Causes, presentation and outcome of lesional adult onset  
mediotemporal lobe epilepsy  

B M Soeder,¹ U Gleissner,¹ H Urbach,² H Clusmann,³ C E Elger,¹ A Vincent,⁴ C G Bien¹  

Abstract  
Background and aim: Mediotemporal lobe (MTL) epilepsy (MTLE) is particularly frequent among human localisation related epilepsies. MTLE usually starts before adulthood and is most frequently associated with hippocampal sclerosis (HS). Here, aetiologies, disease courses and outcomes of adult onset MTLE patients treated at this tertiary epilepsy centre are studied.  

Methods: We collected all patients studied between January 1999 and December 2005 fulfilling the following criteria: (1) MTLE manifestation at age >20 years; (2) time between disease manifestation and assessment <6 years; (3) MTL lesion on brain MRI; and (4) neuropsychological test battery applied. The diagnoses were classified and paraclinical data, neuropsychological performances, and seizure and memory outcomes were documented.  

Results: Diagnoses in the 84 patients (mean age 42 years at MTLE onset) were: limbic encephalitis (LE), n = 23 (27%); tumours I/II, n = 12 (14%); amygdala lesions (increased volume and T2/FLAIR signal), n = 11 (13%); and other, n = 20 (24%). Visible MTL affection was frequently bilateral in patients with LE (57%) and HS (22%). These groups also showed the poorest memory performance. Patients with amygdala lesions were the oldest (mean age 52 years); their lesions were in part immune mediated and in part probably dysplastic. Treatment dependent seizure outcomes were similar to published data without restriction to adult onset cases. Under conservative therapy, memory performance remained stable in patients with HS but improved in a proportion of patients with LE.  

Conclusions: The data suggest that LE is a common and a previously underestimated cause of MTLE in this age group. Its prognosis is variable. Amygdala lesions, also, are in part encephalitic in nature.  

Mediotemporal lobe (MTL) epilepsy (MTLE) is particularly frequent among human localisation related epilepsies, and most cases start in childhood or adolescence. In autopsy and epilepsy surgery series, the most frequently observed morphological substrate of the epileptogenic area is hippocampal sclerosis (HS).¹-⁶ However, there are few data on the causes of adult onset MTLEs. Epidemiological studies in adult onset epilepsies in general suggested vascular, traumatic, tumoral and (in individuals >64 years of age) neurodegenerative aetiologies.⁷-⁹ These studies, however, did not specifically address the subgroup of MTLE. Furthermore, such studies cover large numbers of patients and are not designed to detect subtle disease processes requiring extensive indepth investigations. Therefore, in the present study, we assessed all patients who developed adult onset MTLE with MTL lesions on high resolution brain MRI over a 7 year period from our tertiary epilepsy centre. It extends our previous study, which revealed that limbic encephalitis (LE) was a frequent underlying substrate of lesional adult onset MTLE-HS.⁸ It also identifies a patient group with amygdala lesions in part encephalitic and in part probably dysplastic in origin.  

Patients and methods  
Inclusion criteria  
We selected all patients treated at the Department of Epileptology, University of Bonn, Germany, between January 1999 and December 2005 who fulfilled the following criteria:  
1. Manifestation of epilepsy with seizures compatible with an MTL origin, at the age of ≥20 years.  
2. First comprehensive assessment, including brain MRI, at this centre within 6 years of MTLE onset (this limit was chosen to have a high chance of obtaining detailed data and diagnostic material on the patients).  
3. At presentation to this centre, MRI diagnosis of an MTL lesion by an experienced neuroradiologist (HU). HS is regarded as a lesion in this study.  
4. At presentation to this centre, assessment of cognitive performance by a neuropsychological test battery assessing verbal and visual memory, and attention functions.  

