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Neuropsychiatric tests and cognitive functions before and after epilepsy surgery in patients with drug-resistant epilepsy

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Ghasem Farahmand[1,2], Sina Gharehjeh[1], Seyyed Reza Ebadi[2], Vahid Zolfaghari[1], Sara Ranji[1,2], Sajjad Shafiee[1], Abbas Tafakhori[1,2], Atefeh Behkar[1,3], Mojtaba Shahbazi[1], Vajiheh Aghamollaii[4]

[1] Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Neurology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[3] Occupational Sleep Research Center, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran
[4] Department of Neurology, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

Keywords
Surgery; Epilepsy; Cognitive Functions; Resistant Epilepsy

Abstract
Background: Patients with refractory epilepsy may benefit from epilepsy surgery. However, cognitive decline following epilepsy surgery is a significant concern. In this study, we investigated the effect of epilepsy surgery on cognitive function.
Methods: In this pre-post study, we used a census method to include 15 patients diagnosed with intractable epilepsy based on International League Against Epilepsy (ILAE) criteria, aged 10-65 years, and eligible for epilepsy surgery. We used the Rey Auditory Verbal Learning Test (RAVLT) and Delis-Kaplan Executive Function System (D-KEFS) to evaluate patients' cognitive function. The Wilcoxon test was used to compare cognitive function before and one month after surgery.
Results: Fifteen patients (mean age: 34.2 ± 11.1) were included. The Wechsler Symbol Digit Modalities Test and Wisconsin Card Sorting Test (WCST)/Condition 2-1 (3.26 ± 1.83 to 4.13 ± 2.03, +26.7%, P = 0.01) and WCST/Condition 2-2 (3.33 ± 2.05 to 3.86 ± 2.03, 15.0%, P = 0.021) were the only tests in the total population that showed significant improvement. RAVLT/Step 1-5 (31.00 ± 10.87 to 33.72 ± 13.12, +8.8%, P = 0.02), RAVLT/Step 6 (6.00 ± 3.06 to 7.36 ± 3.66, +22.7%, P = 0.04).

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Corresponding Author: Vajiheh Aghamollaii
Email: vajiheh102@gmail.com

Trail Making Tests (TMT)/Number Sequencing (93.40 ± 52.24 to 68.50 ± 50.54, -26.7%, P = 0.028), WCST/Condition 1-1 (3.63 ± 1.91 to 4.09 ± 2.25, +12.7%, P = 0.023), WCST/Condition 2-1 (2.90 ± 1.70 to 3.72 ± 2.10, +28.3%, P = 0.039), and WCST/Condition 2-2 (3.36 ± 1.91 to 3.90 ± 2.02, +16.1, P = 0.014) demonstrated significant improvements in patients who underwent right-sided surgery. The only significant improvement in the left-sided surgery group was the TMT/switching score (175.50 ± 70.00 to 128.50 ± 74.24, -26.8%, P < 0.05).

Conclusion: Surgery can benefit patients with refractory seizures. We observed that surgical treatment of epilepsy did not impair cognitive function. Postponing epilepsy surgery because of concerns about cognitive deterioration is unnecessary. However, it is important to note the limitations of our study, and future larger studies are needed to confirm and extend our findings.

Introduction

Epilepsy is a common and chronic neurological disorder characterized by abnormal electrical activity in the brain that results in seizures. Epileptic seizures can cause serious health, cognitive, psychological, and social problems. More than 65 million individuals are estimated to be affected globally.[1,2] Despite having a relatively high incidence (1.8%) in Iran,[3] epilepsy does not demonstrate a distinct pattern of peak rise and is mainly associated with gender (women) and poor socioeconomic status.[3,4] Although epilepsy is considered benign in 60 to 70 percent of cases when treated with monotherapy or polytherapy, approximately 30 percent of individuals still experience recurrent seizures despite taking two or more medications.[5] International League Against Epilepsy (ILAE) defines refractory seizures as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[6] In a cohort study of patients with refractory epilepsy, the remission rate was 5% per year, with a 71.2% risk of remission after five years.[7]

