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Original Article**Cognitive impairments in patients with intractable temporal lobe epilepsy**

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Abstract

BACKGROUND: Cognitive impairment associated with temporal lobe epilepsy (TLE) has been recognized in multiple studies. We designed this study to find a specific cognitive profile in patients with TLE who were candidates for epilepsy surgery. We also sought to find if neuropsychological assessment could differentiate left TLE, right TLE and normal subjects.

METHODS: The sample of this study consisted of 29 patients with right TLE, 31 with left TLE, and 32 subjects without history of seizure as the control group. For all recruited patients and controls, demographic questionnaire, Wechsler Memory Scale-III (WMS-III) and Wechsler Adult Intelligence Scale-R (WAIS-R) were administered. Multivariate analysis of variance was carried out to reveal differences in memory and intelligence performance between the three groups.

RESULTS: All of the mean scores of the WMS-III indexes were significantly higher in the control group in comparison with the right or the left TLE groups ($p < 0.001$). There were not any significant differences between mean scores of WMS-III indexes of the right and the left. The WAIS-R also showed significantly better mean scores of full scale intelligence quotient (FSIQ) and performance intelligence quotient (PIQ) in the control groups than both of the right and left TLE patients ($p < 0.001$). Although the verbal intelligence quotient (VIQ) mean scores were significantly different between the left TLE and the control group ($p = 0.037$), there were not any significant differences between the right TLE patients and the control group.

CONCLUSIONS: These findings indicated that WMS-III and WAIS-R can differentiate patients with refractory temporal lobe epilepsy from normal subjects. However, the obtained cognitive profile could not differentiate between the right and the left TLE.

KEYWORDS: Temporal Lobe Epilepsy, Cognitive Impairment, Memory, Wechsler Memory Scale

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Temporal lobe epilepsy (TLE) is the most prevalent form of complex partial seizures (CPS) with specific temporal lobe related symptoms.¹⁻² Some studies showed that recurrent seizures affect all aspects of cognitive functioning including attention, language, praxis, executive function intelligence, judgment, insight, and problem solving.³⁻⁵ Howev-

er, the most important cognitive deficit in TLE is memory impairment.⁶⁻⁷ Damage to the mesial structure of the temporal lobe, particularly the amygdale and hippocampus, has the main role in these memory difficulties.⁸⁻¹¹ Another factors, including the long-term administration of antiepileptic drugs and seizure-related factors, i.e. age of onset, duration of the epilepsy,

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type of seizure, and psychosocial effects may also contribute to the cognitive decline over years.¹²⁻¹³

Approximately 30% to 45% of patients with TLE are refractory to antiepileptic pharmacotherapy.¹⁴⁻¹⁵ In this condition, surgical removal of the epileptogenic tissue would be considered. Resection of brain tissue would be limited to the epileptogenic zone to prevent disruption of normal brain functions.¹⁵⁻¹⁶ A variety of diagnostic and assessment techniques are used to find location of epileptogenic focus and prediction of epilepsy surgery consequences.^{15,17-18} Long term monitoring (LTM) of patients with prolonged electroencephalography (EEG) and video recording is utilized to find the specific source of discharges. Magnetic resonance imaging (MRI) is used to reveal structural abnormalities that may be related to seizures.^{15,19-20} Neuropsychological assessments provide current cognitive profile, which help for lateralization and localization of the damages and prediction of post-surgical outcome.^{2,5,21} For example, if there is significantly lower score of performance intelligence quotient (PIQ) than verbal one, the neuropsychologist may conclude lateralization of the epileptogenic zone in non-dominant brain hemisphere.^{7,15,21}

Temporal lobe, especially its mesial region, is crucial for processing of memory. Studies following lesions of this region have provided material-specific lateralization of information, which the dominant mesial temporal region is specific for verbal and non-dominant for visual memory.^{15,21-22}

Wechsler Memory Scale-Third Edition (WMS-III) is the measure that has been used widely for memory assessment of adults.²³ Vast majorities of epilepsy surgery centers use it as a component of presurgical neuropsychological evaluations.^{21,24} This instrument tries to evaluate verbal and visual domains separately. Several researchers showed that left temporal lobe epilepsy patients had significantly lower scores on the auditory subscale than visual one, while right-sided temporal dysfunction may produce deficits in nonverbal memory

who obtain higher scores on verbal than non-verbal indexes.^{23,25-30} However, there were multiple studies that could not reveal any differences between auditory and visual scores in one-sided mesial temporal epileptogenic focus.^{8,31-32} The most replicable finding in assessment of memory of TLE patients showed significant lower scores of the WMS-III in comparison with normal group.^{30,32}

This study was designed for patients with refractory TLE for two purposes. The first purpose was to evaluate cognitive state of patients who were candidates for epilepsy surgery. We sought to find if there was a specific cognitive profile in TLE patients. The second aim was to determine ability of WMS-III to differentiate left TLE, right TLE, and normal subjects with Persian language.

