

Relationship Between the Wada Test and Preoperative/Postoperative Memory in Mesial Temporal Lobe Epilepsy Patients

Mezial Temporal Lob Epilepsili Olgularda Wada Testi ve Ameliyat Öncesi/Amaliyat Sonrası Bellek İlişkisi

Lütfü HANOĞLU,¹ Nesrin HELVACI YILMAZ,¹ Çiğdem ÖZKARA,² Burcu POLAT,¹ Sema DEMİRCİ,¹ Mustafa UZAN³

¹Department of Neurology, Medipol University Faculty of Medicine, Istanbul

²Department of Neurology, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul

³Department of Neurosurgery, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul, all in Turkey

Summary

Objectives: To study the correlation between Wada memory test and neuropsychometric tests which were applied preoperatively to mesial temporal lobe epilepsy patients associated with hippocampal sclerosis (MTLE-HS) who had undergone selective amygdalohippocampectomy and find out the effects of early onset epileptic seizures on atypical memory dominance.

Methods: Drug-resistant 27 patients (16 left, 11 right MTLE-HS) had video EEG, cranial MRI and Wada test preoperatively. Weschler visual subtest and verbal memory processing tests were applied to all patients before surgery and the first year after the operation.

Results: The number of left hemisphere memory dominant patients was 6 (22.2%) and the number of atypical memory dominant patients was 21 (77.8%) according to the Wada test. There was a significant difference between the two groups when compared for epileptic seizure onset age; ($p=0.042$), and also a significant difference when compared for HS (right/left) side ($p=0.002$). When we analyzed the correlation between preoperative and postoperative verbal and nonverbal tests and left memory Wada dominance; in verbal memory processing tests 'delayed recall' scores between groups were significant ($p=0.042$), on the other hand in patients with atypical memory dominance 'total learning' scores between groups were significant ($p<0.001$).

Conclusion: As a result, we found that the earlier the onset of seizures, the more atypical the memory dominance (right or bilateral). The Wada test was effective for assessing verbal memory; on the other hand, it was inadequate for assessing visual memory dominance. If the scores of 'delayed recall' in verbal memory were high in the patients with typical verbal dominance and 'total learning' scores in the patients with atypical verbal dominance, the scores also tended to rise after the operation.

Key words: Memory dominance; mesial temporal sclerosis; neuropsychometric tests; Wada test.

Özet

Amaç: Selektif amigdalohippokampektomi yapılan hipokampal sklerozla ilişkili mesial temporal lob epilepsili (HS-MTLE) hastalarda ameliyat öncesi dönemde yapılan Wada testi ile nöropsikometrik testler arasındaki ilişkiyi inceleyerek erken yaşta başlayan epilepsi nöbetlerinin belleğin atipikleşmesi üzerindeki etkilerini araştırmak.

Gereç ve Yöntem: Medikal tedaviye dirençli 27 hastaya (16 sol, 11 sağ HS-MTLE) cerrahi öncesi video EEG, kranial manyetik rezonans görüntüleme, Wada testi ile ameliyat öncesi ve sonrası birinci yılda Weschler görsel subtest ve sözel bellek süreçleri testleri uygulanmıştır.

Bulgular: Wada bellek testinde sol hemisfer dominant bulunanların sayısı 6 (%22.2), atipik yerleşimli olanların sayısı 21 (%77.8) idi. Bellek dominansı sol ve atipik olanlarda nöbet başlama yaşı ($p=0.042$), ve HS (sağ/sol) tarafı açısından karşılaştırıldığında da anlamlı fark saptanmıştır ($p=0.002$). Yine sol bellek dominant olanlar ile ameliyat öncesi ve sonrası verbal ve nonverbal testler arasındaki korelasyona bakıldığında sözel bellek süreçleri testlerinden 'gecikmeli hatırlama' puanları arasında anlamlı ilişki bulunurken ($r=0.829$; $p=0.042$) atipik bellek dominansı olanlarda 'toplam öğrenme' puanları arasında anlamlı ilişki bulunmuştur ($r=0.731$; $p<0.001$).

