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Cognitive Changes After Unilateral Cortico-amygdalo-hippocampectomy or Unilateral Selective-amygdalohippocampectomy for Mesial Temporal Lobe Epilepsy

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ABSTRACT

BACKGROUND: The aim of this study was to compare neuropsychological outcome at 1-year follow-up in patients with medically refractory unilateral mesial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis (HS) treated by a cortico-amygdalohippocampectomy (CAH) or a selective-amygdalohippocampectomy (SAH).

METHODS: Data for a series of 72 adult patients who underwent surgery for MTLE/HS were evaluated. Thirty-six patients underwent CAH and 36 SAH. All patients underwent neuropsychological evaluation before and 1 year after surgery.

RESULTS: The intelligence quotient increased postoperatively in both surgical groups. Memory evaluation in the CAH group revealed a postoperative decline in nonverbal memory after right-sided resection and a postoperative decline in verbal memory after left-sided resection. In the SAH group, there was a slight postoperative decline only in verbal memory after left-sided resection, but other memory function was well preserved. However, no significant difference was found between two approaches regarding memory. There was no also statistically significant difference between two approaches in terms of seizure outcome at 1-year follow-up.

CONCLUSIONS: Our results suggest that in the clinical planning of seizure treatment, the optimal type of surgical approach is dependent on the outcome predictions, rather than on any supposed advantages to postoperative memory function.

KEY WORDS: Anterior temporal lobectomy, cortico-amygdalohippocampectomy, epilepsy surgery, hippocampal sclerosis, selective- amygdalohippocampectomy.

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) secondary to hippocampal sclerosis (HS) is the most common medically refractory epilepsy syndrome. Different surgical approaches yielded satisfactory and almost equal success rate in terms of seizure control although different results have been reported. Among the different surgical techniques, Falconer's en bloc anterior temporal lobe resection (ATLR) or cortico-amygdalohippocampectomy (CAH) (8) and Niemeyer's selective-amygdalohippocampectomy (SAH) (25) are the two surgical techniques that have been most commonly used. Both techniques have been modified and surgical results especially in terms of seizure outcome have been found comparable to each other (28, 36). However, in recent years, most epilepsy surgeons shifted to use more selective surgical excision due mostly to advancing imaging and the evolving body of knowledge related to pathogenetic bases of HS. There is still debate on which type of surgical modality results in a better outcome in terms of both seizure and cognitive outcome since some claim that a more restricted resection such as SAH results in better cognitive and seizure outcome (21, 24) than a resection that involves temporal neocortex such as CAH whereas others and even meta-analytic studies have not found significant differences between the two surgical strategies (2, 17, 29).

It is currently difficult to compare surgical results of CAH and SAH at the same medical center since most centers use a single preferred surgical approach in MTLE/HS and comparisons in terms of seizure outcome or cognitive changes can only be made with the results of other centers in which different types of surgical strategies are performed. Little comparative data on the cognitive sequela of either surgical procedure have been published (10, 24, 30). Thus, we compared some postoperative cognitive functions including intelligence quotient (IQ), and verbal and non-verbal memory in patients with mesial temporal lobe epilepsy who underwent either CAH (mostly misinterpreted as anterior temporal lobectomy) or SAH at the same center, Montreal Neurological Institute (MNI).

PATIENTS and METHODS

Patient selection

We describe 72 patients who underwent epilepsy surgery at the MNI and were right-handed or had left hemisphere language dominance revealed by intracarotid sodium amytal (Wada) test. Our inclusion criteria for this study were as follows: patients who 1) were? 16 years old; 2) had a similar clinical picture; 3) had complete clinical, neuroradiological, electrophysiological, neuropsychological and surgical data sets; 4) had interictal and ictal scalp/sphenoidal and intracranial depth electrode electroencephalography (EEGs) displaying unilateral independent antero-mesial temporal epileptic discharges; 5) had MRI or histopathological findings characteristic of HS; 6) had no re-operation and 7) had a follow-up duration of at least 1-year.

