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The impact of cerebrovascular risk factors on postoperative memory decline in patients with left temporal lobe epilepsy

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Abstract

Cerebrovascular risk factors (CVRFs) and comorbid cardiovascular and metabolic disease have been linked to accelerated cognitive aging and dementia in the general population; however, the contribution of these comorbidities to the risk of post anterior temporal lobectomy (ATL) memory decline has been unexamined. We explored the effects of CVRFs on postoperative verbal memory decline in a cohort of 22 patients with left temporal lobe epilepsy (LTLE) who completed pre- and one-year postsurgical neuropsychological testing. Diagnoses of interest included preoperative cardiovascular and metabolic disorders, as well as CVRFs [pulse pressure proxy, body mass index (BMI), and fasting glucose]. Twenty-three percent of patients had a history of cardiovascular disease, 9% of metabolic disorders, and 38% had a BMI indicating overweight or obese status. Higher preoperative BMI and glucose were associated with greater decline in verbal memory. The association between BMI and memory decline remained significant after controlling for age and left hippocampal volume. These findings suggest that modifiable health-related risk factors, including CVRFs, may impact the risk of postoperative cognitive decline, and that BMI in particular could be an important factor to consider and/or target for intervention early in clinical care to protect cognitive health.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of competing interest

None of the authors have any conflicts of interest to disclose.

Keywords

Temporal lobe epilepsy; Vascular risk factors; Body mass index; Verbal memory

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1. Introduction

Vascular and metabolic biomarkers and modifiable health-related risk factors have been linked to accelerated cognitive aging and dementia in the general population [1]. Despite evidence that some patients with temporal lobe epilepsy (TLE) are at increased risk for progressive cognitive decline, the effects of important cerebrovascular risk factors (CVRFs) on cognition are rarely examined in TLE or epilepsy in general [2]. Furthermore, there are no data examining whether these comorbidities increase the risk of postoperative cognitive decline.

Population-based studies in patients with epilepsy have found elevated vascular risks [3–5] [i.e., hyperlipemia, body mass index (BMI)] and poor health behaviors [2,6] (e.g., decreased physical activity, poor social and occupational functioning) that may place them at greater risk for cognitive impairment. An emerging literature in epilepsy has begun to identify CVRFs associated with cognitive impairment [7–10]. Recent studies have found abnormalities in vascular, inflammatory, and metabolic biomarkers in patients with epilepsy that are associated with poorer performance on neuropsychological measures of memory, psychomotor speed, attention, language, and working memory [8,9]. Furthermore, in the general population, elevated health-related risk factors have been linked to reduced hippocampal volume and memory impairments [11].

In this study, we explored for the first time the effects of CVRFs and comorbid vascular and metabolic disease on postoperative verbal memory decline in patients with treatment-resistant left TLE (LTLE). Secondary analyses examined the relationships between CVRFs and preoperative hippocampal volume and the potential mediating effects of CVRFs in hippocampal volume–verbal memory outcomes. Verbal memory was selected given that it is the most common and problematic postoperative cognitive comorbidity after left anterior temporal lobectomy (ATL) [12] and based on emerging evidence linking higher CVRFs with verbal memory impairment in epilepsy.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Boards at UC San Diego and UC San Francisco, and informed consent was collected from all participants. Twenty-two patients had medically-refractory LTLE diagnosed by board-certified epileptologists, in accordance with the criteria defined by the International League Against Epilepsy. All patients completed a full presurgical work-up and subsequently underwent a left ATL with marginal tailoring of the lateral temporal neocortex based on electrical stimulation mapping.

2.2. CVRFS and clinical history

Presurgical diagnosis of cerebrovascular risk factors (i.e., hypertension, hyperlipidemia, hypertriglyceridemia, stroke), metabolic disorders (i.e., diabetes mellitus), smoking status (i.e., former or current smoker), BMI (mass [kg]/height [m] [2]), glucose levels (mg/dl), and pulse pressure proxy (PPP = systolic–diastolic blood pressure [mm Hg]) were collected during standard preoperative clinical examination. For descriptive purposes, patients were divided into the following BMI categories: Underweight BMI < 18.4; Normal weight BMI 18.5–24.9; Overweight BMI 25–29.9; Obese BMI ≥ 30. However, BMI was treated as a continuous variable in all analyses. Variables representing cardiovascular disease and metabolic disorders were dichotomized into present or absent.

