



Anterior temporal lobectomy for older adults with mesial temporal sclerosis



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ARTICLE INFO

Article history:

Received 5 February 2016

Received in revised form 7 September 2016

Accepted 29 September 2016

Available online 30 September 2016

Keywords:

Anterior temporal lobectomy

Mesial temporal sclerosis

Age

ABSTRACT

Objective: To compare postoperative seizure-free survival between older and younger adults.

Methods: A retrospective cohort of 107 temporal lobe epilepsy patients with a diagnosis of mesial temporal sclerosis (MTS) received anterior temporal lobectomy (ATL) between 1993 and 2014. We divided the lower three quartiles (younger) and top quartile (older, all 47+ years) of patients, then reviewed patient registry and electronic medical records to determine time to first self-reported seizure after ATL, the primary outcome (mean = 3.5 years of follow-up, SD = 3.6). We also assessed Engel classifications, intra-operative and postoperative treatment complications, and social disability. We used Cox proportional hazard models to assess the association between individual traits and time of seizure recurrence.

Results: During follow-up, 35/107 (32.7%) patients had post-operative seizure(s). After adjustment for potential confounders there were no significant differences in the probability of post-operative seizures between the older and younger groups, though we had limited precision (hazard ratio of 0.67 [0.28–1.59]), ($p = 0.36$). There were more treatment complications and disability in older patients (18% vs. 1.3% for any complications, 84.62% vs. 58.23% for driving disability, and 84.6% vs. 60.7% for work disability, $p < 0.05$).

Conclusion: Older patients appear to have more complications after ATL, compared with younger patients. Age, however, does not appear to have a large independent association with seizure recurrence.

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1. Introduction

Epilepsy affects over 4.8 million adults in the United States alone. It leads to serious social stigma, reduced income and lower quality of life (Beghi et al., 2005; Brodie and Stephen, 2007; Faught et al., 2012; Galimberti et al., 2006; Griffith et al., 2007; Leonardi and Ustun, 2002; McWilliams et al., 2013; Penberthy et al., 2005; Perucca et al., 2006; Reid et al., 2012; St Germaine-Smith et al., 2012). Nearly 30% of all newly developed epilepsy is diagnosed in the elderly and often more disabling than the younger adults. The incidence of a first seizure is approximately 136–150 per 100,000 in those 65 years and older (Hesdorffer et al., 2011; Kotsopoulos

et al., 2002; Leppik, 2007; Pugh et al., 2007; Ramsay et al., 2007; Ruggles et al., 2001).

Although, anti-seizure drugs (AED) are the first line treatment for epilepsy, (Ramsay et al., 2007; Rowan et al., 2005; Sheorajpanday and De Deyn, 2007) about 20–45% of epilepsy patients still continue to have seizures despite multiple medications or suffer intolerable medication side effects (Choi et al., 2014). Older adults are more vulnerable to AED side effects and are more prone to serious injuries from seizures (Birnbaum et al., 2003; Brodie and Stephen, 2007; Kwan et al., 2010; Ruggles et al., 2001; Sheorajpanday and De Deyn, 2007; Stephen et al., 2006; Tatum, 2010). Older adults with epilepsy are also disproportionately subject to cognitive decline regardless of the number of AEDs prescribed (Griffith et al., 2006; Hermann et al., 2008). Moreover, post-seizure disorientation may last longer, and prolonged seizures are significantly more likely to result in fatality in that age group (Brodie and Stephen, 2007; Galimberti et al., 2006; Griffith et al., 2007; McWilliams et al., 2013; Perucca et al., 2006).

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Many people with epilepsy have temporal lobe epilepsy (TLE) due to mesial temporal sclerosis (MTS), which can be effectively treated by anterior temporal lobectomy (ATL) (Elsharkawy et al., 2009; Kelemen et al., 2006; McIntosh et al., 2012; Téllez-Zenteno et al., 2005). Following ATL, about 70% of patients are seizure free one year after surgery and up to 60% after 5 years (Elsharkawy et al., 2009; Kelemen et al., 2006; McIntosh et al., 2012; Sadek and Gray, 2011; Téllez-Zenteno et al., 2005). Comparing MTS patients managed solely with AEDs, MTS patients with ATL are less likely to require AEDs and even end with better results, such as decreased seizure recurrence and morbidity. Due to the substantial comorbidities associated with AEDs in the elderly and current evidence that suggests surgery within 2 years of diagnosis offers the best chance of preventing a lifetime of disability, (Mcdermott et al., 2012) national practice guidelines recommend clinicians refer both young and elderly patients to be considered for epilepsy surgery (Fountain et al., 2015; Kuehn, 2015; Panayiotopoulos et al., 2005).