Sonuç: Nöbet başlama yaşı ne kadar düşükse bellek dominansı o kadar atipiktir (sağ veya bilateral). Wada testi sırasında yapılan bellek değerlendirmesi verbal belleği değerlendirmede etkili ancak görsel belleği değerlendirmede yetersizdir. Tipik bellek dominansı olanlarda 'gecikmeli hatırlama', atipik olanlarda 'toplam öğrenme' puanları başlangıçta yüksek ise, ameliyat sonrası dönemde de yükselme göstermektedir.

Anahtar sözcükler: Bellek dominansı; mezial temporal skleroz; nöropsikometrik testler; Wada test.

Submitted (Geliş): 28.09.2013

Accepted (Kabul) : 17.10.2013

Correspondence (İletişim) : Nesrin HELVACI YILMAZ, M.D.

e-mail (e-posta) : dnesrin76@gmail.com



Introduction

The Wada test is an invasive procedure that evaluates memory and language functions in drug-resistant mesial temporal lobe epilepsy patients associated with hippocampal sclerosis (MTLE-HS) before surgery.^[1,2] Although formal neuropsychometric tests assess memory functions according to material specific features; Wada test gives different stimulants that can be coded by different ways and by this way it exhibits general hemispheric dysfunction against amnesia risk.^[1] Many previous studies discussed the effectiveness of the Wada test in estimating postoperative amnesia. In some studies, it was mentioned that the Wada test had a predictive importance in determining verbal memory loss in left TLE patients.^[3,4] On the other hand, in some other studies it was pointed out that it was not as effective as expected for estimating postoperative memory deficit.^[5,6]

Memory dominance could shift to the other hemisphere when memory functions were affected by unilateral epileptic activity.^[7] Interhemispheric plasticity for memory was more common in patients with early onset of seizures. Left TLE patients were thought to have interhemispheric reorganization for verbal memory functions while right TLE patients were thought to have interhemispheric reorganization for visual memory functions.^[8]

In our study; we aimed to show the effect of early onset seizures on atypical memory dominance and examine the correlation between memory dominance in the Wada test and preoperative and postoperative verbal and nonverbal memory tests in MTLE-HS patients.

Material and Methods

Twenty-seven MTLE-HS patients who had presented to epilepsy surgery center of Istanbul University, Cerrahpasa Faculty of Medicine and undergone epilepsy surgery procedure between 1997-2004 were included in the study. Data were collected retrospectively. The Wada test and selective amygdalohippocampectomy were applied to all patients. Before surgery, level of education and age at seizure onset were queried. The side that would be operated was determined by cranial MRI, interictal and ictal video EEG and results of neuropsychometric analysis. Hand preference was assessed by questioning. The subjects who had left and bilateral hand preference were classified as 'atypical'. An extensive neuropsychometric battery was a part

of the routine process in our epileptic surgery procedure. [9] The Turkish verbal memory process tests (VMPT) and Wechsler visual subtest were selected from this battery and applied to the patients preoperatively and one year after the operation. Seizure outcome was evaluated by Engel classification.^[10]

Wechsler visual subtest; it is a subtest of Wechsler visual memory test. Four complex intangible geometrical figures in different cards are shown to the patient and later asked to draw. First drawings are evaluated as the 'immediate recall' phase of the visual memory. After 30 minutes, the patient is asked to draw the figures again. This part is evaluated as the 'delayed recall' phase of the visual memory. Maximum point is 14 for these two tests and scored separately.^[11]

Verbal memory process test: Fifteen unrelated words are presented to the patients until he/she learns it completely or questioned after maximum 10 repeats ('total learning' score). The patient is asked how many words he/she remembers in 30 minutes. This is the 'delayed recall' phase of the verbal memory. Furthermore, the words that the patient cannot recall are demonstrated in a multiple choice list and asked the patient to recognize. In statistical analysis; 'total learning' and 'delayed recall' scores are used.^[12]