2.3. Neuropsychological testing

Verbal learning and memory (i.e., both immediate and delayed recall) were evaluated before and one year after surgery using tests of immediate and delayed word list learning (California Verbal Learning Test [CVLT-II] Total score and Long Delayed Free Recall [LDFR]), prose recall (Wechsler Memory Scale [WMS-III] Logical Memory [LM]: LM1-Immediate and LM2-Delayed), and paired-associate learning/recall (WMS-III Verbal Paired Associates [VPA]: VPA1-Immediate and VPA2-Delayed). Reliable change indices accounting for practice effects (RCI-PE) were calculated based on pre- and postsurgery memory scores [13]. This method predicts a given individual's postoperative score by adding the mean practice effect of a reference group (i.e., test–retest normative sample) to the individual's presurgical test score [14]. For this study, a 90% confidence interval (CI) was created around the predicted score and z-scores were generated. With a 90% CI only 5% of scores would be expected to equal or exceed the reliable change in either negative or positive direction. For all the analyses, the raw values corresponded to the 90% CI RCI threshold. Decline was defined as a z-score ≤ -1.64 and improvement was defined as a z-score ≥ 1.64. Test–retest data for the CVLT [15] were based on raw scores and test–retest data for LM and VPA [16] was based on scaled scores. All test–retest normative data were obtained from the test's technical manual. The following raw score change was needed for a reliable decline on the CVLT: 5-word decline for the CVLT-Total and 3-word decline for LDFR. For LM and VPA, the following scaled score change was needed for a reliable decline: LM1: 3 scaled score points; LM2: 2 scaled score points; VPA1: 2 scaled points; VPA2: 3 scaled points.

2.4. Hippocampal volume

Volumetric T1-weighted magnetic resonance imaging (MRI) scans were available for all participants; MRI data were collected on a General Electric Discovery MR750 3T or 1.5T EXCITE HD scanner using a standard 1-mm isotropic acquisition. Individual T1-weighted images were processed with FreeSurfer (v5.1.0) to obtain hippocampal volumes [17]. Visual inspection of hippocampus segmentation accuracy was performed, and any patients whose segmentations failed were excluded from the volumetric analysis. Intracranial volume and scanner type were regressed out from both left and right hippocampal volume.

2.5. Statistical analysis

Spearman's Rho correlations were conducted to evaluate the relationship between memory changes scores (i.e., RCI-PEs) and CVRFs. Linear regression analyses were used to evaluate the contributions of CVRFs to RCI-PEs, after controlling for age and hippocampal volume. All CVRFs (i.e., BMI, glucose, PPP) were evaluated as continuous variables.

3. Results

3.1. Clinical and postoperative memory profiles

Table 1 displays the clinical and demographic characteristics as well as prevalence of CVRFs and comorbid disease in the sample. One year after left ATL, 82% of patients achieved Engel 1 seizure outcome, and the remaining 18% achieved Engel 2 or 3 outcomes. Forty-five percent of the patients had the same number of antiepileptic drugs (AEDs) one-year postsurgery, and the remaining had a reduction in the number of AEDs. Table 2 displays pre- and postoperative scores and postoperative verbal memory change (i.e., decline, stable, gain) at the whole group level and for the normal weight and overweight groups. One patient in the obese category, demonstrated decline across all measures of verbal memory. When comparing decline across the patients who remained on the same AED regimen relative to those who had a change in AEDs, there were no differences in verbal memory decline between the two groups across most tests. We only found a significant difference in delayed paired associates (Fisher's exact = 5.83, p -value = .031), with patients on fewer AEDs demonstrating the most decline.