While the likelihood of post-operative seizure freedom is well characterized in younger adults, the likelihood of seizure freedom is unclear in older patients. The understanding of post-operative seizure freedom in elderly patients is limited due to the fact that older adults are much less likely to be offered surgical intervention (de Tisi et al., 2011; Murphy et al., 2010; Simasathien et al., 2013), (Costello et al., 2009; de Tisi et al., 2011; Mcdermott et al., 2013; Murphy et al., 2010; Simasathien et al., 2013). Avoidance of surgical intervention for the older patients are due to the assumptions of poor surgical candidacy and the likelihood to experience post-operative complications because of their age. The probability of undergoing surgery may also be influenced by different treatment preferences or treatment-related concerns in the elderly.

Some authors have suggested that patients 50 years or older with MTS treated with ATL have seizure outcomes that are comparable to younger patients over the long term (Costello et al., 2009; Murphy et al., 2010). However, these studies analyzed the data with a logistic regression model, which did not account for the confounding factor of follow-up length (censored data).

An appropriate method to address censored data is a cox proportional hazard model, which uses the time of seizure recurrence. In addition, it provides a quantitative assessment of the impact of age at surgery even after adjusting for important variables such as number of AEDs.

A study of patients with temporal lobe epilepsy of various age groups who underwent anterior temporal lobectomy and were diagnosed with mesial temporal sclerosis is needed to compare post-operative clinical outcomes between older and younger adults. Our primary outcome is time-to-seizure recurrence.

2. Methods

2.1. Study population

An epilepsy surgery outcomes protocol and registry was created in 1993 in our epilepsy center (Costello et al., 2009). We sought to systematically and prospectively gather demographic data, clinical characteristics and outcomes among all patients who underwent epilepsy surgery. Patients were seen at the epilepsy unit on a regular basis after their temporal lobectomy. Each visit included a neurologic exam and interviews about seizure recurrence and seizure frequency with antiepileptic medication adjustment as needed.

To examine the association between age and post-operative seizure freedom, we selected all adult patients who had undergone temporal lobectomy (ATL) between June of 1993 and March of 2015 ($n = 186$). We excluded patients who received an alternative histopathology diagnosis such as vascular, tumoral, or devel-

opmental malformation and included only those patients with histologically proven hippocampal sclerosis ($n = 107$).

2.2. Procedure

The lead author trained two research assistants to compare the information obtained from the data registry with that available in the medical record. They were previously trained to abstract relevant medical records and to code information related to patient demographics, clinical traits and outcomes. When conflicting or incomplete information was encountered, the medical record was discussed and reviewed by the lead author. In addition, data reliability was assessed using a random sample of 10% of charts reviewed by each research assistant. Inter-rater reliability revealed a good level of agreement between both research assistants and the lead author with a kappa above 0.9 for demographic measures and numerical objective measures (e.g.: age at first seizure, seizure frequency), and kappa ranging from 0.6 and 0.8 for clinical traits and outcome measures (e.g.: seizure type, degree of disability) (Costello et al., 2009; Moura et al., 2015a,b).

2.3. Measurements

2.3.1. Pre-surgical evaluation and surgical procedure

All of the patients underwent magnetic resonance imaging (MRI), and video-electroencephalography (EEG) monitoring as part of the standard investigations. If these investigations and the seizure pattern were concordant, then neuropsychological and psychiatric assessments were undertaken. Positron emission tomography (PET), single photon emission computed tomography (SPECT) scans, and invasive EEG monitoring were performed as needed. A multidisciplinary team through review of the pertinent data ascertained surgical candidacy. The eligible patients underwent an en bloc anteromedial temporal lobectomy (ATL) performed by one of two experienced surgeons (Sass et al., 1991).

