Amygdalohippocampectomy is a well-established, standard surgery for medically intractable mesial temporal lobe epilepsy (MTLE). However, in the case of MTLE without hippocampal atrophy or sclerosis, amygdalohippocampectomy is associated with decreased postoperative memory function. Hippocampal transection (HT) has been developed to overcome this problem. In HT the hippocampus is not removed; rather, the longitudinal hippocampal circuits of epileptic activities are disrupted by transection of the pyramidal layer of the hippocampus. The present study describes a less invasive modification of HT (transsylvian HT) and presents the seizure and memory outcomes for this procedure.

Methods. Thirty-seven patients with MTLE (18 men and 19 women; age range 9–63 years; 19 with surgery on the right side and 18 with surgery on the left side; seizure onset from 3 to 34 years) who were treated with transsylvian HT were retrospectively analyzed. All patients had left-side language dominance, and follow-up periods ranged from 12 to 94 months (median 49 months). Seizure outcomes were evaluated for all patients by using the Engel classification. Memory function was evaluated for 22 patients based on 3 indices (verbal memory, nonverbal memory, and delayed recall), with those scores obtained using the Wechsler Memory Scale–Revised. Patients underwent evaluation of the memory function before and after surgery (6 months–1 year).

Results. Engel Class I (completely seizure free) was achieved in 25 patients (67.6%). Class II and Class III designation was achieved in 10 (27%) and 2 patients (5.4%), respectively. There were differences in memory outcome between the sides of operation. On the right side, verbal memory significantly increased postoperatively (p = 0.003) but nonverbal memory and delayed recall showed no significant change after the operation (p = 0.718 and p = 0.210, respectively). On the left side, all 3 indices (verbal memory, nonverbal memory, and delayed recall) showed no significant change (p = 0.331, p = 0.458, and p = 0.366, respectively).

Conclusions. Favorable seizure outcome and preservation of verbal memory were achieved with transsylvian HT for the treatment of MTLE without hippocampal atrophy or sclerosis.

(key Words: hippocampal transection mesial temporal lobe epilepsy epilepsy surgery memory outcome)

Abbreviations used in this paper: AH = amygdalohippocampectomy; FIQ = full-scale IQ; HT = hippocampal transection; MTLE = mesial temporal lobe epilepsy; WAIS-R = Wechsler Adult Intelligence Scale–Revised; WMS-R = Wechsler Memory Scale–Revised.)
Transsylvian hippocampal transection for temporal lobe epilepsy

should be prevented. In the hippocampus, seizure generation is dependent on the longitudinal hippocampal circuits. On the other hand, memory function is primarily subserved by the transverse lamellae, whose loops start and end in the entorhinal cortex.25 In HT, the hippocampus is not removed; rather, the longitudinal hippocampal circuits of epileptic activities are disrupted by transection of the pyramidal layer of the hippocampus.

In the present study we describe a less invasive modification of HT (transsylvian HT) for the treatment of MTLE without hippocampal sclerosis or atrophy, and we evaluate the seizure and memory outcomes in patients treated with this procedure. This is the largest case series dealing with HT and the first report evaluating seizure and memory outcomes by using statistical methods.

Methods

Patient Population

Between January 2005 and December 2011, 201 surgeries for drug-resistant MTLE were performed in Osaka City University Hospital and Tokyo Metropolitan neurological hospital by a single surgeon (M. M.). Of these patients, 37 were treated with HT (18 men and 19 women; age range 9–63 years; 19 with surgery on the right side and 18 with surgery on the left side; seizure onset from 3 to 34 years). All patients were right-handed and had left-hemisphere language dominance. Diagnosis of MTLE was made by seizure semiology, MRI findings, scalp electroencephalography with sphenoidal electrode, interictal FDG-PET, N-isopropyl-p(123I)-iodoamphetamine SPECT, interictal magnetoencephalography, and neuropsychological examination. In addition, patients underwent video-electroencephalography monitoring after implantation of subdural electrodes on the bilateral parahippocampal gyrus, temporal base, and lateral temporal cortex, and the ictal discharge from mesial temporal lobe was confirmed.

