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Original Article

The Relationship between Pre-Operative Clinical Characteristics with Changes in Post-Operative Memory Scores on Temporal Lobe Epilepsy Patient

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Abstract

Background : Most temporal lobe epilepsy (TLE) will become seizure-free after anterior temporal lobectomy (ATL) surgery but often result in cognitive decline, specifically in verbal or visual memory. This study examined the relationship between several demographic characteristics and pre-operative clinical conditions with changes in pre-post surgical memory of TLE patients.
Methods : This study used a retrospective cohort in which the subjects were TLE patients who had undergone ATL surgery at Kariadi Hospital or Telogorejo Hospital, Semarang. Demographic variables include the age of onset, duration of illness, level of education, and clinical variables include seizure frequency, EEG waveform, number of AED, lesion site, and IQ score.
Results : Memory re-examination was conducted on TLE patients who had undergone surgery between 2018 and 2021, with 55 subjects who fulfilled the criteria. Characteristics of the subjects were male 31(56%) males, 38% Senior High School education, the mean age of onset was 13.87±6.899, age at surgery was 27.67±9.802, 21 (39%) normal pres-surgical EEG waveform, 31 (56%) lesion on the left and the most frequent seizures occurred in 36 subjects (65%). Statistical test results showed a significant relationship between age of onset and changes in verbal memory recognition scores (p 0.044), lesion side with changes in verbal memory task scores (p 0.018), recall (p 0.005), recognition (0.008), and IQ scores with changes in visual memory construction recall (p 0.041)
Conclusion : Age of onset, lesion side, and IQ score characteristics were related to the changes in memory scores between pre- and post-operative anterior temporal lobectomy in TLE patients.

Keywords : temporal lobe epilepsy, post-operative memory changes, anterior temporal lobectomy

INTRODUCTION

Epilepsy is one of the severe brain disorders afflicting more than 70 million people worldwide.[1] It has become one of the world's health priorities because of the necessity of providing relatively expensive drugs to reduce morbidity, disability, and mortality.[2] It can also have unwanted effects on mental development, cognition, and behavior, as well as decreased intelligence and memory problems.[3] Epilepsy is classified as a seizure,[4] and an estimated 60% manifest as focal seizures.[5] Focal epilepsy patients experience ongoing seizures, are resistant to drugs[6] and site-specific cognitive impairment.[7] Based on localization, temporal lobe epilepsy (TLE) is the most common type of refractory focal epilepsy.[8] Breuer *et al*. found a progressive decline in memory of 20–25% in chronic TLE patients over a 4-year interval. It was associated with lower initial intellectual capacity, duration of epilepsy, seizure frequency, history of status epilepticus, polypharmacy, and progressive hippocampal atrophy.[9]

Mesial temporal lobe epilepsy (MTLE) syndrome with hippocampal sclerosis is one of the epilepsy types with good surgical outcomes.[10] The success rate of post-operative seizure-free is about 60–80% of cases.[11–14] Sallie Baxendale reported that studies analyzing cognitive function (memory) of TLE patients for ≥5 years are rare. Most of those which studied for 1–2 years post-operatively obtained stable results for comparing pre- and post-operative memory function.[15] However, Witt *et al*. analyzed adult MTLE patients with surgery in Germany and found a change in memory between pre- and post-operatively. There was a more significant decrease in verbal task memory and recall on both sides, specifically on the left.[16] Mathon *et al*. also demonstrated that the variable anterior temporal lobectomy (ATL) and hippocampal lesions on the left side worsened post-operative verbal memory outcomes.[17] There are still mixed outcomes regarding the results of pre-operative memory tests compared to post-operative temporal lobe epilepsy patients. Until this day, there has no evidence of research in Indonesia that analize the changed in memory function of post-ATL TLE patients, even though the impact on memory function is very important for the patients and as a consideration in patient care delivery.

Therefore, it is necessary to study the relationship between several individuals and clinical factors with changes in memory before ALT surgery in TLE patients.

OBJECTIVE

This study explored the association between pre-operative demographic and clinical features and memory changes after surgery in Indonesian patients with TLE.

METHODS

This study was conducted using a non-experimental and retrospective cohort design. The samples used were obtained from the human population, namely TLE patients with known epileptic seizures originating from the temporal lobe region of one side. The diagnosis was based on anamnesis, Electroencephalography (EEG), Magnetic resonance imaging (MRI), and Positron emision tomography (PET) scan with normal hippocampus or sclerosis. The examination was carried out within the past 1-4 years when the ATL surgery was programmed. Furthermore, the pre-operative memory scores of the subject were evaluated and compared to post-operative scores.

