Ictal Fear in Temporal Lobe Epilepsy

Surgical Outcome and Focal Hippocampal Changes Revealed by Proton Magnetic Resonance Spectroscopy Imaging

Michael Feichtinger, MD; Elisabeth Pauli, PhD; Iris Schäfer; Knut W. Eberhardt, MD; Bernd Tomandl, MD; Johannes Huk, MD; Hermann Stefan, MD

Background: Ictal fear (IF) is most frequently associated with epileptic discharges from mesial temporal areas.

Objectives: To determine whether patients with IF were more likely to become seizure free after anteromesial temporal lobe resection compared with those without IF and whether they show more anteriorly pronounced metabolic changes assessed by means of multivoxel magnetic resonance spectroscopy (MRS) along the hippocampal axis.

Methods: Surgical outcome was assessed in 33 consecutive patients with temporal lobe epilepsy after a mean follow-up of 25 months (range, 12-38 months). Proton multivoxel MRS of the hippocampal formation was applied to detect regional differences along the axis of the hippocampus in patients with and without IF. Magnetic resonance tomography showed typical features of hippocampal sclerosis in all patients.

Results: Twelve (36%) of the 33 patients reported fear at the beginning of their habitual seizures. Eleven of these patients were seizure free postoperatively. In contrast, only 11 of 21 patients without IF had a favorable outcome. Results of MRS revealed significantly higher pathologic N-acetylaspartate–choline ratios in the anterior portion of the hippocampal formation in patients with than in those without IF, indicating focal metabolic and/or morphologic changes in the head of the hippocampus.

Conclusions: These results indicate the importance of diagnosing auras with IF to provide a more detailed prognosis of the surgical outcome. In addition, our data emphasize that multivoxel MRS is a valuable tool in the presurgical evaluation, as it may reveal different topographical patterns of hippocampal sclerosis.

Arch Neurol. 2001;58:771-777

Fear is among the most common experiential phenomena elicited by temporal lobe epileptic discharge.1-7 The leading role of the amygdala, as well as that of the hippocampus and the parahippocampal gyrus, in the mechanisms of inducing a fearful perception is well established by studies of electrical stimulation performed intraoperatively8 or during presurgical evaluation using intracranial depth electrodes.2,9-12

Surgical resection of the temporal lobe became a widely accepted therapeutic approach to control complex partial seizures.13 In patients with fear as an initial manifestation of their epileptic seizures (IF patients), ictal discharges were reported to originate from the amygdala, the hippocampus, or its near vicinity,2,14 i.e., regions that are removed by temporal lobectomy. We therefore investigated whether the presence of IF may predict a favorable outcome of surgical therapy.

Proton (H) magnetic resonance spectra obtained by magnetic resonance spectroscopic imaging (MRSI) provide detailed information about metabolic changes of the mesial temporal region using signals from N-acetylaspartate (NAA)-, choline (Cho)-, and creatine (Cr)-containing compounds.15-20 Because NAA is primarily located in mature neurons, a reduced NAA signal is generally interpreted as neuronal loss or dysfunction.21-23 Concentrations of Cho and Cr are reported to be higher in the glia22,23; thus, a decrease of levels of Cho and, to a lesser extent, Cr24 may indicate astrocytosis. Unilateral changes (a reduced NAA/Cho ratio) have been shown to be of value for preoperative focus localization in epilepsy surgery.16,17,20,21-23

Because atrophy of the amygdala and the hippocampus correlates with the presence of IF,20 analysis of these structures by means of MRS could confirm the involvement of these regions in the perception of IF. Unfortunately, MRS of the amygdala is not applicable because of its small size, its difficult differentiation to adjacent structures,27,28 and the interference of neighboring cerebral and extracerebral tis-
 PATIENTS AND METHODS

PATIENTS

We included 33 consecutive patients with unilateral medically intractable temporal lobe epilepsy (TLE) (19 male and 14 female) considered for surgical treatment at the Epilepsy Center of the Department of Neurology, University Erlangen- Nuremberg, Erlangen, Germany. The mean age was 34 years (range, 20-48 years). The epileptogenic temporal lobe was identified by means of a comprehensive evaluation, including a detailed history and neurologic examination, prolonged electroencephalographic and video monitoring with scalp and sphenoidal electrodes for ictal analysis, neuropsychological assessment, and MRI. In 5 patients, electrodes for recording intracranially ictal activity were implanted.

