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SHORT RESEARCH ARTICLE

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Histopathologic substrate of drug-resistant epilepsy in older adults and the elderly undergoing surgery

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Summary

Patients 60 years or older are one of the highest risk age groups for development of epilepsy. Clinical and neuroimaging analysis has typically accounted for etiology in two-thirds of these patients, while the data on histopathology are lacking. We provide the first analysis of the histopathological substrates underlying drug-resistant epilepsy (DRE) in older adults/elderly patients who underwent resective epilepsy surgery (RES) at Cleveland Clinic. A total of 78 patients (mean age ± standard deviation: 64.7 ± 3.7 years; 59% female) were included in the study. The most common pathologies included hippocampal sclerosis (HS; 35.9%; all visible on magnetic resonance imaging [MRI]), focal cortical dysplasia (FCD; 25.6%) and remote infarct/ischemic changes (12.8%). Underlying pathology did not differ significantly between the patients achieving a good seizure outcome (Engel class I; 77% [47 of 61 patients]) and the rest of the cohort. With one exception, all MRI-negative cases had FCD type Ib. A receiver-operating characteristic (ROC) curve analysis found a significant association ($P = 0.002$) between seizure-onset age and HS, whereby the odds of its presence were reduced by 4% for every 1 year increase in the age at seizure onset. The model showed that the age cutoff for seizure onset predicting HS was 43 years, with a negative predictive value of 81.6%. None of the 14 patients with late-onset epilepsy (≥60 years of age) were found to have HS; they mostly had acquired lesions. Our study provides histopathologic evidence for the diminished role of late-onset HS in DRE in older adults/elderly who undergo RES.

KEYWORDS

elderly, epilepsy, geriatric epilepsy, hippocampal sclerosis, neuropathology

1 | INTRODUCTION

Population aging is a universal phenomenon and the number of elderly individuals (≥65 years) in the world will more than double by 2050.[1] This provides unique challenges in epilepsy care as the incidence of unprovoked seizures and new-onset epilepsy is known to rise rapidly after the age of 60 years.[2] The etiology underlying this rapid increase in the incidence of epilepsy has been described using a combination of clinical and neuroimaging data[3,4] but remains unknown in

up to one-third of cases.[3] To the best of our knowledge, no study in the literature has specifically analyzed the pathologic substrates underlying epilepsy in the older adult/elderly (≥60 years of age in this study) population.

We recently showed an incremental increase in the number of older adults/elderly patients undergoing resective epilepsy surgery (RES) over the last 15 years at our center.[5] They achieved seizure-freedom rates comparable to the younger adults (25-45 years).[5] This trend of improving RES utilization is less likely a simple manifestation of increased epilepsy incidence in this population then a growing willingness to offer the therapy to older adult/elderly patients. This, in-turn, is likely due to the maturing of epilepsy surgical programs from years of experience of performing RES in younger adults combined with a healthier elderly population.

RES in this patient population provides an opportunity to study the underlying epileptogenic pathology of drug-resistant epilepsy (DRE) in the older adult/elderly. Therefore, the primary aim of our study is to describe the pathology underlying DRE in the older adult/elderly patients undergoing RES and compare it between subgroups divided by age at seizure onset. We also investigated if the age at seizure onset could predict the specific underlying pathology responsible for DRE in the study cohort.

2 | METHODS

After institutional review board approval, we performed a retrospective cohort study by identification of individuals from our prospectively maintained RES database, who underwent RES for DRE at the age of ≥60 years between January 1, 2000 and March 30, 2018. A patient was diagnosed as having developed DRE based on the definition proposed by the International League Against Epilepsy (ILAE).[6] Therefore, patients with a history of seizures who were undergoing tumor resection, without having failed two well-chosen and dosed antiepileptic drugs (AEDs) were excluded. The microscopic slides from the en bloc tissue obtained from the RES were reviewed by a dedicated neuropathologist (R.P.) in all cases to establish the histopathologic diagnosis, which was the primary objective of the study. Patients with an insufficient tissue sample from RES were excluded. ILAE hippocampal sclerosis[7] (HS) and focal cortical dysplasia (FCD)[8] classification was used. Demographic and clinical data were extracted from the electronic medical record review. We subdivided the study into two groups based on the age at seizure onset: late-onset epilepsy (≥60 years of age) and "earlier onset" epilepsy (<60 years of age). These two subgroups were compared against each other based on demographic, clinical, and pathologic variables. Seizure outcome after RES was classified based on Engel's criteria for patients who had at least 1 year of clinical follow-up. We compared the distribution of pathology between patients who achieved Engel class I outcomes and the rest of the study population (Engel class II-IV or insufficient clinical follow-up [<1 year]).