Inclusion criteria were TLE patients of any gender, aged 8–60 years, who underwent pre-operative and surgical examinations at Kariadi Hospital or Telogorejo Hospital in Semarang. Exclusion criteria included a history of brain or meningeal infection, stroke, dementia, post head injury, and other brain structural abnormalities except for focal cortical dysplasia in the temporal lobe.

The materials and tools used are: (1) Pre-operative ATL medical records in patients with TLE who were operated on for the period 2018–2021, including anamnesis: age of onset, age at surgery, last education, number of antiepileptic drugs, seizure frequency, as well as results of an examination of memory scores, IQ scores, EEG recordings, MRI photo impression, lesion side, and anatomic pathology impression. (2) The results of the pathological examination of the anatomy of the hippocampus are based on the description of gliosis and neuronal loss on cornu ammonis 1,2,3,4 stated by a neuropathologist. (3) Memory scores are expressed in numbers from each sub, namely verbal memory of task, recall, recognition, and visual memory of task construction and recall. The examination was conducted with verbal and visual memory (Neurobehavior examination book : Wordlist task & recognition, Neurorestoration study group of Indonesia Neurology Association, 2010). (4) A psychologist conducted the IQ examination using WAIS protocol for adults (16–65 years old) and WISC for children (8–15 years old), and the IQ score is the total IQ. (5) The patients were examined for verbal and visual memory scores evaluation between 1 and 4 years post-operatively. (6) The results of this post-operative memory score examination analyzed changes in the form of an increase/constant or decreased compared to the memory score before surgery. (7) Anatomical pathology laboratory equipment. (8) Statistical analysis was carried out by computer using SPSS for windows version 26.

Comparative tests were performed using Pearson Chi Square and Fisher's Exact test for nominal data. Data with a 2x2 table if it meets the requirements, the Pearson Chi Square test is carried out, if it does not meet the

requirements (expected count < 5), the Fischer's Exact test is carried out. Data with 2x3 and 2x4 tables were tested by Pearson Chi Square. Comparative test between numeric and nominal two groups of data were performed using independent t test if the data has normal distribution, but if it has abnormal distribution it will carried out with Mann Whitney test after the attempt to normalize data is unuseful. the statistic was significance if p<0,05. (9) The ethical clearance was conducted by the Health Research Ethics Commission of the Undip Medical Faculty Semarang with no 451/EC/FK-RSDK/2020, and Telogorejo Hospital Semarang no 20978/TU.710/KEPK/K/2020. The permit of study was received from Kariadi General hospital no DP.02.01/I.II/3746/2020 and Telogorejo Hospital no 29665/TU.710/DIR/K/2020. (10) Informed consent is carried out at the time of initial contact with prospective research subjects, the purpose and benefits of the research are explained and they are given independence whether to participate or to refuse of becoming research subjects. Each research data in the form of identity, documents and the confidentiality will be guaranteed, namely by not including the identity of the subject, and the data is only used for research, education and science purposes.

RESULTS

This study was conducted on TLE subjects who had surgery between 2018 and 2021. Based on data collection, 71 patients with TLE had unilateral hippocampal sclerosis, and 16 subjects were excluded. This is because the anatomical pathology laboratory data were incomplete, refused to be included in this study, the contact number could not be reached, and the location of residence was far from the local referral hospital. Demographic and clinical characteristics included gender, age of onset, education level, age of surgery, length of illness, interictal epileptic wave, number of AEDs, hippocampal lesion site, and frequency of seizures.

From Table 1, the results showed that the subjects were 55, with a male gender distribution of 31 (56.4%), and the level of education that graduated from High School was 25 (38.2%). The mean age of onset was 13.87±6,899, the mean age at surgery was 27.67±9,802 (8-47), and the average length of illness was 13.8±8.818 years. Meanwhile, the EEG showed interictal epileptic discharges in only 9 (17%) subjects, the mean number of AED drugs taken was 2.32±0.976, 24 (43.6%) had hippocampal sclerosing lesions on the right side, 36 (65.5%) had frequent seizures, and the mean total IQ and median score were 87,91 ±16,224 and 92.

In general there are several postoperative memory examinations that show improvement or the same results as in visual construction, visual contraction recall and verbal recognition. However, there are memory examination that have decreased, such as verbal memory recall as shown in Table 2.

