Major depression in temporal lobe epilepsy with hippocampal sclerosis: clinical and imaging correlates

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ABSTRACT

Purpose: Refractory temporal lobe epilepsy (TLE) is often associated with hippocampal sclerosis (HS). Patients with Major Depression (MD) may also show structural abnormalities in the limbic system. Co-occurrence of TLE with HS and MD is not uncommon. We investigate clinical and morphological characteristics of TLE patients in relation to MD.

Methods: Thirty-four TLE patients with HS were assessed at a Comprehensive Epilepsy Program. All relevant clinical data were obtained, including the history of antecedent events to epilepsy. MD was diagnosed based on detailed psychiatric investigation. MRI was used to measure the volume and tissue signal (T2-relaxometry) of the hippocampus and amygdala. The imaging data were expressed as percentage of the values obtained in a series of 55 controls.

Results: A history of MD was present in 15 (44%) of the 34 patients. Patients with MD had a longer duration of their epilepsy ($p<0.05$), and a lower frequency of antecedent events (13% with MD, 58% without MD, $p<0.05$). Both groups had a similar degree of ipsilateral HS (small hippocampal volume, increased hippocampal T2-relaxation time), and demonstrated bilateral amygdaloid atrophy. However, the contralateral amygdala showed lower signal in presence of MD (97 ±9 msec; no MD: 103 ±8 msec, ANCOVA, $p=0.02$).

Conclusion: The integrity of the amygdala may influence mood disturbances in TLE patients with HS, as depression was associated with a relative preservation of the contralateral amygdala. In contrast, hippocampal abnormalities were not related to the presence of depression.

INTRODUCTION

Refractory temporal lobe epilepsy (TLE) is a chronic disease, associated with a major social burden reflected in reduced quality of life. Refractory TLE is often associated with mood disorders, particularly with depression. The incidence of depressive disorders in patients with epilepsy has been estimated to range between 30% and 70% (1, 2), which indicates that depression is the most frequent co-morbidity of epilepsy. It has also been suggested that the presence of depression has an even more negative effect on the quality of life than seizure frequency (3). The clinical presentations of depressive disorders in epilepsy can be identical to that of such disorders in non-epileptic patients and can include major depression, bipolar and dysthymic disorders, and minor depression (4). Kanner suggested that the relationship between epilepsy and depression is 'bi-directional' with the presence of a common pathogenic process facilitating the occurrence of one disease in the presence of the other (4). Supportive for this model is that similar structures of the limbic network are involved in both diseases. In a Single Photon Emission Computerized Tomography (SPECT) study it was demonstrated that depressed epilepsy patients show relatively increased blood flow in the limbic system, when compared to not depressed patients (5), supporting the importance of the limbic system in depression associated with epilepsy. The hippocampus and the amygdala are the prominent mesial temporal structures of the limbic network, and may have significant roles in this 'bi-directional' relationship.

Recent research on patients with depression alone has suggested structural as well as functional changes in the limbic network. Several studies have demonstrated a reduction of the hippocampal volume in patients with major depression (6-8), as well as with post-traumatic stress disorder (9). Whereas the hippocampus is primarily involved in memory consolidation (10), the amygdala has been associated with the processing of emotions, particularly negative emotions (11). The amygdala appears to undergo functional alterations (12, 13), as well as structural changes (12, 14) in patients with depression. However, there is some controversy in the literature on the direction of the volumetric changes of the amygdala (15). The function of the amygdala in the interpretation of emotional meanings may be altered in depression (16).

On the other hand, mesial temporal abnormalities are the most common single abnormality associated with temporal lobe epilepsy (TLE) (17). Hippocampal sclerosis (HS) is the most common lesion in patients with TLE, refractory to antiepileptic medication. Around 60% of HS patients have a history of a precipitating injury, such as prolonged febrile convulsions in early childhood. These antecedent events to the development of TLE are thought to induce an epileptogenic lesion to the hippocampus (18). These observations support that HS is an acquired lesion (19). Hippocampal sclerosis can be diagnosed with MR imaging (20). The reduction in hippocampal volume and the increase in the T2-weighted signal intensity can be quantified (21). Patients with antecedent events have pronounced hippocampal abnormalities, as compared to TLE patients in whom no antecedents have been documented (22).

