Mesial temporal lobe epilepsy: long-term seizure outcome of patients primarily treated with transsylvian selective amygdalohippocampectomy

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OBJECTIVE The aim of this study was to present long-term seizure outcome data in a consecutive series of patients with refractory mesial temporal lobe epilepsy primarily treated with transsylvian selective amygdalohippocampectomy (SAHE).

METHODS The authors retrospectively analyzed prospectively collected data for all patients who had undergone resective surgery for medically refractory epilepsy at their institution between July 1994 and December 2014. Seizure outcome was assessed according to the International League Against Epilepsy (ILAE) and the Engel classifications.

RESULTS The authors performed an SAHE in 158 patients (78 males, 80 females; 73 right side, 85 left side) with a mean age of 37.1 ± 10.0 years at surgery. Four patients lost to follow-up and 1 patient who committed suicide were excluded from analysis. The mean follow-up period was 9.7 years. At the last available follow-up (or before reoperation), 68 patients (44.4%) had achieved an outcome classified as ILAE Class 1a, 46 patients (30.1%) Class 1, 6 patients (3.9%) Class 2, 16 patients (10.4%) Class 3, 15 patients (9.8%) Class 4, and 2 patients (1.3%) Class 5. These outcomes correspond to Engel Class I in 78.4% of the patients, Engel Class II in 10.5%, Engel Class III in 8.5%, and Engel Class IV in 2.0%. Eleven patients underwent a second surgery (anterior temporal lobectomy) after a mean of 4.4 years from the SAHE (left side in 6 patients, right side in 5). Eight (72.7%) of these 11 patients achieved seizure freedom.

The overall ILAE seizure outcome since (re)operation after a mean follow-up of 10.0 years was Class 1a in 72 patients (47.0%), Class 1 in 50 patients (32.6%), Class 2 in 7 patients (4.6%), Class 3 in 15 patients (9.8%), Class 4 in 8 patients (5.2%), and Class 5 in 1 patient (0.6%). These outcomes correspond to an Engel Class I outcome in 84.3% of the patients.

CONCLUSIONS A satisfactory long-term seizure outcome following transsylvian SAHE was demonstrated in a selected group of patients with refractory temporal lobe epilepsy.

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KEY WORDS temporal lobe epilepsy; selective amygdalohippocampectomy; temporal lobectomy

Temporal lobe epilepsy with associated hippocampal sclerosis is the most frequent form of focal epilepsy that is refractory to medical treatment. The benefit of resective surgery has been convincingly demonstrated in multiple studies.14,15,57 While the crucial importance of including medial temporal structures in the resection has been acknowledged since the experience of the Montreal group, the question of the optimal extent of resection (selective limbic resection vs standard anterior temporal lobectomy [ATL]) in the individual patient has not yet been resolved.1,4,27,31,49
was started in Vienna in 1994, the Second Palm Desert Survey documented similar seizure freedom rates between selective limbic resections (68.8%) and ATL (67.9%). These results refuted the argument that a more extensive neocortical resection is necessary to obtain good seizure control. Thus, it has been our strategy to tailor the temporal resection to the results of our preoperative patient investigations, and we have opted for the transsylvian technique in patients assumed to be eligible for selective amygdalohippocampectomy (SAHE).

We present here the experience at our center in using the transsylvian SAHE in patients deemed eligible for selective resection; the same epileptological team and the same surgeon performed all resections.

Methods

Patients

We retrospectively reviewed prospectively collected data on 427 adults who had undergone resective surgery for medically refractory epilepsy at the Vienna Epilepsy Program between July 1994 and December 2014. Of these patients, 295 suffered from temporal lobe epilepsy not associated with structural lesions other than hippocampal sclerosis or temporal lobe atrophy. Based on the criteria outlined below, 158 were assigned to SAHE as the first surgical treatment.

The study protocol was reviewed and approved by the local ethics committee.

