



Original Article

Memory and executive functioning outcomes of selective amygdalohippocampectomy in patients with hippocampal sclerosis: A preliminary study in a developing country

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ABSTRACT

Background: Selective amygdalohippocampectomy (SA) is an effective treatment for drug-resistant cases of epilepsy due to hippocampal sclerosis (HS). However, its neurocognitive outcomes are inconsistent across the previous studies, pointing to potential location-specific confounders. Here, we investigated the neurocognitive outcomes of SA in an Iranian center recently adopting this approach.

Methods: Thirty adults (53.3% of females, age 31.4 ± 6.2 years) with drug-resistant epilepsy due to HS were included in the study. Patients were stratified into surgical ($n = 15$) and medical ($n = 15$) treatment groups based on their preferences. Neurocognitive function was assessed before and 6 months after intervention using Wisconsin Card Sorting Test (WCST), Wechsler Adult Intelligence Scale-Revised, and Wechsler Memory Scale-Third Edition (WMS-III). Postintervention performance changes were compared between the two groups, and predictors of worse postoperative outcomes were investigated.

Results: Longitudinal changes of performance in WMS-III and WCST were significantly different between the surgically and medically treated patients. Postoperative WMS-III performance showed an average 25% decline (mean $\Delta T_2-T_1 = -25.1\%$, $T = -6.6$, $P < 0.001$), and WCST performance improved by an average of 49% (mean $\Delta T_2-T_1 = +49.1\%$, $T = 4.6$, $P < 0.001$). The decline in memory performance was more severe in the left-sided surgery and in patients with higher baseline education (mean $\Delta_{T_2-T_1} = -31.1\%$, $T = -8.9$, $P < 0.001$).

Conclusion: In our center, executive functioning improved or remained stable after SA, but memory functions declined moderately. The left-sided SA and higher education were associated with more severe decline in memory functions, highlighting the need for special considerations for these groups.

Keywords: Drug-resistant epilepsy, Executive function, Hippocampal sclerosis, Memory, Selective amygdalohippocampectomy

INTRODUCTION

Epilepsy is one of the most common disorders of the nervous system, with a lifetime prevalence of around 7.6 per 1000 individuals.^[3] In addition to harmful seizures, epilepsy can have devastating

effects on the social and psychological well-being of the patients^[46] and was responsible for about 0.5% of the global disease burden in 2016.^[3] Patients with epilepsy are also at an increased risk of mortality^[38] due to sudden unexpected death in epilepsy, status epilepticus, trauma, and suicide.^[3] Fortunately, in about 50–70% of the patients, seizures and their ensuing complications can be well controlled by antiepileptic drugs (AED) or are resolved spontaneously. However, about 20–30% of the patients, particularly those with focal seizures, fail to experience a sustained seizure-free state despite appropriate pharmacotherapy with AEDs and are called to have drug-resistant epilepsy (DRE).^[19,28]

In DRE cases, where the seizures originate from a focal and identifiable epileptogenic zone that is not crucial to important brain functions, surgical resection of this region can potentially lead to a cure.^[7] The temporal lobe, and in particular its medial part, is the most common site of focal epilepsies in adult and adolescent patients.^[21] The majority of mesial temporal lobe epilepsies (MTLEs) originate from pathologies in the hippocampus, mostly in the form of hippocampal sclerosis (HS).^[37] HS is characterized by neuronal loss and gliosis in the hippocampus, in addition to the amygdala, parahippocampal gyrus, and entorhinal cortex,^[34] and is estimated to have a prevalence of 30–45% among all patients with epilepsy.^[37] The hippocampus and the amygdala have integral roles in higher-order cognitive and executive brain functions, which are responsible for many functions of human beings, especially verbal memory.^[5,25]

Temporal lobe epilepsy (TLE) most of the time presents resistance to medication, and just about 25% of the patients with MTLE respond to AED.^[31,44] Therefore, surgical resection of the temporal lobe (TLR) is generally considered an effective treatment option for patients with MTLE, resulting in a seizure-free state in 60–70% of the patients.^[22,36] TLE is the most curable type of epilepsy by surgery and the control of the epileptic episode is evidently better than AEDs.^[31] On the other hand, prolonged and repeated seizures too can ameliorate cognitive and executive functions.^[34,35] In addition, the hippocampus's structure, function, and connectivity, and in turn, neurocognitive functions are already impaired in MTLE patients before surgical interventions.^[34,47] Therefore, the overall effects of selective amygdalohippocampectomy (SA) on cognitive and executive functions are unclear. The previous studies have largely reported inconsistent findings regarding the direction and extent of postoperative neurocognitive outcomes,^[30,40,42] which can be attributed to differences in study populations, surgical techniques, and methodology.^[47]