Despite the known relationship between TLE and depression, only a few studies have investigated whether patients with this co-morbidity display a characteristic pattern of clinical and imaging findings, distinguished from patients with isolated TLE. Several

studies demonstrated altered morphology of the mesial temporal structures in TLE patients with associated aggressive behaviour (23) or psychosis (24, 25), whereas others have investigated the predictive value of clinical epilepsy characteristics, such as seizure focus lateralization, on the co-occurrence of depression in TLE (26). However, the relationship between clinical and morphological characteristics on the co-occurrence of TLE and depression has not been investigated to date. We aim to assess whether TLE patients with associated major depression have a different pattern of hippocampal and amygdaloid damage, and of clinical epilepsy characteristics than TLE patients without such mood disorders.

METHODS

Patients

We studied 34 consecutive patients with refractory temporal lobe epilepsy (TLE) associated with hippocampal sclerosis (HS) that had detailed psychiatric assessment as part of their pre-surgical epilepsy evaluation between 1/2003 and 10/2004. All patients were assessed in the comprehensive Epilepsy Program (CEP) of Austin Health, Melbourne. These investigations included clinical characterisation, video-EEG telemetry, psychiatric and neuropsychological assessment, Magnetic Resonance Imaging (MRI), and in the majority of the cases positron emission tomography (PET) as well as ictal and interictal single photon emission tomography (SPECT). The diagnosis of HS was based on an epilepsy-dedicated 1.5T MR protocol using established criteria (27). The diagnosis of TLE was based on the decision of the CEP meeting, which takes all available information from all investigations into account, and formulates a recommendation for epilepsy surgery. The ipsilateral side indicates the side of the seizure focus. Significant antecedent events included severe peri-natal complications, severe post-natal head injury, significant cerebral infection, stroke, and complicated febrile seizures, as previously described by our group (28). All other risk factors (e.g. prematurity, uncomplicated febrile seizures) were not regarded as significant. The age at onset of epilepsy was defined as the age at the first habitual seizure. Seizure characteristics were expressed as frequency of complex partial seizures (CPS), and occurrence of generalized tonic clonic seizures (GTCS). The number of CPS per week was counted based on seizure diaries kept during the three months leading up to the inpatient monitoring (CEP). The patients and their cares received appropriate instructions on how to keep the diary in their outpatient visits. The presence or absence of GTCS as part of seizure semiology was identified based on patient histories.

Diagnosis of depression: The psychiatric assessment was performed routinely in all patients as part of the pre-surgical investigation of the CEP program. It was conducted in all subjects by a consultant neuropsychiatrist, experienced in the assessment of psychiatric aspects of epilepsy (MH). This psychiatric evaluation was based on an approximately hour long semi-structured interview, providing diagnosis according to DSM-IV criteria (APA, 1994). The interview was summarized and the diagnosis recorded in the patients file at the time of the investigation. For the purpose of this study, MH also performed a retrospective file audit of all subjects in order to maximise the classification of psychiatric symptoms. The TLE patients were classified as having the

co-morbidity major depression when they had either current major depression, or had suffered from major depression in the past. Past or current use of anti-depressants was noted. Minor depressive mood swings were not considered as qualifying for the diagnosis. Patients with psychotic disorders, or suffering from other psychiatric diseases were not included in the study.

The study was approved by the Austin Health Human Research Ethics Committee, and all subjects gave informed consent to participate.

MR experiments

Research MR imaging was performed on a 3T GE LX Horizon scanner (Milwaukee, USA). For the volumetric analysis we acquired T1 weighted images using a fast spoiled gradient recalled echo at steady state (FSPGR) sequence (TR/TE 8.9/1.9, flip angle 20, matrix size 256x256 and a field of view (FOV) of 25x18.75cm) with contiguous coronal slices of 1.5mm thickness. For the T2-relaxometry analysis we used a Carr-Purcell-Meiboom-Gill (CPMG) sequence with eight images per location at echo times between 28ms and 231ms (TR 2080ms, 8 echoes per location, 256 x 128 matrix, 1NEX, 24cm FOV, 24 slices 5mm thick, no gap) with an acquisition time of 10 minutes. The images were acquired perpendicular to the long axis of the hippocampus.