Only patients with distinct unilateral focus within the temporal lobe were scheduled for epilepsy surgery. These patients were also included in the current study, since they fulfilled the following inclusion criteria: (1) typical seizure symptoms for TLE, (2) all seizures arising from a single temporal lobe, and (3) typical findings of mesial temporal sclerosis on MRI (ie, atrophy and/or decreased signal on T1- and/or increased signal on T2-weighted images of the hippocampus and/or amygdala). Thus, these patients represented a homogeneous group of good candidates for temporal lobectomy. This homogeneity is crucial for determination of whether IF is a prognostic variable independent from already established predicting factors.

SURGICAL PROCEDURE

All 33 patients underwent anteromesial temporal resection performed by the same neurosurgeon. All patients received at least a selective amygdalohippocampectomy, including the parahippocampal gyrus. Additional neocortical resection was individually tailored, guided by intraoperative electrocorticography to keep resected brain volume restricted to epileptogenic tissue. The mean extent of the resected hippocampus was 24 mm (range, 16-40 mm).

Postoperative seizure control outcome was assessed 3 and 6 months and each year after the operation, using the classification according to Engel. Only patients with a follow-up of at least 12 months were included in the study. For further statistical analysis, outcome was divided into a seizure-free group (Engel class 1) and a non–seizure-free group (Engel classes 2-4).

PATHOLOGICAL FINDINGS

All available brain specimens were prepared and stained for histopathological examination performed by a pathologist blinded to the results of MRSI. Hippocampal sclerosis (HS) was defined as neuronal loss and marked proliferation of astrocytes involving the hippocampus, preferentially in the sectors CA1 and CA3/4. In 3 cases, hippocampal sections did not allow a proper diagnosis of an HS owing to fragmentation of the specimen. Histopathological analysis of the amygdala was not available.

CHARACTERIZATION AND CLASSIFICATION OF IF AND AURAS

Assessment of the presence of IF included a detailed review of available medical records and an accurate inquiry about the type of auras. A standardized interview was used, including the assessment of fear and fear-related emotional, cognitive, and autonomous signs as part of an aura or in the course of a habitual seizure. Care was taken to avoid suggestive questioning. For further investigation, the term ictal fear was accepted only (1) if it was reported as being concomitant with an epileptic seizure; (2) if it arose spontaneously, out of context; and (3) if it could be clearly distinguished from the fear of a seizure. Type and presence of any other sensations or phenomena associated with seizures were assessed in a similar manner.

ROUTINE MRI

Routine MRI examinations were performed on a 1.5-T whole-body MR system (Siemens Magnetom Vision; Siemens, Erlangen, Germany) according to a standard protocol, including transversal and coronal T2-weighted targeted systemic exposure, coronal fluid-attenuated inversion recovery, coronal T1-weighted 3-dimensional-magnetization-prepared rapid acquisition gradient echo, and coronal inversion recovery. Atrophy of the hippocampus and/or amygdala seen by means of visual inspection and/or as hyperintensity inside the hippocampus on T2-weighted images was taken as criterion for mesial temporal sclerosis.

MULTIVOXEL 1H-MRSI

During presurgical evaluation, 27 patients underwent multivoxel 1H-MRSI of the hippocampal formation after written informed consent was obtained.

We acquired MRSI using a 1.5-T whole-body MR system (Siemens Magnetom Vision). To establish normative data, an additional 30 healthy volunteers (17 male and 13 female subjects; age range, 16-47 years; mean age, 31 years) underwent MRSI examinations.