Surgery is an effective and low-risk treatment, with complications in less than 2% of refractory seizures.[5,8] Surgical interventions to treat epilepsy include resection, destruction, disconnection of epileptogenic brain tissue, and neurostimulation to various parts of the brain structures or peripheral nerves.[2,9] Although surgery is not free of complications, particularly neuropsychological complications such as visual memory impairment after left temporal surgery and verbal memory impairment after right temporal surgery, if suitable candidates are selected, surgery is the most effective treatment for patients with refractory epilepsy. Eradication or reduced seizure frequency significantly affects a patient's personal and social life. However, data on the cognitive outcomes of this procedure are incongruent. Therefore, although cognitive decline is a reported complication, some patients demonstrate improved memory and executive functions after surgery.[8,10-14]

Various factors, including seizures and pharmaceutical side effects, affect cognitive function in patients with epilepsy. Several neuropsychological studies have yielded inconsistent data regarding cognitive outcomes of epilepsy surgery.[10,13,15-18] In 2011, Sherman et al. investigated the variations in cognitive function after epilepsy surgery. The naming domain was more severely compromised in patients who underwent left temporal surgery (34% vs. 20% in the right temporal). They observed a slight decline in intelligence quotient (IQ), executive functioning, and attention in only a few patients, while verbal fluency significantly improved with left-sided temporal surgery.[8] In 2006, Baxendale et al. examined memory impairment in patients with temporal lobe epilepsy (TLE) after surgery (anterior temporal lobe resection). 25% of patients experienced postoperative regression in verbal learning, with good pre-operative memory function, left-sided surgery, and older age as predictors.[15] In 2009, Dulay et al. examined the effect of anterior temporal lobectomy (ATL) on spatial and linguistic memory. They found that 40.5% of patients who underwent right ATL had a significant decline in spatial memory, while 62.5% with left ATL surgery had deteriorated language memory.[19]

Previous meta-analyses have revealed a spectrum of cognitive outcomes following epilepsy surgery, with some patients experiencing decline while others showing improvement. However, this analysis has yet to be conducted in Iran, highlighting a crucial gap in understanding and necessitating further investigation.[8] This study aimed to evaluate the effect of surgical treatment on seizure control and cognitive functions in patients with refractory epilepsy.

Materials and Methods

This prospective pre-post observational study was conducted between 2020 and 2021 at the Imam Khomeini Hospital Complex (an academic referral hospital) in Tehran City, Iran. Using census sampling, we included 15 patients with intractable epilepsy based on ILAE.[6] The inclusion criteria were candidacy for epilepsy surgery, age of 10-65 years, the necessary cooperation to perform neuropsychiatric tests, and consent to be enrolled in the study. The exclusion criteria included inability to understand the tests, lack of patient cooperation, and severe speech impairment.

We used a questionnaire to collect the patients' demographic information, number of seizures, and medications.

We used the following tests to evaluate various aspects of the patients' cognitive and executive functions before surgery and one month after surgery:

1. Wechsler Digit Span, Wechsler Digit Symbols and Symbol Search to assess attention and processing speed
2. The Brief Visuospatial Memory Test-Revised (BVMT-R), a commonly used commercial assessment tool to measure visuospatial learning and memory[20]
3. Clock Drawing Test (CDT) to assess visual perceptual and spatial skills
4. The Rey Auditory Verbal Learning Test (RAVLT), a neuropsychological test widely used to assess verbal memory and learning in individuals aged 7-89[21]
5. The Persian version of the Boston Naming Test (BNT), consisting of 60 black and white line drawings of objects and assessing confrontation naming, which takes into account the finding that patients with dysnomia often have greater difficulties in naming low-frequency objects[22]
6. The Controlled Oral Word Association Test (COWAT), a subtest of the Multilingual Aphasia Examination (MAE), used to assess verbal and categorical fluency[23]
7. The Wechsler Symbol Digit Modalities Test and Wisconsin Card Sorting Test (WCST) to assess abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies[24]
8. Trail Making Test (TMT), a subtest of The Delis-Kaplan Executive Function System (D-KEFS), a neuropsychological test to assess verbal and nonverbal executive functions in individuals aged 8-89 years.[25,26]

The same neurology resident administered all tests individually for participants under the supervision of a skilled neurologist. The administrations followed standard procedures. To ensure inter-rater reliability, periodic reliability checks were conducted during which both the neurology resident and the supervising neurologist independently scored a subset of test sessions. Any discrepancies in scoring were resolved through discussion and consensus.