2.3.2. Histologic examination

Resected specimens were sent for histologic examination to confirm diagnosis of MTS. Hematoxylin and eosin (H&E) staining was performed on the neocortical and mesial specimens, including the amygdala and hippocampus. The pathologist reported in the electronic medical record positive cases of hippocampal sclerosis, conventionally defined as a neuronal cell loss of greater than 50% in the CA1 sector. Among the 161/186 (86%) patients who had ATL with presumed diagnosis of MTS, 107 (57%) had confirmed MTS (the remaining 64 (34%) had an unknown diagnosis despite pathology); while 25 (13%) had pre-operative suspicion of other etiologies (e.g.: vascular malformation).

2.3.3. Post-surgical outcomes

The primary endpoint of interest was the time, in days, it took to first self-report seizures after ATL from the date of surgery. In keeping with prior literature, we used the standard Engel classification for seizure outcomes after ATL were recorded in the registry at each visit during a weekly post-clinic conference case discussion after every follow-up visit (Elsharkawy et al., 2008; Engel, 2006). The main Engel categories are the following: Engel Class I: Free of disabling seizures (completely seizure free; non-disabling, simple partial seizures only; some disabling seizures, but free of disabling seizures for at least 2 years; generalized convulsion with antiepileptic drug withdrawal only.); Class II – Rare disabling seizures (initially free of disabling seizures, but rare seizures now; rare disabling seizures since surgery; more than rare disabling seizures, but rare seizures for at least 2 years; nocturnal seizures only.); Class III – Worthwhile improvement (worthwhile seizure reduction; prolonged seizure-free intervals amounting to more

than half the follow-up period, but not less than 2 years.); and Class IV – No worthwhile improvement (significant seizure reduction; no appreciable change; seizures are worse) (Engel, 2006).

Engel classification was only used in the post-operative period. In addition, we categorized seizure frequency into four categories: seizure-free (≤ 1 seizure per year); rare seizures (>1 per year, but ≤ 1 per month); occasional seizures (>1 per month, but ≤ 1 per day); or, frequent seizures (>1 seizure per day). Seizure type was classified into one of three categories: complex partial, complex partial with secondary generalization, or more than one seizure type. Electroencephalography (EEG), while an objective measure of seizure activity, was only performed when clinically indicated (See et al., 2013; Tonini et al., 2004).

Occurrence of surgical complications were ascertained and documented in the registry during each follow-up visit. Neurosurgical complications collected include: intracranial infection of any type, postoperative hemorrhage or stroke (both symptomatic and asymptomatic), and persistent neurologic symptoms such as hemiparesis, significant speech or memory disturbance, and visual field deficits that would affect a patient's ability to drive. Other acute or chronic complications such as urinary tract infections, chest infections, depression or other neuropsychological complications were not systematically gathered.

2.3.4. Additional measures

Additional demographic and clinical variables were gathered through medical records abstraction taking into account: age, gender, race, age at first seizure, number of co-morbidities at the time of surgery, presence of psychiatric comorbidities, and the number and type of anti-epileptic drugs at the time of epilepsy surgery and the last follow-up visit. At the time of each follow-up visit we gathered indicators of driving disability (e.g., whether the patient was able to legally drive), work disability (e.g., when applicable, whether the patient was unable to maintain regular work activities due to seizures, AED toxicity or complications of surgery), and employment status (when applicable, whether the patient was able to maintain regular employment status after the surgery).

Past history of epilepsy risk factors included self-reported history of birth or developmental anomaly, history of head trauma, and family history of epilepsy. Missing data was due to absence of information in both the epilepsy surgery outcomes registry and the longitudinal medical record.

2.4. Statistical analysis

The balance between baseline characteristics of age groups was assessed using two-group *t*-tests to compare continuous variables. For categorical variables such as race, gender, history of birth or development anomaly, history of head trauma, and seizure type, a two-group chi-square test was used.

To provide an adequate representation of "older age," age was modelled as a binary variable divided between younger and older patients with a cut-off at the fourth quartile for the study sample. Age in quartiles has been used as a method of modelling the effect of "older age" in previous studies that retains reasonable sensitivity to detect a difference among age groups (Murphy et al., 2010).