Acquisition of MR spectra was performed using a 2-dimensional (2-D) hybrid chemical shift imaging (CSI) technique. Three orthogonal slice-selective high-frequency pulses were applied for preselection of a region of excitation, avoiding the intensive signal of subcutaneous fat. Phase encoding (16 × 16 matrix) was used for in-plane spatial resolution and chemical shift-selective Gaussian pulses for water suppression. To optimize the homogeneity of the

RESULTS

Twelve patients (36%) reported fear as an initial manifestation of their habitual seizures. Five of these patients described an accompanying epigastric sensation; 2 patients, a cephalic aura; and 3 patients, fear as a single phenomenon. The remaining symptoms included déjà vu...
magnetic field, an automatic multivalue-projection shim was applied.

A series of orthogonal T1-weighted images for localization were obtained, with the transaxial plane approximately parallel to the long axis of the hippocampus. The preselected region of excitation was positioned on 3 orthogonal base images in the left and right temporal lobe. The volume of interest was chosen, including a column of 3 voxels (voxels 1-3) in the transversal plane in the hippocampal formation. As shown in Figure 1, this column was chosen to obtain data mainly from the hippocampus with little or no interference from adjacent regions. The position was carefully checked and meticulously adjusted in all 3 orthogonal sections to ensure identical placement in all subjects. After interactive volume-selective shimming and water suppression (frequency-selective 90° Gauss pulse), a 2-D 1H CSI spin-echo protocol was selected (acquisition variables: repetition time, 1500 milliseconds; echo time, 135 milliseconds; field of view, 200 mm2; matrix, 16 × 16). The nominal result size of individual voxels was 1.2 × 1.2 cm in the sagittal and coronal planes and 1.5 cm in the transversal plane (2.16 cm3). The acquisition time for each hippocampus was 6 minutes 31 seconds. The total time required for MRS measurement was about 45 minutes.

MRS DATA PROCESSING

The CSI raw data were evaluated using a standard automatic CSI postprocessing program (Siemens Magnetom Vision). Spectra were displayed on transversal T1-weighted MRI scans with an overlaid grid indicating the anatomic location from where the data were derived. The postprocessing protocol used k-space filtering, 2-D fast Fourier transformation to real space, gaussian filtering of the time-domain data in each voxel, fast Fourier transformation to the frequency domain, baseline and phase correction, and curve fitting for the peaks of NAA and Cho. The ratios of the fitted peak integrals for NAA and Cho were evaluated and integration of the Cr peak was omitted. Although many studies included Cr for assessment, we preferred the NAA/Cho ratio, as this ratio is reported to be highly reliable in detecting HS in TLE.16,20,24 Spectra of poor quality were excluded from the analyses, for instance, when Cr and Cho peaks were not resolved.

The NAA/Cho ratios of each voxel were compared with the average ratio of the corresponding, homotopically located voxel in the control subjects. Pathologic voxel values (PXpatient) in patients were defined as differences between the patient’s NAA/Cho ratio (R) of the specific voxel (X = 1-3) and the 2-SD threshold of the corresponding voxel (X = 1-3) in controls20,31 as seen in the following equation:

\[ PX_{\text{patient}} = \frac{M(R_{\text{control}}) - 2 \text{ SD}(R_{\text{control}}) - R_{\text{pat}}}{2}, \]

where M indicates the mean voxel value of the controls.

Deviation from the healthy controls is more pronounced as the negative pathologic value (PXpatient) increases. The value 0 was assigned when no abnormality was found.

A CSI score representing the mean pathologic values of voxels 1, 2, and 3 (v1, v2, and v3) was calculated using the following equation20,31,32:

\[ \text{CSI} = \frac{P_{v1} + P_{v2} + P_{v3}}{3}, \]

To determine ipsilateral, contralateral, and bilateral abnormalities, we computed the laterality ratio (r) using the following equation:

\[ r = \frac{(\text{CSI}_{\text{ipsi}} - \text{CSI}_{\text{contra}})}{(\text{CSI}_{\text{ipsi}} + \text{CSI}_{\text{contra}})}, \]

where ipsi and contra refer to the ipsilateral and contralateral sides of resection. Thus, a CSI laterality ratio of r = 1 reflects ipsilateral CSI changes, and a ratio of r = −1 reflects exclusively contralateral CSI changes. A ratio of r = 0 corresponds to bilateral CSI changes but would also be seen in cases of no abnormality. For practical reasons, results were classified as strictly ipsilateral (0.25 < r ≤ 1), strictly contralateral (−0.25 > r ≥ −1), and bilateral (−0.25 < r < 0.25).

