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Cognitive Outcome after Surgery in Patients with Mesial Temporal Lobe Epilepsy

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ABSTRACT

Introduction: The aim of the present study was to evaluate the neuropsychological outcomes of patients with medically intractable unilateral mesial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis (HS) treated either by anterior temporal lobectomy (ATL) or selective amygdalohippocampectomy (SAH).

Methods: This was a retrospective study where 67 patients who had undergone surgery for MTLE were evaluated. Thirty-two patients underwent ATL and 35 underwent SAH. All patients underwent a detailed neuropsychological evaluation before and 1 year after surgery.

Results: The verbal memory outcome was unchanged after left-sided surgery, whereas learning capacity increased after right-sided surgery (p=0.038). The visual memory outcome improved after right-sided surgery. Improvement of executive functions, particularly in the resistance of interference pattern in the Stroop Test, shortened 5th card time (p=0.000), and decreased corrections (p=0.003), after right-sided surgery and increased attention (p=0.027) after left-sided surgery were observed. After both surgery types, although statistically insignificant, there was a marked decrease in incorrect answers in the Stroop Test, which also showed an improvement in the resistance of interference pattern. Moreover, there was a significant decrease in switching errors with word pairs in the Verbal Fluency Test (p=0.008) after right-sided surgery. When the two sides were compared, we observed that the recall phase of the verbal memory worsened (p=0.018); however, the recognition phase improved (p=0.015) after left-sided surgery. Additionally, the short-term visual memory was better for both sides (p=0.035).

Conclusion: Our results showed that patients with left MTLE were not worsened in verbal memory, but despite improved recognition, they have some problems in recalling information and only a minor improvement in attention. Patients with right MTLE improved in their verbal learning capacity, visual memory, and resistance of interference pattern 1 year after surgery. It was thus shown that while epilepsy surgery is associated with some negative cognitive changes, it may also improve some cognitive functions.

Keywords: Cognitive outcome, mesial temporal lobe epilepsy, anterior temporal lobectomy, selective-amygdalohippocampectomy, executive function

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis (HS) is the most common medically intractable and surgically treatable epilepsy syndrome (1,2). Anterior temporal lobectomy (ATL) or selective amygdalohippocampectomy (SAH) is a surgical procedure used to treat intractable temporal lobe epilepsy (TLE) (3). Many groups have reported significantly improved seizure outcome in approximately 60–90% of surgically treated patients (4,5,6,7,8). However, seizure frequency alone after surgery is insufficient to decide whether a patient is in a satisfactory condition, and concerns have been expressed regarding neuropsychological outcomes after surgery (6,9).

Impairments of various cognitive functions, such as verbal memory, visual memory, naming, verbal fluency, and attention, have been reported after left- and right-sided surgeries (10). Verbal memory decline and naming difficulties in left-sided surgery and visual memory decline in right- and left-sided surgeries are the most prominent losses (10). TLE in the speech-dominant hemisphere is associated with a deterioration of verbal episodic memory. Visual memory seems to be less lateralized than verbal memory. In an evaluation of 732 patients with TLE who had undergone temporal lobe surgery at the 12-month follow-up, memory decline was the most frequent cognitive adverse effect within the language-dominant hemisphere (11). Although the results are inconsistent, the impairment of verbal memory before and after left temporal surgery and the impairment of visual memory after right temporal surgery are the most frequently reported findings (9,10,12,13,14,15). Some other authors have reported recovery in these cognitive functions (10). Contralateral improvement in visual memory (9,10,15) and improvements in executive functions and also in memory function have been reported (10,16,17).

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The main purpose of the present study was to compare the neuropsychological outcomes of patients with MTLE after surgery at the 1-year follow-up.

