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ORIGINAL COMMUNICATION

Growing older with drug-resistant epilepsy: cognitive and psychosocial outcomes

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Abstract

We aimed to investigate the cognitive and psychosocial outcomes of patients older than 50 with drug-resistant temporal lobe epilepsy as compared to a younger cohort. One hundred and thirty-one patients with temporal lobe epilepsy (47% age ≥ 50) who underwent comprehensive neuropsychological testing were retrospectively identified. A comparison of percentage of Z scores < -1.5 between the older and younger cohort on Trail Making Tests A and B, Boston Naming Test, Rey Auditory Verbal Learning Test (RAVLT) delayed recall, and Rey–Osterrieth complex figure test delayed recall was performed as well as the presence of disability due to epilepsy and depression scores. Grading of white matter hyperintensities on MRI was also performed. Older patients with epilepsy were more likely to score $Z < -1.5$ on the RAVLT (54.1 vs 32.8%) and were more likely to be on disability due to their seizures (23.0 vs 5.7%). A higher grade of white matter hyperintensities correlated with worse performance on Trail Making Test A, while a higher number of anti-epileptic drugs (AEDs) correlated with worse performance on Trail Making Test B regardless of age. The results of this study reveal that older patients with drug-resistant epilepsy are a vulnerable population with an impaired cognitive profile. In addition, limiting the number of AEDs and addressing markers of small vessel disease should also be prioritized by clinicians.

Keywords Drug-resistant epilepsy · Cognitive outcomes · Memory · Disability · White matter disease · Anti-epileptic drugs

Introduction

Epilepsy is a neurological disorder that represents around 0.70% of global disease burden [1] and carries significant morbidity and mortality across the lifespan. Around a third of patients with epilepsy are resistant to medications, and they experience the majority of the disease burden [2]. Patients with chronic longstanding epilepsy entering their 5th and 6th decade of life are at a disadvantage given that they are starting at a lower cognitive baseline [3, 4] and are thus more susceptible to the effects of aging. There is also the question of whether epilepsy causes a progressive dementing illness later on in life [5]. Studies evaluating the long-term cognitive outcomes of epilepsy have mainly focused on the role of seizure frequency and disease duration [6]. Other factors that have received less attention include the role of increased sensitivity to anti-epileptic drugs (AEDs) [7] and heightened atherosclerosis, thought to possibly be due to the effects of chronic exposure to enzyme-inducing AEDs [8, 9]. The current study evaluates the cognitive profile of older patients with drug-resistant temporal lobe epilepsy (TLE) with a particular focus on the impact of AEDs and of cerebral small vessel disease.

Methods

A retrospective chart review of patients with temporal lobe epilepsy who underwent neuropsychological testing was performed. The research patient data repository software [10] was used to identify cases between 1995 and 2017 relying on

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ICD-9 and ICD-10 diagnosis codes consistent with epilepsy or seizures.

Inclusion criteria included: (1) a diagnosis of temporal lobe epilepsy based on History + EEG and/or neuroimaging confirmed by an epileptologist; (2) absence of high-grade tumors; and (3) drug resistance. Patients were considered to have drug-resistant epilepsy if they failed at least two AEDs [11]. Any patient with a prior intracranial surgery or dual pathology (extratemporal cortical lesions) was excluded.

Neuropsychological testing was performed during an inpatient hospital admission for seizure characterization/pre-surgical work up in the epilepsy-monitoring unit or in the outpatient setting. Patients with IQ scores < 70 or primary sensory/motor impairments affecting test performance were excluded. Only the first neuropsychological assessment was used. Patients were then divided into a younger vs older cohort with an age cutoff of ≥ 50. The study was approved by the Brigham and Women's Hospital institutional review board.

All patients underwent comprehensive neuropsychological testing. Given that the testing was performed across a 20 year span, the following tests were selected because of consistent usage across the cohort: Processing speed: Trail Making Test—Part A (TMT-A), language: Boston Naming Test (BNT), executive functions: Trail Making Test—Part B (TMT-B), verbal memory: Rey Auditory Verbal Learning test (RAVLT) delayed recall [12], visual memory: Rey–Osterrieth complex figure test delayed recall (Rey–O DR). The Beck Depression Inventory (BDI-II) was used to assess for depressive symptoms. Test scores were transformed into normalized *Z* scores (mean = 0, SD = 1) based on normative data for age, sex (all measures), and education (TMT-A and B only).