In handling missing data with respect to seizure outcomes (right censoring), we performed an exploratory multivariate cox proportional hazards (CPH) model which accounts for different follow-up durations between patients. In this analysis, the independent relationship between age as continuous variable and time of seizure-recurrence was tested using Cox proportional hazards regression, adjusting for potential confounders. In a second sensitivity analysis, we compared the outcomes for the patients age ≥ 60 years vs. adults 18–60 years old, as a clinically meaningful comparison. We also performed the same sensitivity analysis using age

≥ 65 years as cut off point. The overall probability of seizure recurrence in this sample was described using Kaplan-Meier curves.

Potential confounders identified a priori which included the following: disease duration (time from first seizure to epilepsy surgery), preoperative seizure type, seizure frequency prior to surgery, number of co-morbidities, and number of antiepileptic medications at the last follow-up visit. The chart abstraction allowed for completion of data collection with respect to these variables (i.e., $n = 107$). Two surgeons with previously established comparability in post-operative outcomes performed all the anterior temporal lobectomies (Costello et al., 2009). Correlations were performed between covariates to confirm that there was no multicollinearity between the variables included in the regression model. Interaction terms were also tested between age and included potential confounders with a priori suspicion for interaction effect.

Statistical significance for analyses was set at a two-sided alpha ≤ 0.05 . All analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, NC).

2.5. Standard protocol approvals, registrations, and patient consents

This study was conducted under a protocol approved by The Partners Healthcare Institutional Review Board.

3. Results

A total of 107 patients were included in the study and age ranges were specified in quartiles (i.e.: 0%, 25%, 50%, 75%, and 100% represented 19, 30, 37, 47, and 68 years old, respectively). In this sample, 80/107 (74.7%) patients in the younger age group and 27/107 (25.2%) patients in the older age group, which included patients older than 47 years. These patients were followed through a mean of 3.5 (SD: 3.6) years. A total of 35/107 (32.7%) patients with post-operative seizure recurrence were identified.

The baseline demographics and clinical characteristics of the study population according to younger and older age groups are displayed in Table 1. Fig. 1 displays the overall distribution of ages within our cohort.

The mean \pm SD age for young patients was 33.7 ± 7.4 years compared to 54.4 ± 6 years for older patients. Females represented 45/79 (56.96%) younger patients and 12/27 (44.4%) older patients. Older patients lived with epilepsy for longer periods before under-

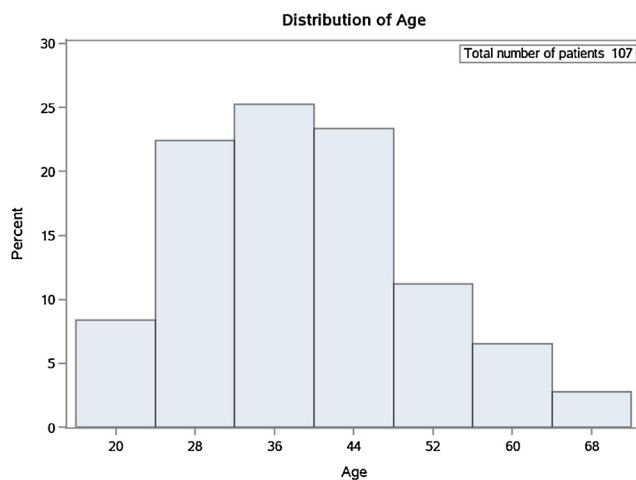


Fig. 1. Distribution of ages within the study cohort. Legend: Age: the bottom of the histogram displays the age categories of patients distributed at 8-years intervals. Percent: the bars represent the proportion of patients within each age category.

Table 1
Baseline characteristics of patients by age group.