To evaluate whether anterior parts of the hippocampus (predominantly the head) show metabolic changes different from those of the posterior parts, separate comparison of single-voxel data (Pv1, Pv2, and Pv3) in patients with and without IF was performed. To assess the prevalence of different distribution patterns, we used the following equation to compute difference score (Ip) of the pathologic values of the anterior (Pv1 and Pv2) and posterior voxels (Pv3):

\[ Ip = \frac{(P_{v1} + P_{v2})}{2} - P_{v3}. \]

STATISTICAL ANALYSIS

Statistical analysis was performed using commercially available software (SPSS E 8.0 for Windows 95; SPSS Inc, Chicago, Ill). Inference statistical decisions were based on a significance level of α ≤ .05.

We performed χ2 tests (Fisher exact test) to evaluate the relation between the presence or absence of IF with seizure outcome and the prevalence of different spectroscopic results.

For evaluation of the severity of abnormality ipsilateral to the side undergoing operation in IF and non-IF patients, 1-way analysis of variance (ANOVA) with IF as between-subject factor was computed separately for the following dependent variables: CSI score; pathologic values of voxels 1, 2, and 3; and the NAA/Cho ratio of voxels 1, 2, and 3.

IF AND OUTCOME

Postoperative outcome assessment was possible in all 33 patients (average postoperative period, 25 months [range, 12-38 months]). According to the Engel classification, 22 patients became seizure free (Engel class 1), 8 patients had rare disabling seizures (Engel class 2), 1 pa-
tient had an improvement in seizure frequency of greater than 80% (Engel class 3), and 2 patients reported no improvement (Engel class 4).

Eleven of 12 IF patients had an excellent outcome, whereas only 11 of 21 non-IF patients were classified as seizure free (Engel class 1) (2-sided Fisher exact test, \( P = .03 \)) (Figure 2). No other aura showed a clear relation to postoperative outcome.

PATHOLOGIC CSI SCORES AND THEIR RELATION TO HS AND IF

In 24 patients, comparison of ipsilateral CSI scores with the histopathological diagnosis of an HS was possible. Pathologic CSI scores were measured in 10 (59%) of 17 cases with histologically proven HS; normal CSI scores were found in 6 of 7 patients without HS. Two of 3 cases with insufficient specimen for histological analysis also showed pathologic CSI scores ipsilaterally.

Concerning the frequency of bilateral or contralateral CSI score changes, no significant difference could be found between the IF and the non-IF patient groups.

IPSILATERAL NAA/Cho RATIOS AND IF

Separate comparison of the ipsilateral NAA/Cho ratio in voxels 1, 2, and 3 revealed marked differences between IF and non-IF patients; results of 1-way ANOVA showed significantly lower ratios in the anterior part of the hippocampus (voxels 1 and 2) in IF patients (voxel 1, \( F_{1,25} = 4.78 \) \( P = .04 \); voxel 2, \( F_{1,26} = 9.29 \) \( P = .005 \)) (Figure 3 and Table 1).

IPSILATERAL PATHOLOGIC CSI VALUES AND IF

A similar relation was found when ipsilateral pathologic values for each voxel (\( P_{v1}, P_{v2}, \) and \( P_{v3} \)) were compared between groups (voxel 1, \( F_{1,25} = 5.93 \) \( P = .02 \); voxel 2, \( F_{1,25} = 14.98 \) \( P = .001 \)) (Table 1). Pathologic values of voxel 3 did not differ significantly between IF and non-IF patients.
The mean pathologic value of all 3 voxels (CSI score) also showed significantly lower scores (ie, more abnormal compared with the controls' 2-SD threshold) in IF patients compared with non-IF patients (1-way ANOVA, $F_{1.26} = 5.41$ [P = .03]) (Table 1).