Presurgical Evaluation

All patients were subjected to extensive evaluation before surgery. The presurgical workup comprised neuropsychological examination and history, prolonged video electroencephalography (EEG) monitoring, high-resolution MRI, Wada testing or functional MRI for assessment of language and memory function, formal neuropsychological testing, and visual field examination using the standard automated perimetry examination. In the majority of patients, interictal PET was performed. Video EEG monitoring was recorded for an average of 5 days; the EEG activity was recorded according to the extended international 10-20 system, including bilaterally placed true anterior temporal electrodes and sphenoidal electrodes. Seizure semiology, including clinical localizing and lateralizing signs, was evaluated with respect to predicting the side of the epileptogenic zone. Absolute spike frequency and location of interictal epileptiform discharges (IEDs) were assessed by visual analyses over the entire recording time. The distribution of IEDs was defined as unilateral if > 90% of the spikes occurred over the affected temporal lobe. Ictal scalp EEG patterns were determined by morphology, location, and time course of ictal EEG changes.

All patients underwent high-resolution MRI, which was initially performed with a 1.5-T unit. MRI, Wada testing or functional MRI for assessment of the rostral prolongation of the collateral sulcus including the unco-hippocampal arteries passing through the uncal collateral fissure, a corticotomy on the temporal side of the limen insulae was performed. By resection and suction of the amygdala and adjoining uncal cortex up to the level of the optic tract, the anterior roof of the temporal horn was opened. After detaching the choroid plexus from its tenia fimbriae and dissecting the arterial branches to the hippocampal sulcus, subpial dissection of the medial parahippocampal gyrus was started. The posterior margin of the resection was defined by a transverse transependymal cut through the most posterior part of the hippocampus. The collateral sulcus was exposed through the ventricular wall lateral to the hippocampus. This incision was connected to the posterior transverse hippocampectomy incision, and the lateral limit of the resection was defined by following this sulcus rostrally, taking into account information on the individual sulcal pattern provided by MRI. After dissecting around the hippocampal head in a subpial plane, cutting the unco-hippocampal arteries passing through the uncal sulcus, and lastly coagulating and cutting the vein usually present at the anterior end of the choroid fissure and draining into the basal vein, the parahippocampal-hippocampal specimen was removed en bloc. Finally, in every case an effort was made to resect by suction the cortex medial to the optic tract, the anterior roof of the temporal horn was opened. After detaching the choroid plexus from its tenia fimbriae and dissecting the arterial branches to the hippocampal sulcus, subpial dissection of the medial parahippocampal gyrus was started. The posterior margin of the resection was defined by a transverse transependymal cut through the most posterior part of the hippocampus. The collateral sulcus was exposed through the ventricular wall lateral to the hippocampus. This incision was connected to the posterior transverse hippocampectomy incision, and the lateral limit of the resection was defined by following this sulcus rostrally, taking into account information on the individual sulcal pattern provided by MRI. After dissecting around the hippocampal head in a subpial plane, cutting the unco-hippocampal arteries passing through the uncal sulcus, and lastly coagulating and cutting the vein usually present at the anterior end of the choroid fissure and draining into the basal vein, the parahippocampal-hippocampal specimen was removed en bloc. Finally, in every case an effort was made to resect by suction the cortex medial to the rostral prolongation of the collateral sulcus including the posterior superomedial polar cortex. The resected tissue was sent for histopathological analyses in all cases.

Outcome Assessment

Follow-up was conducted at 4 months and 1, 2, 5, 10, 15, and 20 years postoperatively. The face-to-face interview included neurological examination, scalp EEG, neuropsychological testing, and visual field examination. Magnetic resonance imaging was performed at 4 months after surgery. In addition, seizure outcome and current AEDs were...
evaluated yearly based on telephone interviews. Outcome was scored using the stringent classification of the International League Against Epilepsy (ILAE),8 which allows for the identification of patients who have been completely seizure free since surgery. Furthermore, we apposed the ILAE classification and the Engel classification as proposed by Wieser et al. for better comparability with the literature.15,59 Accordingly, ILAE Classes 1, 1a, and 2 are comparable to Engel Class I, ILAE Class 3 is comparable to Engel Class II, ILAE Class 4 is comparable to Engel Class III, and ILAE Classes 5 and 6 are comparable to Engel Class IV. The patients with seizures on attempted AED withdrawal were considered to be not seizure free.