First cohort: patients with CAH

The first cohort or group included the first 36 patients who had undergone CAH for MTLE/HS between March 1986 and January 1990 and who met our inclusion criteria. These individuals were drawn from a total of 336 patients who had undergone surgery for intractable epilepsy during the same period. This group consisted of 13 males and 23 females with a mean age of 36.0 ± 12.4 years. The mean age of the patients at seizure onset was 13.4 ± 10.8 years and all had complex partial seizures. Fifteen and 21 patients underwent surgery on the right and left side, respectively.

Second cohort: patients with SAH

The SAH group consisted of the first 36 patients who met our inclusion criteria and had undergone SAH for MTLE/HS between January 1991 and April 2001. These individuals were drawn from a total of 741 patients who had undergone surgery for intractable epilepsy during the same period. This group consisted of 9 males and 27 females with a mean age of 39.1 ± 11.6 years. The mean age of the patients at seizure onset was 14.8 ± 12.2 years. All had complex partial seizures. Twenty-two patients underwent surgery on the right side, whilst 14 patients underwent surgery on the left side.

Data regarding clinical and surgical variables in patients who have undergone each technique are listed in Table I.

Preoperative Evaluation

At the MNI, the preoperative evaluation of patients with medically refractory MTLE/HS includes electrophysiological, neuroradiological and neuropsychological testing.

All patients underwent preoperative MRI assessments (1.5 T, Philips Gyroscan; Philips Medical Systems, Eindhoven, the Netherlands) including high-resolution T1/T2-weighted, and fluid-attenuated inversion recovery (FLAIR) scans were routinely obtained.

Electrophysiological evaluations included scalp/sphenoidal interictal and ictal EEGs, and intraoperative electrocorticography (ECoG). Intracranial stereoelectroencephalography (SEEG) was performed if indicated. Prolonged video-EEG with scalp/sphenoidal electrodes was performed to record interictal and ictal spikes during wakefulness and sleep in all patients. SEEG recording with stereotaxically implanted electrodes were performed in patients in whom the extracranial EEG recordings

Table I: Clinical data of the patient groups

Factors	**CAH (n = 36)**	**SAH (n = 36)**	**P**
Age (yr)	36.0 ± 12.4	39.1 ± 11.6	0.22, NS*
Gender, Male/Female	13 / 23	9 / 27	¯2 = 0.44, NS
Age at onset of epilepsy (yr)	13.4 ± 10.8	14.8 ± 12.2	0.70, NS*
Age at surgery (yr)	36.9 ± 11.8	38.8 ± 12.0	0.33, NS*
Side of surgery, Right/Left	15 / 21	22 / 14	¯2 = 0.15, NS
Seizure outcome at 1-year (F/UF), %	94.4 / 5.6	100 / 0	¯2 = 0.11, NS

CAH: Cortico-amygdalohippocampectomy; F: Favorable seizure outcome (Engel class I and II); NS: Not significant; SAH: Selective-amygdalohippocampectomy; UF: Unfavorable seizure outcome (Engel class III and IV).
* stands for non-parametric "Wilcoxon test" test.

did not provide clear localization or lateralization of seizure onset. Furthermore, ECoG recording was used in patients in order to see whether there was epileptic activity coming from the neocortex when needed.

Neuropsychological studies with emphasis on verbal and visual memory, visuospatial abilities and language functions, were performed preoperatively in all patients. A standardized neuropsychological test battery included the full intelligence scale (IQ) [Wechsler Adult Intelligence Scale–Revised (WAIS-R)], verbal (story learning test, abstract words learning test and the Rey auditory verbal learning test), non-verbal and learning (the Rey-Osterrieth complex figure recall memory test and abstract design learning test) tests. Cognitive functions were evaluated before and 1-year after surgery for this study as follows: By IQ [verbal IQ (VIQ), performance IQ (PIQ), and full scale IQ (FIQ)], as determined with the WAIS-R. By verbal memory, as determined with Rey's Auditory Verbal Learning test (RAVT) or 15-Word test, consisting of 5 successive presentations of a list of 15 words followed by free recall on each trial. The tests yield two measures: the total words recalled across the five trials as a measure of list learning or acquisition (immediate recall), and the long delay, free recall score as a measure for consolidation and retrieval (delayed recall). By non-verbal memory, as determined with the Rey-Osterreith Complex Figure Task in which the patient has to copy a figure and after 10 minutes, is asked to reproduce the figure just copied.