Data collection from the time point of initial assessment  
We retrospectively assessed the following data from patient records: date of epilepsy onset, history of potential causative antecedent events ("initial precipitating injuries")¹⁰-¹¹, monthly seizure frequency (all types of epileptic seizures) and drug therapy, including antiepileptic drugs (AED). The MRI interpretation based on images obtained by a dedicated epilepsy protocol¹² was noted (and rechecked with an experienced neuroradiologist (HU) if doubtful). Results of standard CSF analyses and tests for autoantibodies known to be associated with LE were noted. Sera were tested by immuno-dot-blotting for Hu, Yo, Ri, CV2/CRMP5, amphiphysin, Ma1 and Ma2 antibodies on a commercially available blotting kit¹³ and by indirect immunohistochemistry, both performed by the Department of Clinical Chemistry, University of Cologne, Cologne, Germany, according to internationally accepted practice.¹⁴ Sera were also tested for VGKC antibodies by radioimmunoprecipitation performed by AV, with values >100 pmol/l regarded as positive.¹⁵ ¹⁶
Neuropsychological performance at the initial visit was assessed with the following tests:

- The Verbal Learning and Memory Test (a German adaptation of the Rey Auditory Verbal Learning Test) assessed the following parameters for verbal memory: learning capacity (sum of recalled words in five consecutive learning trials), loss in delayed recall (recalled words after a time delay of 30 min minus recalled words in the fifth trial) and recognition (correctly recognised words minus false alarms).

- The Diagnostikum für Cerebralschädigung, revised version, assessed visual memory: nine abstract designs have to be reconstructed by use of five wooden sticks; the parameter of interest was the learning capacity (sum of reconstructed designs across five learning trials).

- Attentional speed was assessed with the d2 test, a visual cancellation task, and the Trail Making Test, parts A and B, for the assessment of attention functions. Parameters of interest were the total score (correct cancellations minus failures) for the d2 test and time (in seconds) for the Trail Making Test.

All parameters were transformed into standardised values or percentiles according to the norms provided in the manuals.

Diagnostic classification
Where available, histopathology was used to determine the precise diagnoses of tumours and other well defined lesions such as cavernomas. If no surgical brain specimen was available, diagnoses were made by MRI interpretation according to established criteria including VGKC antibodies as diagnostic markers. "Possible LE" was diagnosed using criteria of serial MRI (evolution from mediotemporal signal increase and swelling to atrophy over several months) as described previously (see also fig 1). Post-traumatic epilepsy was diagnosed if there was a history of severe brain injury and mediotemporal postcontusional findings on histopathology or characteristic post-traumatic MRI lesions on the appropriate sequences, including T2*.

Other less common diagnoses were made in accordance with established standards.

Treatment categorisation
The treatment administered after the first visit to this centre was categorised as follows:

- "Surgery": epilepsy surgery after comprehensive presurgical assessment following commonly accepted principles with subsequent ongoing administration of AEDs for at least 1 year after operation.

- "AED only": anticonvulsive pharmacotherapy only.

- "AED+immunotherapy": anticonvulsive pharmacotherapy plus immunointerventions (as detailed in the results section).

Outcome assessment
Seizure outcome
For the most recent follow-up visit, the interval to surgery or to the first visit (as applicable) was noted. A minimum follow-up of 6 months was required; otherwise "no follow-up" was noted. Seizure outcome was assessed in a dichotomous way: "seizure free" (if the patient was free of all types of epileptic manifestations including auras for at least the previous year or the total available follow-up if this was <1 year) or "not seizure free".

Neuropsychological outcome
Neuropsychological re-tests after at least 6 months were evaluated as available in the conservatively treated patients (because it was not intended here to assess the effect of tissue removal by resective epilepsy surgery). The significance of individual changes in verbal memory performance (domains verbal learning, loss in delayed recall and recognition) was evaluated using the categories "gain", "stable" or "loss". This was done using reliable change indices according to previous proposals. Reliable change indices provide an index of significant and reliable alteration in test performance, a change that cannot be attributed to common sources of measurement error inherent in test/re-test designs (eg, practice effects, regression to the mean). Individual changes were classified as being worse or improved if they exceeded the 90% confidence interval for the before and after difference scores derived from 81 healthy controls (mean age 50 (SD 12) years, range 16–68 years, 22 men) who had been tested twice (mean re-test interval 5.3 (SD 1.7) months).