The patients whose first operation failed were offered reevaluation according to the criteria described above and, if possible, reoperation. The decision regarding the type of reoperation to perform was made individually for each patient after the reevaluation and case discussion at a multidisciplinary epilepsy conference were completed. The extent of the temporal pole resection was dependent on the laterality of language and memory, with 3–4.5 cm on the dominant side and 4.5–5.5 cm on the nondominant side.

Statistical Analysis

For unifactorial analysis between groups defined by outcome, the Student t-test was used for statistical comparison of continuous prognostic variables if the distribution was normal, and the Wilcoxon test was used if the distribution was not normal. Dichotomous discrete variables were analyzed using the chi-square test or the Fisher exact test. All analyses were performed using SPSS version 18.0 (SPSS Inc.).

Results

Seizure Outcome After SAHE

We performed an SAHE in 158 patients (78 males, 80 females; 73 right side, 85 left side) with a mean age of 37.1 ± 10.0 years (median 37.5 years, range 16.0–62.0 years) at surgery. We excluded from further analysis the data for 4 patients (2.5%) who were lost to follow-up and 1 patient (0.6%) who committed suicide 4 months after surgery.

Seizure outcomes were documented up to 20 years following surgery, with a mean follow-up time of 9.7 years (median 10.0 years, range 18 months–20.1 years). At the last available follow-up (or before reoperation), complete cure of seizures since surgery (ILAE Class 1a) had been achieved in 68 patients (44.4%). Forty-six patients (30.1%) had been seizure free at least 12 months before the last follow-up visit (ILAE Class 1), 6 patients (3.9%) had only auras (ILAE Class 2), and 31 patients (20.3%) benefited from surgery, with 16 (10.4%) achieving ILAE Class 3 and 15 (9.8%) achieving ILAE Class 4. Two patients (1.3%) did not benefit from surgery and were classified as ILAE Class 5. The corresponding outcomes according to the Engel classification were Engel Class I in 78.4% of patients, Engel Class II in 10.5%, Engel Class III in 8.5%, and Engel Class IV in 2.0%. No patient had an appreciable worsening of epilepsy (IEEA Class 6 or Engel Class IVC).

During the follow-up period, seizure freedom rates remained stable when applying ILAE Class 1 (that is, no seizures during a 12-month period prior to assessment). One hundred eight (70.6%) of 153 patients were seizure free at 1 year, 96 (64.9%) of 148 patients at 3 years, 101 (78.9%) of 128 patients at 5 years, 80 (81.6%) of 98 patients at 10 years, 46 (88.5%) of 51 patients at 15 years, and 4 (57.1%) of 7 patients at 20 years after SAHE. Figure 1 shows the number of patients with or without seizures at different time points after surgery and the number of patients changing between the seizure-free and non–seizure-free groups.

When analyzing our cohort using the stringent but clinically more relevant definition of seizure freedom (that is, ILAE Class 1a, patients completely seizure free since surgery), we found a smaller number of successfully treated patients and a decrease in the number of patients without recurrence of seizures and auras over time: 70.6% at 1 year, 61.3% at 2 years, 54.3% at 5 years, 50% at 10 years, 50% at 15 years, and 28.6% at 20 years (Fig. 2).

Our analysis of potential predictors of seizure outcome such as age at surgery; age at seizure onset; number of AEDs; history of traumatic brain injury, meningitis, or febrile seizures; and seizure frequency did not reveal any significant findings.

FIG. 1. Long-term postoperative outcome among 153 MTLE patients after SAHE according to ILAE Class 1. Figure is available in color online only.
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Temporal Lobectomy After Unsuccessful SAHE