Indications for HT

Lack of hippocampal atrophy or sclerosis on preoperative MRI (T1-weighted, T2-weighted, and FLAIR images) is a minimum requirement of HT for several reasons. First, the sclerotic hippocampus and parahippocampal gyrus are difficult to transect safely because of their hardness. Second, in the sclerotic hippocampus most functions have already been lost, and there is usually minimal memory impairment after removing the hippocampal formation in this context. In addition to the findings on MRI, bilateral ictal onset and higher preoperative memory score were taken into consideration to decide whether HT was indicated. The study was approved by the ethics committees of Osaka City University Hospital and Tokyo Metropolitan Neurological Hospital. Written informed consent was obtained from each patient or his or her parents.

Surgical Procedures

There are 3 steps in transsylvian HT: approaching the inferior horn of the lateral ventricle via the sylvian fissure, transection of the pyramidal layer, and transection of the parahippocampal gyrus.

Step 1. After induction of general anesthesia, the patient is placed supine on the operating table with the head tilted approximately 10° degrees to the side opposite the surgeon. A standard frontotemporal craniotomy can be performed, but slightly wider exposure of the temporal lobe is necessary to permit intraoperative electrocorticography.13

After wide exposure of the sylvian fissure, the inferior perinsular sulcus can be identified at the most inferior point of the insular gyri. Along this sulcus, the inferior horn of the lateral ventricle is opened with a cortical incision 15 mm in length (Fig. 1A). Care is taken to avoid injuring the uncinate fasciculus, which passes through the anterior part of the limen insula. After reaching the inferior horn of the lateral ventricle, the hippocampus can be seen to form the floor of the inferior horn. The amygdala faces the hippocampus and forms part of the roof of the inferior horn of the lateral ventricle. The inferior part of the amygdala is removed to obtain the surgical field for the remainder of the procedure. Then, hippocampal recording is performed to confirm the paroxysmal epileptic discharge from the hippocampus.16 Typically, positive biphasic spikes are identified on the hippocampus (Fig. 2 upper).

Fig. 1. Schematic drawings of HT. A: After the wide exposure of the sylvian fissure, the inferior perinsular sulcus can be identified at the most inferior point of the insular gyri. Along this sulcus, the inferior horn of the lateral ventricle is opened with a cortical incision 15 mm in length. The dotted line indicates the line of approach to the hippocampus. B: The alveus is sharply incised with microscissors. The incisions (dotted lines) are perpendicular to the long axis of the hippocampus, in 5-mm intervals. Usually, 5 or 6 incisions are made on the hippocampal surface. C: A round, flat knife 2.3 mm in diameter is inserted from the incision lines of the alveus to transect the pyramidal cell layer. At the bottom of the incision, arteries and veins in the hippocampal fissure (white arrow) can be seen through the arachnoid membrane. Special care should be taken to avoid injury to the fimbria (asterisk). D: A ring-shaped, blunt dissector 4 mm in diameter is inserted from the innominate sulcus along the incision lines of the alveus to transect the parahippocampal gyrus and entorhinal area.
Step 2. The concept of HT has been described previously. In short, the direct intrahippocampal pathway is the most important connection for verbal memory in humans. The input fibers of the direct hippocampal pathway mainly originate from the inferior temporal association cortex (area 37) and reach the entorhinal cortex through the perirhinal cortex. The main objectives of HT are to preserve this pathway and to disrupt only the circuits of epileptiform discharge. Because most of the fiber tracts that form hippocampal pathways are organized perpendicular to the long axis of the hippocampus, the vertical transections of the hippocampus at 5-mm intervals disrupt seizure circuits while preserving hippocampal function.