Characteristic	Young patients ^a	Old patients ^a	p-value
Mean age (years ± SD)	33.8 ± 7.4	54.4 ± 6	
Mean age at 1st seizure (years ± SD)	16.1 ± 10.9	18.48 ± 18.2	<0.0001
Disease duration (years ± SD)	17.77 (10.7)	35.9 (17.3)	<0.0001
Gender: 106 (%)			0.260
Male	34 (43.04)	15 (55.6)	
Female	45 (56.96)	12 (44.4)	
Race: n = 89 (%)			0.889
White	23 (33.3)	7 (35)	
Non-White	46 (66.7)	13 (65)	
Past medical history: n, (%)			
Birth or development anomaly: n = 102 (%)	4 (5)	0 (0)	0.245
History of head trauma: n = 101 (%)	8 (10.5)	4 (16)	0.502
Family history of seizure: n = 100 (%)	13 (17.3)	0 (0)	0.025
Psychiatric condition: n = 104 (%)	39 (49.4)	9 (36)	0.242
Seizure type n = 103:			0.641
More than one type	12 (15.4)	2 (8)	
Complex partial	15 (19.23)	5 (20)	
Complex partial + secondary generalized	51 (63.4)	18 (72)	
Number of comorbidities: n = 96 (%)			0.0033
0	22 (29.3)	10 (47.6)	
1–3	45 (60)	5 (23.8)	
>3	8 (10.6)	6 (28.6)	
Preoperative seizure frequency ^b : n = 100 (%)			0.320
Seizure free	29 (38.7)	15 (60)	
Rare seizures	20 (26.7)	4 (16)	
Occasional seizures	22 (29.3)	5 (20)	
Frequent seizures	4 (5.3)	2 (4)	
Number of current AEDs ^c : n = 105 (%)			0.9209
0	3 (3.8)	1 (3.8)	
1	24 (30.4)	9 (34.6)	
2	26 (32.9)	10 (38.5)	
3	21 (26.6)	5 (19.2)	
4	5 (6.3)	1 (3.8)	
Operated hemisphere: n = 107 (%)			0.380
Left	52 (65)	15 (55.6)	
Right	28 (35)	12 (44.4)	

^a Old patients defined as ≥46.8 years old (75th percentile). Young patients defined as <46.8 years old.

^b Preoperative seizure frequency was divided into four categories: seizure-free (≤1 seizure per year); rare seizures (>1 per year, but ≤1 per month); occasional seizures (>1 per month, but ≤1 per day); or, frequent seizures (>1 seizure per day).

^c Number of previous anti-epileptic drugs at the epilepsy surgery day.

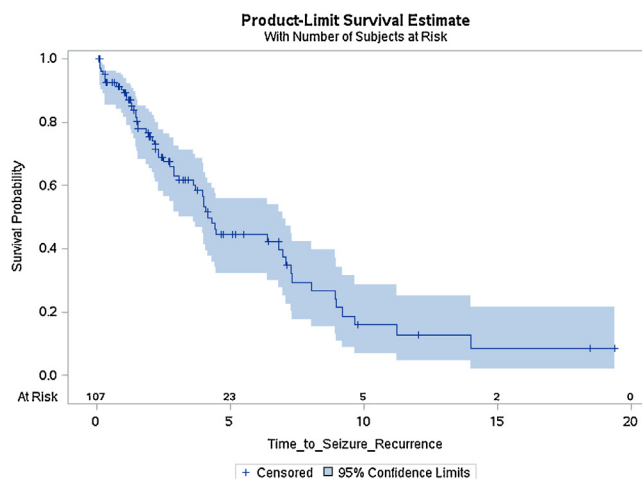


Fig. 2. Kaplan-Meier curve representing the probability of post-operative seizure recurrence among the entire sample through 20 years of follow-up.

Legend: Time to seizure recurrence in years. At risk: the bottom of the graph displays the number of patients that were still being followed at the outlined time-points.

going surgery (disease duration = 35.9 ± 17.3 years) compared to younger patients (17.7 ± 10.7 years), $p < 0.0001$. Age at first life-

time seizure was also higher for older ATL patients, with a mean ± SD age of 16.1 ± 10.9 years for the younger group compared to 18.48 ± 18.2 years for the older group.

There was a higher proportion of participants with a family history of epilepsy in the younger group compared to none in the older group 13/75 (17.3%) v. 0/25 (0%); ($p = 0.025$). The majority of older patients submitted to ATL had no comorbidities, whereas the majority of younger patients had between 1 and 3 comorbid conditions (10/21 (47%) vs. 45/75 (60%); $p = 0.0033$). With regard to seizure type, complex partial seizures with secondary generalization was most common, followed by stand-alone complex partial seizures.