With the development of surgical equipment and techniques in our country, we have recently started to perform SA in Razavi Hospital for the 1st time in East Iran. To the best of our knowledge, the neurocognitive outcomes of SA surgery have

not yet been investigated in this country. Given the inconsistent findings of the previous studies and the potential location-specific confounders (e.g., the study population, surgical expertise, facilities, and postsurgical care) on surgical outcomes, here, we set to investigate the changes in cognitive and executive functioning in patients undergoing SA due to suspected HS in our center, as compared to medically treated controls.

MATERIALS AND METHODS

Participants

Thirty adults with DRE referred to Razavi Hospital, Mashhad, Iran, from 2014 to 2020 were recruited in this study. We included patients between the age of 20 and 40 years old who were proved to have DRE due to HS and were diagnosed by epilepsy MRI protocol and video EEG monitoring. The local ethics committee reviewed and approved the study protocol, and informed consent was obtained from each patient before their participation. The treatment was chosen based on patients' preferences in discussion with their treating neurologist. Accordingly, 15 patients opted for SA surgery (cases), whereas 15 received medical treatment only (controls). The SA was performed through the Transylvian approach to all the patients. We followed all the patients prospectively for 6 months to assess seizure outcome and neurocognitive function before the surgery (T1) and at the end of follow-up (T2).

Seizure outcome assessment

Seizure outcomes were assessed 6 months after SA surgery in all patients using the Engel classification.^[10] Patients were assigned to two subgroups: patients completely free of any seizures (Engle Ia) and patients with recurrent seizures (Engel Ib-IVc).

Neurocognitive assessment

Executive functioning, particularly the ability to reason, understand concepts, and react to a changing environment, was partly assessed using Wisconsin Card Sorting Test (WCST), the most commonly used test in this matter in our country.^[18] This test consists of 64 cards including shapes with different colors (red, blue, yellow, or green), forms (crosses, circles, triangles, or stars), or numbers (one to four), and the participant is asked to sort these cards to match either color, form, or number. There is a sorting rule during the task that, unbeknownst to the participant, continually changes between color, form, or number. The participant is expected to implicitly understand the sorting rule based on the feedback received from the examiner (i.e., saying "correct" or "incorrect"). We recorded the perseveration error as the measure of performance in WCST.

In addition, to assess performance in visual processing, verbal comprehension, and abstract reasoning, we used, another well-established test, the short form of Wechsler Adult Intelligence Scale-Revised (WAIS-R) with the following components: (1) “arithmetic,” which evaluates concentration, immediate memory, and basic mathematical skills, (2) “similarities,” which measures the ability of verbal conceptualization and abstract reasoning, (3) “picture completion,” which assesses visual concentration and visual processing performance, and (4) “block design,” which is a test of nonverbal intelligence, evaluating problem-solving, visual processing, and visual comprehension.^[27]

We also used a validated Persian translation of the Wechsler Memory Scale-Third Edition (WMS-III) to evaluate memory performance.^[26] This battery includes subtests measuring immediate recall, delayed recall and recognition, auditory memory (immediate and delayed), visual memory (immediate and delayed), and working memory. In addition to the individual scores for each subtest, WMS-III calculates a composite score called “General Memory,” which measures delayed recall, and was the outcome of interest in this study.

In all tests, raw scores were adjusted for age based on published normative data and were transformed to z-scores for ease of comparison.

Statistical analysis

In-house Python 3.7 scripts with *pandas*, *NumPy*, *SciPy*, and *pingouin* packages were used for the statistical analyses. Descriptive summaries of study variables were reported as mean \pm standard deviation of continuous variables, or frequency and percent of categorical variables. The effect of SA on neurocognitive performances was assessed using mixed-design analysis of variance (ANOVA) with time as the within-subject factor and study group as the between-subjects factor. If group \times time interactions were significant, *post hoc* paired t-tests were used to characterize the direction and magnitude of changes in each group. In addition, we investigated the association of changes in performance with the side of HS, level of education, gender, age, and preoperative performance for the neurocognitive measures with a significant postoperative change, using mixed-design ANOVAs and Pearson’s correlations limited to the SA group. It was ensured that the data met assumptions of parametric tests, and visual analysis was carried out as well. As there was no missing data, we did not use any method of missed data handling. The statistical significance threshold was set at $P < 0.05$.

