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The neurophysiology and seizure outcomes of late onset unexplained epilepsy

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HIGHLIGHTS

- Late onset unexplained epilepsy LOUE is pharmacosensitive with 8% drug resistant.
- In patients with discharges, LOUE is mostly temporal, with left predominance.
- As compared to controls, patients with LOUE have more vascular risk factors.

ABSTRACT

Objective: To investigate neurophysiologic and neuroimaging characteristics of patients with late onset unexplained epilepsy (LOUE).
Methods: We performed a retrospective chart review of elderly patients with ICD9 diagnosis codes consistent with epilepsy/seizures. Inclusion criteria included unprovoked seizures, and absence of cortical lesions on magnetic resonance imaging (MRI). Electroencephalograms (EEGs) findings were also analyzed. MRI images were scored for degree of white matter hyperintensities (Fazekas Scale) and mesial temporal atrophy (MTA). Vascular risk factors, and Framingham Heart Study general cardiovascular disease (FHS-CVD) risk scores were compared to controls from the Harvard Aging Brain study (HABS).
Results: We identified 224 LOUE patients and 8% were drug resistant. Epileptiform abnormalities were captured on EEG in 35%. The location was temporal with left sided predominance in 49%. Fazekas scale consisted of 25% beginning of confluent lesions, and 10% large confluent lesions. MTA scores consisted of 21% moderate-severe hippocampal atrophy. LOUE patients had on average a 2.3% (adjusted), 7.4% (unadjusted) increased FHS-CVD score.
Conclusions: Our findings highlight LOUE as pharmacosensitive and left temporal predominant. Given the higher prevalence of vascular risk factors, investigations are needed to study their role in pathophysiology.
Significance: Physicians caring for patients with LOUE should evaluate for vascular risk factors and investigate the presence of hippocampal atrophy.

1. Introduction

The incidence of epilepsy increases with age, and its prevalence is projected to continuously rise (Hauser et al., 1991). By the age of 75, the prevalence of epilepsy is twice the rate of younger adults (Hauser et al., 1991) and can reach 7.7% in nursing home residents (Birnbaum et al., 2017). Epilepsy in the elderly has been tied to increased per patient per month costs, inpatient admissions and readmissions as well as mortality (Lhatoo et al., 2001; Fitch et al., 2019). The most common etiologies in the elderly include cerebrovascular disease, neurodegenerative conditions, and neoplasms (Ghosh and Jehi, 2014). However, 25–50% of cases do not have an identifiable etiology and have late onset unexplained epilepsy

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(LOUE) (Luhdorf et al., 1986; Hauser et al., 1993). LOUE remains a poorly understood entity, and its neurophysiology and seizure outcomes have not been well described. The current prevailing hypothesis is that LOUE is tied to occult cerebrovascular disease (Gibson et al., 2014). In addition, seizure outcomes have not been well described, and it is unclear if patients also have rates of drug resistance of up to 30% similar to other epilepsy cohorts (Kwan and Brodie, 2000).

In the current study we aimed to retrospectively identify patients with LOUE, evaluate their vascular risk factors at time of presentation, and assess their neurophysiologic features and seizure outcomes. We hypothesized that LOUE patients would have more vascular risk factors, and that neuroimaging features would correlate with the presence of focal slowing or epileptiform abnormalities on electroencephalogram (EEG).

2. Methods

2.1. Cohort identification

We performed a retrospective chart review covering a 10-year period (2005–2015) of outpatient and inpatient records at Brigham and Women's Hospital and Faulkner Hospital using a research patient data repository (RPDR) tool (Nalichowski et al., 2006). The search was restricted to patients equal to or older than 65 years, who had ICD9 diagnosis codes consistent with epilepsy (345.x), seizure disorder (780.39) or transient alteration of awareness (780.02). Patients were included if age of onset was ≥65. Each chart was then individually reviewed including clinical notes, neuroimaging results, and EEG findings. The etiologies were then divided into cerebrovascular, neoplastic, toxic/metabolic, traumatic, infectious, and unexplained (Supplementary Table 1). Given that the diagnosis of epileptic seizures is difficult later in life, we only included patients who met at least one of the following set of requirements: 1- At least one witnessed generalized tonic clonic seizure; 2- transient neurologic symptoms not explained by any other etiology and an epileptiform EEG; 3- recurrent stereotyped neurologic symptoms that decreased in frequency with antiseizure medications (ASM) treatment. We only included patients in the unexplained category, if no clear provoking factors or etiologies were identified for the seizures/epilepsy, if they had a 1.5 T or 3 T magnetic resonance imaging (MRI) of the brain during their work up with no identifiable cortical lesions (lacunar strokes were included) and did not carry a clinical diagnosis of dementia by their treating physician. The study was approved by the Brigham and Women's Hospital IRB.