In this study we used delayed recall score for non-verbal memory measurements since this test is supposed to measure long-term visual memory.

Surgical Procedures

The surgical procedure was not randomized in this study. CAH was considered the standard procedure for treatment of MTLE/HS between 1986 and 1990 at the MNI. In CAH, the aim is to perform a temporal neocortical resection, extending habitually 5 cm along the sylvian fissure and 5 to 5.5 cm along the bottom of the middle fossa on the non-dominant side and 4.5 to 5 cm in the dominant side, together with total or partial resection of the amygdala and uncus, and 2.5 to 3 cm removal of the hippocampus and parahippocampal gyrus. The surgical procedure has been described in detail elsewhere (27). The main surgical procedure became SAH between 1991 and 2001. Briefly, trans-cortical SAH, a procedure that has been described in greater detail elsewhere (28), involves performance of either a pterional craniotomy or a centered craniectomy with corticectomy along the superior bank of the middle temporal gyrus, subpial extension of this line of entry down along the superior temporal sulcus, across the temporal white matter, and into the temporal horn of the lateral ventricle. Once inside the ventricle, the hippocampus, amygdala, entorhinal cortex, and uncus are resected. All steps of the procedure were done by neuronavigation and were performed by the same surgeon (A.O.). The choice of surgical procedure paralleled the advancements in neuroimaging and electrophysiological techniques and understanding of the epileptogenic bases of MTLE/HS. At the MNI, our work with chronic depth electrode recording has confirmed the overwhelming predominance of temporal seizure onset from the limbic structures. Relying more and more heavily on the morphological changes seen in the limbic structures on MRI and on the results obtained from SEEG, we have carried out more and more frequently the trans-cortical SAH which has become the procedure of choice in cases of mesio-temporal limbic epilepsy, i.e. when the seizure pattern, the EEG findings and the morphological stigmata are congruent.

Histopathological Study

Hippocampal tissue sufficient for histopathological diagnosis was available in all patients. The resected specimens were histopathologically examined with previously described techniques (23). The qualitative assessment of pattern of cell loss, gliosis and HS in hippocampal subfields CA1, CA3 and in the dentate gyrus was applied.

Postoperative Evaluation

Patients were discharged on therapeutic dosages of at least one first-line anti-epileptic drug (AED). The first follow-up was performed at 6 weeks following the surgery and 6 months in the 1st year and yearly thereafter, either through outpatient visits or telephone interviews. Outcome was assessed independently by the neurological and neurosurgical teams. Patients and relatives were instructed to report seizure recurrences by telephone between scheduled outpatient visits, and these data were entered onto a structured outcome data sheet. Interviews for follow-up purposes involved questioning patients or relatives about the recurrence of symptoms and signs suggestive of complex partial, partial motor, or generalized tonic–clonic seizures. All patients had MRI, scalp EEG and neuropsychological evaluations during the follow-up period.

Seizure outcome at 1-year follow-up in relation to seizure control was based on Engel's classification, using all 12 subclasses (modified Engel classification) (7). For categorical comparisons in this study, seizure outcome was divided into two groups: favorable outcome (Engel class I and II) and unfavorable outcome (Engel class III and IV).

Statistical analysis

All data collected from each patient were organized in a database (Excel; Microsoft Corp., Redmond, WA). Numeric variables were provided as mean ± standard deviation. For statistical analysis, we used the "chi-square test (¯2)" to compare nominal data (seizure outcome, gender, and side of surgery) for different surgical procedures. For smaller contingency tables, we used Fischer's exact test. For comparison of patient groups in relation to mean age and cognitive functions (IQ and memory), nonparametric statistics were preferred because of the relatively small size of some samples and non-normal distribution of some variables. For this purpose, the Wilcoxon test (Z) was used. Repeated measures for comparison of cognitive functions were made by using multiple analyses of variance (MANOVA). A probability value was considered as statistically significant if less than 0.05. All statistical calculations were performed using commercially available software (SPSS version 11.0.1; SPSS Inc., Chicago, IL).

RESULTS

The follow-up period was more than 1 year for all patients and all data were available at 1-year follow-up in all patients.