In all 6 IF patients with a pathologic CSI score, changes in the anterior hippocampus ($I_{ap} < 0$) were more pronounced, whereas in 6 of 7 non-IF patients, abnormality was predominantly located posteriorly ($I_{ap} > 0$). One non-IF patient had higher pathologic values in the anterior hippocampus (2-sided Fisher exact test, P = .005) (Table 2).

### Table 1. NAA/Cho Ratio, Pathologic Values for Voxels, and CSI Score in Relation to Ictal Fear*

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 30)</th>
<th>IF Patients (n = 10)</th>
<th>Non-IF Patients (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cho ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voxel 1</td>
<td>1.23 ± 0.24</td>
<td>0.76‡</td>
<td>1.00</td>
</tr>
<tr>
<td>Voxel 2</td>
<td>1.38 ± 0.24</td>
<td>0.95‡</td>
<td>1.16</td>
</tr>
<tr>
<td>Voxel 3</td>
<td>1.75 ± 0.26</td>
<td>1.53</td>
<td>1.43</td>
</tr>
<tr>
<td>Pathologic values§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voxel 1</td>
<td>...</td>
<td>−0.08‡</td>
<td>−0.01</td>
</tr>
<tr>
<td>Voxel 2</td>
<td>...</td>
<td>−0.01‡</td>
<td>0.00</td>
</tr>
<tr>
<td>Voxel 3</td>
<td>...</td>
<td>−0.03</td>
<td>−0.06</td>
</tr>
<tr>
<td>CSI score¶</td>
<td>...</td>
<td>−0.07‡</td>
<td>−0.02</td>
</tr>
</tbody>
</table>

* NAA indicates N-acetylaspartate; Cho, choline; CSI, chemical shift imaging; and IF, ictal fear.
† Values represent mean NAA/Cho ratio ± 1 SD.
‡ P < .05
§ Values represent mean pathologic value of voxels 1 to 3 in IF and non-IF groups.
¶ Pathologic voxel values are calculated as difference between each patient's NAA/Cho ratio of the specific voxel (1 to 3) and the 2-SD threshold of the corresponding voxel of controls. Lower score stands, therefore, for higher pathologic metabolic changes in voxel area compared with healthy control subjects.

### Table 2. Frequencies of Different Distribution Patterns in Patients With and Without Ictal Fear*

<table>
<thead>
<tr>
<th>Distribution Pattern†</th>
<th>IF Patients</th>
<th>Non-IF Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior ($I_{ap}&lt;0$)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Posterior ($I_{ap}&gt;0$)</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

* IF indicates ictal fear, P = .005, 2-sided Fisher exact test.
† Calculated applying a difference score ($I_{ap}$) between pathologic value of the 2 anterior and the posterior voxels ($P_{an}$, $P_{ap}$, and $P_{pp}$), according to the following formula: $I_{ap} = [(P_{an} + P_{pp})/2] - P_{ap}$. Because pathologic voxel values have negative signs, $I_{ap}<0$ refers to predominantly anterior abnormality and $I_{ap}>0$ refers to posteriorly accentuated abnormality.

There is no doubt that the mesial temporal regions and especially the amygdala play a pivotal role in the mediation of fearful emotion. This is supported by numerous studies in the production of fear by electrical stimulation of the amygdala. Stimulation of the hippocampus and the parahippocampal gyrus produced fear less often. However, this research indicates that these structures are involved in the mediation of fear, at least under certain circumstances.

We hypothesized that the presence of IF could be related to a satisfying seizure outcome after surgical treatment, when resections include the amygdala, the hippocampus, and the parahippocampal gyrus. Our study confirmed this hypothesis in demonstrating a close relation between favorable postoperative seizure control and the presence of IF. This was not seen for any other aura. Previous studies have addressed the prognostic significance of the type of aura concerning postoperative seizure control and could not find any aura to be of predictive value. This discrepancy might be explained by differences in patient selection criteria, classification of aura types, or assessment of IF. The term ictal fear should be used exclusively for a sudden, often short, fearful affect at the beginning of or during an epileptic seizure, without context or any relation to a precedent causal perception or cognition. The intensity may vary from a slight trace of anxiety to a feeling of intense terror. The predominance of other auras or anterograde amnesia may reduce subjective awareness of fear in some individuals. Thus, only a direct and standardized questioning, as performed in our study, enables the most reliable assessment of IF.