METHODS

We retrospectively reviewed the charts of 73 consecutive patients with medically intractable unilateral MTLE due to HS, assessed at Bakirkoy Hospital for Psychiatric and Neurological Diseases, who had undergone ATL or SAH between 2001 and 2014. Candidates for surgery were determined after a comprehensive presurgical evaluation. Clinical features, seizure semiology, and antiepileptic treatment were noted before and after surgery. Long-term video EEG monitoring was performed on all patients, and at least 3 ictal seizures were recorded to confirm the location of ictal onset. All patients underwent pre- and postoperative 1.5-Tesla MR imaging (MRI) with an epilepsy protocol. A detailed neuropsychological evaluation was applied to all patients. One patient who could not complete the tests due to mental retardation before and 1 year after surgery and 5 patients with left-hand dominance were excluded. Of the remaining 67 patients, 32 underwent ATL and 35 underwent SAH. HS was confirmed by pathological analysis.

Neuropsychological evaluation for the epilepsy surgery patients comprised a standard battery of psychometric tests assessing various cognitive functions such as intellectual abilities, hand dominance, attention, executive functions, and verbal, logical, and visual memory. The following tests were used: Wechsler Adult Intelligence Scale IQ Test for IQ evaluation, Edinburgh Hand Dominance Test for handedness, Digit Span Test (with forward, backward, and total scores) for attention, Wisconsin Card Sorting Test (with total score), Stroop Test (with 1st and 5th card times, mistake, and correction) and Verbal Fluency Test (semantic fluency with animals per minute, word pairs per minute, perseverations, and switching errors) for executive functions, Verbal Memory Processes Test (with short-term memory, maximum and total learning, recall, recognition, and total recall), Wechsler Memory Scale (WMS) story subtest for (with short- and long-term) verbal and logical memories, Boston Naming Test for language skills, WMS visual memory subtest (with short- and long-term memories, recognition, and total score) for visual memory, and Benton Facial Recognition Test and Line Orientation Test for visuospatial skills and construction ability. All patients had at least 4 years of education. Informed consent was obtained from all patients or their relatives. All procedures were performed in agreement with the general recommendations of the Declaration of Helsinki.

Statistical Analyses

Statistical analyses was performed using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 18. Numeric variables of the groups were assessed with the independent t-test, while non-numeric but categorical variables were assessed with chi-square tests. Pre- and postoperative variables within groups (left and right side) were assessed by the paired sample t-test. Differences of cognitive domains between the groups were assessed by ANOVA for repeated measures, with laterality used as the variable. P<0.05 was considered statistically significant.

For some patients, some subtests of verbal or nonverbal memory were not performed due to their lack of cooperation, resulting in missing data for these scores. These events occurred at random and are shown as 0 in the analyses.

RESULTS

Sixty-seven patients, comprising 28 (41.6%) females and 39 (58.4%) males, were included. The mean age was 27.28±8.08 (varying between 10 and 47 years) with 16.36±8.6 years as the mean duration of disease. Of these patients, 40 (59.7%) had left-sided HS, while 27 (40.3%) had right-sided HS. The demographic features of the patients are given in Table 1.

In the assessment of left-sided MTLE/HS patients, there was a significant improvement in attention after surgery (p=0.027).

For the right-sided MTLE/HS patients, there was a significant improvement of visual memory functions, especially in the short-term (p=0.035) and long-term (p=0.049) subtests which investigate the recording and recall phases. Also, a significant improvement of the verbal memory function, especially in the recording phase, was observed. Improvement of the executive functions, especially in the Stroop Test, a shortened 5th card time (p=0.000), and decreased corrections (p=0.003), showed the significant improvement of the resistance of interference pattern. Moreover, we observed a significant decrease in switching error of word pairs in the Verbal Fluency Test (p=0.008) after right-sided surgery.

After both surgery types, although statistically insignificant, there was a marked decrease in incorrect answers in the Stroop Test, which also demonstrates an improvement in the resistance of interference pattern.

Pre- and postoperative neuropsychological test results for each side are shown in Table 2. Differences in the cognitive domains between the right and left TLE groups were assessed by ANOVA test, and the results are shown in Table 3.

Pre and postoperative scores of right- and left-sided temporal resections were compared; whereby, despite the significant improvement in the recognition phase (p=0.015) in the verbal memory test in left-sided surgery patients, the recall phase (p=0.018) results worsened. The recording phase of the visual memory test (p=0.035) was better for both sides.

