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Age at surgery as a predictor of cognitive improvements in patients with drug-resistant temporal epilepsy

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ABSTRACT

Temporal lobe epilepsy (TLE) surgery is an effective procedure that can produce cognitive changes. However, the prognostic factors related with cognitive outcomes need to be better understood. The aim of the present study is to know if age at surgery is a reliable predictor of verbal memory competence and considering factors such as: hemisphere; type of surgery; pre-surgical seizure frequency; and epilepsy duration. Sixty-one typically dominant patients with drug-resistant TLE (34 with left TLE [L-TLE] and 27 with right TLE [R-TLE]) underwent a neuropsychological assessment before and a year after surgery. Results showed that R-TLE patients had better evolution in short- and long-term verbal memory and naming than L-TLE patients (for all, $p > .04$). L-TLE patients also more frequently showed a strong and reliable decline in these functions than R-TLE patients. No effects for gender or type of surgery were found. From a multivariate approach, patients with improvements in verbal competence underwent surgery at earlier ages and suffered epilepsy for less time (for all, $p < 0.4$). The relevance of age at surgery was confirmed as a predictor of long-term verbal memory changes, although the frequency of partial seizures also explains, at least partially, these changes. In addition, the frequency of partial seizures explains short-term verbal memory changes. These results emphasize the importance of early intervention, independently of the resected hemisphere, in order to minimize the cognitive side-effects of epilepsy treatment, as well the need to consider cognitive functions as related processes and network dependent.

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1. Introduction

Epilepsy is a condition that affects more than 50 million people worldwide [1]. While most patients with epilepsy achieve adequate seizure control with antiepileptic drugs (AEDs), approximately 30% of patients continue to have seizures despite appropriate trials of two or more AEDs [2–4]. In these cases, surgery may be a suitable treatment to achieve seizure control [5,6].

The goal of epilepsy surgery is to remove the epileptogenic region while preserving as much functional tissue as possible [7]. Surgery for temporal lobe epilepsy (TLE) represents the most frequent surgical procedure [8] and usually involves resection of various structures of the temporal lobe, including the hippocampus, amygdala, entorhinal cortex, and temporal neocortex [9]. Surgery for TLE is an effective procedure [10] that decreases the number of seizures in approximately 70% of patients [3,11]. Despite these advantages, the surgery may produce various sequelae in patients, including impairments in verbal and nonverbal memory, language, attention, and visual-constructive function [7]. Among these cognitive domains, verbal memory disruption is one of the most frequently reported complaints by patients [7,12–14]. Various factors have been suggested to explain cognitive performance changes after surgery, although their predictive capability has not been confirmed [15]. These proposed factors include variables of the patient such as gender [5,16,17]; characteristics of the epilepsy course such as age at onset, duration, seizure-free period, and frequency of seizures [15,18]; as well as variables related to surgical procedures such as type of surgery and age at surgery [5,9]. In addition to the identification of relevant factors, notable efforts have been made to minimize variability in cognitive performance due to confounding variables (such as the practice effect). From among these efforts, the reliable change index (RCI) has been widely used to detect if cognitive changes are clinically relevant [19–22].

It is crucial to determine the appropriate age of the patient to perform epilepsy surgery in order to optimize seizure control and minimize cognitive sequelae. Age at surgery has been identified as an important modulator of the cognitive reserve capacity of the patient [5,7] since there are critical phases of cerebral functional plasticity such as

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childhood until language acquisition at 6 years of age, puberty until 15 years, and a decline from 30 years of age [16,17]. Although neural plasticity could be compromised in adult patients and the risk of cognitive decline after surgery is a frequent concern in older patients [23], few studies have analyzed the importance of age at surgery in the verbal memory of adult patients with TLE and the results are inconsistent. The relationship between verbal memory and age at surgery has been studied using two strategies: comparing age groups and considering age as a continuous variable from a regression approach. In studies where verbal memory is compared in groups of patients classified by age, poorer performance and more frequent declines have been found in patients older than 50 in comparison with younger patients [23]. However, an absence of significant differences has also been reported [24]. Other studies with the same methodological strategy have suggested an age effect depending on the hemisphere, showing lower declines in older patients than in younger patients with left-sided TLE (L-TLE) and no differences in those with right-sided TLE (R-TLE) [25]. Studies that considered age at surgery as a continuous variable capable of predicting changes in verbal memory after surgery are also inconsistent. Wagner et al. [26] found that the age at surgery explained, among other factors, changes in verbal learning but not verbal recall. However, Baxendale et al. [27] found that age at surgery, as well as the preoperative IQ, were predictors of verbal memory only in patients with R-TLE. Other factors that were not considered (such as seizure frequency and patients with atypical dominance) could explain, at least in part, the discrepancy in results.