2.1 | Statistical methods

Categorical variables were described using frequencies and percentages. Continuous variables were described using means and standard deviations (for normally distributed data) or medians and quartiles (for non-normal distributions). Group differences among earlier- and late-onset epilepsy were examined using Student *t* test or chi-square analysis. A receiver-operating characteristic (ROC) curve analysis was performed to evaluate the overall diagnostic ability of age at onset to predict each pathology. Discrimination was evaluated using the area under the ROC curve (AUC). The best age cutoff to predict a pathology was determined based on the highest combination of sensitivity and specificity. Sensitivity and specificity, along with positive and negative predictive values, were calculated for various ages. Analyses were performed using SAS software (version 9.4; Cary, NC).

3 | RESULTS

A total of 78 patients (59% female) were included in the study. The mean age at seizure onset was 37.4 (±20.8) years and the mean age at the time of RES was 64.7 (±3.7) years. Temporal lobectomy was the most common RES (56 patients; 71.8%) followed by frontal (12 patients; 15.4%), multilobar (6 patients, 7.7%), and parietal (3 patients, 3.8%) resections and 1 hemispherectomy. A total of 14 patients (17.9%) were found to have late-onset epilepsy. As noted in Table 1, the late-onset group was slightly, but significantly, older (66.9 ± 2.7 years) at the time of RES compared to the "earlier-onset" group (64.2 ± 3.7 years) and had epilepsy for a much shorter (4.1 ± 3.0 years) duration ($P < 0.001$). The two subgroups were otherwise not statistically different, including seizure outcomes, with the exception of a higher likelihood of the "earlier-onset" group to undergo temporal lobectomy (odds ratio [OR] 4.76, 95% confidence interval [CI] 1.42-16; *P* 0.01).

The most common pathologies included HS (35.9%), FCD (25.6%), and remote infarct/ischemic changes (12.8%; Table 2). HS was present in 28 of the 56 (50%) temporal lobectomies. Seventeen of 28 patients (60.7%) with HS had associated FCD as well (ILAE FCD type IIIa; 11 morphologically resembled FCD 1b and 6 resembled FCD Ic). One patient each had HS and FCD associated with remote infarct. All histopathologically confirmed HS was noted on the magnetic resonance imaging (MRI). MRI findings did not match pathology in 14 cases (18%), including 11 patients (14.1%) with nonlesional MRI, all found to have FCD Ib except one patient with gliosis. Of the

TABLE 1 Demographic, disease, and outcome variables in the study population as well as subgroups based on seizure onset (earlier-onset [<60 years of age] epilepsy and late-onset [≥60 years of age] epilepsy)

Characteristic	Study population (%) (N = 78)	Seizure onset <60 y (%) (n = 64)	Seizure onset ≥60 y (%) (n = 14)	Odds ratio[a] (95% confidence interval)	*P*- value
Gender (female)	46 (59)	41(64.1)	5 (35.7)	3.2 (0.96-10.72)	0.1
Age at surgery (y)	64.7 (±3.7)	64.2 (±3.7)	66.9 (±2.7)	N/A	0.01
Age at seizure onset (y)	37.4 (±20.8)	31.8 (±18.8)	62.8 (±2.9)	N/A	<0.001
Duration of epilepsy (y)	27.3 (±20.1)	32.4 (±18.6)	4.1 (±3.0)	N/A	<0.001
Duration of follow-up (y)	2.2 (±2.1)	2.3 (±2.0)	1.9 (±2.2)	N/A	0.54
Side of RES (Left)	36(46.2)	31(48.4%)	5 (35.7)	1.7 (0.5-5.6)	0.55
MRI					
Unilateral	62 (79.5)	50 (78.1)	12 (85.7)	0.59 (0.11-2.98)	0.72
Negative/bilateral	16 (20.5)	14 (21.9)	2 (14.3)		
Intracranial EEG evaluation					
Yes	19 (24.4)	16 (25)	3 (21.4)	1.22 (0.3-4.94)	1
No	59 (75.6)	48 (75)	11 (78.6)		
Surgical resection					
Temporal	56 (71.8)	50 (81.3)	6 (42.9)	4.76 (1.42-16.0)	0.01
Extratemporal/multilobar	22 (28.2)	14 (18.7)	8 (57.1)		
Follow-up ≥1 y	61 (80.2)	52 (81.3)	9 (64.3)	2.41 (0.68-8.49)	0.28
Seizure outcome[b] (n = 61)					
Engel class I	47 (77)	41 (78.8)	6 (66.7)	1.86 (0.4-8.67)	0.67
Engel class II-IV	14 (23)	11 (21.2)	3 (33.3)		