Wada (intracarotid amobarbital) procedure

We firstly catheterized the internal carotid artery of the operation side if there was no obstacle for classical angiography procedure. Average dose of 100-125 mg sodium amobarbital in 10 cc isotonic was injected in 3 to 5 seconds. After the patient had contralateral hemiplegia/paresis, we examined the presence of aphasia in order to identify the language dominant hemisphere. The examination of language functions were held by asking open-labeled questions, giving verbal orders, naming objects and reading of written words. Then, a memory test of totally 10 items including real objects, printed words and unfamiliar designs was applied. When the muscle weakness was improved approximately in 15 minutes after the injection, we started to evaluate the delayed recall part of the memory functions. First the patient was asked to remember the items spontaneously and then asked to recognize the same items among a group of other items. Contralateral injection was held in the same way after 30 minutes of the first injection. We could not apply EEG during this procedure because of technical reasons.^[13]

According to the results of the Wada test; patients were classified into two groups: 'left dominance for language' (aphasia developed only after left side injection) and 'atypical dominance for language' (aphasia developed after only right and/or both sides injection; or aphasia did not develop after both side injections). Only dysarthria or speech arrest after the injection was not accepted as aphasia. Comprehension failure, impairment of expression and the presence of paraphasia were also accepted as aphasia.

Furthermore, the patients were classified into two groups according to the performances in Wada memory test: 'left dominance for memory' (memory impairment developed only after left side injection) and 'atypical dominance for memory' (memory impairment developed after only right and/or both side injections; or memory impairment did not develop after both side injections). The presence of memory impairment was evaluated by the performance in recognition, not by recall. Under seven score out of ten items was accepted as impaired recognition performance.

Statistical analysis

Shapiro Wilk test was used to test the normality of variables. Continuous variables meeting normality assumption were presented as mean ± standard deviation, otherwise median (minimum-maximum) values were given. Mann-Whitney's

U-test was used to compare two independent groups and Wilcoxon test was used to compare two dependent groups. Categorical variables were expressed by counts and percentages. Comparisons between the groups were performed with Fisher's exact chi-square test. Correlations between the variables were analyzed using the Spearman's correlation coefficient. A p value of <0.05 was considered significant.

Results

The mean age of the patients (16 female, 11 male) was 23.1±5.9. The mean age of seizure onset was 10 years (1-17 years) and the mean duration of education period was 5 years (12-15 years). The number of right-handed patients were 24 (88.9%) and left-handed were 3 (11.1%). Sixteen of them had left language dominance (59.3%) while 11 (40.7%) had atypical language dominance according to the Wada test. The subjects that had left memory dominance was 6 (22.2%), and atypical memory dominance was 21 (77.8%). The number of patients with left HS who would be operated from the left side was 16 (59.3%); the number of patients with right HS who would be operated from the right side was 11 (40.7%). When the patients were separated into groups according to Engel classification; 19 patients did not have any seizures (70.4%) (Engel 1), 3 of them were almost

Table 1. The characteristics of the patients according to the Wada memory dominance

	Wada memory left (n=6)		Wada memory atypical (n=21)		p
	n	%	n	%	
Gender					
Male	4	36.36	7	63.64	0.187
Female	2	12.50	14	87.50	
HS					
Left	0	0.00	16	100.00	0.002
Right	6	54.55	5	45.45	
Hand preference					
Right	4	16.67	20	83.33	0.115
Atypical	2	66.67	1	33.33	
Wada language					
Left	4	25.00	12	75.00	1.000
Atypical	2	18.18	9	81.82	
	n (min-max)		n (min-max)		
Age	21 (17-33)		23 (14-38)		0.589
Education	6.5 (5-15)		5 (2-15)		0.512
The age of seizure onset	12 (1-17)		8 (1-13)		0.042

without seizures (11.1%) (Engel 2), 2 of them had (7.4%) rare seizures (Engel 3) following surgery. Seizure outcome of three patients could not be reached (Table 1).

Difference scores were used to compare preoperative and postoperative visual and verbal memory test scores according to the Wada memory dominance (Table 2, Table 3).

Correlation between preoperative and postoperative verbal and nonverbal tests and the Wada memory test results in the left dominant group, revealed no significant correlation between preoperative and postoperative WIR ($p=0.461$), WDR ($p=0.156$) and VMPT-TL ($p=0.072$) scores, but a significant correlation existed between VMPT-DR scores ($r=0.829$; $p=0.042$).