2.2. Clinical and neurophysiologic data

Data extracted included age at first seizure, first seizure semiology and state during first seizure (wakefulness or sleep), history of depression or anxiety disorders, family history of epilepsy or dementia. We also assessed number of ASMs used during the follow-up period and how many patients were drug resistant based on International League Against Epilepsy criteria at last follow-up if they were followed for at least a year (Kwan et al., 2010). We looked at all EEGs done during the follow-up period at our institution; all studies were reviewed by a board certified epileptologist. We noted the findings of the first routine 10–20 system EEG (generalized slowing <8 Hz, focal slowing, epileptiform or not), and whether epileptiform abnormalities or seizures were captured during the follow-up period. The localization of epileptiform abnormalities was divided into frontal, temporal, or posterior quadrant (includes parietal and occipital) based on the location of the electrode with the maximal electrical activity. We also identified whether the patient was diagnosed with dementia by their treating physician during the follow up period.

2.3. Vascular risk factors

We assessed the following vascular risk factors at time of first seizure: treatment for hypertension, current smoking, diabetes, body mass index, and systolic blood pressure (first blood pressure measurement obtained during the outpatient appointment after the seizure), and obstructive sleep apnea. We compared vascular risk factors, and family history to subjects ≥65 years old recruited to the Harvard aging brain study (HABS) (Dagley et al., 2017), a study following cognitively normal older adults without any known neurological conditions affecting cognition or behavior, scored 11 or less on the Geriatric Depression

Scale, and had a similar age range to our cohort. For both samples we calculated the Framingham Heart Study general cardiovascular disease (FHS-CVD) risk score (D'Agostino et al., 2008), which provides a 10-year probability of future cardiovascular events (defined as coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure).

2.4. Neuroimaging

White matter hyperintensities (as a marker of cerebral small vessel disease) were assessed on axial FLAIR images from a 1.5 or 3 T MRI performed using the visually-rated Fazekas scale (Wahlund et al., 2001) (0: none or single lesion 1: multiple punctate lesions, 2: beginning of confluency, 3: large confluent lesions). We used the medial temporal atrophy score (MTA) to analyze T1-weighted coronal sections through the level of the pons and examined the following features with a range of 0–4: width of the choroid fissure, width of the temporal horn of the lateral ventricle and the height of the hippocampus (Duara et al., 2008).

2.5. Statistical analyses

Statistical analyses were performed using JMP software (SAS). A 2-sided P-value < 0.05 was considered statistically significant. To compare the vascular risk factors between the LOUE patients and HABS subjects, the independent two sample *t* test was used for continuous variables and Pearson's Chi-squared test for categorical variables. We then performed a multiple linear regression analysis with FHS-CVD as the dependent variable and group (LOUE vs. HABS) as predictor while controlling for age.

Given the limited number of MTA data available due to the absence of coronal sections in several MRI studies, we first compared the age of the patients with and without MTA scores using the independent two sample t test.

In addition to identifying the vascular risk factors in this population, we were also interested in whether the neuroimaging features reflective of vascular and neurodegenerative pathologies correlated with neurophysiologic findings. To determine whether there was a correlation between the MRI and first EEG findings, we performed separate logistic regression with EEG findings (epileptiform, focal slowing, generalized slowing) as dependent variables, and MTA (>1, ≤1) as a categorical predictor, or Fazekas scale as ordinal predictor while controlling for age.

3. Results

3.1. Clinical characteristics

A total of 224 patients were identified from the retrospective review (Supplementary Fig. 1). Patients' average age was

76.4 ± 7.7, median follow up 5.8 years (range 0.2–21.2). The clinical characteristics of the cohort are summarized in Table 1. The patients were diagnosed with seizures based on a witnessed generalized tonic clonic seizure (103/224), a transient neurologic symptom with epileptiform activity on EEG (51/224), and recurrent stereotyped neurologic symptoms responding to an ASM (70/224). Thirty-six patients had a single seizure with 12/36 having an epileptiform EEG.

Seven patients were not started on an ASM. At last follow-up 92% were pharmacosensitive and seizure free; after excluding those who were included in the cohort due to the AED response the pharmacosensitive rate remained high at 90%.

The most common ASM regimen at last follow up consisted of levetiracetam monotherapy (42%), phenytoin monotherapy (11%), lamotrigine monotherapy (10%), polytherapy (16%), and no ASM (16%) (Supplementary Table 1). Sixteen patients were not on ASM at last follow up, 11 were weaned after 1–10 years of seizure-freedom, 4 patients did not tolerate the ASM, and 1 patient felt the seizure frequency and severity was tolerable.