DISCUSSION

The main finding of the present study include that the overall verbal memory was not worsened after left-sided surgery with the improvement of attention. Increased learning capacity for verbal memory and improvements of the short- and long-term visual memory and resistance of interference pattern were found after right-sided surgery. Independent of the surgical technique performed, although statistically insignificant, there was a marked decrease in incorrect answers in the Stroop Test, which also demonstrates an improvement in the resistance of interference pattern and the recovery of executive functions. Also, a decreased switching error of word pairs in the Verbal Fluency Test after right-sided surgery was observed. All these findings reveal an improvement in frontal functions as well as memory.

Table 1. Demographic features of the patients

		Left MTLE /HS (n=40)	Right MTLE /HS (n=27)	p
ATL/SAH (n)		18/22	14/13	
Age, years (mean±SD)		16–47 (27.57±8.62)	10–41 (27±7.55)	0.780
Gender	Female, n	17 (42.5%)	11 (40.7%)	0.581
	Male, n	23 (57.5%)	16 (59.3%)	
Mean age at seizure onset (years)		1–36 (9.7±6.37)		
Mean duration of disease (years)		2–36 (16.36±8.6)		
IQ		78.34±12.84	80.35±12.74	0.639

MTLE/HS: Mesial temporal lobe epilepsy/hippocampal sclerosis

Table 2. Comparison of pre- and postoperative neuropsychological test results of the patients for each side

Tests		Right				Left			
		n	Pre-op (mean±SD)	Post-op. (mean±SD)	p*	n	Pre-op. (mean±SD)	Post-op. (mean±SD)	p*
DST	Forward	22	4.72±0.82	4.81±0.95	0.492	40	4.80±1.04	4.80±1.04	1.000
	Backward	22	3.50±1.18	3.31±1.04	0.257	33	3.69±0.88	4.00±1.29	0.077
	Total	22	8.22±1.77	8.13±1.83	0.648	33	8.63±1.79	9.15±2.13	0.027
VMPT	STM	21	9.66±20.2	5.52±1.88	0.358	32	5.34±1.28	5.00±1.96	0.35
	MLS	21	11.90±2.40	12.76±2.11	0.038	32	11.78±2.02	11.06±2.36	0.106
	TLS	21	93.95±18.68	99.57±24.39	0.092	32	91.40±19.18	85.25±22.14	0.124
	Recall	21	9.57±2.87	9.80±2.46	0.682	32	8.25±2.94	7.71±2.90	0.280
	Recognition	21	4.76±2.42	4.71±2.26	0.925	32	5.93±2.35	6.31±2.29	0.425
	Total recall	21	14.33±1.65	14.52±1.16	0.540	32	14.15±1.72	14.03±1.57	0.580
WMS LM	STM	15	8.53±3.04	9.13±3.13	0.407	22	9.05±4.85	8.36±4.71	0.301
	LTM	14	7.14±3.80	9.00±3.23	0.051	21	7.86±4.90	7.19±4.22	0.305
WMS Visual	STM	19	8.63±2.90	9.57±3.28	0.035	32	10.37±2.70	11.03±2.46	0.155
	LTM	18	7.44±3.45	8.94±3.38	0.049	32	8.84±3.12	9.62±2.82	0.070
	Recognition	17	3.00±2.26	2.23±1.67	0.304	32	2.43±2.44	2.09±2.08	0.523
	Total	18	10.27±2.84	11.05±3.18	0.369	32	11.28±2.56	11.71±2.12	0.342
BNT		6	28.0±2.19	27.5±1.76	0.624	16	26.5±2.98	26.75 ± 2.93	0.33
Visuospatial skills	BLOT	20	17.65±6.31	19.05±6.64	0.323	27	20.78±5.78	20.56±7.23	0.842
	BFR	20	38.75±3.94	38.85±4.45	0.929	32	40.75±3.33	39.56±4.33	0.128
Stroop	1st card time (s)	20	12.90±5.12	11.75±2.42	0.246	30	12.90±4.82	12.57±4.39	0.638
	5th card time (s)	20	39.10±14.27	31.00±11.13	0.000	30	31.40±10.35	28.17±11.97	0.112
	Mistake	20	0.95±1.60	0.25±0.44	0.054	30	0.83±1.85	0.17±0.46	0.064
	Correction	20	2.20±1.57	0.90±1.20	0.003	30	1.20±1.29	0.87±1.10	0.224
WCST		7	128.00±0.00	128.00±0.00	1.000	14	126.64±5.07	126.71±4.81	0.336
Categorization		8	2.75±2.55	3.63±2.56	0.262	16	2.63±2.27	3.31±2.60	0.060
VFT	Semantic	21	16.42±3.95	15.61±5.36	0.341	31	15.00±4.13	15.74±5.01	0.418
	Perseveration	21	0.23±0.62	0.19±0.40	0.74	31	0.09±0.30	0.09±0.39	1.00
	Word pairs	19	6.89±2.07	7.42±1.86	0.135	31	6.45±1.87	7.00±2.33	0.146
	Pair perseveration	19	0.68±1.41	0.84±1.50	0.73	31	0.77±1.56	0.51±1.28	0.174
	Switching error	17	0.71±1.10	0.18±0.52	0.008	24	0.21±065	0.37±087	0.426