Paired sample t -test were conducted to evaluate differences between pre- and postoperative memory scores at the whole group level. These results revealed that patients with LTLE showed a significant decline in prose recall (p = .014; LM-Immediate), but not on other memory measures. Linear regressions were conducted to examine the contribution of important clinical variables (i.e., age of onset, mesial temporal sclerosis (MTS) status, preoperative memory scores) to each RCI-PE score. For delayed prose recall (LM-Delayed), the overall model was significant ($F(3,16) = 3.74$, p = .039); however, the individual predictors were not significant (age of onset: $\beta = -0.061$, p = .092; MTS: $\beta = -1.58$, p = .082; preoperative score: $\beta = -0.221$, p = .116). No other models were significant.

3.2. Relationship between CVRFs and epilepsy-related variables

Higher BMI was associated with higher systolic pressure ($r = 0.398$, p = .003) and overall PPP ($r = 0.405$, p = .002). Higher glucose was associated with a greater number of AEDs ($r = 0.419$, p = .001), and higher systolic pressure was associated with older age ($r = 0.356$, p = .008). Higher BMI was associated with a smaller right hippocampus ($r = -0.405$, p = .043) but not with left hippocampal volume or other CVRFs (p -values > .05).

3.3. Relationship between CVRFs and postoperative verbal memory decline

Table 3 and Fig. 1 demonstrate the relationship between CVRFs (i.e., BMI, glucose, PPP) and the RCI-PE scores for each of the memory measures. Higher presurgical BMI was associated with greater decline in immediate word list learning (CVLT-Total), as well as with greater decline in delayed recall for all types of information (word list, prose, and

paired associates; CVLT-LDFR, LM-Delayed, and VPA-Delayed). Higher glucose was associated with decline in immediate word list learning and delayed list recall (CVLT-Total, CVLT-LDFR). These correlations were significant ($p < .05$) after controlling for age at surgery. Because left hippocampal volume is known to be associated with verbal memory decline following left ATL, linear regression was used to determine the independent contribution of left hippocampal volume and BMI to each memory change score. After controlling for left hippocampal volume as well as age at surgery, BMI remained a significant predictor of delayed prose recall (LM-Delayed: R^2 change = 0.344, $\beta = -0.240$, $p = .021$), paired-associate learning (VPA-Immediate: R^2 change = 0.402, $\beta = -0.293$, $p = .039$), and delayed paired-associate recall (VPA-Delayed: R^2 change = 0.387, $\beta = -0.237$, $p = .022$).

3.4. Mediation effect of BMI

A posthoc causal mediation analysis was conducted to explore whether BMI mediates the relationship between hippocampal volume (left and right) and decline in verbal memory. The right hippocampus was examined given its role in maintaining verbal memory after resection of the left hippocampus [18]. To increase statistical power, we used a nonparametric bootstrap sampling procedure to test significance of the mediation effect [19]. Unstandardized mediation effects and the 95% CIs were computed for each of the 1000 bootstrapped samples. Body mass index mediated the relationship between right hippocampal volume and delayed recall of prose material (LM-Delayed: average causal mediation effects (ACME) = 0.0019, $p = .004$), and approached significance for right hippocampal volume and paired-associate learning (VPA-Immediate: ACME = 0.00337, $p = .052$) and delayed recall of paired associates (VPA-Delayed: ACME = 0.00163, $p = .054$; Total Effect: 0.0027, $p = .014$). No mediating effects were found for BMI and left hippocampal volume.

4. Discussion

In this study, we found that elevated CVRFs were associated with greater postoperative verbal memory decline in patients with LTLE. In particular, BMI played an important role, with higher BMI being associated with greater memory decline across multiple dimensions of verbal memory (word list learning, prose recall, and paired-associate learning). These findings suggest that early targeted patient interventions may benefit from the inclusion of modifiable health-related risk factors (e.g., BMI) that may improve cognitive health and reduce the risk of further cognitive decline.