In 11 patients who were not seizure free after SAHE (ILAE Class 5 in 2 patients, ILAE Class 4 in 7 patients, ILAE Class 3 in 2 patients), reoperation via temporal lobectomy was performed after a mean period of 4.4 years from the SAHE (left side in 6 patients, right side in 5 patients). In none of these patients did histology reveal cortical dysplasia in the resected tissue. Magnetic resonance imaging after SAHE revealed residual mesiotemporal structures corresponding to the entorhinal and/or perirhinal cortex in 10 cases and residual hippocampal tissue in 3 cases. In none of these patients was selective resection of residual mesial structures alone intended since the potential for additional benefit in terms of seizure control due to the removal of neocortical tissue could not be dismissed preoperatively. In 4 of these patients (2 patients with ILAE Class 4 outcome, 2 patients with ILAE Class 5 outcome), a second operation was performed early, between 12 and 24 months after SAHE. The 7 remaining patients were temporarily free from seizures or had only rare disabling seizures (ILAE Classes 1–3), and 4 of these patients were completely seizure free between 5 months and 3.2 years after SAHE (ILAE Class 1a). Reoperation in these 7 patients was performed after a mean period of 8.0 years from SAHE. After a mean follow-up of 10.1 years from reoperation, 8 (72.7%) of these 11 patients were seizure free (ILAE Class 1a). Among the 3 remaining patients, 1 had only auras (ILAE Class 2), 1 had rare seizures (ILAE Class 3), and 1 did not improve (ILAE Class 5). These data correspond to improvement to an Engel Class I outcome in 82% of the 11 patients.

Overall Seizure Outcome

After a mean follow-up of 10.0 years (median 10.1 years, range 12 months–20.1 years), 72 patients (47.0%) were completely seizure free since (re)operation (ILAE Class 1a), 50 patients (32.6%) were classified as ILAE Class 1, 7 patients (4.6%) as ILAE Class 2, 15 patients (9.8%) as ILAE Class 3, 8 patients (5.2%) as ILAE Class 4, and 1 patient (0.6%) as ILAE Class 5. These data correspond to an Engel Class I outcome in 84.3% of the patients.

Surgical Complications

There were no deaths associated with surgery and no complications that resulted in a permanent neurological deficit. Complications with temporary morbidity were seen in 7 patients (4.6%). Three of the patients needed surgery for a complication. In 2 of these patients, a hemispheric hygroma formation leading to intractable headaches required drainage through a burr hole 1 month and 5 months after SAHE, respectively. In the remaining patient, a hematoma in the resection cavity needed evacuation on the 2nd postoperative day due to progressive impairment of consciousness, which did not result in any permanent neurological compromise.

One patient had an infarct in the territory of the lateral posterior choroidal artery with severe hemiparesis that fully resolved 6 months after surgery. One patient had intermittent aphasia without any correlate on CT or follow-up MRI, although it had fully resolved by discharge on Day 12 after surgery. Transcranial Doppler ultrasonography of the middle cerebral artery was normal throughout that period. Two patients experienced temporary oculomotor nerve palsy.

No complications occurred in any of the patients who underwent reoperation.

Discussion

Although 2 recent meta-analyses of studies comparing selective medial temporal resections and standard ATL have noted a moderate advantage with the latter procedure, and despite the fact that an assumed reduction in the
risk of selective surgery–related neuropsychological deterioration did not unequivocally stand the test of time, obtaining a good long-term seizure outcome with less extensive brain tissue resection remains an intuitively appealing concept.\textsuperscript{5,17,26,27,31,52,56} Our study provides information on long-term seizure outcome in a cohort of 153 consecutive adults with mesial temporal lobe epilepsy (MTLE) and hippocampal sclerosis on MRI who were selected for transsylvian SAHE at a single center, representing the largest consecutive series of patients treated in the MRI era with the most long-term follow-up information.\textsuperscript{59} After a median follow-up of 10 years, 78.4\% of the patients had a good SAHE outcome (Engel Class I). At 10 years, half of the patients had been completely seizure free since surgery (ILEA Class 1a or Engel Class IA).

Taking into account information available at the start of our epilepsy surgery program in 1994,\textsuperscript{15,16,21,44,50} we decided to propose SAHE to all patients fulfilling electroclinical and radiological criteria for unilateral MTLE. Therefore, our practice does not allow for a comparison between the selective procedure and ATL, as the latter procedure was used only when the patient did not fulfill the diagnostic criteria for SAHE. In contrast, most investigators have discussed this selective surgery group of patients in comparison with patients assigned to ATL or patients with lesional MTLE including tumors and vascular malformation.\textsuperscript{23,24,41,52,59}

While previous series have reported a lost-to-follow-up rate between 8.6\% and 32.9\%, the referral pattern of our patients allowed for strict long-term observation with only 4 patients (2.5\%) lost to follow-up.\textsuperscript{5,19,23,24,41,59,63} This also allowed for reoperation (ATL) in 11 cases of unsatisfactory seizure control or seizure recurrence. This strategy led to an excellent overall outcome (Engel Class I and ILEA Classes 1 and 2) in 84.3\% of the patient population.