Statistical evaluation
Because of the limited group sizes, non-parametric tests were performed for statistical comparisons (χ² test and the Kruskal–Wallis-test, as appropriate). A p value <0.05 was considered significant.

RESULTS
Eighty-four patients with adult onset MRI positive MTLE fulfilled the inclusion criteria. Their clinical and paraclinical data in the diagnostic subgroups are given in table 1.
Only 13 (10%) patients were ≥60 years, and no more than seven patients (8%) were ≥64 years. For serum antibody and CSF findings, see supplementary table 1 (available online); for the neuropsychological performance, see supplementary table 2 (available online).

Limbic encephalitis (n = 23, 27%)
Six patients proved to have paraneoplastic definite LE. The detected tumours were: small cell lung cancer (n = 2), testicular cancer (n = 1), uterine leiomyosarcoma (n = 1), rectal carcinoma (n = 1) and undetected in the presence of Hu antibodies (n = 1). Three of these patients had onconeural antibodies (Hu, n = 2; Ma2, n = 1). Five patients had non-paraneoplastic definite LE associated with VGKC antibodies. Twelve patients were classified as having possible LE on the basis of evolving mediobasal MRI features in the absence of detected autoantibodies or a tumour. A typical example is given in fig 2C–E. At the initial visit to this centre after a median of 7.4 months, 20 of the 23 patients already had hippocampal atrophy (and had therefore been included in our previous study). Disease onset was indicated by recurrent seizures in all patients (often accompanied by memory decline) apart from one who had memory impairment only for 2.4 years before epilepsy onset. On formal neuropsychological assessment at initial presentation to this centre, memory performance was poor. At least half of the patients performed below 1 SD of controls in the different verbal memory domains.

Hippocampal sclerosis not related to LE (n = 18, 22% of the total cohort)
Eleven of the patients in this group had HS which was preceded by an initial precipitating injury (childhood meningitis, n = 1; febrile seizures, n = 1; brain trauma, n = 2; status epilepticus, n = 3; note, patients with HS evolving from LE were included in the LE subgroup, described in the previous paragraph) or in the context of another brain lesion (“dual pathology”: old ipsilateral posterior cerebral artery infarctions, n = 2; ipsilateral parietal porencephalic cyst, n = 1; neurofibromatosis type I, n = 3; of note, patients with HS evolving from LE were included in our previous study). The MRI appearance of these HS by MRI and neuropathology (if surgery was done) was indistinguishable from that of patients with disease onset before adulthood (see fig 2A). Four of the 18 patients had bilateral HS (22%). Memory performance in the patients with HS at first assessment was poor: more than half of the patients performed below 1 SD of controls in each of the verbal and non-verbal memory domains.

Tumours WHO I/II (n = 12, 14%)
In seven patients, the diagnosis was made by histopathological study of brain tissue obtained at epilepsy surgery. The detailed diagnoses were: dysembryoplastic neuroepithelial tumour (DNT) WHO I (n = 2; an example is given in fig 2B), ganglioglioma I (n = 4) and ganglioglioma II (n = 1). In the remaining five cases, MRI suggested low grade tumours (DNT I, ganglioglioma I, astrocytoma II); these patients did not undergo epilepsy surgery at this stage because they were either not yet pharmacoresistant or refused surgical treatment. Left-sided temporal damage is often associated with verbal memory deficits. However, even though in this group the left side was more often affected than the right (9:3), mean verbal memory performance of this group was within 1 SD of normal controls (ie, within the average range); on the individual level, the performance was clearly better than in the previous two groups.