*p<0.05 were considered statistically significant. DST: Digit Span Test; VMPT: Verbal Memory Processing Test; WMS_LM: Wechsler Memory Scale story subtest; WMS_Visual: Wechsler Memory Scale visual memory subtest; BNT: Boston Naming Test; BFR: Benton Facial Recognition Test; BLOT: Benton Line Orientation Test; WCST: Wisconsin Card Sorting Test; LTM: Long-term memory; STM: Short-term memory; MLS: Maximum learning score; TLS: Total learning score; VFT: Verbal Fluency Test

Patients with MTLE have refractory seizures originating from the mesial temporal lobe (MTL) structures, including the hippocampus, amygdala, and parahippocampal gyrus. The MTL has been associated with encoding, storage, and the retrieval of long-term memories and has extensive connections with the prefrontal cortex, which plays important functions in memory. MTLE is a network disorder involving areas that are closely linked to cognitive functions. The epileptogenic network in MTLE also varies between individuals. These networks are asymmetrically distributed and organized in left and right TLE. Apart from seizure freedom, cognitive function is one of the most important criteria for a successful epilepsy surgery. Cognitive decline usually has a specific pattern associated with the side of the resection.

Verbal memory decline typically occurs after left-sided operations (9,10,15,21,22). In concordance with Oddo et al. (17), we found that the recall phase of verbal memory was impaired but the recognition phase was improved after surgery, leading to unchanged total scores. Therefore, we did not observe verbal memory dysfunction after left-sided resection. Improved verbal memory was reported after left-sided surgery, both in SAH or ATL (2,6,23). We also observed an improvement of the verbal memory functions, especially in the recording phase in patients with right-sided resection. Frequently, cognitive impairment affects the contralateral temporal and frontal functions (10,18,19,20). Epileptic activity spreading from the right TLE may worsen left hemisphere functional activity. After right temporal resection, a left temporal lobe released from this spreading could support memory more effectively (19). Consistent with this finding, studies that have examined neuroplasticity after epilepsy surgery have found compensatory functional MRI activation contralateral to the resection site and enhanced connectivity to the remaining hippocampus (24,25,26).