The epilepsy surgery for patients was conducted by a highly skilled neurosurgeon specializing in this field. The surgical approach was determined based on the precise localization identified through long-term monitoring (LTM) and magnetic resonance imaging (MRI) scans.

To calculate sample size, we used the Tang et al.[27] study with a significance level (α) of 0.05, power ($1-\beta$) of 0.80, standard deviation (SD) (σ) of 5.5, an effect size (δ) of 0.05, a 4.3 difference between population means, and attrition rate of 10%.

All statistical analyses were conducted using the SPSS software (version 26, IBM Corporation, Armonk, NY, USA). The mean and SD were used to report quantitative variables, and the frequency was used to report qualitative variables. The Shapiro-Wilk test was used to assess normality before analysis and the Wilcoxon test was used to compare the results of the cognitive tests before and after surgery.

Results

Fifteen patients (7 men) with refractory epilepsy underwent epilepsy surgery. The average age of the participants was 34.2 ± 11.1 years, and the average level of education was 10.00 ± 3.93 years. Eleven patients underwent right hemisphere surgery, and four patients underwent left hemisphere surgery. Eleven patients were seizure-free, three had a significant reduction in the number of seizures, and only one did not experience a decrease in the number of seizures (Table 1).

Memory: There were no statistically significant changes in the total population or in patients who underwent left-sided epilepsy surgery after surgery. However, patients who underwent right-sided epilepsy surgery showed a significant improvement in RAVLT/Step 1-5 (31.00 ± 10.87, 33.72 ± 13.12, P = 0.020) and RAVLT/Step 6 scores (6.00 ± 3.06 to 7.36 ± 3.66, P = 0.041) (Table 2).

Language: There were no statistically significant differences between the pre-surgery and post-surgery BNT and COWAT scores (P > 0.050) (Table 2).

Table 1. Patients' characteristics

Variable	Value
Age (year)	34.2 ± 11.1
Gender (men)	7 (46.6)
Education (year)	10.0 ± 3.9
ILAE classification	
1	11 (73.3)
3	2 (13.3)
4	1 (6.7)
5	1 (6.7)
Surgery site	
Right	11 (73.3)
Left	4 (26.7)

Data are presented as mean ± standard deviation (SD) or number (%)
ILAE: International League Against Epilepsy

Executive function: In the study of all patients, significant improvements were seen before and after surgery in the WCST/Condition 2-1 (3.26 ± 1.83 to 4.13 ± 2.03, P = 0.010) and WCST/Condition 2-2 (3.33 ± 2.05 to 3.86 ± 2.03, P = 0.021) (Table 2).

In patients with right TLE surgery, TMT/Number Sequencing (93.40 ± 52.24 to 68.50 ± 50.54, P = 0.028), WCST/Condition 1-1 (3.63 ± 1.91 to 4.09 ± 2.25, P = 0.023), WCST/Condition 2-1 (2.90 ± 1.70 to 3.72 ± 2.10, P = 0.039), and WCST/Condition 2-2 (3.36 ± 1.91 to 3.90 ± 2.02, P = 0.014) were improved significantly. In patients who underwent left TLE surgery, TMT/switching was the only executive function test with a significant improvement (175.50 ± 70.00 to 128.50 ± 74.24, P < 0.050).

Discussion

This study aimed to compare the cognitive function of patients with refractory epilepsy before and after epilepsy surgery. The D-KEFS has been used in a limited number of studies to measure cognitive functioning following epilepsy surgery. To the best of our knowledge, this is the first study in Iran to employ the D-KEFS to evaluate the cognitive effects of epilepsy surgery.

73.3% of the patients in this study became seizure-free after the surgery. Moreover, we found no significant cognitive impairment following the procedure. The results of the language-related tests (COWAT and BNT) showed no significant changes, indicating the preservation of language skills. The WCST showed significant improvements in all patients and those who underwent right-sided surgery. In addition, RAVLT/Step 1-5 and RAVLT/Step 6 demonstrated significant improvement in right-sided surgery.