Demographic data and seizure outcome

Demographic and clinical data are summarized in Table I. Patients who underwent a CAH or SAH had very similar clinical and demographic characteristics. There was no statistically significant difference between the two groups in terms of patient demographics and seizure outcome at 1-year follow-up. ($p > 0.05$).

Intelligence quotient

Table II lists the IQ scores before and one year after surgery in both groups. Overall, all IQ scores, including VIQ, PIQ, and FIQ increased following both types of surgery. There were no statistically significant differences between CAH and SAH in either pre- or post-operative period. However, we found significant differences when we compared pre- and post-operative IQ. In patients who underwent right CAH or SAH, both VIQ and FIQ showed a marked increase compared to the pre-operative level. There was a significant post-operative increase in PIQ and FIQ scores after left

Table II: Intelligence quotient before and 1-year after surgery.

	Right CAH (n = 15)			Left CAH (n = 21)		
Intelligence Quotient	**Preop.**	**Postop.**	**P**	**Preop.**	**Postop.**	**P**
Verbal	88.2±13.1	90.9±13.2	0.04	94.0±19.0	94.8±19.3	0.4
Performance	89.2±13.0	91.7±13.9	0.1	97.0±15.5	102.0±15.3	0.03
Full Scale	89.4±16.0	92.7±16.3	0.01	94.7±18.7	97.7±18.9	0.002
	Right SAH (n = 22)			**Left SAH (n = 14)**		
Intelligence Quotient	**Preop.**	**Postop.**	**P**	**Preop.**	**Postop.**	**P**
Verbal	89.0±16.6	91.8±17.4	0.005	87.5±11.7	90.9±11.5	0.01
Performance	92.0±18.2	92.9±16.4	0.5	95.0±17.4	96.1±13.2	0.5
Full Scale	91.6±17.2	94.4±18.4	0.002	90.7±12.6	94.5±12.6	0.005

CAH: Cortico-amygdalohippocampectomy; Preop: Preoperative; Postop: Postoperative; SAH: Selective-amygdalohippocampectomy.

CAH. However; patients who had left-sided SAH showed a marked increase in VIQ and FIQ.

Taken together, MANOVA with approach and laterality as inter-group factors indicated that there were no significant post-operative changes with respect to VIQ, PIQ, and FIQ.

Memory

Verbal memory

Pre- and 1-year post-operative verbal and non-verbal memory scores regarding immediate and delayed memory are listed in Table III. The MANOVAs with approach and laterality as inter-group factors showed no significant difference from pre-operative verbal memory.

In CAH group, there were decline in verbal memory after right- and left-sided resections and the difference reached significance only for delayed memory in left-sided resection. The decline in verbal memory after left-sided resection was somewhat more than for right-sided resection in CAH patients.

We found a tendency for verbal memory to decline following both right- and left sided-resection in the SAH group. Decline in verbal memory was found to be more marked with right-sided SAH than with left-sided SAH. Overall, memory function was better preserved in the SAH group than in the CAH group.

Non-verbal memory

Pre- and 1-year post-operative verbal and non-verbal memory scores regarding immediate and delayed memory are listed in Table III. The MANOVAs with approach and laterality as inter-group factors showed no significant difference from pre-operative verbal memory.

In the CAH group, there were declines in nonverbal memory after both right- and left-sided resection but the differences were not statistically significant.

In the SAH group, there was also decline in non-verbal memory function but no marked post-operative difference was found when compared to pre-operative scores regarding the side of surgery. More decline in non-verbal memory was noted in the CAH group compared to the SAH group, although the MANOVAs with approach and laterality as inter-group factors showed no significant difference between post-operative non-verbal memory.

Complications

There were no intraoperative or postoperative deaths or any significant neurological deficits in this series.

DISCUSSION

It has been shown that both CAH or anterior temporal resection, or what is sometimes

Table III: Verbal and non-verbal memory before and 1-year after surgery.