The older patients had higher incidence of complications compared to younger patients (5/27 (18%) v. 1/78 (1.3%), $p = 0.001$) (Table 2). The most serious complication was a perioperative left capsular-lenticular infarction affecting a 56-year-old female treated with left ATL. Self-reported disability was also significantly higher among older patients after surgery.

Kaplan-Meier curve representing the probability of post-operative seizure recurrence among the entire sample through 20 years of follow-up, are shown in Fig. 2. Fig. 3 shows Kaplan-Meier curves comparing the probability of post-operative seizure recurrence among the age groups. During one year, 86/97 (88%) patients

Table 2
Outcomes after anterior temporal lobectomy for hippocampal sclerosis by age group.

Outcome	Young patients ^a	Old patients ^a	p-value
Follow-up length (years ± SD)	3.6 (3.5)	2.9 (2.5)	0.332
Engel categories ^b (%)			0.877
1A	46 (57.5)	17 (62.9)	
1B	8 (10)	3 (11.1)	
2	20 (25)	6 (22.2)	
3	3 (3.7)	0 (0)	
4	3 (3.7)	1 (3.7)	
Complications, n = 105 (%)	1 (1.3)	5 (18)	0.001
Self-reported driving disability, n = 105 (%)			0.014
Yes	46 (58.23)	22 (84.62)	
No	33 (41.77)	4 (15.4)	
Self-reported work disability, n = 105 (%)			0.025
Yes	48 (60.7)	22 (84.6)	
No	31 (39.2)	4 (15.4)	
Employed, n = 89, (%)			0.028
Yes	45 (67.16)	9 (40.9)	
No	22 (32.8)	13 (59.1)	

^a Old patients defined as ≥46.8 years old (75th percentile). Young patients defined as <46.8 years old.

^b Engel classification: Engel Class I: Free of disabling seizures (A: completely seizure free; B: non-disabling, simple partial seizures only; Class II – Rare disabling seizures; Class III – Worthwhile improvement; and Class IV – No worthwhile improvement.

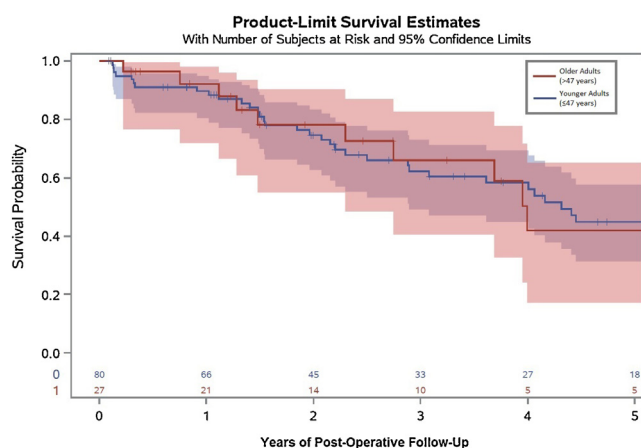


Fig. 3. Kaplan-Meier curve representing the probability of post-operative seizure recurrence among the age groups through 5 years of follow-up.

Legend: At risk: the bottom of the graph displays the number of patients that were still being followed at the outlined time-points. This graph used the follow-up data through 20 years but was truncated at 5 years follow-up for better visualization of specific data points when there was still 5 or more patients in each group. Non-parametric (log-rank test) comparison of the seizure recurrence risk among the age groups showed no statistical significance, $p=0.44$. Blue = Younger age group. Red = Older age group (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

attained seizure freedom, while 22/65 (33.8%) remained seizure free at 5 years.

The relationship between age groups and seizure recurrence was fit using the Cox proportional hazards model, adjusting for disease duration, seizure type, number of co-morbidities, number of current anti-epileptic drugs, and seizure frequency (Table 3). We found that the probability of post-operative seizures was not significantly greater in the older group compared to the younger group (hazard ratio of 0.67 [0.28–1.59]). The number of current anti-epileptic drugs (hazard ratio of 1.58 [1.14–2.19]) was the only statistically significant factor associated with seizure recurrence.

Sensitivity analysis using age as a continuous variable yielded similar results (hazard ratio of 1.00 [0.97–1.04]). The second sensitivity analysis using 60 years as the cut-off also yielded similar

results (hazard ratio 0.62 [0.10–3.7]). Similar results were also found using 65 years as the cut-off (hazard ratio 0.77 [0.07–8.3]).