Amygdala lesions (n = 11, 13%)
Eleven patients presented with homogenously increased amygdala volumes and signal intensities on FLAIR or T2 MRI sequences. In four cases, the hippocampal head appeared to be involved in the same process. None of these lesions showed contrast enhancement. The 11 patients in this group had the oldest mean age at epilepsy onset of all groups (52 years). Neuropsychological performance at initial assessment was better than in the HS and LE patients and more like that of patients with tumours I/II, even though the left side was more often affected than the right (8:2; one patient showed bilateral affection). Three patients underwent MTL resections. Two patients had a follow-up, and both were seizure free.

CSF findings, histopathology or a temporary evolution of the amygdala lesions (regression of MRI-T2/FLAIR signal increases over time, see fig 2F–H) suggested a chronic inflammatory origin in five patients (median age at onset 66 years, range 45–71 years; only one patient <50 years). In the remaining six patients, CSF findings, non-encephalitic histopathology or long term stability of amygdalar MRI lesions did not speak in favour of an underlying encephalitis (see fig 2I–L). These patients were younger (median age 46 years, range 23–61 years; only two patients >50 years) than their encephalitic counterparts. It is likely that some form of dysplastic lesion underlies the MRI changes. Individual data are given in supplementary table 3 (available online).

Table 1 Clinical and paraclinical features at initial presentation

<table>
<thead>
<tr>
<th>Group</th>
<th>No (female)</th>
<th>Proportion of all 84 patients (%)</th>
<th>Age at epilepsy onset (years) (median (range))</th>
<th>Time since seizure onset (years) (median (range))</th>
<th>Right/left/bilateral affection (according to MRI)</th>
<th>Seizure frequency (month) (median (range))</th>
<th>No of AEDs (median (range))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group</td>
<td>84 (28)</td>
<td>100</td>
<td>42 (20–79)</td>
<td>1.6 (0.0–6.0)</td>
<td>25/35/24</td>
<td>6 (0–600)</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>Four main groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LE</td>
<td>23 (6)</td>
<td>27</td>
<td>41 (23–66)</td>
<td>0.6 (0.0–5.6)</td>
<td>5/5/13</td>
<td>10 (0–600)</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>HS</td>
<td>18 (6)</td>
<td>21</td>
<td>38 (21–79)</td>
<td>2.4 (0.0–6.0)</td>
<td>8/6/4</td>
<td>6 (0–150)</td>
<td>3 (0–3)</td>
</tr>
<tr>
<td>Tumours I/II</td>
<td>12 (4)</td>
<td>14</td>
<td>32 (20–44)</td>
<td>3.0 (0.0–6.0)</td>
<td>3/9/0</td>
<td>10 (1–34)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Amygdala lesion</td>
<td>11 (5)</td>
<td>13</td>
<td>52 (23–71)</td>
<td>1.0 (0.0–4.2)</td>
<td>2/8/1</td>
<td>4 (1–100)</td>
<td>3 (0–1)</td>
</tr>
<tr>
<td>Group differences: p value</td>
<td>Sex NS* 0.008†</td>
<td>Bilaterality &lt;0.001† NS† 0.011†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20 (5)</td>
<td>24</td>
<td>44 (28–60)</td>
<td>2.0 (0.6–5.7)</td>
<td>7/7/6</td>
<td>14 (1–450)</td>
<td>1 (0–3)</td>
</tr>
</tbody>
</table>

*χ2 test. †Kruskal–Wallis test.
AEDs, antiepileptic drugs; HS, hippocampal sclerosis (not related to LE); LE, limbic encephalitis.
Other (n = 20, 24%)
In these remaining patients, the following conditions underlying MTLE were diagnosed: tumours III/IV (n = 6), post-traumatic lesions (n = 5), cavernoma (n = 3), chronic herpes simplex encephalitis (n = 2), cerebral amyloid angiopathy with inflammation (n = 1) and not further specified mediobasal MRI lesions (n = 3). In the patients with tumours III/IV, the diagnosis was made histopathologically. Two constellations occurred: either surgery was performed when signs of malignancy were unexpectedly found during the presurgical work-up (resulting in resection for neurosurgical indication, n = 2) or a I/II<sup>+</sup> tumour was suspected during work-up for epilepsy and only histopathology revealed the diagnosis of a grade III/IV<sup>+</sup> tumour (n = 4). The neuropathological diagnoses were: glioblastoma multiforme (n = 1), anaplastic oligodendroglioma (n = 1), anaplastic astrocytoma (n = 3) and anaplastic oligoastrocytoma (n = 1).