Measurements: Volumetric measurements were performed using NIH-image software (NIH-image 1.63, available at http://rsb.info.nih.gov/nih-image). Measurement of hippocampal, amygdaloid and whole brain volumes used previously described methods (29). Standard anatomical atlases and relevant previous publication were used as guidelines for the hippocampal and amygdaloid measurements (30). Hippocampi and the amygdalae were manually outlined at each second slice, from posterior to anterior, and the slice volumes were summed.

The T2 relaxation times were measured with Functool® (GE Medical Systems, Milwaukee, WI). The analysis fits a single exponential to signal intensity values of corresponding pixels from each of the eight images per slice location. Measurement of the T2 relaxation times was achieved by placing a circular region of interest over a predefined area of anatomy, carefully avoiding inclusion of CSF. All measurements were performed bilaterally, using anatomical landmarks. We measured the T2-relaxation time bilaterally in the hippocampus and amygdala. In each subject, the ROI comprised of the maximal possible circular region within the boundaries of the structure, as previously described (21). This approach has been previously validated to give precise and reliable measurements for the most complex ROI included, the hippocampus.

All measurements were performed blinded to the psychiatric diagnosis of the subjects. All values were expressed as ipsilateral and contralateral to the seizure focus. As normative data of volumetric measurements are gender dependent, all values were expressed as percentage of corresponding values obtained from controls of the same gender, as described previously by our group (31). The control series consisted of 55 controls (mean age 34 ±9 years, 29 men). These controls were free of any neurological or psychiatric disease, as based on a routine questionnaire, and had normal MR imaging. The mean hippocampal volume of these controls was 2661±378 mm3, the amygdaloid volume 1083 ±179 mm3, and the brain volume 1184 ±135 cm3. The T2-relaxation time was in the hippocampus 90±3 msec, and in the amygdala 84 ±3 msec.

Data analysis: Differences in clinical and imaging findings were assessed between patients with and without major depression. Continuous data were assessed using analysis of variance (ANCOVA), with the age at examination included as a co-variate. For the volumetric analysis, the brain volume was added as a second co-variate. Categorical data were assessed using Chi Square tests (Fisher's exact p-value given). A p-value of ≤ 0.05 was regarded as significant.

RESULTS

Epilepsy characteristics and depression

Of the 34 TLE-HS patients, 15 (44%) had a diagnosis of Major Depression (MD). At the time of the investigation, five HS patients with MD displayed current symptoms of depression and nine were on anti-depressants. Gender (15 males: 7 with MD, 8 without MD) and seizure focus side (24 left HS: 12 with MD, 12 without MD) was not different between depressed and not depressed HS patients (table 1). The age at examination, and the age at the first habitual seizure did not differ between HS patients with and without MD. However, HS patients with Major Depression had in average a 10 year longer duration of their epilepsy ($p<0.05$, ANOVA). The frequency of significant antecedent events was reduced in depressed HS patients (2/15 patients with MD, 13%), as compared to not-depressed HS patients (11/19 patients without MD, 58%, Chi Square $p=0.01$). There was no difference in the frequency of CPS per week (table 1). However, in both patient groups, seizure frequency showed large individual differences. Furthermore, there was also no difference in the number of patients who had experienced GTCS, in both groups around 60% had occasional generalization of their seizures.

table 1

Clinical epilepsy characteristics in all patients

		Major Depression	no Depression	
n=		15 (44%)	19 (56%)	
gender	male	7 (47%)	8 (42%)	
	female	8 (53%)	11 (58%)	
age at examination		42 ±10 years	35 ±10 years	
age at onset epilepsy		10 ±12 years	14 ±12 years	
duration epilepsy		31 ±17 years	21 ±12 years	*
frequency of CPS		2.1 ± 3.5 per week	2.6 ± 4 per week	
presence of GTCS	present	9 (60%)	12 (63%)	
	absent	6 (40%)	7 (37%)	
side of seizure focus	right	3 (20%)	7 (37%)	
	left	12 (80%)	12 (63%)	
significant antecedents	present	2 (13%)	11 (58%)	*
	absent	13 (87%)	8 (42%)	