3.2. EEG findings

The first routine EEG was performed within a month of seizure onset in 68% of patients (Table 2), and stage N2 sleep was captured in 50.8% of the studies. Patients whose N2 sleep was captured during the routine EEG were more likely to have epileptiform abnormalities (35.4% vs. 19.4%, p = 0.013). In the 14 patients who had seizures captured on EEG during the follow-up period, 57% were left temporal and 43% right temporal. Two of the seizures were captured on a routine EEG. At last follow-up, 34.8% of patients had a documented epileptiform abnormality on EEG with left temporal predominance 38/78 (Fig. 1). Of the patients followed for at least a year, 46 (23.4%) were ultimately diagnosed with a dementia with an average of 6.1 ± 3.7 years after epilepsy onset. Dementia was diagnosed by the treating neurologist in 39/46, while 7/46 were diagnosed by their primary care physician.

3.3. Vascular risk factors

As compared to the HABS cohort, the patients with LOUE were more likely to have diabetes, obstructive sleep apnea, and receive treatment for hypertension (Table 3). However, they had lower BMI, and systolic blood pressure. The unadjusted FHS-CVD score difference was 7.4% between the groups (Table 3). Using linear regression we found that patients with LOUE had on average a 2.3% higher FHS-CVD score as compared to HABS subjects while controlling for age (p = 0.0055).

Table 1
Clinical characteristics of the cohort.

	N = 224
Age at first seizure in years (mean ± SD)	76.4 ± 7.7
Male/Female	115 (51%)/109 (49%)
Race	
White	186 (83%)
Black	15 (7%)
unknown	22 (10%)
Duration of follow-up in years (mean ± SD)	6.6 ± 4.8
At least 1 year follow-up	196 (88%)
First Seizure Semiology	
GTC	83 (37%)
FIA	86 (43%)
FA	43 (19%)
First seizure occurred during sleep	50 (24%)
At least 1 GTC during follow-up	103 (47%)
Did not tolerate first ASM	76 (34%)
Drug resistant epilepsy at last follow-up	18 (8%)

ASM: antiseizure medication, FA: focal aware, FIA: focal impaired awareness, GTC: generalized tonic clonic.

Table 2
Neurophysiologic characteristics of the cohort.

First EEG epileptiform (n = 219)	57 (26%)
Average number of EEGs during follow-up (range)	2 (0–11)
Generalized slowing on first EEG	42 (19%)
Focal slowing on first EEG	113 (50%)
Temporal (Left/Right/Bilateral)	67 (59%)/11 (10%)/15 (13%)
Fronto-temporal (Left/Right/Bilateral)	4 (4%)/4 (4%)/2 (2%)
Frontal (Left/Right/Bilateral)	1 (1%)/1 (1%)/2 (2%)
Long-term inpatient monitoring obtained	25 (11%)
Ambulatory EEG obtained	32 (15%)
Seizure captured on routine EEG	2 (1%)
Seizures captured on any EEG	16 (7%)

3.4. Neuroimaging

A summary of hippocampal volume (MTA) scores and Fazekas (white matter disease) scores is represented in Fig. 2. Lacunar infarcts were noted in 9.4% of the cohort. There was no difference in age, gender, or EEG findings between those with or without MTA or Fazekas scores. Epileptiform abnormalities were more likely in the absence of mesial temporal atrophy; the odds ratio for having epileptiform abnormalities on first EEG in the setting of MTA score $\leq$1 is 5.7 [95% CI 1.09–29.67, p = 0.02), while controlling for age. Age was also associated with generalized slowing with an odds ratio of 1.13 [95% CI 1.03–1.24, p = 0.004), such that the older a patient is the more likely the patient is to have generalized slowing. No other associations between neuroimaging and EEG findings were identified.

4. Discussion

In this retrospective review of patients with LOUE, we found that seizures were pharmacosensitive in most of the cases, and epileptiform abnormalities when identified had left temporal predominance (49% of those captured). Patients had more vascular risk factors as compared to their peers, and those with more severe medial temporal atrophy were less likely to manifest epileptiform abnormalities on EEG.