In patients with atypical memory dominance however, no significant correlation was present between preoperative and postoperative WIR ($p=0.161$), WDR ($p=0.223$) and VMPT-DR ($p=0.109$), whereas, pre and post-operative VMPT-TL scores ($r=0.731$; $p<0.001$) were significantly correlated.

Discussion

In our study, Wada memory dominance (left/atypical) presented no significant difference on the basis of gender, age, duration of education, HS side (left/right), hand preference (right/atypical) and Wada language dominance (left/atypical). But the age of seizure onset in atypical memory dominance group was significantly younger (Table 1). Concordant with some previous studies these results were in favor with the view that early onset of seizures result with atypical memory dominance. Kim et al. reported that as the patient with left TLE had right-shifted verbal memory dominance, both verbal and nonverbal memory representation was found to be in the right hemisphere.^[8] In the study of Griffin et al., 70% of the patients with seizure-onset before age 9, had atypical cerebral reorganization. Also, these patients had significant improvement in verbal tests in the postoperative period.^[14]

Powell et al., indicated that both right and left HS patients had partial reorganization in verbal and nonverbal memo-

Table 2. Preoperative and postoperative verbal and nonverbal memory test scores (n=27)

Tests	Preoperative scores	Postoperative scores	p
WIR	10 (1-14)	11 (2-14)	0.045*
WDR	8 (0-14)	8 (1-14)	0.774
VMPT-TL	103 (50-128)	98 (42-137)	0.115
VMPT-DR	9 (1-14)	9 (2-14)	0.840

WIR (Wechsler Test- Immediate Recall); WDR (Wechsler Test-Delayed Recall); VMPT-TL (Verbal Memory Process Test-Total Learning); VMPT-DR (Verbal Memory Process Test- Delayed Recall). Fisher's chi-square test was used for the statistical analysis. * $p<0.05$ significant.

Table 3. Comparison of test scores according to the Wada memory dominance

	Wada memory left Median (min-max)	Wada memory atypical Median (min-max)	p
Preoperative scores			
WIR	10.5 (3-14)	10 (1-14)	0.712
WDR	9 (4-13)	9 (1-13)	0.476
VMPT-TL	111.5 (65-126)	99 (50-128)	0.712
VMPT-DR	10.5 (4-14)	9 (1-13)	0.476
Difference scores			
WIR	0 (-5-4)	2 (-7-8)	0.175
WDR	-1.5 (-4-5)	1 (-10-12)	0.408
VMPT-TL	-3 (-11-3)	-5 (-48-25)	0.798
VMPT-DR	1 (-2-2)	0 (-9-5)	0.842

WIR (Wechsler Test- Immediate Recall); WDR (Wechsler Test-Delayed Recall); VMPT-TL (Verbal Memory Process Test-Total Learning); VMPT-DR (Verbal Memory Process Test- Delayed Recall).

ry functions by using functional MRI preoperatively. They showed that the more the severity of hippocampal pathology, the worse the memory and less ipsilateral and greater contralateral activation on functional MRI.^[15] In our study; consistent with the literature, we found that patients with left HS had shifted memory dominance and as a result, all the patients with typical dominance had left HS (Table 1).

Cognitive deficits emanating after the surgery were complex and multifactorial. Cognitive performance during the postoperative period seemed to be related to many factors; as the age of seizure onset, epilepsy duration, age at the surgery, the side of the epileptogenic focus, antiepileptic drugs and behavioral factors.^[16] In the study of Morino et al., a significant improvement in verbal memory tests was found after surgery in 62 unilateral HS patients who underwent selective amygdalohippocampectomy.^[17] Another study on patients who had anterior temporal lobectomy, disclosed that visual memory tests (especially 'delayed recall') were improved significantly during the postoperative 6th and 12th months when compared with the preoperative results. There was no difference in verbal memory tests, however.^[18] Generally, right TLE patients had improvement in verbal learning and memory after surgery. Patients who had higher memory potential in language dominant hemisphere were prone to an increased amnesia risk after the operation.^[19]