Methods

Participants

From May 2007 to February 2009, all of 132 patients with refractory epilepsy who were referred to Ayatollah Kashani Comprehensive Epilepsy Program, Isfahan University of Medical Sciences (Isfahan, Iran), were evaluated to establish TLE based on EEG and MRI findings. Sixty patients with established TLE were recruited. The inclusion criteria were age between 15 and 40, full scale intelligence quotient (FSIQ) more than 70, at least elementary school education and absence of major mental or neurological disorders except for epilepsy. The exclusion criteria were informed consent withdrawal and exacerbation of seizures that led to invalid neuropsychological test performance.

Control subjects who were matched for age and education, were selected from the patients' accompanying persons. They met inclusion criteria and did not have history of epilepsy. Finally, 29 right TLE, 31 left TLE, and 32 control subjects were recruited in this study.

Measures

A demographic checklist was completed for each patient. This checklist included questions about age, education, seizure duration, handedness and marital status. The WMS-III was

used to assess auditory and visual declarative memory and working abilities in adults and adolescents. It includes 11 subtests, 6 of which are considered primary and 5 optional. Primary subtests must be given to obtain index scores and optional subtests can be given to obtain supplementary information. In this study, primary subtests were used including logical memory I and II, face I and II, verbal paired associates I and II, family picture I and II, letter-number sequencing and spatial span. The index scores are obtained by summing these primary subtests.³³ One study in Iran revealed internal consistency of 0.65 to 0.85 for WMS-III subtests and 0.76 to 0.83 for WMS-III indexes by Cronbach's alpha coefficient.³⁴ WMS-III was administered by a student of PhD in psychology.

Measures of full scale, verbal, and performance intelligence quotient (IQ) were obtained using Wechsler Adult Intelligence Scale-R (WAIS-R). In one Iranian study, reliability and validity of WAIS-R were studied.³⁵ The WAIS-R subscales showed reliability from 0.69 to 0.87 on test-retest stability and their internal consistency was 0.77 to 0.88 with Split-half coefficient.³⁶ WAIS-R was administered by a student of PhD in psychology.

Statistical Analysis

All data were compared between patients (right TLE and left TLE) and controls. Discrete

variables were analyzed by the chi-square test. Analysis of Variance (ANOVA) was employed for continuous variables. The Multivariate Analyses of Variance (MANOVA) was used to analyze the data of WMS-III and WAIS-R between groups. The results were analyzed by SPSS version 14.

Results

The demographic characteristics of right TLE patients, left TLE patients and the control subjects were summarized in table 1. Homogeneity of variance between the groups for each of the dependent variable was checked. Various measures of memory were analyzed by MANOVA. The results of MANOVA revealed a significant difference between groups [Pillai's Trace $F(12,170) = 6.57, p < 0.001$].

As shown in table 2, results of MANOVA revealed significant differences between the groups for mean scores on PIQ subscale of WAIS-R ($p < 0.001$), FSIQ subscale of WAIS-R ($p < 0.002$) and all primary indexes of WMS-III ($p < 0.001$). There were no significant differences between right and left TLE regarding mean scores of WAIS-R and WMS-III.

Although the verbal intelligence quotient (VIQ) mean scores were significantly different between the left TLE and the control group ($p = 0.037$), there were not any significant differences between the right and the control group.

Table 1. Demographic characteristics by group

Participant characteristic	RTL epilepsy	LTL epilepsy	Control group	Statistical test	P-value
N	29	35	32		
Age (years)	26.93 (6.59)	25.91 (7.01)	26.53 (5.27)	$F = 0.21$	0.81
Education (years)	11.31 (3.71)	10.9 (3.28)	12.87 (3.2)	$F = 2.89$	0.06
Seizure duration (years)	13.48 (7.66)	15.28 (7.98)	-	$F = 0.83$	0.36
Handedness					
Right	25 (86.2)	28 (80)	29 (90.6)	$\chi^2 = 1.54$	0.46
Left	4 (13.8)	7 (20)	3 (9.4)		
Marriage					
Married	19 (65.5)	21 (60)	19 (59.4)	$\chi^2 = 0.29$	0.86
Single	10 (34.5)	14 (40)	13 (40.6)		

RTL: Right Temporal Lobe, LTL: Left Temporal Lobe
The results are presented as number (Percent)

Table 2. Wechsler Adult Intelligence Scale-R and Wechsler Memory Scale-III primary indexes and their subscale scores and comparisons by group