	Right CAH (n = 15)			Left CAH (n = 21)		
Factors	**Preop.**	**Postop.**	**P**	**Preop.**	**Postop.**	**P**
***Verbal Memory**						
Immediate 15-word recall	9.3±3.6	8.2±3.0	0.17	10.0±3.0	8.9±2.7	0.03
Delayed 15-word recall	8.9±4.3	9.3±4.1	0.75	9.2±3.6	8.2±3.5	0.16
****Non-verbal Memory**						
Rey's complex figure	11.3±8.7	10.6±7.6	0.78	15.0±4.7	14.5±5.2	0.43
	Right SAH (n = 22)			**Left SAH (n = 14)**		
Factors	**Preop.**	**Postop.**	**P**	**Preop.**	**Postop.**	**P**
***Verbal Memory**						
Immediate 15-word recall	10.2±3.5	9.6±3.2	0.006	8.8±3.5	8.2±2.8	0.50
Delayed 15-word recall	9.1±3.6	8.6±3.3	0.03	7.4±4.1	7.5±3.7	0.65
****Non-verbal Memory**						
Rey's complex figure	12.8±7.6	12.9±7.2	0.86	9.3±7.0	10.3±8.0	0.26

CAH: Cortico-amygdalohippocampectomy; Preop: Preoperative; Postop: Postoperative; SAH: Selective-amygdalohippocampectomy.

* Number of words that patients recalled.

** Number of figures that patients recalled (copied).

inappropriately called a temporal lobectomy and SAH are effective and safe procedures in patients with intractable MTLE/H (2-6, 26). The comparison between two modalities is difficult because most centers usually perform one preferred procedure and comparison usually relies on the results reported by other centers. To our knowledge, there have been only three studies that specifically compared the surgical results of CAH and SAH in terms of seizure outcome and/or cognitive changes at a single center (10, 24, 30). The first one was from Goldstein et al. (10) who studied 42 patients with MTLE/HS at one and four-month follow-up. CAH and SAH were performed in 19 and 23 patients and the results in terms of cognitive function were compared. No statistically significant differences were found between the groups on pre- and post-operative IQ measures. However, they showed that CAH patients showed an improvement in PIQ and SAH was followed by mild deterioration irrespective of the side of surgery. Moreover, right-sided surgery was followed by a relative decrease in verbal skills, while the reverse was true for left-sided operations. Left-sided surgery was associated with deterioration in immediate recall as with right-sided CAH (but to a lesser degree). For delayed recall, both left-sided groups' scores fell, whereas both right-sided groups (SAH more than CAH) showed some improvement. Right CAH showed better results than right SAH, but left CAH performed worse than left SAH on verbal memory. When considering non-verbal memory, they found that right CAH showed more deterioration than right SAH but left CAH showed less deterioration than left SAH. In the second study, Paglioli, et al. (30) compared long-term seizure and cognitive outcome in 80 patients with CAH and 81 patients with SAH. They demonstrated that verbal memory scores with left-sided operations declined compared to right-sided surgery. Right CAH showed worse non-verbal scores than the right SAH group. A recently published study compared the cognitive functions in 17 and 32 patients who underwent CAH and SAH, respectively, at 1-year follow-up (24). They found that IQ increased in both groups after surgery, without a marked difference between the groups. In the CAH group, there was a significant postoperative increase in IQ scores for all except verbal IQ and FIQ after left-sided resection. In the SAH group, there was a significant postoperative increase in IQ scores for all except PIQ after right-sided resection. A repeated-measures MANOVA with approach and laterality as inter-group factors indicated that there were no significant postoperative change in respect to VIQ, PIQ, and FIQ scores. Furthermore, they also revealed that CAH showed declines in both non-verbal memory after right-sided resection and verbal memory after left-sided resection, but the decline in verbal memory after left-sided resection was particularly marked. Verbal memory after left-sided-resection declined slightly in the SAH group, as in the CAH group,. Repeated-measures MANOVA with approach as an inter-group factor revealed no significant postoperative changes in verbal and non-verbal memory. They concluded that memory function was better preserved in the SAH group than in the CAH group, although the differences did not reach a markedly significant level.