Information related to epilepsy characteristics (duration, focal impaired aware seizure frequency per month, frequency of generalized tonic–clonic seizures [GTC] per year, history of GTC, antiseizure medications, and lateralization on EEG), family history of epilepsy or dementia, a history of depression, psychosocial factors (ever employed, on disability due to epilepsy), and neuroimaging (lesion type) was also extracted. White matter hyperintensities (as a marker of cerebral small vessel disease) were assessed only on axial FLAIR images from a 1.5 or 3T MRI performed within 2 years of the neuropsychological assessment using the Wahlund scale [13] (absent, grade 0; punctuate, grade 1; early-confluent, grade 2; confluent, grade 3).

Statistical analysis

To compare the demographic, clinical, neuroimaging, and psychosocial factors between the two groups, the independent two sample *t* test was used for continuous variables if normally distributed, the Wilcoxon rank sum for non-normally distributed continuous variables, and Pearson's Chi-squared test for categorical variables.

A one sided *t* test was used to compare the average *Z* scores of the older cohort to normative data.

To determine whether the older vs younger groups differed in cognitive outcomes, the percentage of patients with a *Z* score < − 1.5 was calculated. The cutoff of − 1.5 was chosen, since it is considered to signify mild cognitive impairment [14].

To identify predictors of impaired performance on the cognitive measures, the outcomes were then fit into a logistic regression adjusting for known covariates of age, number of AEDs, white matter disease status (Wahlund grade ≥ 1), epilepsy laterality, depression, and years of education. For outcomes of TMT-A and B, the level of education was not included in the model as the *Z*-score conversion already accounted for it. An impaired visual memory prediction model was not generated due to the large number of missing variables.

All the outcomes measured as continuous variables were converted to binary variables and coded as 1 if they were less than − 1.5 and 0 otherwise. Age was also converted to a binary variable in which those at or greater than age 50 were coded as 1 and the others as 0. Number of AEDs, years of education, and depression index were treated as continuous variables. The reference group of the epilepsy laterality was right sided for the RAVLT. An age × AED variable was also included in the model to determine whether there is an interaction between the age category and medications. To correct for multiple comparisons, the false discovery rate method was used with a *p* value less than 0.05 considered significant. The goodness of fit for each logistic regression model of each outcome of interest was assessed using the Hosmer–Lemeshow test.

Results

A total of 131 patients fulfilled inclusion criteria including 61 older than 50. The clinical and neuroimaging characteristics of the cohort are summarized in Table 1. The older cohort had a longer duration of epilepsy. Pathologies other than mesial temporal sclerosis included the following; younger cohort: cavernoma 1, cyst 1, low-grade tumors 2, malformation of cortical development 1, for the older cohort: 4 low-grade tumors, 1 malformation of cortical development. The average age at receipt of social security disability benefits due to the epilepsy for the older cohort was 48.2 years (range 25–63 years), while that of the younger cohort was 42.0 (range 30–49 years).

In 24.4% of the patients, the neuropsychological testing was performed in the outpatient setting with no difference

Table 1 Clinical and neuroimaging characteristic of the cohort

	Younger patients (18–49) $N = 70$	Older patients (≥ 50) $N = 61$
Age at testing mean (± S.D.)*	33.87 (7.79)	59.16 (7.32)
Years of education mean (± S.D.)	14.34 (2.43)	14.17 (2.62)
Females	62.9%	54.1%
FHx of epilepsy	35.7%	29.5%
FHx of dementia	7.14%	14.75%
Hx of depression	25.7%	27.9%
Ever employed	97%	100%
Currently disabled due to epilepsy*	5.7%	23.0%
Age of onset median (range)*	18 (1–44)	29 (0.5–87)
Duration of epilepsy median (range)*	13.79 (1.1–43.7)	30.65 (0.7–66.0)
Focal impaired awareness seizures per month median (range)	1 (0.1–20)	1 (0.1–6)
Hx of GTCS	80.0%	77.0%
GTCS per year median (range)	0.3 (0–6)	0.2 (0–24)
Num of AEDs median (range)	2 (1–4)	2 (1–4)
Epilepsy lateralization		
Bilateral	5.8%	8.3%
Left	43.5%	55.0%
Right	50.7%	36.7%
Lesional MRI	41.2%	38.3%
Mesial temporal sclerosis on MRI	38.3%	32.2%
Wahlund grade*		
0	95.6%	49.1%
1	2.9%	41.5%
2	1.5%	9.4%

Fhx family history, *GTCS* generalized tonic–clonic seizure, *Hx* history, *S.D* standard deviation

*Indicates p value < 0.05

between the cohorts. The cohorts were also evenly distributed across years of testing.