Variable	RTL epilepsy (n = 29) Mean (S.E)	LTL epilepsy (n = 35) Mean (S.E)	Control group (n = 32) Mean (S.E)	F	P-value	Eta Squared	Observed Power
WAIS							
VIQ	89.72±2.08	87.87 ± 2.02	93.87 ± 1.98	2.36	0.1	0.05	0.46
PIQ	82.2 ± 2.24	85.03 ± 2.17	95.18 ± 2.14	9.85	0.001	0.18	0.98
FSIQ	85.21 ± 1.93	85.42 ± 1.87	93.56 ± 1.84	6.54	0.002	0.13	0.9
WMS-III index							
Auditory immediate	18.69 ± 1.05	17.41 ± 1.02	28.62 ± 1.00	36.97	0.001	0.45	1.00
Visual immediate	12.2 ± 0.92	12.06 ± 0.9	22.21 ± 0.87	43.65	0.001	0.49	1.00
Immediate memory	30.89 ± 1.7	29.48 ± 1.64	50.84 ± 1.62	53.26	0.001	0.54	1.00
Auditory delayed	18.03 ± 1.03	17.13 ± 0.99	28 ± 0.98	37.33	0.001	0.46	1.00
Visual delayed	11.89 ± 0.85	12.29 ± 0.82	22.06 ± 0.81	49.32	0.001	0.53	1.00
Auditory recognition delayed	8.27 ± 0.54	7.48 ± 0.52	13.4 ± 0.52	37.98	0.001	0.46	1.00
General memory	38.21 ± 2.04	36.9 ± 1.97	63.46 ± 1.9	58.14	0.001	0.56	1.00
Working memory	12.27 ± 0.89	11 ± 0.86	16.53 ± 0.85	11.38	0.001	0.2	0.99

RTL: Right Temporal Lobe, LTL: Left Temporal Lobe; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; FSIQ: Full Scale Intelligence Quotient; WAIS-R: Wechsler Adult Intelligence Scale-R

Discussion

Many investigators have reported specific cognitive deficits that differentiate TLE from the other types of epilepsy. Problems in memory have been the most shared cognitive deficit in patients with TLE.³⁷ Early neuropsychological studies indicated that resection of the left temporal lobe may impair the ability to learn verbal materials while right temporal resection can produce a deficit in learning of nonverbal and visuospatial information.^{24,38} These phenomena were also found in patients with unilateral temporal lobe seizures with less power.³⁹⁻⁴⁰ However, there were other studies that failed to show material specific of memory impairment to lateralize right or left TLE.⁴¹⁻⁴²

In our study, patients with TLE as a single group, had significant lower scores in all of the memory indexes and in the most subscales in comparison with control subject. In addition, a comparison of the IQ scores between patients with epilepsy and subjects in control group showed significantly higher scores in FSIQ and PIQ scores. This findings were consistent with those studies that showed cognitive dysfunction in temporal lobe epilepsy.^{30,32}

In patients with the right TLE or the left TLE as two different groups, there were no significant differences between the two groups regarding scores of WAIS-R and WMS-III indexes and subscales. These results were not consistent with findings of Doss et al.²³ and Wilde et al.²⁹ that showed material-specific dichotomized deficits in TLE patients who were undergone anterior temporal lobectomy. However, some researchers have reported non-specific memory deficits in right or left TLE. Baker et al.³² and Vannucci³¹ found that there were no significant disparities between auditory and visual scores of patients with left temporal focal epilepsy group. Bachtler and Dordrill showed that no significant group differences were found for visual immediate or delayed or auditory immediate indexes.⁴³ These results were consistent with our finding.

We can suggest three possible explanations for these results. First, most of the findings that revealed material-specific memory problems were based on patients who were undergone anterior temporal lobectomy. Our results derived from pre-surgical evaluation of the TLE patients. Second, wilde et al. reported that the

ability of the WMS-III to predict lateralization was particularly weak for those with left temporal dysfunction.²⁹ Finally, although many of the neuropsychological tests possessed face validity, their genuine capabilities to assess what was prepared for them were in doubt. In WMS-III, the visual memory items invite verbal encoding during inspection, thus contralateral temporal lobe may have alternative or supplementary strategy for encoding of seemingly visual items in non-dominant hemisphere temporal lobe epilepsy. The results of this study showed ability of the WMS-III to find cognitive decline in patients with TLE. However, it has limitation in lateralizing epileptogenic zone.

This study had several limitations. We could not discontinue antiepileptic drugs because of medical ethics. Although the sample size had enough power to reveal difference between patients with TLE and control group, it was not able to differentiate right versus left epileptogenic zone. The WMS-III has multiple subscales but it would have been better if more cognitive assessment tools had been used to raise validity of the findings.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

This study has been derived from Ph.D. thesis of MT. All neuropsychological assessments, data gathering, and analysis were carried out by MT. MB was the main designer of this study and involved in all clinical and neuropsychological evaluations. HTN and HM were Ph.D. supervisors. RKN were advisors of Ph.D. thesis. AM was consultant of WMS-III administration and its psychometric properties. JM and MZ selected patients and localized the site of epileptogenic focus. All authors have read and approved the content of the manuscript.

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