Bivariate analysis of the relationship between clinical variables and changes in verbal task memory scores at Table 3 shows that the results of postoperative memory examination have significant in lesion side with RR 1.830 (p=0.018).

The relationship between clinical variables and changes in verbal recall memory scores in bivariate analysis at Table 4 shows that the results of postoperative memory examination have significant in lesion side with RR 2.296 (p=0.005) .

The relationship between clinical variables and changes in verbal recognition memory scores in bivariate analysis of at Table 5 shows that the results of postoperative memory examination have significant in age of onset (p=0.044) and lesion side with RR 1.722 (p=0.008).

Bivariate analysis of the relationship between clinical variables and changes in visual construction recall memory scores at Table 6 shows that the results of postoperative memory examination have significant in

TABLE 1
Demographic and Clinical Characteristics of Pre-operative Subjects (n=55)

Characteristics	Limit	Frequency (%)	Mean ±SD (Min–Max)	Median (Min–Max)
Gender	Male	31 (56.4%)		
	Female	24 (43.6%)		
Education	Special School	2 (3.6%)		
	Elementary School	6 (10.9%)		
	Junior High School	1 (1.8%)		
	Senior High School	25 (38.2%)		
	College	21 (25.5%)		

TABLE 1. Continued.

Characteristics	Limit	Frequency (%)	Mean ±SD (Min–Max)	Median (Min–Max)
Age of onset	Year		13.87 ± 6.899	13.00
Operated age	Year		27.67 ± 9.802	25.00
Ill duration	Year		13.8 ± 8.818	12.00
Seizure frequency	Often (>3x per month)	36 (65.5%)		
	Moderate (1-2x per month)	15 (27.3%)		
	Infrequent (<1x per month)	4 (7.3%)		
Number of AED	Tablet per day		2.32 ± 0.976	2.00
Interictal EEG wave	- Normal	21 (39.6%)		
	- Slow general/focal	9 (15.1%)		
	- Ipsilateral focal epilepsy	10 (17%)		
	- Epilept bilatr/general ± slow	15 (28.3%)		
Lesion side	Right	24 (43.6%)		
	Left	31 (56.4%)		
IQ Score	Number		87.91 ± 16.224	92

AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 2
Changes in Pre- and Post-operative Memory Score

Memory Type	Pre-operative	Post-operative	Score Change	
			Increase/keep	Decrease
Verbal *Task*	19.00 ± 4.944	18.16 ± 5.776	29 (52.7%)	26 (47.3%)
Verbal *Recall*	6.27 ± 2.181	5.15 ± 2.415	25 (45.5%)	30 (54.5%)
Verbal *Recognition*	9.10 ± 1.222	8.85 ± 1.495	35 (63.6%)	20 (36.4%)
Construction Visual	9.42 ± 2.455	10.31 ± 1.574	52 (94.5%)	3 (5.5%)
Visual Construction Recall	8.22 ± 3.083	8.71 ± 3.154	47 (85.5%)	8 (14.5%)

IQ score (p=0.041).

DISCUSSION

The results obtained a significant relationship between the hippocampal lesion side and verbal memory scores consisting of task, recall, and recognition changes. However, there was no significant relationship between the lesion side and changes in visual memory scores. This finding is consistent with previous studies showing that lesions on the left side adversely affected verbal memory both pre- and post-operatively.

In epilepsy patients, memory deficits result from disrupted normal cognitive networks by epileptic activity. The left hemisphere also plays a vital role in reorganizing verbal and non-verbal memory. Therefore, TLE in the left hemisphere indicates more severe memory impairment. Allone *et al*. showed that in the pre-operative condition, the dominant verbal disorder was the most common form in both the left (65.9%) and right (48.8%) sclerosis groups. The verbal memory index was lower than the visual, specifically in patients with left sclerosis. In the post-operative condition, improvement in memory index was found in 23.3–36.6% of patients. Memory improvement was similar between left and right hippocampal sclerosis, as well as verbal and visual domains.[13] Hypocampectomy can improve memory index regardless of the surgical site or the domain of

TABLE 3
Bivariate Analysis on the Relationship of Clinical Variables with Changes in Verbal Task Memory Score