During the 20-year study period (1994–2014), we did not change our approach as we felt confirmed by our evolving data and the data provided in the literature.\textsuperscript{8,24,25,30,34,52,59} Long-term seizure freedom rates at experienced centers were, indeed, similar between SAHE (54.4\%–80.4\%) and ATL (56\%–83\%). Recently, 2 meta-analyses of studies that compared epilepsy outcome between a selective and a standard approach pointed to a moderate advantage for the standard ATL.\textsuperscript{27,31} Methodological limitations of the included nonrandomized studies were addressed and comprise a lack of standardized follow-up, comparisons mostly with historical controls, and different SAHE techniques. Moreover, MRI findings and invasive recordings biased the choice of the surgical approach in some of the included studies.\textsuperscript{2,36}

Beginning with Niemeyer in 1958, several authors have suggested that selective resection of the mesial temporal structures could be sufficient by having the same effect in terms of seizure outcome as a complete resection of the anterior temporal lobe.\textsuperscript{38,40,61}

Regardless of the surgical corridor used to approach the medial temporal lobe, the different techniques somewhat incorrectly designated as “SAHE” aim to include the uncus and anterior parahippocampal gyrus into the resection volume.

We systematically used a transsylvian approach as developed by Yaşargil\textsuperscript{62} and Wieser.\textsuperscript{60} In every single case we tried to maximize the amygdala resection and include all of the presumed entorhinal and perirhinal cortex into the resection volume, tailoring the resection to the individual sulcal pattern visualized on MRI.\textsuperscript{4,11,28,39}

The failure of surgery to control seizures in MTLE can be discussed under various perspectives, differing in their practical relevance.\textsuperscript{1,13,22} The question regarding the optimal extent of resection in the individual patient probably cannot be answered with absolute certainty prior to resection of the epileptogenic zone.\textsuperscript{49} The critical involvement of the “temporopolar cortex” in a subgroup of patients with MTLE has been very well characterized based on stereo-EEG (SEEG) investigations,\textsuperscript{1} with mostly the mediobasal parts of the pole showing early involvement and considered to be part of the epileptogenic zone. Subpially resecting the temporal pole medial to the dorsal temporopolar gyrus and down and laterally to the prolongation of the collateral sulcus would include the whole of the entorhinal and perirhinal transitional cortex in the resection.\textsuperscript{11,46} This region has been resected in the original descriptions of the transsylvian SAHE by a perional craniotomy.\textsuperscript{3,162} Furthermore, postresection MRI studies, including a series by our group, have highlighted the importance of resecting this region with respect to seizure control, substantiating earlier observations.\textsuperscript{4,21,50,64} The variability of the sulcal anatomy in this basal temporopolar region must be taken into account, as certain anatomical variants of the temporobasal anatomy can misdirect the entorhinal resection during SAHE.\textsuperscript{11,39}

While some authors reporting on SAHE deliberately do not include the parahippocampal gyrus in the resection,\textsuperscript{2} the postoperative MRI included in some reports has shown what we would consider an insufficient resection of anterior entorhinal and/or perirhinal cortex.\textsuperscript{37} As we have demonstrated in previous reports, however, residual entorhinal cortex represents the most important factor in SAHE failures.\textsuperscript{3,62} Working through a limited corticotomy without a retractor necessitates precise planning of the available angular range through this “cortical keyhole” to be able to access the structures to be resected. Lesions in the dorsal part of the anterior medial temporal lobe can be resected through a lateral subfrontal-transsylvian approach with supraorbital craniotomy. However, this approach does not allow for selective transamygdaloid resection of cortex partially lying under the sphenoid wing on the anterior middle fossa floor.\textsuperscript{17,37,47}