Uncontrolled seizure is one reason for cognitive impairment; thus, controlling seizures can improve cognition.[8] Surgery is one of the most promising treatments for controlling drug-resistant epilepsy. Moreover, successful surgery has been proven to reduce the number of seizures and improve quality of life.[8] However, cognitive dysfunction following epilepsy surgery, especially temporal lobe surgery, has always been a significant concern. This study used a wide range of neuropsychological tests to examine cognitive function before and after surgery for epilepsy.

Preliminary results of this study showed that out of 15 patients who underwent epilepsy surgery, 11 (73%) became seizure-free, two had a significant reduction in seizures, one had a relative decline, and one had no change. Compared to prior research, more patients became seizure-free.[17,28-30] Moreover, there was no decline in cognitive function and improvement of executive function and memory in patients who underwent right-sided surgery, as well as the improvement of executive functions in all patients, contradicting the results of a previous systematic review.[8] Variability in surgical techniques across studies may contribute to the observed discrepancies. However, despite this inconsistency, verbal memory scores seemed to show consistency across various studies.[8]

After surgery, 33% of patients showed improved verbal memory, most of whom were in the right-sided epilepsy group, while 46.6% had no gains in this domain. Visual memory also improved post-surgery in 26.6% of patients, while there were no changes in 60.0%. Generally, compared to previous studies with a similar design, the improvement in memory domains overweighs the deterioration in these domains.[31] The most significant improvement among patients was executive function, with 66.6% improvement, where no decline was observed. Finally, the language domain had the most intact cognitive function among all those examined, with 91.3% of the patients without any changes in their language test scores. Given that most of our patients were in the right ATL surgical group (8 out of 15), a 37.5% improvement in verbal memory versus no decline (0%) in this group was an excellent achievement in our study. However, in a study by Baxendale et al., 25% of patients experienced a significant decline in verbal learning scores at the 1-year follow-up after surgery.[10]

Table 2. Cognitive and executive test results before and after epilepsy surgery

Test	Total (n = 15)		Right side (n = 11)		Left side (n = 4)	
	Before	After	Before	After	Before	After
Memory						
RAVLT/step 1	3.80 ± 1.65	4.06 ± 1.48	3.45 ± 1.75	4.09 ± 1.57	4.50 ± 1.29	4.00 ± 1.41
RAVLT/step 1-5	33.13 ± 12.71	34.12 ± 12.34	31.00 ± 10.87	33.72 ± 13.12*	39.00 ± 17.26	35.75 ± 11.55
RAVLT/delayed	6.93 ± 3.28	6.80 ± 2.93	6.45 ± 2.58	7.27 ± 3.25	8.25 ± 4.99	5.50 ± 1.29
RAVLT/step 6	6.53 ± 3.58	6.53 ± 3.62	6.00 ± 3.06	7.36 ± 3.66*	8.00 ± 4.96	4.25 ± 2.62
BVMT-R/step 1	3.20 ± 2.04	3.80 ± 1.65	2.90 ± 1.92	3.45 ± 1.63	4.00 ± 2.44	4.75 ± 1.50
BVMT-R/step 2	4.26 ± 1.70	4.33 ± 1.67	4.09 ± 1.81	4.18 ± 1.77	4.75 ± 1.50	4.75 ± 1.50
BVMT-R/step 3	4.93 ± 1.33	4.93 ± 1.27	4.63 ± 1.43	4.72 ± 1.34	5.75 ± 0.50	5.50 ± 1.00
BVMT-R/delayed	4.53 ± 1.45	4.60 ± 1.45	4.36 ± 1.56	4.54 ± 1.50	5.00 ± 1.15	4.75 ± 1.50
Language						
BNT	48.82 ± 1.97	48.92 ± 1.80	49.10 ± 2.02	49.20 ± 1.75	48.33 ± 2.08	48.00 ± 2.00
COWAT/verbal	15.93 ± 9.84	17.60 ± 10.30	14.00 ± 8.60	16.45 ± 9.79	21.25 ± 12.41	20.75 ± 12.57
COWAT/categorical 1	25.20 ± 8.14	26.20 ± 8.93	25.54 ± 7.90	27.27 ± 8.11	24.25 ± 9.97	23.25 ± 11.72
COWAT/categorical 2	8.60 ± 3.56	8.33 ± 3.47	8.54 ± 3.35	8.54 ± 3.67	8.75 ± 4.64	7.75 ± 3.30
Executive function						
TMT/visual scanning	61.80 ± 36.61	61.06 ± 41.40	64.54 ± 40.54	58.27 ± 44.98	54.25 ± 25.92	68.75 ± 33.87
TMT/letter sequencing	108.50 ± 77.83	107.37 ± 88.49	118.85 ± 77.88	116.85 ± 91.09	NA	NA
TMT/number sequencing	91.85 ± 52.55	73.00 ± 46.89	93.40 ± 52.24	68.50 ± 50.54*	88.00 ± 61.24	84.25 ± 40.32
TMT/switching	144.14 ± 79.34	122.14 ± 47.05	131.60 ± 86.77	119.60 ± 43.75	175.50 ± 70.00	128.50 ± 74.24*
TMT/motor speed	85.16 ± 45.54	83.33 ± 43.07	86.33 ± 48.02	83.55 ± 49.65	81.66 ± 46.45	82.66 ± 18.58
Design fluency#/filled dots	5.60 ± 2.77	5.66 ± 2.74	5.18 ± 2.96	5.36 ± 2.61	6.75 ± 2.06	6.50 ± 3.31
Design fluency/empty dots	6.80 ± 4.85	5.86 ± 3.22	6.45 ± 5.14	5.72 ± 3.00	7.75 ± 4.50	6.25 ± 4.27
Design fluency/switching dots	4.66 ± 3.45	4.40 ± 2.09	4.00 ± 3.00	4.09 ± 2.21	6.50 ± 4.27	5.25 ± 1.70
WCST/condition 1-1	3.66 ± 1.87	4.13 ± 1.95	3.63 ± 1.91	4.09 ± 2.25*	4.50 ± 1.73	4.25 ± 0.95
WCST/condition 1-2	3.40 ± 1.91	3.80 ± 1.85	3.27 ± 1.79	3.81 ± 2.13	3.75 ± 2.50	3.75 ± 0.95
WCST/condition 2-1	3.26 ± 1.83	4.13 ± 2.03*	2.90 ± 1.70	3.72 ± 2.10*	4.25 ± 2.06	5.25 ± 1.50
WCST/condition 2-2	3.33 ± 2.05	3.86 ± 2.03*	3.36 ± 1.91	3.90 ± 2.02*	3.25 ± 2.75	3.75 ± 2.36