Another interesting relation to the presence of IF could be detected when we analyzed $^1$H-MRS data of the ipsilateral hippocampus (related to the side that underwent operation). The IF patients had significantly higher pathologic values in the anterior 2 voxels (voxels 1 and 2). These results indicate different distribution patterns concerning the degree of neuronal loss (or dysfunction) and reactive astrogliosis along the hippocampal axis in IF and non-IF patients. On the basis of postmortem or postoperative histopathological examination, topographical differences of neuronal loss within the hippocampus have been described repeatedly. When qualitative and volumetric MRI techniques were applied for differentiation between focal and diffuse HS, contradicting results were reported. Several studies described a focal accentuated atrophy in the anterior portion of the hippocampus in most of their patients. However, 2 studies reported diffuse atrophy to be the most frequent HS variant. Actually, it is controversial whether a different distribution of sclerotic changes bears any significance for seizure outcome. Kim et al suggested that distinction of focal and diffuse abnormality did not appear to be essential for predicting postoperative seizure control. In contrast, Babb et al classified the following 2 patterns of HS with implications concerning surgical outcome: a diffuse pattern (ie, equally distributed neuronal loss in the hippocampal head and body) with less favorable surgical outcome, and a focal pattern (neuronal loss predominantly in the head of the hippocampus).

The present study confirms the latter observation and stresses the value of the assessment of different distribution patterns. That IF is related to focal anterior abnormality is important, as the resected brain volume should be restricted to epileptogenic tissue. Moreover, the extent of resection influences the degree of postoperative neuropsychological dysfunction.

Previous studies assessing the value of MRS in TLE have paid little attention to the detection of different

©2001 American Medical Association. All rights reserved.
Because the total volume of all 3 selected voxels is somewhat larger (>6.48 cm³) than the estimated volume of the hippocampus (approximately 4 cm³), a certain influence of adjacent tissue could not be prevented. This may be particularly true in cases with atrophied hippocampus. To assess whether this volume loss influences MRS data, further correlation studies between MRSI and volumetric measurements along the hippocampal axis are needed. In our patient population, atrophy (assessed by means of visual inspection) was not related to a higher prevalence of pathologic MRSI spectra.

When looking for differences along the hippocampal axis in IF patients, we assumed the anterior voxel (voxel 1) would show the highest pathologic values because of its close vicinity to the amygdala. Indeed, our results demonstrate a significant relation of anterior abnormality in the IF patients, which allows speculations about a concomitant sclerosis of the amygdala. The fact that voxels 1 and 2 are similarly associated with IF argues for higher involvement of the anterior hippocampal portion in the mechanisms of fear than previously presumed. Interestingly, Miller et al.34 found IF in a higher percentage when amygdala and hippocampus were both sclerotic compared with sole sclerosis of amygdala. Actually, several authors estimated sclerosis of the amygdala to be combined with HS in up to 60% of patients.28,47–50 To confirm our findings, future studies concerning the correlation between amygdala volume and spectroscopic findings of the hippocampus and studies on higher numbers of patients (to rule out possible sample bias due to small patient number) are currently planned.

CONCLUSIONS

Our study supports the concept that IF is related to a measurable abnormality within the anterior mesial temporal regions. It underlines the role of the hippocampus in the presence of this affective ictal state and emphasizes the importance of MRS for detecting different topographical patterns of HS. Our observation that IF patients represent a population with favorable seizure relief after anteromesial lobectomy may be clinically significant when planning surgical therapy and when counseling patients with TLE.

Accepted for publication October 4, 2000.

Corresponding author and reprints: Hermann Stefan, MD, Department of Neurology, University Erlangen–Nuremberg, Schwabachanlage 6, D-91054 Erlangen, Germany (e-mail: hermann.stefan@neuro.med.uni-erlangen.de).

REFERENCES