Table 3. Comparison of the two sides for the pre- and postoperative neuropsychological test results

Tests		Right			Left			
		n	Pre-op (mean±SD)	Post-op. (mean±SD)	n	Pre-op. (mean±SD)	Post-op. (mean±SD)	p*
DST	Forward	27	4.70±0.82	4.70±0.82	40	4.80±1.04	4.80±1.04	0.689
	Backward	22	3.50±1.18	3.31±1.04	33	3.69±0.88	4.00±1.29	0.125
	Total	22	8.22±1.77	8.13±1.83	33	8.63±1.79	9.15±2.13	0.161
VMPT	STM	21	9.66±23.27	5.52±1.88	32	5.34±1.28	5.00±1.96	0.293
	MLS	21	11.90±2.40	12.76±2.11	32	11.78±2.32	11.06±2.36	0.100
	TLS	21	93.95±18.68	99.57±24.39	32	91.40±19.18	85.25±22.14	0.115
	Recall	21	9.57±2.87	9.80±2.46	32	8.25±2.94	7.71±2.90	0.018
	Recognition	21	4.76±2.42	4.71±2.26	32	5.93±2.35	6.31±2.29	0.015
	Total recall	21	14.33±1.65	14.50±1.16	32	14.15±1.72	14.33±1.57	0.406
WMS_LM	STM	15	8.53±3.04	9.13±3.13	22	9.05±4.85	8.36±4.71	0.923
	LTM	14	7.14±3.80	9.00±3.23	21	7.86±4.90	7.19±4.22	0.687
WMS Visual	STM	19	8.63±2.90	9.57±3.28	32	10.37±2.70	11.03±2.46	0.035
	LTM	18	7.44±3.15	8.94±3.38	32	8.84±3.12	9.62±2.82	0.223
	Recognition	17	3.00±2.26	2.23±1.67	32	2.43±2.44	2.09±2.08	0.463
	Total	18	10.27±2.84	11.05±3.18	32	11.28±2.56	11.71±2.12	0.195
BNT		6	28±2.191	27.5±1.76	16	26.50±2.98	26.75±2.93	0.386
Visuospatial skills	BLOT	20	17.65±6.31	19.05±6.64	27	20.78±5.70	20.56±7.23	0.183
	BFR	20	38.75±3.94	38.85±4.45	32	40.75±3.33	39.56±4.33	0.154
Stroop	1st card time (s)	20	12.90±5.12	11.75±2.42	30	12.90±4.82	12.57±4.39	0.718
	5th card time (s)	20	39.10±14.27	31.00±11.13	30	31.40±10.35	28.17±11.97	0.097
	Mistake	20	0.95±1.60	0.25±0.44	30	0.83±1.85	0.17±0.461	0.714
	Correction	20	2.20±1.57	0.90±1.210	30	1.20±1.29	0.87±1.106	0.086
WCST		20	128.00±00	128.00±00	30	126±5.07	126.71±4.81	0.494
Categorization		8	2.75±2.55	3.63±2.56	16	2.63±2.27	3.31±2.60	0.832
VFT	Semantic	21	16.42±3.95	15.61±5.36	31	15.00±4.13	15.74±5.01	0.570
	Perseveration	21	0.23±0.62	0.19±0.40	31	0.96±0.30	0.96±0.39	0.194
	Word pairs	19	6.89±2.07	7.42±1.86	31	6.45±1.87	7.00±2.33	0.426
	Pair perseveration	19	0.68±1.41	0.84±1.50	31	0.77±1.56	0.51±1.28	0.746
	Switching error	17	0.71±1.10	0.17±0.52	24	0.21±0.65	0.37±0.87	0.490

Paired sample t-test was used. *p<0.05 were considered statistically significant. DST: Digit Span Test; VMPT: Verbal Memory Processing Test; WMS_LM: Wechsler Memory Scale story subtest; WMS_Visual: Wechsler Memory Scale visual memory subtest; BNT: Boston Naming Test; BFR: Benton Facial Recognition Test; BLOT: Benton Line Orientation Test; WCST: Wisconsin Card Sorting Test; LTM: Long-term memory; STM: Short-term memory; MLS: Maximum learning score; TLS: Total learning score; VFT: Verbal Fluency Test