Data are presented as mean ± standard deviation (SD)

*Significant results with P-value < 0.05; #Design fluency is a subtest of Delis-Kaplan Executive Function System (D-KEFS)

RAVLT: Rey Auditory Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; BNT: Boston Naming Test (Persian version); COWAT: Controlled Oral Word Association Test; TMT: Trail Making Test; WCST: Wisconsin Card Sorting Test

This might be due to our study's more precise and updated surgical treatment techniques. Moreover, Hamberger and Drake demonstrated that left temporal surgeries impacted verbal memory the most.[13] In our study, the improvement in visual memory was more significant than the decline in the right ATL group (25% vs. 12.5%). Positive findings of the present study were mostly prominent in executive functions among patients with right ATL, with 75% improvement and no decline.

For the language domain, Vega et al. observed regression in the confrontational naming function during left temporal resection in children.[28] In another comprehensive study, Dulay and Busch observed language problems in the form of a decline in word-finding functions (54%-29%) in anterior left temporal lobe surgery and loss of visual memory (6%-32%) in anterior right temporal lobe surgery.[29] Several other studies have also reported similar results.[32,33] A systematic review by Sherman et al. found that left temporal lobe surgery could improve verbal fluency.[8] However, there was no significant difference in the pre- and post-operative language tests in the present study, possibly because of the small number of patients who underwent left lobe surgery in our study.

The limitations of this study were the short-term follow-up (1 month) and the small number of patients who underwent left-sided epilepsy surgery. Future studies should include more patients with types of surgery other than right lobe surgery and longer follow-up periods.

Conclusion

The findings of this study suggest that epilepsy surgery can be an effective intervention for preventing seizures or significantly reducing their frequency, with no significant cognitive impairment observed post-operatively and, in some cases, even showing improvements in cognitive function. These results highlight the potential benefits of surgery in appropriately selected candidates. Further research is needed to confirm these findings in larger, more diverse patient populations.

Conflict of Interests

The authors declare no conflict of interest in this study.

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