Results shown as mean ± standart deviation, or as frequency (percentage).
Differences between patients with and without MD were assessed using
CPS means complex partial seizures, measured per week over a 3 months observation period; GTCS means generalized tonic clonic seizures, assessed as being part of patient's seizure history or not
ANCOVA (continuous variables) and Chi Square tests (categorical variables).
Significant results are highlighted with an asterix.
Patients with Major Depression had a longer duration of the epilepsy and a lower incidence of antecedent events to the development of epilepsy

Structure of mesial temporal lobe and depression

In refractory TLE patients the volume of the ipsilateral hippocampus and amygdala was, in average, reduced by more than 25% of corresponding control values (table 2). The contralateral hippocampal volumes were only slightly reduced, whereas the contralateral amygdala showed atrophy of a similar degree as the ipsilateral amygdala. However, these volume deficits were not different between patients with and without major depression. The ipsilateral hippocampal T2-relaxation time was markedly increased, again without a difference in relation to the depression status (table 2). Interestingly, the T2 signal in the

contralateral amygdala was increased in patients without depression (103 ±8 msec), as compared to patients with depression (97 ±9 msec, ANCOVA, p=0.02).

DISCUSSION

Major depression was found in 44% of refractory TLE patients, consistent with earlier studies on this topic (1). As expected, these TLE patients with visual diagnosis of hippocampal sclerosis showed characteristic quantitative atrophy and signal increase in the ipsilateral mesial temporal structures. The degree of ipsilateral hippocampal damage did not predict the presence of Major Depression. This is in agreement with a recent study assessing hippocampal volumes of HS patients in relation to depression scores (32). This study did not investigate T2-relaxation times, or the degree of amygdaloid damage. Utilising these tools, we documented a relatively preserved contralateral amygdala in TLE patients with associated MD. Furthermore, a long duration of epilepsy and the absence of precipitating insults were associated with an increased risk of MD. There was no apparent association between seizure characteristics and the presence of MD. This may support that depression is not merely a consequence of having (a lot of) seizures (3),

table 2

Structural measurements in HS patients relation to mood state

		Major Depression	**no Depression**	
n=		15	19	
Volumetrics				
Hippocampus	ipsi	64 ±13	71 ±18	
	contra	93 ±18	97 ±17	
Amygdala	ipsi	76±19	76 ±19	
	contra	71 ±21	80 ±21	
T2-relaxometry				
hippocampus	ipsi	117±15	120 ±10	
	contra	102 ±7	102 ±6	
amygdala	ipsi	102 ±15	105 ±9	
	contra	97 ±10	103 ±8	*

volumes and T2-relaxation times expressed as percentage normal values based on control values obtained in subjects of the same gender
Differences between depressed and not-depressed patients assessed with ANCOVA, with age and total brain volume included as co-variates for the volumetric measurements, and age for the T2-relaxation times
Only patients without depression had contralateral T2 increase in the amygdala (*)

but may also reflect intrinsic difficulties in measuring seizure severity and their impact on the patients mood.

For the purpose of our study, we have combined patients with past and current symptoms of Major Depression, as we aimed to assess whether certain structural abnormalities, commonly part of the spectrum of TLE with HS would predispose to Major Depression. Structural changes typically associated with hippocampal sclerosis are most commonly stable over time, and are postulated to be present early in the evolution of the epilepsy (17, 19). On the other hand, both symptoms of depression and epilepsy vary over time, and it cannot be excluded that acute exacerbations could have an additional impact on the structure of the mesial temporal lobe. Our cross-sectional study design does not allow assessing these questions, however, can give information about an underlying difference between temporal lobe epilepsy patients with and without associated depression.

We documented a relative sparing of signal change in the contralateral amygdala in TLE patients with associated Major Depression. Contralateral mesio-temporal abnormalities have been described in TLE patients (33-36). Volume deficits are typically contributed to neuronal cell loss, whereas an increase in T2-relaxation time, at least in the ipsilateral hippocampus, is thought to reflect gliosis (37, 38). Therefore, our findings could be interpreted as reflecting relatively less gliotic changes in the contralateral amygdala of patients with Major Depression.