Outcome
In the following, outcome data were analysed only for the four main groups delineated above (64 patients). Because of the retrospective nature of this study, outcome data were available only for some of the patients, as indicated below.

Seizure free outcome
Data were available for 43/64 patients: for 18/19 surgically treated patients, for 9/25 AED only treated patients and for 16/20 AED+immunotherapy patients. Four types of immunotherapy were applied in patients with follow-up data available: (1) monthly pulses of 3–9 g of intravenous methylprednisolone, applied over a period of 1–24 months (n = 10); (2) intravenous methylprednisolone as before over 4 or 8 months, followed by oral prednisone, tapered from 100 mg/day to <7.5 mg, total application duration 2.5 or 36 months (n = 2); (3) oral prednisone, dosing as in (2), administered over 13–78 months (n = 4); (4) one pulse of intravenous methylprednisolone as in (1) followed by 15 doses of intravenous immunoglobulins at 0.4 g/kg body weight (n = 1). There were no serious adverse events. After a median follow-up of 1.9 years (range 0.5–6.0 years), 23/43 patients were seizure free (53%). Patients with benign tumours had a very favourable seizure free outcome (6/7) after resective epilepsy surgery. Four out of seven surgically treated HS patients became seizure free, but only one of five conservatively treated HS patients. Patients with LE achieved an intermediate seizure free outcome rate under conservative treatment of 5/13 (4/11 patients became seizure free under AED+immunotherapy, two of them had been VGKC antibody positive and two antibody negative). For further details, see supplementary table 4 (available online).

Neuropsychological outcome
Verbal memory outcome data were available from 15/25 conservatively treated patients in the four main groups (for the purposes of this study, neuropsychological outcome data of the operated patients were not considered, as explained in the methods section): 3/25 AED only and 12/20 AED+immunotherapy patients; in the latter, treatment types according to the categories given in previous paragraph were as follows: (1) n = 6; (2) n = 1; (3) n = 4; (4) n = 1. Patients were re-tested after a minimum period of 6 months (median follow-up 15 months, range 6–44 months). Whereas the four patients with HS had a stable verbal memory performance, there was an improvement in 1–4 (depending on the test domain) of eight patients with LE treated with AED+immunotherapy. For details, see supplementary table 5 (available online).
DISCUSSION

We studied causes, presentation and outcome of an adult onset MTLE cohort with lesional brain MRI (≥20 years) collected retrospectively at our tertiary epilepsy referral centre. The largest group (more than 25%) was made up of patients with LE, as defined by the criteria for paraneoplastic neurological syndromes,34 by VGKC antibodies35 or by evolutionary mediotemporal MRI changes.25,26

The cohort studied here was younger than that of classical studies in the elderly (≥60 or ≥65 years at onset),27,30,31 and thus represented the depressed part in the tub-shaped incidence curve of epilepsies.28,32 Such patients have not previously been studied extensively. The cohort was homogenous in terms of localisation of the epileptogenic area because all had MTLE. A potential selection or referral bias must, however, be taken into account as the patients were recruited in a tertiary epilepsy centre that is likely to take care of particular patients.

LE has a strong tendency to bilateral mediotemporal involvement, as evident by MRI findings and by the poor memory performance indicating extensive MTLE dysfunction. The second largest group was made up of cases of HS (unrelated to LE) accounting for about one-fifth of cases. A considerable group (15% of the total cohort, which is almost the same as the proportion with tumours I/II) had amygdala lesions. This is a spectrum of causes clearly different from the typical childhood–adolescent onset MTLE among which HS cases predominate. It also differs from that of adult onset epilepsy cohorts studied for epidemiological purposes. In the Icelandic epilepsy incidence study, one subgroup consisted of patients aged 15–64 years (the age range in this subgroup largely resembles ours, in which the ≥64-year-old patients were a minority). In this Icelandic subgroup, a cause underlying the unprovoked seizures was identified in only 51% of cases.8 The comparability of these data to ours, however, is limited for two reasons. Firstly, in the Icelandic study, epilepsies other than MTLE were included. Secondly, only 85% of all patients underwent structural neuroimaging, and this was in an unspecified proportion only done by a CT scan. Therefore, more subtle lesions such as HS, LE or amygdala lesions may have been missed in some of the patients.