The alveus, composed of tough fibers covering the hippocampal surface, is sharply incised with microscissors. The incision lines are perpendicular to the long axis of the hippocampus in 5-mm intervals (Fig. 1B). Usually, 5 or 6 incisions are made on the hippocampal surface. Next, a round, flat knife 2.3 mm in diameter (Fig. 3A) is inserted from the incision lines of the alveus to transect the pyramidal cell layer (Fig. 1C), which is within 2 mm of the hippocampal surface. At the bottom of the incision, arteries and veins in the hippocampal fissure can be seen through the arachnoid membrane (Fig. 3C). Special care should be taken to avoid injury to the fimbria, in which fibers run parallel to the long axis of the hippocampus, because it is important in the memory-processing pathway (Fig. 3D).

Step 3. A ring-shaped, blunt dissector 4 mm in diameter (Fig. 3B) is inserted from the innominate sulcus along the incision lines of the alveus to transect the parahippocampal gyrus and entorhinal area (Figs. 1D and 3E). The entorhinal area seems to play important roles in the propagation of epileptic discharges, and this step is important to disrupt the circuit of epileptiform discharge. This step inevitably consists of blind manipulation. Careless manipulation is associated with a risk of injuring the important vessels running in the ambient cistern or of injuring the midbrain. Gentle manipulation with a soft, blunt dissector made of silver is necessary to avoid tearing the arachnoid membrane of the parahippocampal gyrus.

After transection is complete, hippocampal recording is repeated over the hippocampus to confirm that active epileptiform discharges have completely disappeared (Fig. 2 lower).

On postoperative T1-weighted MRI sequences, the transected lines were demonstrated on the hippocampal head and body, and the lateral side of the temporal lobe remains intact.

Outcome Evaluation

Seizure outcomes were evaluated in all patients by using the Engel classification. Patients with more than 1 year of follow-up were included in this evaluation.

Neuropsychological memory function was evaluated with 3 indices (verbal memory, nonverbal memory, ...
and delayed recall) obtained with the WMS-R\textsuperscript{6,26} except in children less than 16 years old. The WAIS-R\textsuperscript{10} score was also determined in all patients. Memory function was evaluated in all patients before and after surgery (6 months–1 year).

Memory score change was assessed in the patients with a preoperative FIQ higher than 65 by WAIS-R, because in patients with a low FIQ it can be difficult to evaluate memory function adequately by using WMS-R.\textsuperscript{1,21} Patients with more than 1 year of follow-up were included in this evaluation.

Possible variables influencing memory score change were analyzed using a multiple regression model. Side of operation, age at operation, seizure onset, and seizure outcome were defined as independent variables, and differences between the postoperative and preoperative scores of the 3 memory indices were defined as dependent variables.

If there were significant variables, patients were stratified into 2 groups according to those variables, and memory score changes were evaluated with the paired t-test.

**Statistical Analysis**

Statistical analyses were conducted using JMP version 9.0 (SAS Institute, Inc.). Statistically significant differences were accepted at $p < 0.05$ in all analyses. The mean values are expressed as $\pm$ SE.

**Results**

There were no surgical complications. Follow-up periods were from 12 months to 94 months (median 49 months).

**Seizure Outcome**

All 37 patients were included in this evaluation. Engel Class I (completely seizure free) was achieved in 25 patients (67.6%). The Class II and Class III designation was achieved in 10 (27%) and 2 patients (5.4%), respectively.

**Memory Score Change**

Four patients were excluded from analysis because of their young age (< 16 years). Another 11 patients were excluded because of their low preoperative FIQs (< 65). The remaining 22 cases were included in this evaluation.