An average of the Z scores according to the cognitive domain is depicted in Fig. 1. When compared to the normative data, the average Z scores of the older cohort were all significantly different with $p < 0.05$. None of the averages were significantly different between the two groups.

When analyzing the percentage of scores with a Z score < -1.5, the older cohort exhibited a higher percentage of verbal memory scores below the pre-specified cutoff (Table 2).

Prediction models of Z scores < -1.5 across the domains were then generated except for visual memory given the large number of missing data (even with the limited sample size, the only predictor that revealed a trend towards significance was the presence on an MRI lesion: 0.092). All the rest of the models had p values greater than 0.05, failing to reject the null hypothesis of correct model specification at 0.05 confidence level. On the binary level, the probability of scoring lower than -1.5 in verbal memory score was greater in the older cohort ($p = 0.012$ unadjusted, $p = 0.0728$

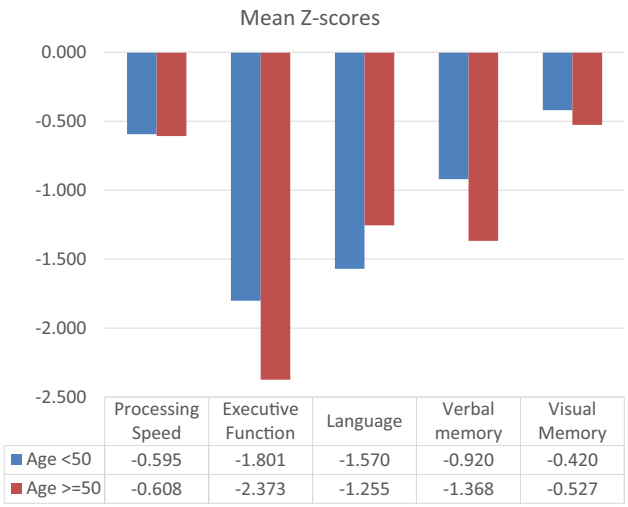

Fig. 1 Average Z scores per cognitive task

Table 2 Neuropsychological testing

Number of available values	Younger patients (18–49) $N = 70$	Older patients (≥ 50) $N = 61$
FSIQ (median, range) (51, 35)	102 (74–120)	102 (74–123)
BDI (median, range) (53, 52)	9 (0–35)	9 (0–26)
Executive functions		
TMT-B (66, 54)	33.3%	48.15%
Processing speed		
TMT-A (66, 56)	19.7%	17.86%
Language		
BNT (70, 58)	40%	36.06%
Visual memory		
ROCF-delayed recall (40,28)	12.50%	3.57%
Verbal memory		
RAVLT-delayed recall (64, 48)*	32.81%	54.17%

BDI-II Beck Depression Inventory II, *BNT* Boston naming test, *FSIQ* Full Scale Intelligent Quotient, *RAVLT* Rey Auditory Verbal Learning test, *ROCF* Rey–Osterrieth complex figure test, *TMT-A* Trail Making Test—Part A (TMT-A), *TMT-B* Trail Making Test—Part B

Percentage of Z scores < -1.5

*$p < 0.05$

adjusted) and those with lower education level ($p = 0.0135$ adjusted and unadjusted). Being at or older than age 50 was associated with a 2.42 times greater odds of having a verbal memory score < -1.5. For processing speed, Wahlund grade > 0 was associated with a 16.60 times greater odds of a score < -1.5. While for executive functions, each additional AED was associated with a 3.13 times greater odds of having a score < -1.5. For the language outcomes, only the years of education showed significance with each additional year of education associated with a 28% lower odds of having a score < -1.5.

Discussion

In this cross-sectional analysis of patients with drug-resistant TLE, we found that older patients were more likely to have significantly impaired verbal memory performance as compared to their same-age peers and there was a trend for impaired performance compared to a younger patient population. The older patients were also more likely to be on disability due to their disease. We also found that the small vessel disease burden negatively correlated with processing speed, while the number of AEDs negatively correlated with executive functions regardless of age category.