RES, resective epilepsy surgery; EEG, electroencephalography; MRI, magnetic resonance imaging. Time duration presented by means (± standard deviation[a] of "seizure onset <60 y" and "seizure onset ≥60 y" groups. [b]Patients who had ≥1 y of clinical follow-up).

rest (n = 3), one patient with temporal pole encephalocele on MRI was found to have gliosis. The other two were thought to have HS on MRI; one of them was false positive based on histopathologic analysis (found to have FCD Ib), and the other patient only underwent a superior temporal gyrus resection.

The ROC analysis found that the presence of FCD ($P = 0.9$), remote infarct ($P = 0.32$), and gliosis ($P = 0.58$) could not be predicted better than chance alone using the age at seizure onset. However, ROC analysis for HS showed a significant association with seizure-onset age, with an OR of 0.96 (95% CI 0.94-0.99, $P = 0.002$). The area under the ROC curve was 0.733. The best cutoff for predicting HS pathology was 43 years (shown in Figure 1), with a sensitivity and specificity of 0.75 and 0.62, respectively. The positive predictive value (PPV) of 43 years at age cutoff for the presence of HS was 0.525, whereas its negative predictive value (NPV) was 0.816.

The comparison of underlying pathology between late-onset and "earlier-onset" epilepsies, as noted in Table 2, shows that none of the 14 patients with late-onset epilepsy had HS. This is remarkably in contrast ($P = 0.001$) to the "earlier-onset" group, where 43.8% of patients had HS as the underlying pathology for their DRE. Apart from HS, no other pathology was significantly different between the two subgroups. However, a trend toward a higher likelihood of presence of gliosis in the late-onset epilepsy group ($P = 0.07$) was noted. Details about underlying pathology and individual clinical information about the late-onset epilepsy subgroup are provided in Table 3. As a corollary to the above-mentioned results of RES type, the late-onset epilepsy group was significantly more likely to undergo extratemporal resections ($P = 0.01$, Table 1). The details in Table 3 shows that 4 (28.5%) of these patients required multilobar resection and two were found to have remote infarct.

There were 61 patients (80.2%) with at least 1 year of clinical follow-up and 47 (77%) of them achieved Engel class I outcome at the last follow-up. There was no significant difference in pathology between patients with Engel I outcome and the rest of study population (Table S1).

4 | DISCUSSION

Although some case series have investigated patients older than 50 years undergoing RES, only two studies have specifically looked into older adult/elderly (≥60 years) individuals.[9,10] They found that HS was the most common underlying pathology, accounting for little more than 50% (11 of 19

TABLE 2 Details of various surgical pathology in patients undergoing RES at the age of 60 years or older

Pathology	Study population (%) (N = 78)	Seizure onset <60 y (%) (n = 64)	Seizure onset ≥60 y (%) (n = 14)	Odds ratio (95% CI[a]; *P*-value)
Hippocampal sclerosis	28 (35.9)	28 (43.8)	0	N/A ($P = 0.001$)
ILAE type Ia	7			
ILAE type Ib	17			
ILAE type 2	2			
ILAE type 3	2			
Hippocampal sclerosis with FCD (or FCD ILAE IIIa)	17			
Focal cortical dysplasia (excluding ILAE IIIa)	20 (25.6)	18 (28.1)	2 (14.3)	0.43 (0.09-2.1; 0.34)
ILAE Ib	16			
ILAE Ic	2			
ILAE IIb	1			
ILAE IIId	1			
Remote infarct/ischemic damage	10 (12.8)	7 (10.9)	3 (21.4)	2.22 (0.5-9.94; 0.37)
Gliosis	10 (12.8)	6 (9.4)	4 (28.6)	3.87 (0.92-16.19; 0.07)
Cavernoma	4 (5.1)	3 (4.7)	1 (7.1)	1.56 (0.15-16.3; 1)
Tumor[c]	3 (3.8)	1 (1.6)	2 (14.3)	10.5 (0.89-125.2; 0.08)
Miscellaneous[b]	3 (3.8)	1 (1.6)	2 (14.3)	10.5 (0.89-125.2; 0.08)

FCD, focal cortical dysplasia; RES, resective epilepsy surgery; ILAE, International League Against Epilepsy.
[a]CI, confidence interval; N/A, not applicable. [b]Miscellaneous = One each of a benign cyst, an atypical lymphocytic infiltrate (both in late-onset subgroup) and hamartia.
[c]Tumor = One each of oligodendroglioma (World Health Organization [WHO] grade III), ganglioglioma (WHO grade I), diffuse astrocytoma (WHO grade II).

