Previous studies suggest that 60% to 80% of patients fulfilling MRI criteria of mesial temporal sclerosis can expect a good seizure outcome after temporal lobe surgery.1,4 Reasons for surgical failure in those satisfying the MRI criteria are poorly understood. Possibilities include bilateral mesial temporal sclerosis, conservative amygdalohippocampal resection,9 and occult dual pathology among others. Another possible explanation is the presence of more widespread mesial temporal structural damage, such as amygdalar atrophy or involvement of other limbic structures.7

Previous studies by our group have found concurrent fornix atrophy in a high percentage of patients with ipsilateral hippocampal atrophy.7 These findings reflect analogous pathologic changes to limbic circuit interconnected structures. The relevance of the limbic system as a neural circuitry to temporal lobe epilepsy is well recognized. Part of this circuit is known as the circuit of Papez.8 The limbic system constitutes hippocampal formation and additional structures such as the fornix, mammillary bodies, thalamus, cingulum, amygdala, and orbitofrontal cortex.

The importance of the fornix as an independent preoperative determinant of surgical outcome has not been examined and the best combination of MRI criteria for outcome is unknown. This study evalu-
ates the contribution of the fornix as a predictor of seizure outcome in patients with medically intractable temporal lobe epilepsy.

METHODS

SUBJECTS

We selected patients who had undergone anterior temporal lobectomy for intractable temporal lobe epilepsy at the University of Alabama at Birmingham Epilepsy Center during a 24-month period and who had a final diagnosis of mesial temporal lobe epilepsy. Inclusion criteria were preoperative MRI volumetric findings indicating unilateral isolated hippocampal atrophy, unilateral hippocampal atrophy with ipsilateral fornix atrophy, or isolated fornix atrophy without hippocampal atrophy, and at least 3 years of postoperative follow-up. Patients with foreign tissue lesions, dual pathology, MRI volumetric findings of bilateral hippocampal atrophy, and those with no evidence of hippocampal or fornix atrophy were excluded from the study. Seventy-eight patients met the inclusion criteria (37 with unilateral isolated hippocampal atrophy, 35 with unilateral hippocampal atrophy with ipsilateral fornix atrophy, and 6 with isolated fornix atrophy without hippocampal atrophy).

MRI ACQUISITION

The MRI studies were performed using a 1.5-T unit (ACS unit; Philips, Best, the Netherlands). A fast scout scan (axial and coronal images, 90 seconds) was obtained for proper positioning of the subject. After angulation correction, a series of sagittal T1-weighted spin-echo images were obtained with 5-mm sections. After these sagittal localizing images were taken, a 3-dimensional acquired image through the entire brain was obtained within an angulation perpendicular to the long axis of the hippocampus (repetition time, 20 milliseconds; echo time, 6.1 milliseconds; matrix size, 218 × 236 pixels; and field of view, 23 cm). In most patients, about 110 to 130 slices were obtained in the coronal plane. Image slice thickness was 1.5 mm with no gaps. If any set of images had motion artifact, it was repeated.

MRI ANALYSIS

The images were transferred to a workstation (Gyroview; Phillips) and analyzed using commercially available software (ISG Technologies Inc, Malton, Ontario). To minimize partial volume effect, the 3-dimensional MRI data were resampled as 1-mm-thick images (no gap) using multiple planes of reconstruction to follow the anatomical structure of the fornix. Volumetric measurements were performed using an interactive hand-contouring device. Zooming the image by power of 2 and optimizing contrast to facilitate differentiation between tissues enlarged each image. The hippocampus and fornix were measured. The slice volume was calculated by multiplying the area outlined by slice thickness. The total volume of the structures enlarged each image. The hippocampus and fornix were measured. The slice volume was calculated by multiplying the area outlined by slice thickness. The total volume of the structure then was calculated by adding each slice volume for the structure. Individual variance of the volume of structure of interest was normalized by the subject’s total intracranial volume using a previously validated method as follows:

\[ NV = OV - \text{Grad} \times (TCV1 - TCV\text{mean}), \]

where NV is the normalized hippocampal volume; OV, the observed hippocampal volume; Grad, the regression gradient or slope of the regression line of hippocampal regressed on total intracranial volume (TCV) for the control subjects; and TCV1 and TCV\text{mean}, the patient under study and the mean, respectively. The cranial volume was estimated from area measurements on 14 sagittal 5-mm-thick sections equally spaced throughout the cerebrum, using the same volume analysis program as that for the hippocampal volume measurements. The mean, SD, and 95% confidence interval were also determined for the healthy controls.