No significant improvement in the verbal memory test scores in preoperative versus postoperative period was detected in the present study. But there was a significant improvement in 'immediate recall' scores in the visual memory tests. It was reported that two third of drug-resistant TLE patients were free of seizures after surgery.^[20] Similarly, in our group only 7.4% of the patients had ongoing seizures, post-operatively. One of the reasons of improvement in visual memory functions might be the good seizure outcome after the operation. On the other hand, it was remarkable that there was no improvement or worsening in other test results. The follow-up period on memory could also be an important factor. In the first year after the operation, the improvement in test results was minimal however, after 5 to 10 years, memory functions showed mild but significant improvement.^[21]

It was controversial whether the Wada test performed before temporal lobectomy in TLE patients assessed memory functions correctly, or not. Chiaravalotti et al., applied tests to 70 patients who underwent intracarotid amobarbital

test and appraised verbal and nonverbal memory functions 3 weeks after the surgery. Evaluation of material specific memory during the Wada test helped to estimate verbal memory changes after anterior temporal lobectomy but nonverbal tests had no correlation with postoperative visuospatial facial recognition.^[3] The study of Vingerhoets et al., on 89 patients, showed that the Wada test was effective for evaluating verbal memory in left TLE patients; but it did not expose nonverbal memory functions in right TLE patients, sufficiently.^[22] Later on, Baxendale et al., reported that verbal and nonverbal stimuli given during the Wada test was not informative for postoperative verbal 'learning' and 'recall' scores in right TLE patients but it had a strong predictive value for left TLE patients.^[23] White et al., showed that both Wada memory test and preoperative memory reserve were helpful for predicting postoperative verbal memory loss in left TLE patients.^[24]

In our study; there was no significant difference between preoperative scores and the degree of difference scores (first year postoperative score-preoperative score) in the patients with typical and atypical memory dominance. In patients with left Wada dominance, tests evaluating verbal memory revealed a positive correlation between 'delayed recall' scores. In the patients with atypical dominance however, there was a significant correlation between 'total learning' scores and no significant correlation in visual memory test scores. Results show that, if the 'delayed recall' scores for verbal memory were high preoperatively, postoperative values also increased in patients with typical (left) memory dominance. Similarly, if the 'total learning' scores for verbal memory was high preoperatively, postoperative values also increased in patients with atypical (right/bilateral) memory dominance.

Consequently, although our study group was small, we thought that Wada memory dominance was effective for evaluating verbal memory but it was inadequate for visual memory assessment. In this study, the subtests of verbal memory which were affected in regards to memory dominance were determined irrespective of the HS side. Further prospective studies will be necessary as our knowledge about memory grows.