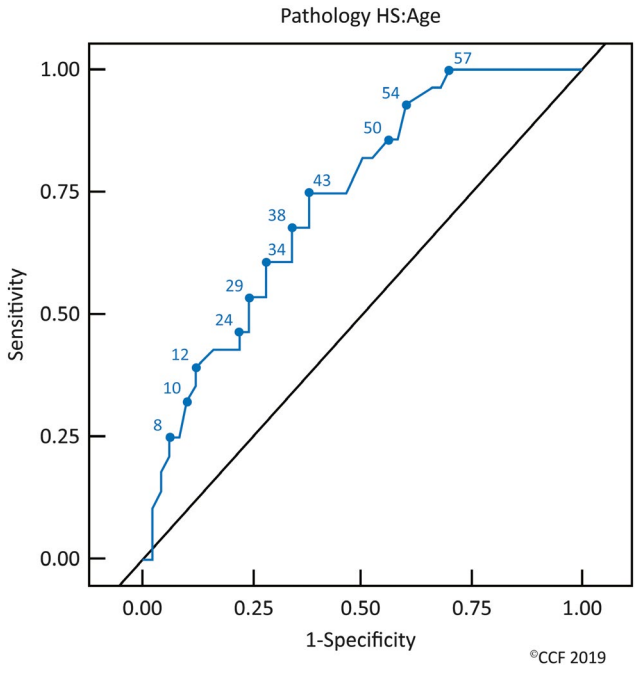

FIGURE 1 Receiver-operating characteristic (ROC) curve for hippocampal sclerosis (HS). Points labeled by the age of epilepsy onset. Age of 43 years was the best cut-off for predicting HS

combined cases) of cases.[9,10] Apart from the above, the tissue histopathology analysis from RES has typically been reported in young adults. The literature now includes single case series of several thousands of patients.[11,12] Therefore, the existing literature serves as a good historical comparison group to our older adult/elderly cohort, obviating the need for a separate young adult cohort in our study.

In this first dedicated study of the pathologic substrates underlying DRE in older adult/elderly patients undergoing RES, we found that HS (with or without associated FCD) accounts for around one-third of all such cases and half of all the temporal lobe resections. The latter proportion is comparable to 52% of 2812 temporal lobectomies found to have HS on pathologic examination.[11] However, the recently published description of the histopathologic findings from 9523 RES cases, including almost 7000 adults,[12] found HS to account for 44.5% of all adults undergoing RES in comparison to 35.9% in our cohort. This difference may be secondary to the two major differences among the adult populations of our studies: a much later age at seizure onset in the current cohort (37.4 ± 20.8 years) compared to the above study (15.0 ± 11.8 years) and an even larger age difference at the

TABLE 3 Epilepsy- and pathology-related findings in patients with late-onset (≥60 y) epilepsy

Patient no., Gender	Age at epilepsy onset	Age at RES	Baseline MRI	Type of RES	Pathology
1, F	60	65	Negative	Frontal	FCD Ib
2, M	60	72	Unilateral	Temporal	Remote infarct
3, M	60	66	Unilateral	Frontal	Cavernomas
4, M	61	66	Unilateral	Frontal	Astrocytoma
5, M	61	62	Unilateral	Multilobar	Oligodendroglioma
6, M	61	68	Unilateral	Multilobar (perirolandic)	Atypical lymphocytic infiltrate
7, M	62	65	Negative	Temporal	Gliosis
8, F	62	68	Unilateral	Multilobar	Remote infarct
9, F	63	67	Unilateral	Parietal	Benign cyst
10, F	64	65	Unilateral	Temporal	Gliosis
11, M	64	64	Unilateral	Temporal	Gliosis
12, M	64	67	Unilateral	Temporal	Gliosis
13, F	66	69	Unilateral[a]	Temporal	FCD Ib
14, M	71	72	Unilateral	Multilobar	Remote infarct

[a]False-negative: MRI suggested HS. FCD, focal cortical dysplasia; F, female; M, male; RES, resective epilepsy surgery.

time of RES (35.2 ± 11.2 years[12] vs 64.7 ± 3.7 years in our study). This suggests that HS may be less often noted in DRE among older adults/elderly who undergo RES compared to young adults.