Cognitive outcomes in the setting of longstanding epilepsy have always been of interest [3, 4, 15–20]. There is an ongoing debate as to whether epilepsy has neurodegenerative features [4, 21] especially in light of the fact that neuroimaging studies point towards an element of progressive atrophy with disease duration [22]. This becomes particularly important for the older patients with longstanding epilepsy as they age. A cross-sectional analysis of a large cohort of TLE patients using the German version of the RAVLT dissociated a pattern of decline mediated by cognitive impairment and mental aging from what would be expected in a neurodegenerative disease [4]. In another cohort of patients with TLE aged 14–60, a significant number of patients scored $Z < -1.5$ across a number of cognitive tests (including the BNT, TMT-A and B) as compared to controls with long epilepsy duration, high burden of seizures, and low educational levels as predictors of worse performance [16]. Meanwhile, in a homogeneous cohort of unilateral mesial temporal sclerosis patients with an onset before age 18, the age category (18–30 vs 30–45 vs 45–65) was not associated with the normalized Z scores of the verbal and visual memory tasks [3]. Longitudinal follow-up studies of TLE patients have also consistently shown a decline in test scores when patients are tested several years later as compared to controls [15, 17–19]. Ultimately, our findings indicate that around half of older patients with epilepsy will have a significantly impaired verbal memory performance for their age, while a longer duration of education was protective. A Z score < -1.5 places the performance below the 7th percentile and is often used to identify patients with mild cognitive impairment [14].

This impairment is also noticeable across a host of other cognitive domains including executive function, processing speed, naming, and visual memory similar to what has been described in other studies [23]. Viewing TLE as a network disease rather than an isolated abnormal pathological "spot" helps explain some of these findings [24]. This profile makes patients with epilepsy ill equipped to handle another "hit" such as the development of Alzheimer-type plaques and tangles pathology. It has to be noted that the younger cohort had a significantly shorter duration of epilepsy and would also have been more likely to have the onset of their disease during crucial stages of neurodevelopment in childhood. These factors are of interest and could also have contributed to the differing cognitive profiles.

Another concern in older patients with epilepsy is the risk of increased atherosclerotic markers especially due to long standing exposure to enzyme-inducing AEDs [8, 9] with long-term studies revealing a higher burden of white matter disease as compared to controls [25]. We found that the patients with a significant burden of small vessel disease on MRI mostly had worse performance on processing speed regardless of age, likely through disruption of frontal subcortical connections [26]. We were also interested in the effect of medications, and found that they had a negative correlation with executive functions. AED polytherapy is known to adversely impact cognitive functions even when controlling for disease severity

with executive functions the most vulnerable to its effects [27–29]. We found that each additional AED is associated with a 3.13 times greater odds of having a score $Z < -1.5$ on executive functions. Although older patients are considered to be more sensitive to medications [7], we did not find the interaction between age category and the number of AEDs to have a significant correlation with cognitive outcomes. Finally, we also found that older patients with epilepsy were more likely to be on disability due to their disease. Nearly, all patients were employed at some point during their lifetime. It is unclear whether older patients ultimately decide no longer to seek employment and prefer to transition to long-term disability due to their longstanding disease process.

Our findings should highlight the fact that older patients with drug-resistant epilepsy are a vulnerable population with an impaired cognitive profile. Physicians should incorporate cognitive screening tests in their examinations to monitor for any progression, provide long-term planning advice, and be mindful of safety issues such as medication supervision. In addition, limiting the number of AEDs and addressing markers of small vessel disease should also be prioritized.

Limitations

The study has a number of limitations; the main limitation is that the study spanned a period of 22 years and the neuropsychological tests were not consistently administered to all of the patients; however, he cohorts were evenly distributed across the years of testing.

Due to the number of missing test scores for example, we could not adequately assess predictors of visual memory outcomes. Larger cohorts would be able to delineate several other predictors of interest and be able to account for multiple comparisons. The cohort also included variable pathologies including bitemporal epilepsies; however, no significant difference in the pathologies between the groups was noted. The cross-sectional design limits inferences about the course of cognitive changes within an individual with drug-resistant temporal lobe epilepsy as they age.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard The study was approved by the Brigham and Women's Hospital Institutional review board and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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