References

1. Feinberg T, Farah M. Behavioral neurology and neuropsychology. 1st ed. New York: McGraw-Hill Companies; 1996.

2. Meador KJ, Loring DW. The Wada test: controversies, concerns, and insights. *Neurology* 1999;52(8):1535-6. [\[CrossRef\]](#)
3. Chiaravalloti ND, Glosser G. Material-specific memory changes after anterior temporal lobectomy as predicted by the intracarotid amobarbital test. *Epilepsia* 2001;42(7):902-11. [\[CrossRef\]](#)
4. Sabsevitz DS, Swanson SJ, Morris GL, Mueller WM, Seidenberg M. Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. *Epilepsia* 2001;42:1408-15. [\[CrossRef\]](#)
5. Lacruz ME, Alarcón G, Akanuma N, Lum FC, Kissani N, Koutroumanidis M, et al. Neuropsychological effects associated with temporal lobectomy and amygdalohippocampectomy depending on Wada test failure. *J Neurol Neurosurg Psychiatry* 2004;75(4):600-7. [\[CrossRef\]](#)
6. Kirsch HE, Walker JA, Winstanley FS, Hendrickson R, Wong ST, Barbaro NM, et al. Limitations of Wada memory asymmetry as a predictor of outcomes after temporal lobectomy. *Neurology* 2005;65(5):676-80. [\[CrossRef\]](#)
7. Powell GE, Polkey CE, Canavan AG. Lateralisation of memory functions in epileptic patients by use of the sodium amytal (Wada) technique. *J Neurol Neurosurg Psychiatry* 1987;50(6):665-72. [\[CrossRef\]](#)
8. Kim H, Yi S. The effect of early versus late onset of temporal lobe epilepsy on hemispheric memory laterality: an intracarotid amobarbital procedure study. *J Korean Med Sci* 1997;12(6):559-63.
9. Ozkara C, Ozyurt E, Hanoglu L, Eskazan E, Dervent A, Koçer N, et al. Surgical outcome of epilepsy patients evaluated with a noninvasive protocol. *Epilepsia* 2000;41:41-4. [\[CrossRef\]](#)
10. Engel J Jr. Outcome with respect to epileptic seizures. In: Engel J Jr, editor. *Surgical treatment of the epilepsies*. New York: Raven Press; 1987. p. 553-71.
11. Wechsler D. *Wechsler Memory Scale-Revised (WMS-R)*, Manual: The Psychological Corporation. San Antonio TX: Harcourt, Brace, Jovanovich; 1987.
12. Oktem O. *Oktem sozel bellek süreçleri testi (SBST) el kitabı*. Ankara: Turk Psikologlar Dernegi Yayınları; 2011.
13. Hanoglu L. Wada testi ve epilepsi cerrahisinde kullanımı. İçinde: Bora I, Yeni N, Gurses C, editörler. *Epilepsi*. İstanbul: Nobel Tıp Kitabevi; 2008. s. 559-66.
14. Griffin S, Tranel D. Age of seizure onset, functional reorganization, and neuropsychological outcome in temporal lobectomy. *J Clin Exp Neuropsychol* 2007;29(1):13-24. [\[CrossRef\]](#)
15. Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, et al. Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Epilepsia* 2007;48(8):1512-25. [\[CrossRef\]](#)
16. Alpherts WC, Vermeulen J, Hendriks MP, Franken ML, van Rijen PC, Lopes da Silva FH, et al. Long-term effects of temporal lobectomy on intelligence. *Neurology* 2004;62(4):607-11. [\[CrossRef\]](#)
17. Morino M, Ichinose T, Uda T, Kondo K, Ohfuji S, Ohata K. Memory outcome following transylvian selective amygdalohippocampectomy in 62 patients with hippocampal sclerosis. *J Neurosurg* 2009;110(6):1164-9. [\[CrossRef\]](#)
18. Oddo S, Solis P, Consalvo D, Seoane E, Giagante B, D'Alessio L, et al. Postoperative neuropsychological outcome in patients with mesial temporal lobe epilepsy in Argentina. *Epilepsy Res Treat* 2012;2012:370351.
19. Andelman F, Kipervasser S, Neufeld MY, Kramer U, Fried I. Predictive value of Wada memory scores on postoperative learning and memory abilities in patients with intractable epilepsy. *J Neurosurg* 2006;104(1):20-6. [\[CrossRef\]](#)
20. Jardim AP, Neves RS, Caboclo LO, Lancellotti CL, Marinho MM, Centeno RS, et al. Temporal lobe epilepsy with mesial temporal sclerosis: hippocampal neuronal loss as a predictor of surgical outcome. *Arq Neuropsiquiatr* 2012;70(5):319-24.
21. Loring DW, Meador KJ. Neuropsychological assessment for epilepsy surgery. In: Hefta JA, Sheinis LA, editors. *Behavioural neurology and neuropsychology*. New York: The McGraw-Hill Companies; 1997. p. 657-66.
22. Vingerhoets G, Miatton M, Vonck K, Seurinck R, Boon P. Memory performance during the intracarotid amobarbital procedure and neuropsychological assessment in medial temporal lobe epilepsy: the limits of material specificity. *Epilepsy Behav* 2006;8(2):422-8. [\[CrossRef\]](#)
23. Baxendale S, Thompson P, Harkness W, Duncan J. The role of the intracarotid amobarbital procedure in predicting verbal memory decline after temporal lobe resection. *Epilepsia* 2007;48(3):546-52. [\[CrossRef\]](#)
24. White JR, Matchinsky D, Beniak TE, Arndt RC, Walczak T, Leppik IE, et al. Predictors of postoperative memory function after left anterior temporal lobectomy. *Epilepsy Behav* 2002;3(4):383-9.