RESULTS

Thirty patients (53.3% of females, age 31.4 ± 6.2 years) with a suspected HS participated in the study. We observed no

significant difference between the two SA and medically treated groups in their gender, age, level of education, and the more prominently affected hemisphere [Table 1].

Seizure outcome

At the time of the neurocognitive assessment (6 months after surgery), 9 patients (60%) were seizure free and assigned to Engel Class I, and 7 patients (46.7%) were Engel Ia. Four patients (26.7%) were Class II and Class III was achieved in 2 patients (13.3%).

Memory outcome

Baseline memory performances were not significantly different between cases and controls. However, postintervention changes of performance in memory function significantly differed between the two groups ($F = 31.8$, $\eta^2_p = 0.53$, and $P < 0.001$) [Table 2]. *Post hoc* paired t-tests showed a significant decline of memory performance in the SA group (mean $\Delta_{T2-T1} = -25.1\%$, $T = -6.6$, and $P < 0.001$) but not in medically treated patients (mean $\Delta_{T2-T1} = -2.0\%$, $T = -1.2$, and $P = 0.23$). In additional analyses limited to the SA group, we observed a significant association between postoperative change of memory performance and the side of surgery ($F = 16.6$, $\eta^2_p = 0.56$, and $P = 0.001$), and the *post hoc* tests showed a significant deterioration of memory in the left-sided SA (mean $\Delta_{T2-T1} = -34.8\%$, $T = -9.3$, and $P < 0.001$), but no significant changes in the right-sided SA (mean $\Delta_{T2-T1} = -7.4\%$, $T = -3.0$, and $P = 0.06$). The level of education was also significantly associated with the postoperative changes of memory performance ($F = 11.9$, $\eta^2_p = 0.48$, and $P = 0.004$), with the *post hoc* tests showing that although memory performance declined in both groups, the decrease was more prominent in patients having some education (mean $\Delta_{T2-T1} = -31.1\%$, $T = -8.9$, and $P < 0.001$), as compared to those with none (mean $\Delta_{T2-T1} = -16.0\%$, $T = -3.0$, and $P = 0.03$). The magnitude of changes in memory function was significantly correlated with the preoperative performances ($r = -0.52$ and $P = 0.045$), but not with age ($r = 0.02$ and $P = 0.930$). We also observed no significant gender \times time interaction ($F = 0.6$, $\eta^2_p = 0.01$, and $P = 0.804$). Among 15 patients who underwent SA surgery for HS, 13 had good seizure outcomes (nine Class I and four Class II), and two had poor seizure outcomes (Class III) at the 6-month follow-up. Among 13 patients with good seizure outcomes, 10 (patients 1–7, 10–12) demonstrated more than 20% decline in memory scores compared to preoperative scores. In contrast, changes in memory scores of two patients with poor seizure outcomes (Class III) were negligible. Among those whose memory declined, the average reduction over preoperative memory scores was 30.82% (from 20% to 44.44%) [Table 3]. Statistical analysis using the Mann–Whitney U-test indicated that individuals with good seizure outcomes after SA surgery

showed a significant decline in memory scores compared with patients with poor seizure outcomes ($P = 0.041$).

Executive functioning outcome

There were no significant between-group differences in preintervention executive functioning performances. Postintervention changes of performance were significantly different between the two groups in WCST ($F = 23.6$, $\eta^2_p = 0.46$, and $P < 0.001$), but not in WAIS-R components [Table 2]. *Post hoc* tests showed a significant increase of

postoperative WCST performance in the SA group (mean $\Delta_{T2-T1} = +49.1\%$, $T = 4.6$, and $P < 0.001$), but no significant change in the controls (mean $\Delta_{T2-T1} = -5.0\%$, $T = -1.8$, and $P = 0.09$). In the subgroup analyses limited to the SA group, we observed no significant interaction of time with the side of surgery ($F = 2.1$, $\eta^2_p = 0.14$, and $P = 0.165$), gender ($F = 0.3$, $\eta^2_p = 0.02$, and $P = 0.589$), or level of education ($F = 1.8$, $\eta^2_p = 0.12$, and $P = 0.201$). However, the magnitude of changes in WCST performance was significantly correlated with its preoperative performances ($r = -0.68$ and $P = 0.005$), but not with age ($r = -0.28$ and $P = 0.297$).

Table 1: Characteristics of the study population.