A few theories have been proposed to explain memory deficits in patients with MTLE. McCormick et al. (26) demonstrated that individualized connectivity patterns between the posterior cingulate cortex and the epileptogenic hippocampus and the contralateral hippocampus explain the differences in memory change following surgery (26). Furthermore, two models have been discussed to explain memory deficits after surgery. The traditional model of hippocampal function suggests that postsurgical memory deficits depend on the capacity or functional reserve of the contralateral temporal lobe to support memory functions after surgery. The second model suggests that postsurgical memory deficits are dependent on the functional adequacy of the tissue to be resected (27). Similarly, Malikova et al. (20) found a significant relationship between the parameters of memory and the volumes of the residual hippocampus and amygdala. They suggested that the longer the posterior hippocampal residue, together with partial destruction of the rest of the amygdalohippocampal complex and a completely spared lateral neocortex, the better the cognitive outcomes (20).

Visual memory deficits have been reported after right-sided resections in some studies, but not in others (1,6,7,9,22). We observed an improvement in visual memory functions, particularly in short- and long-term memories after right-sided resection. Other authors have reported similar findings (6,9,15,17). As reported by Tanrıverdi et al. (9) and Lee et al. (15), a contralateral improvement in visual memory after left-sided surgery was observed in our study.

Although it is controversial, executive dysfunction, such as perseverative responding, abstraction, and problem-solving difficulties, has been reported in TLE associated with HS (13,28,29). The underlying mechanism of executive dysfunction in patients with TLE is not clear.

One of the theories suggests that the temporal discharge propagation toward the frontal lobe interferes with the executive function (28). Another theory is that the memory deficit may alter the results of tests assessing frontal function (16,17). In our population, significant improvements were observed in executive functions, mainly in attention after left-sided surgery and the resistance of interference pattern after right-sided surgery. Helmstaedter et al. (7) reported an improvement of attention independent of the side or type of surgery. In a systematic review, improvement of the executive functions after surgery for both sides was more prominent than losses (10). Twenty-five to fifty percent of patients with TLE without apparent frontal damage have shown impaired executive performance on WCST (16), and some studies have also found an improvement on the WSCT performance after ATL (17,28). Consistent with our findings, investigators reported no changes on WCST regardless of surgery side or seizure freedom (10,30). We observed an improvement in the Stroop Test performance as revealed by the shortened 5th card time and decreased corrections, which demonstrates the improvement of the resistance of interference pattern. Although statistically insignificant, there was a marked decrease in incorrect answers in the Stroop Test after either side surgery. This also suggests an improvement in the resistance of interference pattern. We conclude that the Stroop Test may be more specific than WCST for the documentation of an improvement in executive functions in patients with MTLE.

Furthermore, a decrease in switching errors of word pairs in the Verbal Fluency Test after right-sided surgery was found. Consistent with the nociferous cortex hypothesis, an improvement in the Verbal Fluency Test following ATL was reported by other authors (17,31). They explain it through extrahippocampal metabolic normalization after surgery (31). Overall, an improvement in the frontal functions seems to be remarkable in our study.

There is increasing evidence that more restricted or selective surgical approaches can help reduce the cognitive sequelae of surgery compared to standard extended ATL (7,14,23,32,33). From a neuropsychological viewpoint, restricting surgery to lesional and nonfunctional tissues should help minimize cognitive losses resulting from surgery. On the other hand, the functional adequacy of the to-be-resected brain tissue appears to be a major determinant of the cognitive outcome after surgery (8,27,34).

Cross-sectional analyses demonstrate that an increased duration of epilepsy is associated with poor cognitive function (35). In our study, the mean epilepsy duration was 16 years, and this might be associated with the poor cognitive outcome, as shown particularly by the insufficient verbal memory recovery. It is also known that cognitive functions may be influenced by seizure frequency, education level, comorbid conditions, and cognitive capacity, and these were the limitations of our study. Further, we did not compare the cognitive outcomes according to surgical techniques in this study.

In conclusion, our findings suggest that the 1-year outcomes of cognitive functions of patients with MTLE undergoing SAH or ATL showed satisfactory results not only for right-sided but also for left-sided resections. The improvements of the executive functions, along with the memory functions, were remarkable.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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