The aim of this study was to determine if age at surgery is a reliable predictor of verbal memory competence in typically lateralized TLE, considering other factors such as hemisphere, type of surgery, seizure frequency, and epilepsy duration.

2. Material and methods

2.1. Sample

The inclusion criteria of the study comprised: 1) patients with a diagnosis of drug-resistant TLE who underwent resective epilepsy surgery; 2) a chronological age of at least 18 years; 3) typical language dominance; 4) and a neuropsychological assessment performed prior to surgery and 1 year after the surgery. The initial sample was composed of 67 adult patients with drug-resistant TLE who underwent surgical treatment. Four patients with atypical language dominance and two patients with postsurgical neuropsychological assessment after >1 year were excluded to reduce the variability of the sample. Therefore, the final sample included 61 patients (30 women and 31 men).

Participants were divided in two groups according to the hemisphere of surgery: R-TLE and L-TLE. Descriptive statistics are shown in Table 1.

2.2. Procedure

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe. Signed informed consent was obtained from all participants.

Medical history provided characteristics of the patients such as sex, age, level of education, age at epilepsy onset, duration of epilepsy (years), frequency of seizures (seizures per month), and pre-surgical number of AEDs.

Table 1
Characteristics of the total sample and groups based on resected hemisphere (M ± SD or %).

Characteristics	Total (N = 61)	L-TLE (n = 34)	R-TLE (n = 27)	p
Age	40.33 ± 12.70	41.71 ± 13.16	38.59 ± 12.11	.35
Sex				.71
Female	30 (49.2%)	16 (47.1%)	14 (51.9%)	
Male	31 (50.8%)	18 (52.9%)	13 (48.1%)	
Educational level				.51
Early childhood education	4 (6.6%)	2 (5.9%)	2 (7.4%)	
Primary education	31 (50.8%)	20 (58.8%)	11 (40.7%)	
Secondary education	10 (16.4%)	6 (17.6%)	4 (14.8%)	
Lower-university education	11 (18.0%)	4 (11.8%)	7 (25.9%)	
University education	5 (8.2%)	2 (5.9%)	3 (11.1%)	
Verbal IQ	94.15 ± 18.05	94.62 ± 17.44	93.54 ± 19.15	.82
Performance IQ	102.98 ± 16.03	101.09 ± 16.48	105.70 ± 15.31	.29
Age at epilepsy onset	14.26 ± 10.76	15.94 ± 11.35	12.15 ± 9.77	.17
Age at surgery	38.87 ± 12.39	40.09 ± 13.04	37.32 ± 11.58	.39
Years of epilepsy	24.61 ± 13.32	24.16 ± 14.27	25.18 ± 12.26	.77
Etiology of pathology				.07
Hippocampal sclerosis	31 (50.8%)	18 (52.9%)	13 (48.1%)	
Cavernous angioma	4 (6.6%)	2 (5.9%)	2 (7.4%)	
Cortical malformations	3 (4.9%)	3 (8.8%)	0 (0.0%)	
Hippocampal sclerosis + dysplasia	3 (4.9%)	0 (0.0%)	3 (11.1%)	
Tumor	6 (9.8%)	3 (8.8%)	3 (11.1%)	
Non-specific pathology	7 (11.5%)	6 (17.6%)	1 (3.7%)	
Non-assessable	5 (8.2%)	1 (2.9%)	4 (14.8%)	
Number of AEDs	6.08 ± 2.25	6.07 ± 2.40	6.10 ± 2.07	.97
Pre-surgical seizures per month	12.84 ± 23.72	10.53 ± 20.03	15.76 ± 27.81	.73
Surgical approach				.50
TL	11 (18.0%)	6 (17.6%)	5 (18.5%)	
TL + AH	42 (68.9%)	22 (64.7%)	20 (74.1%)	
Lesionectomy	8 (13.1%)	6 (17.6%)	2 (7.4%)	
Type of surgery				.43
With AH	42 (68.9%)	22 (64.7%)	20 (74.1%)	
Without AH	19 (31.1%)	12 (35.3%)	7 (25.9%)	
Engel I	53 (86.9%)	31 (91.2%)	22 (81.5%)	.27
Postsurgical seizures per month	0.24 ± 0.83	0.08 ± 0.38	0.44 ± 1.16	.19

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