Variable		Verbal Task Memory Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	13.28 ± 6.06	14.54 ± 7.80	0.55€	
	Median	12 (5–36)	13 (1–33)		
Ill duration	Mean	14.34 ± 8.06	13.19 ± 9.72	0.35€	
	Median	13 (3–33)	10 (3–34)		
Seizure Frequency	Often	22 (61.1%)	14 (38.9%)	0.19*	
	Moderate	5 (33.3%)	10 (66.7%)		
	Infrequent	2 (50%)	2 (50%)		
Education level	Special School	2 (100%)	0 (0%)	0.29*	
	Elementary School	2 (33.3%)	4 (66.7%)		
	Junior High School	1 (100%)	0 (0%)		
	Senior High School	15 (60%)	10 (40%)		
	College	9 (42.9%)	12 (21.8%)		
Interictal EEG Wave	Normal	12 (57.1%)	9 (42.9%)	0.89*	
	Slow general/focal	5 (62.5%)	3 (37.5%)		
	Ipsilateral focal epilepsy	4 (44.4%)	5 (55.6%)		
	Bilateral/generalized	8 (53.3%)	7 (46.7%)		
	Epilepsy/± slow wave				
Number of AED	Mean	2.38 ± 1.08	2.25 ± 0.85	0.81€	
	Median	2 (1-5)	2 (1–5)		
Lesion Side	Right	17 (70.8%)	7 (29.2%)	0.018$	1.830 (1.097–3.053)
	Left	12 (38.7%)	19 (61.3%)		
IQ score	Mean	86.72 ± 17.57	89.23 ± 14.81	0.57&	
	Median	93 (47–108)	91.5 (54–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test
AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 4
Bivariate Analysis on the Relationship of Clinical Variables with Changes in Verbal Task Memory Score

Variable		Verbal Recall Memory Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	13.44 ± 6.97	14.23 ± 6.94	0.81€	
	Median	13 (1–36)	12 (5–33)		
Ill duration	Mean	11.92 ± 5.74	15.37 ± 10.58	0.48€	
	Median	12 (3–25)	11 (4–34)		

TABLE 4. Continued

Variable		Verbal Recall Memory Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Seizure Frequency	Often	17 (47.2%)	19 (52.8%)	0,69*	
	Moderate	7 (46.7%)	8 (53.3%)		
	Infrequent	1 (25%)	3 (75%)		
Education level	Special School	0 (0%)	2 (100%)	0.29*	
	Elementary School	3 (50%)	3 (50%)		
	Junior High School	0 (0%)	1 (100%)		
	Senior High School	10 (40%)	15 (60%)		
	College	12 (57.1%)	9 (42.9%)		
Interictal EEG Wave	Normal	13 (61.9%)	8 (38.1%)	0.35*	
	Slow general/focal	3 (37.5%)	5 (62.5%)		
	Ipsilateral focal epilepsy	4 (44.4%)	5 (55.6%)		
	Bilateral/generalized	5 (33.3%)	10 (66.7%)		
	Epilepsy/± slow wave				
Number of AED	Mean	2.26 ± 0.92	2.37 ± 1.03	0.68€	
	Median	2 (1–5)	2 (1–5)		
Lesion Side	Right	16 (66.7%)	8 (33.3%)	0.018$	2.296 (1.23–4.26)
	Left	9 (29%)	22 (71%)		
IQ score	Mean	88.04 ± 15.50	87.80 ± 17.07	0.96&	
	Median	93 (47–108)	91 (47–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test
AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 5
Bivariate Analysis on the Relationship of Demographic and Clinical Variables with Verbal Recognition Memory Score Changes

Variable		Verbal Recognition Memory Score Changes			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	15.37 ± 7.35	11.25 ± 5.21	0.044€	
	Median	14 (5–36)	10.50 (1–22)		
Ill duration	Mean	13.49 ± 8.32	14.35 ± 9.83	0.92€	
	Median	12 (3–34)	12 (3–33)		
Seizure Frequency	Often	25 (69.4%)	30.6 (20%)	0.46*	
	Moderate	8 (53.3%)	46.7 (12.7%)		
	Infrequent	2 (50%)	50 (3.6%)		
Education level	Special School	2 (100%)	0 (0%)	0.28*	
	Elementary School	3 (50%)	3 (50%)		
	Junior High School	1 (100%)	0 (0%)		