Intrarater and interrater reliability of volume measurements was assessed by repeated measurements performed by 2 observers (R.I.K. and E.B.) and repeated twice in the same control by the same observer. A control group of 17 healthy volunteers (mean age, 35 years; age range, 24–41 years) was used for comparison. One control was scanned twice because of motion artifact in the first study. There were 9 women and 8 men. Our group has described the method and anatomical boundaries for measuring the fornix previously. Abnormal volumes were defined as 2 SDs below the mean for the normalized data of the controls (see the “Results” section). Side-to-side hippocampal asymmetry was not considered.

PRESURGICAL EVALUATION

A complete evaluation included videoelectroencephalographic evaluation, MRI of the brain, and neuropsychological evaluation. In patients with non–MTS-temporal lobe epilepsy, positron emission tomographic scans followed by intracranial placement of electrodes was pursued.

SURGERY AND OUTCOME

Subpial aspiration technique was used for temporal resections, which included uncus, amygdala, and the anterior 2 cm of the hippocampus with minimal neocortical resection. Patients were assessed regularly for postoperative seizure control. All had at least 3 years of follow-up. Outcome at most recent follow-up was classified as either seizure free (ie, Engel’s classes 1: a, b, or c) or not seizure free.

PATHOLOGY

Representative tissue samples of the hippocampus were routinely obtained for analysis. Specimens were fixed in formalin and embedded in paraffin. Histologic sections of the hippocampus and temporal lobe were stained with hematoxylin-eosin and with glial fibrillary acidic protein. Pathologic classification using previous diagnostic criteria for mesial temporal sclerosis was used. Adequate hippocampal tissue was available for the diagnosis of hippocampal sclerosis in all subjects.

STATISTICAL ANALYSIS

The \( \chi^2 \) test was used to compare categorical data between the 3 groups. Determination of any relationship between volumes and duration of epilepsy, as well as age at seizure onset, was planned to be performed based on the initial findings.

RESULTS

Seventy-eight patients (47 females, 31 males; mean age, 32 years; age range, 13–58 years) met the inclusion criteria. The mean age of seizure onset was 9.7 years and the mean duration of epilepsy was 21.3 years. Eight patients were excluded because of inadequate follow-up. Based on MRI volumetry, 35 patients (45%) had unilateral isolated hippocampal atrophy while 29 (37%) had unilateral hippocampal atrophy with ipsilateral fornix atrophy. Six patients (8%) had isolated fornix atrophy with-
out hippocampal atrophy corresponding to the side of surgery. The mean (SD) volumes for healthy controls were as follows: right hippocampus, 3692 (293) mm$^3$; left hippocampus, 3575 (292) mm$^3$; right fornix, 47.0 (6.9) mm$^3$; and left fornix 46.0 (7.6) mm$^3$.

The mean age for the 35 patients with unilateral isolated hippocampal atrophy was 32.3 years (age range, 13-58 years). The mean age of epilepsy onset was 8.5 years (range, 10 months to 29 years). The mean duration of epilepsy was 22.8 years (range, 5-54 years). The mean affected hippocampal volume was 2430.2 mm$^3$. The mean fornix volume was 23.5 mm$^3$.

For the 29 patients with unilateral hippocampal atrophy with ipsilateral fornix atrophy, the mean age at evaluation was 29.4 years (age range, 14-61 years). The mean age of epilepsy onset was 10.3 years (age range, 9 months to 26 years). The mean duration of epilepsy was 19.2 years (range, 6-40 years). The mean hippocampal volume was 2316.7 mm$^3$. The mean fornix volume was 30.5 mm$^3$.

Six patients in this study were found to have isolated fornix atrophy without hippocampal atrophy (Table and the Figure). The mean age at evaluation was 35.2 years (age range, 20-46 years). The mean age at epilepsy onset was 13.5 years (age range, 4-23 years). The mean duration of epilepsy was 22.5 years (range, 15-38 years). The mean hippocampal volume was 3592.3 mm$^3$. The mean fornix volume was 29.0 mm$^3$. In this small group, the histopathological analysis revealed mesial temporal sclerosis in 3 patients, while gliosis of varying degrees was seen in the other 3 patients. No significant differences in patient features were found between the 3 groups.

### SURGICAL RESULTS

Twenty-eight (80%) in the unilateral isolated hippocampal atrophy group were seizure free (Engel class 1) at last follow-up, compared with 21 (73%) in the unilateral hippocampal atrophy with ipsilateral fornix atrophy group, and 6 (100%) in the isolated fornix atrophy group. No statistical differences between the 3 groups were found ($\chi^2$, 1.81; $P = .40$). The isolated fornix atrophy group was small and potential differences may not result from the statistical analysis, although all patients were seizure free in the postoperative period of analysis. The lack of significant difference in outcome between the groups precluded any further statistical correlation such as fornix volume loss and duration of epilepsy or age of seizure onset.