	Cases (n=15)	Controls (n=15)	All (n=30)	P-value
Age (year), mean + SD	30.7±6.4	32.1±6.3	31.4±6.3	0.549 ^t
Females, n (%)	7 (46.7%)	9 (60.0%)	16 (53.3%)	0.714 ^c
Level of education, n (%)				0.100 ^f
Uneducated	6 (40.0%)	4 (26.7%)	10 (33.3%)	
<High school diploma	3 (20.0%)	9 (60.0%)	8 (26.7%)	
High school diploma	6 (40.0%)	2 (13.3%)	12 (40.0%)	
Left-sided HS, n (%)	11 (73.3%)	9 (60.0%)	20 (66.6%)	0.698 ^c
Length of time since initial diagnosis (year), mean + SD	19.13±6.4	19.6±6.36	19.37±5.87	0.832 ^t

P-value represents the comparison of study variables between cases and controls using independent *t*-test (*t*), Chi-squared test (*c*), or Fisher's exact test (*f*). No significant difference was identified between the two groups

DISCUSSION

In this prospective cohort, we investigated short-term seizure outcomes and neurocognitive functional outcomes of SA surgery for the 1st time in an Iranian center with a few years of experience in this type of surgery. Engel Class I (seizure freedom) was achieved in 9 patients (60%) at 6-month follow-up after transsylvian SA, whereas four and two patients were allocated to Engel II and Engel III, respectively. These results, apart from shorter follow-up duration, are approximately comparable to seizure freedom percentages in the previous studies following transsylvian SA of about 70%.^[1,29,43,45]

Six months after SA, the patients showed an average 25% decline in memory performance, while the controls showed no significant change. In contrast, the functional outcome of SA with respect to executive functioning was generally good. As measured by WCST, the set-shifting ability was on average improved by 49% following SA but showed no significant change in medically treated patients. However, the longitudinal changes of other components of executive functioning, as measured by WAIS-R, including abstract reasoning, verbal comprehension, visual processing, and

Table 2: Neurocognitive outcomes of selective amygdalohippocampectomy.

Test	Time	Cases	Controls	Between-group P	Group×Time interaction		
					F	P	η^2_p
WMS-III General Memory	Before	82.8±14.3	83.7±14.2	0.868	31.8	<0.001	0.53
	After	61.1±11.0*	82.0±14.7	<0.001			
WCST	Before	50.1±30.3	50.6±29.6	0.960	23.5	<0.001	0.46
	After	64.1±27.0*	49.3±30.8	0.173			
WAIS-R Picture Completion	Before	6.0±2.8	6.4±2.6	0.734	3.2	0.083	0.10
	After	6.0±2.6	5.8±2.4	0.827			
WAIS-R Block Design	Before	6.0±3.1	5.5±2.7	0.624	0.5	0.491	0.02
	After	6.5±3.1	5.7±2.8	0.468			
WAIS-R Similarities	Before	5.7±2.4	5.0±2.6	0.425	2.5	0.124	0.08
	After	4.7±2.7	4.9±2.6	0.839			
WAIS-R Arithmetic	Before	7.0±1.6	6.7±1.9	0.678	0	1	0
	After	7.0±1.5	6.7±1.9	0.678			

The mean±standard deviation of pre- and postintervention test scores is shown separately for each group. The results of between-group independent *t*-tests at each time point and the group×time interaction term of mixed-design analyses of variance are reported. *Significant pre- to postintervention change in *post hoc* paired *t*-test

Table 3: Seizure outcomes and memory evaluation following selective amygdalohippocampectomy.

Seizure outcomes	Memory preoperative score	Memory postoperative score	Difference (preoperative-postoperative)
Engel Class I (good outcome)			
No. 1 ^α	84	58.3	25.7
No. 2 ^α	74	58	16
No. 3 ^α	77	50	27
No. 4 ^α	90	58	32
No. 5 ^α	100	74	26
No. 6 ^α	108	82	26
No. 7 ^α	60	48	12
No. 8 ^β	90	83	7
No. 9 ^β	96	57	19
Engel Class II (good outcome)			
No. 10 ^α	92	60	32
No. 11 ^α	90	50	40
No. 12 ^α	83	53	30
No. 13 ^β	70	65	5
Mean (SD)			22.9 (10.43)
Engel Class III (poor outcome)			
No. 14 ^β	61	55	6
No. 15 ^β	67	65.3	1.7
Mean (SD)			3.85 (3.04)

^α>20% decline over preoperative memory scores. ^β<20% decline over preoperative memory scores

concentration, were not significantly different between the SA and control groups.