TABLE 5. Continued

Variable		Verbal Recognition Memory Score Changes			RR (95% CI)
		Increase/Keep	Decrease	*p*	
	Senior High School	13 (52%)	12 (48%)		
	College	16 (76.2%)	5 (23.8%)		
Interictal EEG Wave	Normal	14 (66.7%)	7 (33.3%)	0.70*	
	Slow general/focal	6 (75%)	2 (25%)		
	Ipsilateral focal epilepsy	5 (55.6%)	4 (44.4%)		
	Bilateral/generalized	8 (53.3%)	7 (46.7%)		
	Epilepsy/± slow wave				
Number of AED	Mean	2.26 ± 0.92	2.44 ± 1.10	0.65€	
	Median	2 (1–5)	2 (1–5)		
Lesion Side	Right	20 (83.3%)	4 (16.7%)	0.008$	1.722 (1.148–2.583)
	Left	15 (48.3%)	16 (51.6%)		
IQ score	Mean	88.11 ± 17.93	87.55 ± 13.15	0.90&	
	Median	93 (47–110)	91.5 (54–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test
AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 6
Bivariate Analysis on the Relationship of Clinical Demographic Variables with Visual Memory Construction Recall Score Change

Variable		Visual Memory Construction Recall Score Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	14.19 ± 7.40	12 ± 1.69	0.54€	
	Median	13 (1–36)	12 (10–15)		
Ill duration	Mean	13.64 ± 8.80	14.75 ± 9.47	0.79€	
	Median	12 (3–34)	11 (4–29)		
Seizure Frequency	Often	29 (80.6%)	7 (19.4%)	0.35*	
	Moderate	14 (93.3%)	1 (6.7%)		
	Infrequent	4 (100%)	0 (0%)		
Education level	Special School	2 (100%)	0 (0%)	0.07*	
	Elementary School	4 (66.7%)	2 (33.3%)		
	Junior High School	0 (0%)	1 (100%)		
	Senior High School	23 (92%)	2 (8%)		
	College	18 (85.7%)	3 (14.3%)		
EEG interictal	Normal	18 (85.7%)	3 (14.3%)	0.57*	
	Slow general/focal	7 (87.5%)	1 (12.5%)		
	Ipsilateral focal epilepsy	9 (100%)	0 (0%)		
	Bilateral/generalized	12 (80%)	3 (20%)		

TABLE 6. Continued

Variable		Visual Memory Construction Recall Score Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
	Epilepsy/± slow wave				
Number of AED	Mean	2.27 ± 1.01	2.63 ± 0.74	0.17€	
	Median	2 (1–5)	2.5 (2–4)		
Lesion Side	Right	22 (91.7%)	2 (8.3%)	0.25$	1.137 (0.921–1.403)
	Left	25 (80.6%)	6 (19.4%)		
IQ score	Mean	89.74 ± 15.05	77.13 ± 19.69	0.041&	
	Median	94 (50–110)	79 (47–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test

impaired memory function.

In preoperative conditions, dominant verbal disturbances were the most common form of disturbance in both the left and right-sided sclerosis groups (65.9% and 48.8%) where the verbal memory index was lower than the visual memory index, especially in patients with left sclerosis.[19] Visual memory impairment was only observed in 11.6% of patients with right-sided sclerosis and 7.3% of patients with left-sided sclerosis. In the postoperative condition, memory index improvement was found in 23.3–36.6% of patients where memory improvement was found to be similar between left and right sided hippocampal sclerosis and between verbal and visual domains.[19] Impaired verbal memory was the most common disorder found in patients with ELT caused by hippocampal sclerosis both on the left and right side. Hippocampectomy can improve the memory index in ELT patients regardless of the side of surgery or the domain of impaired memory function.

There was a significant relationship between IQ scores and visual memory construction recall changes. Patients with high IQ scores experienced an increase in visual memory construction recall or persisted. Furthermore, Rzezak (2017) showed that calculating IQ differences between patients and controls impact the cognitive impairment profile observed in TLE children and adolescents with short- and long-term memory deficits and semantic memory.[20] Furthermore, people with higher intelligence may have less cognitive dysfunction associated with brain pathology. Patients with high IQ showed better immediate visual memory before surgery than those with average and no post-operative changes. Surgery did not impact those with high IQ in verbal fluency and memory, showing that cognitive reserve positively affects function, even after TLE surgery.[21]

Limitations in this study were the non-uniform post-operative evaluation period, unanalyzed subjects due to incomplete data on hippocampal preparations, subjects who refused to be studied and living far from the referral hospital.

CONCLUSION

There is a significant relationship between age of onset and changes in verbal recognition memory scores, as well as IQ and changes in visual recall memory scores. Multivariate analysis found that the lesion location on the dominant side affected changes in verbal recognition memory scores.

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