Much emphasis has recently been put on the different white matter tracts transgressed or deliberately transected during the different approaches.\textsuperscript{9,12} The lateral transtemporal approaches, besides theoretically dissecting parallel to the optic radiation fibers and reducing the risk of a upper quadrant field defect, avoid injury to fiber tracts localized in the temporal stem in the roof of the ventricle.\textsuperscript{3,48} Although the uncinate fascicle can be preserved in the transsylvian approach, as evidenced by postoperative diffusion tensor imaging,\textsuperscript{61} we deliberately extended the resection to the upper margin of the amygdala, at least partially interrupting this fascicle as well as parts of the anterior commissure radiation. At this time we hypothesize that this disconnection is part of the procedure as
there was a lack of evidence for relevant deficits related to it, but this aspect needs to be critically addressed in future studies.\textsuperscript{12,24} It seems more important to restrict the latero-posterior extension of the corticotomy along the inferior insular sulcus into the temporal stem to minimize the risk of interrupting the occipitofrontal fiber bundles that are an important component of the “ventral” language network.\textsuperscript{12}

The lateral subtropical SAHE approaches through either the parahippocampal or, more commonly, the fusiform gyrus, aiming at circumventing the optic radiation altogether, are interesting alternatives, with seizure outcomes reported in the same range as with the other techniques.\textsuperscript{25,34,42,53} Current difficulties in preoperatively assessing the course of the temporobasal veins, the angulation of the collateral sulcus changing from anterior vertical to posterior mediolateral-horizontal and hindering a strictly transsulcal access to the whole extent of the ventricle, as well as a steep working angle to access the upper amygdala-uncal region, can eventually lead to changing the intended corticotomy site to restrict damage to the inferior temporal gyri.\textsuperscript{53}

In our experience, no permanent surgical morbidity has occurred after transsylvian SAHE, and we encountered no surgical complications in the 11 patients who had been treated with a second operation to complete the temporal resection. Minor complications were seen in only 7 patients (4.6%) after SAHE. Similarly, other authors who compared the outcomes for transsylvian SAHE with those for ATL in MTLE did not report a difference in the complication profile. For instance, in the largest series reported by Clusmann et al., no difference in the complication profile among 3 resection types (ATL, transsylvian SAHE, lateral neocortical lesionectomy) was reported.\textsuperscript{8}

Even though there has been no clear-cut evidence that SAHE in MTLE provides a better seizure control rate than ATL over the study period, the fact that a tailored approach avoids a potentially unnecessary resection of neocortical temporal lobe lets us stick to our standard practice.\textsuperscript{8,24,25,34,52,59} In light of this, the aim of complete resection of the medial structures (entorhinal cortex, amygdala, hippocampus, parahippocampus) eliminated the question of whether to perform a second resection limited to mesial structure remnants in cases of unfavorable seizure control. In our series, 114 patients (74.5%) were seizure free (ILEA Class 1) at a mean follow-up of 9.7 years after SAHE. In other words, 114 (74.5%) of the 153 patients would have undergone resection of the anterior temporal lobe unnecessarily if we had followed the strategy of performing an upfront ATL. Only 11 patients (7.2%) underwent reoperation to complete the resection to an ATL due to unsatisfactory seizure outcome, 8 of whom became completely seizure free. Thus, the overall seizure freedom rate of this tailored approach was 79.7% according to the ILAE classification and 83.6% according to the Engel classification, which is comparable to studies using upfront ATL.\textsuperscript{1,29}

In terms of the individual long-term seizure outcome, the rate of recurrence and late cure due to the “running-down phenomenon” needs to be scrutinized. These rates were speculated to be more prominent in selective resections. As in the series by Wieser et al., we observed that a change from seizure freedom to the recurrence of seizures and vice versa could occur at any time after surgery.\textsuperscript{59} More importantly, however, this observation did not differ from data obtained after standard ATL in MTLE patients, arguing against the notion that seizure recurrence and late cure may be higher after SAHE.\textsuperscript{1}

Conclusions

We demonstrated a satisfactory long-term seizure outcome for transsylvian SAHE in a selected group of patients with refractory temporal lobe epilepsy. Having proved that the second-line strategy of an ATL (in the small percentage of patients whose SAHE failed) is highly effective, we think that we can reasonably propose SAHE to selected patients.

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Disclosures
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