In line with our findings, several other studies have also reported a decrease in memory performance following selective or nonselective temporal lobe surgery in MTLE patients. In 2011, a meta-analysis of 12 studies reported an average rate of 44% and 20% decline in verbal memory performance in the left- and right-sided temporal lobe surgery, respectively.^[30] Decreased long-term memory function has also been observed in more selective methods of temporal lobe surgery, including SA^[4,35] and laser ablation.^[13] On the other hand, several other studies have reported improvement^[17,42] or no significant change^[2,40] of memory function following SA. The inconsistency of findings across different studies can be attributed to differences in the side of the resection, the usage of various AEDs, the proportion of patients with histopathological HS, preoperative memory functions, age of the patients, the success of seizure control before or after the surgery, and center-specific idiosyncrasies.^[35,47]

Contrary to the previous studies,^[8,9,24] we evaluated overall memory scores rather than material-specific scores to

represent better a patient's overall functional status. The correlation between favorable seizure outcomes and improved memory scores has been considered unlikely.^[20,41] Likewise, our low sample study demonstrated that good seizure outcomes might result in significant memory decline in patients who underwent SA surgery at the 6-month follow-up. We found that 10 out of 13 patients with good seizure outcomes showed a reduction more than 20% over preoperative scores, whereas two patients who were allocated Engle Class II had trivial changes in memory scores postoperatively.

The heterogeneity of post-SA cognitive outcomes can also be observed at the level of individuals, with some patients being more susceptible to memory deterioration after SA. For example, we found that a higher level of education was associated with more severe decline in memory function. Interestingly, this effect was attributable to a better baseline cognitive function of patients with higher education, and there was no difference in postoperative memory performances between educated and uneducated patients. The association of preoperative performance and education with verbal memory outcomes of temporal lesionectomy has also been shown in another cohort of patients with TLE and concurrent low-grade tumors.^[12] In addition, we showed that the left SA is associated with significantly more severe postoperative memory decline compared to the right SA. This left-sided asymmetry has also been observed in the previous studies on SA^[6,11,35] as well as a meta-analysis on temporal lobe surgery.^[30] This effect may result from the left-right lateralization of hippocampal function, which traditionally has been associated with their specificity for verbal and nonverbal memories, respectively, although some have argued against such a clear-cut dichotomy.^[16] Accordingly, some studies have reported no asymmetry of surgical outcomes,^[17] or an opposite asymmetry, showing worse verbal memory performance after the right-sided surgery.^[4]

The improved postoperative executive functioning of our SA cases in set-shifting and their stability in other aspects of executive functioning is not unprecedented. Several other previous studies have also reported enhanced^[35,39,40,42] or stable^[2,23] executive functioning following selective/nonselective temporal lobe surgery. The executive dysfunction in MTLE has been attributed to the impaired function of the hippocampus and amygdala in memory retrieval and emotional processing, but also to the dynamic epileptiform abnormalities in temporofrontal networks, which may be regularized following temporal lobe surgery and lead to restored executive functioning.^[39] Although investigating this hypothesis requires further investigation, aberrant effective connectivity of epileptogenic zone with the executive control network has been observed in a

functional imaging study on MTLE.^[15] Improved executive functioning following temporal lobe surgery may also result from a decreased rate of seizures.^[39] For instance, in a study on patients undergoing anterior temporal lobectomy, postoperative executive functioning was significantly better in seizure-free patients.^[23] Similarly, a study on patients undergoing SA showed that seizure outcome for patients with improved intelligence quotient is generally favorable.^[40]

Our study had some limitations. As we have just recently developed the technique and expertise to perform SA in our center, this surgery is not routinely carried out, and only a few patients were available for this study. In addition, our study was not a randomized controlled trial, and patients received surgical or medical treatments based on their personal preferences. As a result, and because of our small sample size, we were limited in controlling for potential confounds, although we observed no significant differences in the characteristics and preoperative cognitive performances between the two groups. Furthermore, our cohort did not include patients with university/college-level education, and therefore, our results cannot be generalized to this group. Finally, it should be clearly stated that the 6-month follow-up is too short to draw any conclusion regarding the relationship between postoperative seizure outcomes and neurocognitive outcomes.

CONCLUSION

Taken together, in this prospective cohort on neurocognitive outcomes of SA surgery which was performed in an Iranian center recently adopting this approach, we showed that SA is generally safe or beneficial with regard to executive functioning but can lead to moderately impaired memory functions. The decline in memory functions was more severe in patients with higher education and those undergoing left-sided SA, highlighting the importance of additional considerations before selecting these patients for the surgery. In addition, a significant decline in memory scores seems to be associated with favorable seizure outcomes. Furthermore, this finding points to the need for identifying data-driven biological, imaging, or clinical predictors of post-SA neurocognitive outcomes.^[14,32,33]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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