The second finding related to antecedent events. An antecedent event or an initial precipitating insult is a neurological event occurring prior to the onset of habitual seizures, and poses a risk for the development of epilepsy (19). Serial neuroimaging studies documented the evolution of HS after antecedent events (18, 39). Antecedent events are typically found in up to 60% of refractory TLE patients (17, 40), but were much less frequent in our patients with Major Depression. One could argue that these events may have been missed either at the time of their occurrence, or when the patient was investigated for refractory epilepsy. However, our CEP pays careful attention to record these events, and there is no reason to believe that this should have been different between the two patient groups. Alternatively, the aetiology of the epileptogenic lesion in patients with MD may be independent from antecedent events. Several studies have suggested that some TLE patients have developmental, pre-natal structural abnormalities underlying their epilepsy (41), or a genetic pre-disposition for their seizures (42). However, the mechanisms of seizure focus generation in absence of antecedent events are not well understood (42, 43). It is possible that this process is more focal and unilateral, as HS patients without antecedent events show generally less abnormality in the region of the seizure focus, and also less widespread damage to other ipsilateral and contralateral temporal lobe structures (22). One may argue that the amygdala shows less impairment because these patients were not exposed to initial precipitating events.So far, we have provided a potential explanation for the relationship between a low frequency of antecedent events and contralateral amygdaloid damage, it remains to be discussed whether these findings are related to Major Depression. On a psychological level, one could speculate that the absence of recognized antecedent events represents a higher risk for mood disorders, as these patients have no explanation of what might have caused their epilepsy. Epilepsy has a long history of misconceptions and social stigma, so the lack of a causative event may lead to a negative emotional reaction. Furthermore, the long duration of the disease may pose additional burden to the patients, aggravating their mood disturbance. Alternatively, the absence of antecedent events may indicate a pre-existing abnormality of the limbic network, which may not only cause TLE, but also predispose to

depression (4). In patients with major depression alone, histopathological studies found evidence for developmental disturbances in the limbic system (14).

The importance of the amygdala volume in relation to psychiatric co-morbidities has already been noticed in previous studies on the mesial temporal lobe integrity (23, 44, 45). Particularly interesting in relation to our findings is that a relative preservation of the right amygdala was found in patients with refractory TLE and associated anxiety (44). As the majority of our patients had left HS, one could postulate a side-specific involvement of the amygdala in mood disorders. The relative preservation of the contralateral amygdala may lead to increased or altered processing of negative emotions. Several studies have reported an increase in the metabolism of the amygdala in untreated major depression, when occurring as a sole disorder (12, 46). There is also indication for an alteration of the functional connectivity between the two amygdaloid nuclei in depressed patients (13). Major depression has also been linked to a reduction in amygdaloid glial density, without an associated change in neuronal density (47). This finding mirrors our structural findings in depressed TLE patients, where the signal change, but not the volume change showed an association with MD.

Depression as a sole disease is a clinically heterogenous condition (12). Depression associated with TLE is probably similarly heterogenous, lowering the power to detect differences related to depression. Structural and functional changes may be further altered during the course of the disease, with evidence for different findings during the first episodes, as compared to chronic depression (7). The vast majority of our depressed patients have had more than one episode when examined, so our findings reflect a more chronic disease state. Furthermore, antidepressants may also alter particularly the functional activity of the amygdala (12). Some effects of depression may be reflected in changes of brain function, but not structure, and may thus not be detectable with the methods used in this study. Finally, for this study, we identified depression based on semi-structured interviews, and combined the patients with past and current symptoms of Major Depression in one single group. This approach may have affected our ability to detect abnormalities in brain structure, as it is conceivable that these abnormalities could be more pronounced in the acute stages of the disorder.

In conclusion, in the uncommon situation when TLE associated with HS develops without a precipitating event there may be an increased risk for depression. A relatively preserved contralateral amygdala may lead to altered processing of negative emotions, and symptoms of depression may become clinically evident.

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