We reported findings that were similar to Goldstein et al. (10), Paglioli et al. (30), and Morino et al. (24) who compared CAH and SAH in a homogeneous large group of patients with MTLE/HS in long-term follow-up. Our results demonstrated that verbal memory decreased after left-sided resection in both CAH and SAH but the decline was much more pronounced in the left-sided SAH group. On the other hand, the post-operative memory function was better preserved in the SAH group compared to the CAH group in patients with right-sided resections,. However, we were not able to demonstrate significant post-operative differences in terms of both memory and IQ scores between two surgical modalities when analyzed by MANOVA. Thus, we agree with Jones-Gotman, et al. (17) that our results indicate that there is no particular advantage or disadvantage of one type of surgical excision over another with respect to the aspects of memory, since a similar degree of disturbance was observed in both groups, with no systematic difference between the groups. Thus, our data do not support the conclusion that one type of surgical approach entails more sparing of memory ability than another. It is therefore probably reasonable to determine the optimal type of surgical approach based on outcome predictions, rather than on any supposed advantages to postoperative memory function in the clinical planning of seizure treatment. The similarity in cognitive function despite two different surgical resections may be an unexpected finding. However, CAH and SAH are functionally the same procedures in which resection of either limbic structures or neocortex disconnects one region from the other. The circuit is interrupted, and is essential for normal storage and retrieval (15).

A recent study compared cognitive function after selective amygdalohippocampectomy with trans-sylvian versus trans-cortical approaches (21). They stated that both approaches resulted in a significant decline in verbal memory with left-sided surgery, but phonemic fluency was significantly improved after surgery with the trans-cortical but not the trans-sylvian approach. The authors concluded that either surgical modality can be chosen independent of cognitive outcome criteria.

Overall, our findings are similar to a large number of reports linking the left temporal lobe to verbal and the right temporal lobe to non-verbal memory function (1, 9, 11, 12, 14, 16, 22, 31-34, 37).

Surgery

At MNI, surgical strategy was changed in 1990 and the cohorts in the present study were chosen according to resection strategies and were not randomized. Before 1990, CAH was the surgical procedure of choice and included anterior temporal lobe resection plus amygdalohippocampectomy. After 1990, with systemic use of neuronavigation and great advances in neuroimaging and diagnostic modalities including invasive (frameless, neuronavigation-based inserted depth electrodes since 1992 at MNI) and non-invasive preoperative EEG evaluations, we have attempted to limit resections to the presumed epileptogenic focus with SAH becoming the method of choice. We chose trans-cortical SAH approach initially proposed by Niemeyer to avoid manipulation of the sylvian vessels and to prevent disconnection of the anterior portion of the temporal stem, which results from the trans-sylvian technique. The main finding regarding these two cohorts is that the success rate remained stable despite the reduction in the amount of resected tissue. A comparison of CAH and SAH performed in this series revealed a similar rate of seizure control and cognitive function. There has been no common consensus in the literature that states the extent of the resection has an effect on the seizure and cognitive outcome. Some studies reported that the extent of the mesial resection had no effect (2, 6, 17, 20) but others reported that a greater extent of mesial temporal resection (in patients with a mesial or unilateral anterior temporal lobe focus) had a significant association with a good outcome (19, 13, 22, 18). It should be noted that if the site of seizure origin resides in the damaged structures, these should then be resected as radically and selectively as possible. The larger cortical removal in standard resection should not become, or remain, simply a method of exposing the limbic structures. Finally, the trans-cortical SAH approach has the major advantage of minimizing or completely abolishing the impact of dividing several venous and arterial blood vessels which is tedious, time consuming and, at times, associated with some degree of cerebral swelling.

CONCLUSION

In this study, we have demonstrated that the two basic surgical modalities used in treatment of patients with MTLE/HS can lead to similar favorable seizure control and cognitive outcome. Thus, seizure or cognitive outcome is likely not to be a decisive factor in favoring one technique over the other. Temporal "en bloc" lobectomy may still have its place in specific instances. However, advances in intracranial recording and brain imaging, as well as consideration of patients with impaired memory, has imposed upon the surgeon the need to consider various types of resection individualized for each specific patient. Over the last 20 years, there has been a definite trend towards reducing the extent of neocortical resection and increasing the amount of limbic structure removal. This has led surgeons in many centers to use selective limbic removal by a variety of approaches more and more frequently. We have found that the trans-cortical selective approach has the major advantage of minimizing or completely abolishing the impact of dividing several venous and arterial blood vessels which is tedious, time consuming and, at times, associated with some degree of cerebral swelling.

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