4. Discussion

This study consisted of a retrospective cohort of adults with epilepsy, who were treated with ATL, in order to determine whether the groups deferred in rate of post-operative seizure-free survival. Our results suggested that for patients with intractable temporal lobe epilepsy due to hippocampal sclerosis, increasing age at the time of surgery does not adversely impact the time to seizure recurrence, adjusting for preoperative seizure frequency, disease duration, seizure type, number of comorbidities and current number of AEDs.

This study included a wider range of patient ages and longer follow up period than is found in most studies of surgical outcomes in epilepsy patients. (Benedetti-Isaac et al., 2013; Costello et al., 2009; Murphy et al., 2010) The follow-up included most patients within the first year, and some for up to 20 years thereafter, which is greater than the traditional post-operative follow-up for surgical outcomes that typically ranges within a 5-year timeframe.

Patients should be appropriately selected for surgical treatment, as the long-term physical, cognitive, social, and neuropsychological consequences of failed treatment can be significant. Many studies have tried to assess the prognostic significance of age at surgery with respect to long-term outcomes, but these results have been conflicting (Benedetti-Isaac et al., 2013; Costello et al., 2009; Murphy et al., 2010).

Our data supports the findings of Acosta et al. who retrospectively examined the results of patients older than 60 undergoing temporal lobectomy and compared them to those under age 60. Although Acosta et al. found comparable safety and efficacy of epilepsy surgery in those 60 years and older, heterogeneous underlying pathology and a small sample size of patients older than 60 (3% of cases) was described (Acosta et al., 2008).

Previous authors reported outcomes in a clinically heterogeneous cohort of patients submitted to various types of epilepsy surgery (Costello et al., 2009; Murphy et al., 2010). These authors did not address the confounding contribution of covariates and did not account for the bias introduced with right-censored data.

A secondary finding of this study is that older patients had a higher incidence of complications (18%). The general risk of any

Table 3
Cox proportional hazard model of seizure recurrence risk after epilepsy surgery.

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Old age ^a	0.673	0.284	1.594
Disease duration	1.014	0.988	1.041
Seizure type categories (reference = more than one type)			
Complex partial seizure (CPS)	1.064	0.443	2.554
CPS with secondary generalization	0.410	0.151	1.111
Number of comorbidities	0.942	0.735	1.206
Number of current anti-epileptic drugs	1.580	1.140	2.190
Seizure frequency categories ^b (reference = frequent seizures)			
Seizure-free	0.282	0.072	1.096
Rare seizures	0.859	0.222	3.333
Occasional seizures	0.612	0.164	2.277

^a Old patients defined as ≥ 46.8 years old (75th percentile). Young patients defined as < 46.8 years old.

^b Preoperative seizure frequency was divided into four categories: seizure-free (≤ 1 seizure per year); rare seizures (> 1 per year, but ≤ 1 per month); occasional seizures (> 1 per month, but ≤ 1 per day); or, frequent seizures (> 1 seizure per day).

operative procedure is greater in older patients, given the effects of aging on organ systems and the increased likelihood of significant concurrent diseases. It has been shown that the risk of complications from epilepsy surgery also correlates with increasing age (Kelemen et al., 2006; Murphy et al., 2010).

In Sweden, a study was conducted using 654 heterogeneous surgical procedures for the treatment of epilepsy and founded a positive correlation between increasing age at the time of surgery (in patients older than 35 years) and postoperative complications (Rydenhag and Silander, 2001). The investigators studied adult and pediatric patients who underwent various procedures and whose epilepsy was caused by a variety of pathologies. In contrast, Murphy et al. only included patients with proven hippocampal sclerosis, subjected all patients to the same operative technique by the same surgeon, included a large number of patients older than 50, and did not demonstrate any greater neuropsychological impairment secondary to anterior temporal lobectomy in older patients (Murphy et al., 2010). The difference might be partially explained by the population characteristics, measurements and operational definitions of complications.