The most common postoperative comorbidity in patients undergoing left ATL is verbal memory impairment [20]. Several epilepsy-related factors have been identified as increasing the risk for postoperative memory decline, including late age of epilepsy onset, high preoperative memory performance, left hemisphere language dominance, and the absence of left MTS [21]. However, these factors cannot be modified, and they only estimate the risk of memory decline. In the general population, several modifiable health factors have been found to reduce the size of the hippocampus including cardiovascular disease, diabetes, hypertension, mood disorders, and obesity [11]. Obesity has been associated with

hippocampal atrophy, increasing the risk of cognitive impairment in older adults (for review see [11]). Furthermore, in a sample of young to middle-aged patients with epilepsy, Baxendale et al. [7] found that obesity was associated with lower global intelligence quotient (IQ), slowed processing speed, and poor performance on multiple measures of memory. In our study, BMI was the strongest predictor of decline in multiple types of verbal memory, even after controlling for left hippocampal volume. Given that 77% of the patients in our study had left MTS, the structural and functional integrity of the right hippocampus would be critical for maintaining verbal memory through functional reserve, including possible reorganization of memory functions to the contralateral side [18]. In fact, we found that higher BMI was associated with a smaller right hippocampus and mediated the relationship between right hippocampal volume and memory decline. Thus, it is possible that BMI may play a role in the brain's capability of reorganizing following an insult. These preliminary findings more generally highlight the importance of assessing the role of nonepilepsy related factors that may shape the cognitive trajectories of individual patients with epilepsy. Furthermore, integrating weight management in the care of patients with epilepsy may reduce the risk of further memory decline as well as improve overall health and quality of life.

Patients with TLE may be at increased risk for a host of neurophysiological and brain changes, as well as lifestyle factors that result in premature deterioration of cognitive functions and brain health [2,12]. However, the underlying causes of accelerated cognitive decline in TLE have not been well established. Despite our sample being young to middle-aged adults, we found an increased prevalence of hypertension, dyslipidemia, obesity, and smoking. The presence of midlife vascular and metabolic risk factors as well as poor health habits has been shown to predict the risk of developing dementia [12], and many of these risk factors are overrepresented in epilepsy [22]. The cumulative effect of health-related factors and epilepsy-related factors is not well understood, and therefore, prospective longitudinal studies are needed to determine this risk and disentangle causality.

Several limitations of this study should be addressed. First, we only examined a small number of CVRFs (i.e., BMI, PPP, glucose), and thus, future studies with a larger sample examining a greater range of somatic variables are needed. Second, we only examined verbal memory given that it is the most pervasive postoperative cognitive impairment. However, studies with a broader examination of different cognitive domains are warranted in order to understand the impact of CVRFs on other important functions (e.g., language, executive function).

5. Conclusion

In conclusion, this study adds to an emerging literature emphasizing the importance of nonepilepsy potentially modifiable factors that impact the cognitive health and risk of adverse cognitive changes in people with epilepsy that could be integrated into the care of patients with epilepsy undergoing surgical therapy.

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Fig. 1.

Relationship between verbal memory decline and cerebrovascular risk factors. Reliable change indices accounting for practice effects (RCI-PE) are reflected as z-scores for all memory tests. Decline was based on a 90% CI RCI (z-score -1.64).

Table 1

Demographic and clinical variables at baseline.

	LTLE
N	22
Age at surgery (years)	32.09 (11.73)
Education (Years)	13.68 (1.73)
Age of onset	15.9 (10.7)
Duration of epilepsy	16.45 (13.8)
Number of AEDs	2.4 (1.0)
Seizure frequency	10.27 (15.65)
Pulse Pressure Proxy	47.47 (11.29)
Systolic blood pressure	118.33 (13.23)
Diastolic blood pressure	70.43 (12.39)
Glucose	102.1 (28.4)
Sex: M/F	13/9
MTS: Yes/No	17/5
Vascular Hx: Yes/No	5/17
Metabolic Hx: Yes/No	2/20
Smoking Status: Former/Current	5/2
BMI Category: Normal/Overweight/Obese	14/7/1

LTLE: left temporal lobe epilepsy; AEDs: antiepileptic drugs; F: females; M: males; MTS: mesial temporal sclerosis; Hx: history; BMI: body mass index. Standard deviations are presented inside the parentheses.