On multiple regression analysis, side of operation was the only significant variable influencing verbal memory change ($p = 0.026$). There were no significant variables influencing nonverbal memory or delayed recall changes. Therefore, patients were divided into 2 groups based on the side of operation (12 on the right side, 10 on the left side). There were no significant differences between the 2 groups in sex, age at operation, age at seizure onset, preoperative FIQ, seizure-free rate, and follow-up period ($p = 0.231, 0.198, 0.154, 0.687, 0.624,$ and $0.692$, respectively, by Student t-test, Wilcoxon rank-sum test, and Fisher exact test) (Table 1).

On the right side, verbal memory significantly increased postoperatively ($p = 0.003$). Nonverbal memory and delayed recall demonstrated no significant change after the operation ($p = 0.718$ and $0.210$, respectively). On the left side, all 3 indices (verbal memory, nonverbal memory, and delayed recall) demonstrated no significant changes after the operation ($p = 0.331, 0.458$, and $0.366$, respectively) (Fig. 4, Table 2).

**Discussion**

In the patients with hippocampal atrophy or sclerosis, memory impairment after transsylvian AH was relatively small, as we previously reported.\textsuperscript{13} However, in patients without these pathological changes, functions of the hippocampus are thought to remain to some degree, and postoperative memory losses were reported to be more severe.\textsuperscript{9}

In our study we retrospectively analyzed 37 patients who underwent transsylvian HT for the treatment of MTLE without hippocampal sclerosis or atrophy. Engel Class I (completely seizure free) was achieved in 25 patients (67.6%), whereas Engel Class II and Class III were achieved in 10 patients (27%) and 2 patients (5.4%), respectively. There were differences in memory outcome between the sides of operation. On the right side, verbal memory significantly increased postoperatively. On the other hand, nonverbal memory and delayed recall showed no significant change after the operation on that side. On the left side, all 3 indices (verbal memory, nonverbal memory, and delayed recall) did not change after the operation.

Hippocampal transection was first described by Shimizu et al.,\textsuperscript{18} and then was performed in a limited number of institutions.\textsuperscript{22,23} Although the concept of HT was a proposed hypothesis, not an accepted doctrine, recent studies

**TABLE 1: Characteristics in 22 patients who underwent HT, based on the side of operation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Rt Side</th>
<th>Lt Side</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>7:5</td>
<td>3:7</td>
<td>0.231</td>
</tr>
<tr>
<td>age range in yrs at op (median)</td>
<td>20–48 (28.5)</td>
<td>26–63 (34.5)</td>
<td>0.198</td>
</tr>
<tr>
<td>age range in yrs at seizure onset (median)</td>
<td>5–25 (20)</td>
<td>8–31 (16)</td>
<td>0.154</td>
</tr>
<tr>
<td>preop FIQ (mean ± SE)</td>
<td>82.8 ± 5.4</td>
<td>85.8 ± 4.9</td>
<td>0.687</td>
</tr>
<tr>
<td>seizure-free rate</td>
<td>83%</td>
<td>70%</td>
<td>0.624</td>
</tr>
<tr>
<td>follow-up range in mos (median)</td>
<td>15–91 (55)</td>
<td>12–94 (61.5)</td>
<td>0.692</td>
</tr>
</tbody>
</table>

* The Student t-test, Wilcoxon rank-sum test, and Fisher exact test were used, as appropriate.
have described detailed electrophysiological observations in humans\textsuperscript{25} and memory preservation in rat models\textsuperscript{12} that support the theory and efficacy of HT. However, in the previous literature, the important processes of the surgery and the depth and extent of transection were ambiguous. These points are clarified in the present report. First, it is necessary to completely transect from the alveus to the dentate gyrus. When the dentate gyrus is transected completely, the arachnoid membrane of the hippocampal sulcus can be seen. Next, it is important to transect the lateral aspect of the hippocampus and parahippocampal gyrus by using the ring-shaped, blunt dissector. However, this step inevitably consists of blind manipulation, and gentle manipulation is necessary to avoid tearing the arachnoid membrane of the parahippocampal gyrus. On the other hand, at the medial aspect of the hippocampus, the fimbria should be preserved. Disappearance of the abnormal discharges in the hippocampal recording is the only objective index to judge the completion of HT. These procedures may directly influence the postoperative seizure outcome, and surgeons should perform them appropriately.