Prior investigation into the predictors for the presence of HS found an earlier age at seizure onset to be a significant factor.[13] Of interest, the authors in the later study modeled the probability of presence of HS based on seizure onset from 1 to 40 years of age and found it to be <10% for patients with onset after the age of 40 years. However, they studied young adults (31.1 ± 8.9 years) with early age at seizure onset (12.1 ± 10.8 years). By virtue of being a study in the older adults/elderly, our study had a unique sampling of the widest possible range of age at seizure onset in a single cohort. This allowed us to study the association between age at seizure onset and the underlying pathologic substrate. We found that for each year of increase in the age at seizure onset, the odds of underlying pathology to be HS decreased by 4% (OR 0.96, CI 0.94-0.99, $P = 0.002$). This model showed that the best cutoff age at seizure onset to predict a significantly low likelihood of underlying pathology to be HS was 43 years. Although 52.5% of patients with seizure onset prior to the age of 43 were found to have HS, only 18.4% with a later onset had this pathology. Almost one in every five patients in our study belonged to the late-onset epilepsy group and none of them were found to have HS. Similar lack of HS was noted in a recent neuroimaging-based analysis of 79 elderly patients with epilepsy onset after the age of 65 years.[14] These findings support the observation that HS may be early postnatal pathology,[15] with seizure onset stretching into the 40s. On the other hand, the effect of a remarkably shorter duration of epilepsy in the late-onset group on the absence of HS is unknown and open to interpretation. Similar to the recently reported analysis of ILAE classification–based HS subtypes and outcomes by our group, where 79% of 307 HS cases had associated FCD,[16] a large majority (60.7%) of current cohort also has similar findings.

In addition, as noted in Tables 2 and 3, our data suggest that late-onset epilepsies are due mainly to later acquired pathologies. Infarcts or strokes lead to epilepsy in one-third to one half of all elderly patients, followed by tumors, accounting for 16%-36% of cases.[3,4] Among 14 patients with late-onset epilepsy in our study, half were found to have remote infarcts or gliosis and 21% had tumor or cavernoma. The ROC analysis for rest of the pathologies was nonsignificant, which may be due either to the low number of patients in each pathology group or a true lack of interaction between these pathologies and the age at onset.

One of the limitations of our study is the small number of patients with late-onset epilepsy who underwent RES. We have shown previously that the mean delay from epilepsy onset to RES in the older adults/elderly is 28 years.[5] Such long delay along with reported higher response rate to AEDs in the elderly[3,17] may be a reason behind the above limitation. As most of the patient in this cohort are referred for RES,[5] we lack the data on the exact time point at which the patient actually failed two well-chosen and properly dosed AEDs (in other words, developed DRE[6]). In absence of such data, it may be argued that late-onset epilepsy may still be secondary to HS but takes a much longer time to become DRE and therefore is not present in our cohort of patients undergoing RES.

Cognitive decline with aging, especially in patients with longstanding epilepsy treated with AEDs, is a major concern. Recent analysis of patients undergoing temporal lobectomy after the age of 50 years showed "epilepsy-related tauopathy" contributing to accelerated cognitive decline.[18] Although this is of great scientific interest, the goal of the current study was not to analyze dementia-related markers like β-amyloid or tau through immunohistochemical staining. These staining procedures are not part of the standard histopathologic analysis of RES tissue at our center, irrespective of the age of a patient. Of note, we have previously reported no significant differences in neuropsychological outcomes in the older adults/elderly compared to younger adults after RES, except for confrontational naming.[5]

In conclusion, our findings provide histopathologic evidence of a diminished role of HS as a pathologic substrate in DRE in the older adults/elderly. Each year increase in the age at seizure onset reduces the odds of HS as an underlying pathology by 4%, and patients with seizure onset after the age of 43 years are significantly less likely to have HS as the underlying cause for their DRE. Conversely, this also highlights that underlying HS may lead to seizures much later (up to fifth decade) in life as well. Patients with late-onset epilepsy lacked HS and as suggested by neuroimaging findings in the past, were found to have remote stroke, gliosis, or tumor as the underlying pathology. Future histopathologic studies, exclusively from late-onset epilepsy, are required to understand the etiopathogenesis of epilepsy in this most vulnerable age group.

DISCLOSURE

Vineet Punia, James Bena, Jorge Gonzalez-Martinez, William Bingaman, Imad Najm, Andrey Stojic, and Richard Prayson report no disclosures. 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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