### COMMENT

This study demonstrates no statistically significant differences in surgical outcome between patients with unilateral isolated hippocampal atrophy and those with unilateral hippocampal atrophy with ipsilateral fornix atrophy. These findings suggest that identification of fornix atrophy by MRI in the presence of hippocampal atrophy is not an important preoperative determinant of surgical outcome. The findings may also suggest that hippocampal atrophy and fornix hippocampal atrophy may have a similar pathogenesis. Finally, these findings may suggest that the presence of fornix and hippocampal atrophy probably does not represent a distinct subgroup of mesial temporal lobe epilepsy. This is also supported by the absence of significant demographic and clinical differences between these 2 groups.

A myriad of qualitative MRI studies have suggested that certain limbic structures, such as the fornix and mammillary bodies, are atrophic in patients with mesial temporal sclerosis.13-16 These findings have been confirmed by quantitative analysis techniques.7 The coexistence of fornix atrophy in patients with epilepsy and hippocampal atrophy may suggest that these 2 abnormalities share a common pathogenesis and that certain limbic structures, such as the fornix and mammillary bodies, are atrophic in patients with mesial temporal sclerosis.
Pal atrophy initially was felt not to be coincidental but probably reflected analogous pathologic changes to limbic circuit interconnected structures. 

The existence of fornix atrophy may be secondary to wallerian degeneration from hippocampal cell damage, or as a result of abnormal excitotoxic damage to axonal flow. 

Evidence of increased excitability and inhibition may be associated with the sprouting of new excitatory and inhibitory hippocampal connections in the well-documented synaptic reorganization that is associated with hippocampal sclerosis. 

Furthermore, these changes are not observed in patients with extralimbic onset epilepsy. Although the cornu ammonis and the dentate gyrus are the major site of disease in mesial temporal sclerosis, studies have demonstrated the presence of histologic changes in other temporal structures such as the amygdala, entorhinal cortex, subiculum, and parahippocampal gyrus. 

Furthermore, neuronal loss and gliosis have been found in the thalamus and cerebellum. The pathologic abnormalities beyond the cornu ammonis often are less severe, suggesting that mesial temporal sclerosis is a peripherad (worse in the center and less abnormal toward the periphery) process that involves other interconnected limbic and extralimbic structures.

To our knowledge, the findings of this study have not been previously reported, although studies of outcome in patients undergoing temporal lobectomies for the treatment of temporal lobe epilepsy comparing amygdalal hippocampal vs only hippocampal atrophy have been performed. 

Arruda et al compared outcomes 1 year after surgery in patients with unilateral, bilateral, or no amygdala-hippocampal formation atrophy, based on volumetric MRI findings. Although they found a better outcome in patients with unilateral mesial temporal atrophy, the 2 surgical procedures applied to the different groups were equally effective, regardless of the pattern of atrophy. 

Ho et al found a better outcome in patients with a presurgical diagnosis of isolated hippocampal atrophy vs amygdalal hippocampal atrophy. From these studies one may conclude that the groups with only hippocampal atrophy vs amygdalal hippocampal atrophy probably have different pathogenesis. Our findings, however, contradict to a certain extent the above outcome studies in amygdalar and hippocampal atrophy models. 

Our study supports the hypothesis of secondary wallerian degeneration of the fornix owing to deafferentation, which indicates a similar pathogenic mechanism. Why some patients developed ipsilateral fornix atrophy while others with the same degree of hippocampal damage do not is perplexing. Although no obvious clinical or electrophysiologic differences were observed between groups, it is likely that a number of possible etiopathogenic mechanisms may explain the differences. Further studies are needed to elucidate these findings.

The presence of isolated fornix atrophy in the framework of a normal hippocampus in a small subset of patients with temporal lobe epilepsy raises the possibility that fornix atrophy in isolation may represent an independent structural marker of limbic damage similar to hippocampal sclerosis. The findings of seizure-free outcome in all patients with isolated fornix atrophy, albeit in a small group, are interesting. Given the difficulty of confidently localizing and determining prognosis for surgery in patients with normal hippocampi on MRI, this finding is important. Multiple studies indicate that the absence of hippocampal atrophy in a given patient undergoing temporal lobe surgery precludes good outcome with only 50% achieving seizure-free status. However, none of the previous studies investigated whether fornix atrophy was present in patients achieving seizure-free status. 

These findings parallel to some degree those of Jackson et al in patients with hippocampal end-folium sclerosis without hippocampal atrophy. End-folium sclerosis although rare (5%-10%) is important because surgical outcome is favorable. In these patients, hippocampal signal changes reflecting pathologic changes can be visualized. On this basis, some authors consider end-folium sclerosis as a subtype of mesial temporal sclerosis. 

Thus, even though isolated fornix atrophy may be less common, it may be associated with excellent surgical outcome following temporal lobe epilepsy surgery. If this holds true, it may be useful to investigate more in detail this issue since it may help predict outcome more accurately.

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REFERENCES


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