In previous reports, the inferior horn of the lateral ventricle was approached through the superior temporal gyrus\textsuperscript{18,23} or middle temporal gyrus\textsuperscript{15,25}. On the other hand, we modified the original HT approach and adopted a transsylvian approach to access the inferior horn of the lateral ventricle. In the transsylvian approach, there are some potential risks of cortical damage to the temporal and frontal opercula when splitting the sylvian fissure. However, this approach has two advantages when compared with the transcortical procedure. First, the lateral temporal cortex is preserved. Second, the medial aspect of the hippocampus can be accessed easily, thereby facilitating preservation of the fimbria (Fig. 5).

In our study, the seizure-free rate was 67.6\% (25 of 37), which is lower than that seen in previous reports.\textsuperscript{13} However, previous studies dealt mainly with patients who had hippocampal sclerosis, and the seizure-control rate is lower in patients without hippocampal atrophy. In addition, our study may have included patients with bilateral MTLE. Considering these points, the seizure-free rate seen in this study might be favorable. In the evaluation of the memory score change, side of operation was a significant variable influencing this change. The language-dominant side was reported to be associated with verbal memory and learning, and the right side was associated with spatial/visual memory and cognition. According to subgroup analysis (right vs left side), verbal memory significantly increased and nonverbal memory and delayed recall demonstrated no significant change after the operation on the right side. On the other hand, all 3 indices demonstrated no significant change after the operation on the left side. These findings are consistent with those from previous studies dealing with the AH procedure and were considered to be reasonable clinical results.

**TABLE 2: Memory scores in 22 patients who underwent HT, based on the side of operation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rt Side</th>
<th>LT Side</th>
<th>p Value†</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>verbal memory</td>
<td>99.1 ± 6.0</td>
<td>110.7 ± 6.4</td>
<td>0.003</td>
<td>91.5 ± 4.3</td>
</tr>
<tr>
<td>nonverbal memory</td>
<td>93.8 ± 4.6</td>
<td>95.6 ± 5.8</td>
<td>0.718</td>
<td>96.7 ± 4.8</td>
</tr>
<tr>
<td>delayed recall</td>
<td>96.6 ± 4.9</td>
<td>104.5 ± 6.5</td>
<td>0.210</td>
<td>84.9 ± 6.1</td>
</tr>
</tbody>
</table>

* Scores assigned using the WMS-R. Values are expressed as the mean ± SE.
† According to the paired t-test.
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One limitation of this study is the relatively small sample size. As previously stated, we consider that AH is generally preferable to HT for the treatment of MTLE. Therefore, in patients with positive MRI findings (atrophy or sclerotic change), AH has invariably been used. However, in patients without MRI findings, HT should be considered to avoid postoperative memory decline and to control seizures. In our series, only 37 (18.4%) of 201 surgically treated patients with MTLE were treated with HT. Additional study of HT in a large, multicenter, prospective randomized trial is necessary. However, HT is not a well-established surgery for MTLE, and it is difficult to set a study with such a high evidence level. Therefore, in the present study we have described the results in our limited case series, and we emphasize the notification of epilepsy surgeons about appropriate procedures.

Conclusions

Favorable seizure outcome and preservation of memory function were achieved with transsylvian HT. This procedure may be established as a surgical option for MTLE manifesting without hippocampal atrophy or sclerosis, to control seizures and to avoid postoperative memory decline.

Disclosure

None of the authors has any conflict of interest to disclose. The authors confirm that they have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author contributions to the study and manuscript preparation include the following. Conception and design: Uda, Morino. Acquisition of data: Uda, Morino. Analysis and interpretation of data: all authors. Drafting the article: Uda. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Uda. Statistical analysis: Uda.

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