Table 2

Pre- and postoperative verbal memory performance.

	Pre-op	Post-op	% Change		
			Decline	Stable	Gain
Whole group level					
CVLT-Total	42 (13.1)	37.5 (13.1)	52.9	47.1	0
LDFR	7.4 (4.5)	6.63 (4.3)	33.3	61.1	5.6
LM-Immediate	7.3 (2.5)	6.8 (3.3)	47.1	52.9	0
LM-Delayed	7.5 (2.8)	7.4 (3.5)	35.3	64.7	0
VPA-Immediate	8.9 (2.4)	7.8 (3.9)	42.9	57.1	0
VPA-Delayed	9.6 (3.5)	8.9 (4.2)	21.4	64.3	14.3
Normal weight					
CVLT-Total	42 (14.4)	42.1 (15.3)	40	50	0
LDFR	7.5 (4.9)	7.5 (5.1)	18.2	81.8	0
LM-Immediate	7.4 (2.1)	7.0 (3.7)	45.5	54.5	0
LM-Delayed	7.2 (2.7)	8.0 (3.8)	18.2	81.8	0
VPA-Immediate	8.8 (2.7)	8.7 (3.9)	22.2	77.8	0
VPA-Delayed	9.3 (3.5)	9.6 (4.3)	11.1	66.7	22.2
Overweight					
CVLT-Total	40.8 (13.8)	32.2 (5.6)	60	40	0
LDFR	7.0 (4.9)	5.7 (3.4)	40	40	20
LM-Immediate	6.2 (3.3)	6.8 (2.9)	25	75	0
LM-Delayed	7.2 (3.3)	7.0 (3.4)	50	50	0
VPA-Immediate	8.8 (2.2)	6.0 (3.6)	75	25	0
VPA-Delayed	9.8 (4.6)	7.5 (4.4)	25	75	0

CVLT and LDFR are presented as total raw scores and LM and VPA tests are presented as scaled scores. Change was based on the test-retest normative data from the technical manuals. Standard deviations are presented inside the parentheses.

CVLT-Total: California Verbal Learning Test total score; LDFR: CVLT long delay free recall; LM-Immediate: Logical memory immediate; LM-Delayed: logical memory delayed; VPA-Immediate: verbal-paired associates immediate; VPA-Delayed: verbal-paired associates delayed.

Table 3

Spearman's Rho correlation analysis.

	BMI		Glucose		PPP	
	Rho	<i>p</i>	Rho	<i>p</i>	Rho	<i>p</i>
Verbal Memory						
Word list learning (CVLT-Total)	<i>-0.585</i>	<i>.017</i>	<i>-0.644</i>	<i>.010</i>	0.015	.957
Delayed word list recall (LDLR)	<i>-0.525</i>	<i>.030</i>	<i>-0.562</i>	<i>.010</i>	0.045	.865
Prose recall (LM-Immediate)	-0.319	.228	0.068	.809	-0.223	.407
Delayed prose recall (LM-Delayed)	<i>-0.664</i>	<i>.005</i>	-0.479	.071	-0.129	.635
Paired-associate learning (VPA-Immediate)	-0.440	.133	-0.370	.237	0.439	.134
Delayed paired-associate recall (VPA-Delayed)	<i>-0.602</i>	<i>.030</i>	-0.099	.759	0.379	.202

BMI: body mass index; PPP: pulse pressure proxy; CVLT-Total: California Verbal Learning Test total score; LDLR: CVLT long delay free recall; LM-Immediate: Logical memory immediate; LM-Delayed: logical memory delayed; VPA-Immediate: verbal-paired associates immediate; VPA-Delayed: verbal-paired associates delayed.

Bold and italics represent significant with false discovery rate correction per CVFR (BMI, Glucose, PPP).

BMI FDR $q^*:0.033$.

Glucose FDR $q^*:0.016$.

PPP did not survive FDR correction.