Another finding of this study is that older adults self-reported more driving and work disabilities compared to younger adults. In accordance with previous studies, older adults living with epilepsy appear to be more concerned with social life and work restriction (Griffith et al., 2006; Martin et al., 2005). In fact, the elderly patients could have disabilities not related to the epilepsy. Nevertheless, the findings are within the wide range of previously reported rates of unemployment and social disability before and after surgery and even among those who did not undergo surgery (Carreño et al., 2011; Seiam et al., 2011). This variation highlights the unmet need for validated outcomes with a focus on patient's perspectives and a rigorous assessment of pre versus post-op disability. It would be more useful to prospectively measure pre versus post-operative disability scores using validated scales to explore the impact of age on disability scores adjusted for individual's baseline scores.

An important limitation of this study is the absence of an objective assessment of disability at baseline. For instance, it would be useful to have a disability score at baseline and at every follow-up visit. Another unmeasured information is the type of work that each patient was unable to perform. In our favor, disability in the care of patients with epilepsy is essentially a subjective measure and only the self-reported degree of disability represents each individual's burden.

Another limitation of this study is that the proportion of older patients was relatively lower than younger patients. Age was modelled as a binary variable divided between younger and older patients with a cut-off at the fourth quartile (47 years) to provide an adequate representation of "older age." While the age group

between 47 and 60 years old is not typically considered elderly or at higher risk for co-morbidities or procedural complications, the population of TLE patients undergoing ATL are historically skewed towards younger decades of life. This is because ATL patients are typically selected by an interdisciplinary committee to maximize the likelihood of improved post-operative functional outcome. To illustrate the robustness of the study findings, sensitivity analysis yielded similar results while using age as continuous variable and also using age as a binary variable (i.e.: "older age" being above 60 or 65). Although the sample size is limited, it does however, represent a sizeable sample of older adult TLE patients undergoing ATL, given how infrequently this procedure is performed in older patients in most medical centers (Brodie and Stephen, 2007; Murphy et al., 2010; Ruggles et al., 2001).

The literature remains controversial about the predictors of outcomes after ATL (de Tisi et al., 2011; Murphy et al., 2010; Simasathien et al., 2013), (Costello et al., 2009; de Tisi et al., 2011; Mcdermott et al., 2013; Murphy et al., 2010; Simasathien et al., 2013). Heterogeneity of patient population is one of the main limitations of most of these studies. We selected a single procedure type (i.e., anterior temporal lobectomy) instead of multiple procedures (e.g., frontal lobe surgeries, lesionectomies) to allow for a less biased comparison among age groups. Also, previous studies included other causes of temporal lobe epilepsy such as hippocampal sclerosis but did not adjust for seizure types. In our multivariable analysis, we included seizure type as a covariate to try to account for the fact that patients may have different risk for seizure recurrence depending on their seizure type (e.g., simple partial vs. complex partial with secondary generalization).

We found that older age at the time of surgery was not associated with higher probability of seizure recurrence, after adjusting for pertinent covariates. In some cases ATL does not achieve complete seizure freedom but it still results in a significant reduction in seizure frequency which leads to improved health-related quality of life for patients with TLE (Martin et al., 2005).

The difference in probability of seizure recurrence increases substantially between younger and older age groups as the time of observation increases. This effect is likely due to accumulation of age-related diseases, time-varying dose adjustments and other factors that we were unable to account for in the hazard model. However, the results are concordant with prior literature (Elsharkawy et al., 2008, 2009; Massager et al., 2013).

Finally, there may have been unmeasured bias impacting the pre-surgical decision making process such as the different perspectives of multiple stakeholders (e.g.: patients, caregivers, neurosurgeons, neurologists). In fact, the selection process for elderly versus young patients for surgery appears to be subjectively different. For instance, 47.6% of older patients submitted to ATL

had no known comorbidities in our sample, in contrast to 60% of younger patients that had between 1 and 3 comorbid conditions. This illustrates our center's likelihood to select younger patients for surgery with a lower threshold, similar to many other centers. To address that, the multivariable analysis accounts for number of comorbid conditions.

5. Conclusion

Age at time of anterior temporal lobectomy (ATL) for mesial temporal sclerosis (MTS) does not appear to be an independent predictor of seizure freedom. However, patients older than 47 years appeared to have a higher risk of complications and disabilities in driving and working. Future studies will benefit from a greater focus on patient-centered outcomes such as independent days gained, long-term work and social disabilities.

Funding

None.

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