Amygdala lesions

The existence of MTLE patients with amygdala lesions characterised by increased volume and T2/FLAIR signal has been suggested by a previous report.36 Our observations suggest underlying encephalitis in about half of the patients. The other half of the amygdala lesion cases in our sample—younger than the other half—seem to have had a stable underlying pathology without features suggestive of encephalitis. It is likely that they had dysplastic or benign tumoral lesions, as assumed by the authors of a previous study.37 Future research will be required to disentangle the histopathological abnormalities in these amygdala lesions. It may be speculated that the progressively atrophic encephalitic amygdala lesions may end up as amygdala sclerosis.38,39 In line with this hypothesis is the observation that MTLE patients with amygdala atrophy on MRI had a history of encephalitis more frequently than MTLE patients with normal amygdala volumes.40

Seizure outcomes related to aetiology and treatment

Seizure free outcome rates of surgically treated patients due to benign tumours (86%) or HS (57%) were as high as from those in published series without restriction to cases with adult onset epilepsies.37–40 The low proportion of conservatively treated HS patients becoming seizure free (20%) is also comparable with seizure outcome in AED treated MTLE-HS patients in general.41 The seizure free outcome rate in conservatively treated LE patients was intermediate (58%). A beneficial role of immunotherapy in patients with LE may emerge in the near future. The present uncontrolled retrospective study with non-uniformly treated patients cannot, however, provide treatment efficacy data.

Memory outcomes

Whereas the verbal memory performance of patients with non-LE related HS remained stable over time, a proportion of patients in the LE group undergoing AED+immunotherapy improved. This indicates that LE is not a static condition, and affected cognitive performance may benefit from immunotherapy.

Management of patients with adult onset MTLE

In patients with adult onset MTLE, an immune mediated condition should always be considered unless another well defined type of disorder (such as a tumour) can be identified. In cases with MTLE lesions suspicious of representing encephalitis, tumour search, tests for onconeural and VGKC antibodies and follow-up MRIs are suggested to confirm and refine the preliminary diagnosis.

Acknowledgements: The authors thank Professor Dr Albert J Becker, University of Born, Department of Neuropathology, for generously providing paraffin embedded brain specimens, Mrs Hannelore Storma and Mr Mathias Theek for expert assistance with the artwork, Mrs Claudia Ullmann for excellent technical assistance with histological stainings and Ms Linda Clover for the VGKC antibody testing.

Competing interests: AV and her department receive royalties and payments for antibody tests. The remaining authors have no conflicts of interest.

REFERENCES


898

Causes, presentation and outcome of lesional adult onset mediotemporal lobe epilepsy

B M Soeder, U Gleissner, H Urbach, H Clusmann, C E Elger, A Vincent and C G Bien

J Neurol Neurosurg Psychiatry 2009 80: 894-899 originally published online April 8, 2009
doi: 10.1136/jnnp.2008.165860

Updated information and services can be found at:
http://jnnp.bmj.com/content/80/8/894

These include:

Supplementary Material
Supplementary material can be found at:
http://jnnp.bmj.com/content/suppl/2009/07/22/jnnp.2008.165860.DC1.html

References
This article cites 33 articles, 13 of which you can access for free at:
http://jnnp.bmj.com/content/80/8/894#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Epilepsy and seizures (807)
- Stroke (1422)
- Immunology (including allergy) (1855)
- Infection (neurology) (471)
- Neuroimaging (378)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/