4.1. Seizure outcomes

Late onset seizures regardless of etiology are more medically responsive as compared to earlier onset ones (Huang et al., 2016). Several studies have documented seizure response rates >80%; in a study of 90 patients older than 65 with newly diagnosed epilepsy, 84% achieved seizure freedom at last follow-up with medication manipulations (Brodie and Stephen, 2007), and in a cohort of post-stroke epilepsy after the age of 67 only 12.9% were resistant to ASMs(Burneo et al., 2019). Our findings of medication responsiveness in 92% are also not unexpected since in the absence of cortical structural lesions the recurrence risk is lower (Krumholz et al., 2015). In a longitudinal study of patients with longstanding epilepsy, aging was one of the predictors of spontaneous remission (Novy et al., 2013). However, it remains possible that patients were still experiencing seizures but these may have gone undetected due to the subtle semiology in the elderly (Silveira et al., 2011).

We also found that patients with LOUE were more likely to have a family history of seizures as compared to the control population. We believe that one possibility is that a subset of LOUE patients

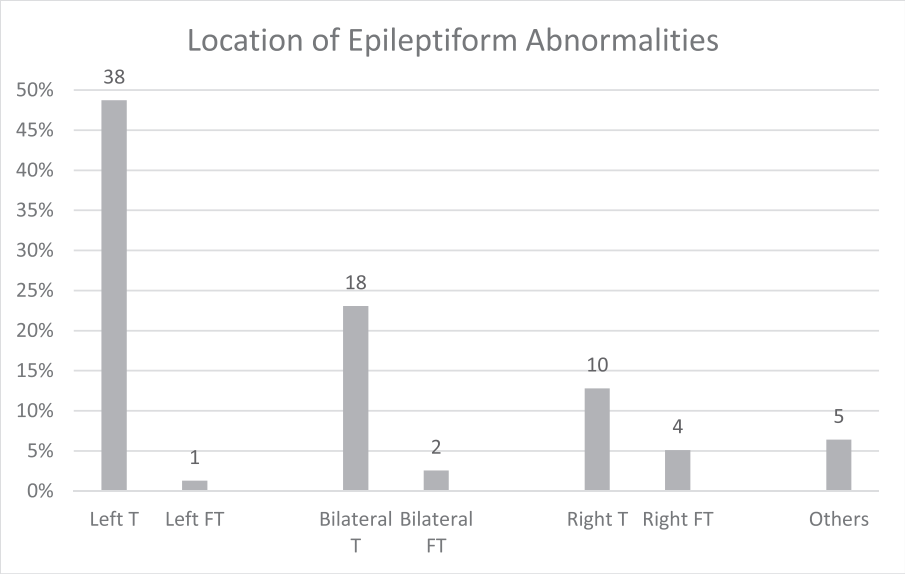

Fig. 1. Location of epileptiform abnormalities documented on EEG during the follow-up period N = 78/219. Y-axis shows percentage of epileptiform abnormalities noted in specific locations, patients were included only once (n on top). Location is a summary of all epileptiform EEG findings. F: frontal, T: temporal.

Table 3
Vascular risk factors in LOUE as compared to HABS.

	LOUE n = 224	HABS n = 293	p-value
Female	109 (49%)	167 (57%)	0.059
Age in years	76.4 ± 7.7	73.9 ± 6.3	<0.001
Race: White	186 (83%)	237 (81%)	
Race: Black	15 (7%)	44 (15%)	
Treatment with antihypertensive medication	187 (83.4%)	150 (51%)	<0.001
Current Smoker	17 (7.9%)	13 (4.4%)	0.107
Diabetes Mellitus	57 (25.4%)	27 (9.2%)	<0.001
SBP	135.0 ± 17.8	140.2 ± 17.6	0.001
BMI	25.8 ± 4.4	26.8 ± 4.4	0.020
FCVDR	40.1 ± 19.8	32.7 ± 19.0	<0.001
Diagnosed with OSA	46 (20.5%)	19 (6.5%)	<0.001
History of depression	85 (37.9%)	47 (16.0%)	<0.001
History of anxiety	84 (37.5%)	16 (5.5%)	<0.001
Family Hx of dementia	26 (11.6%)	75 (25.6%)	<0.001
Family hx of seizures	24 (10.7%)	7 (2.4%)	<0.001

BMI: Body mass index, FCDVR: Framingham Heart Study general cardiovascular disease risk score, HABS: Harvard Aging Brain Study, LOUE: Late Onset Unexplained Epilepsy, OSA: Obstructive sleep apnea, SBP: systolic blood pressure.

already have a lowered seizure threshold due to their family history and the acquired pathologies were thus more likely to cause seizures.

4.2. Location of epileptiform abnormalities and seizures

Interestingly, we found an asymmetry with respect to the lateralization of interictal discharges in this patient sample with the left temporal lobe more commonly involved as opposed to the right. Our findings are consistent with those of Aanestad et al. (2020) who found increased lateralization of interictal discharges with age also with left sided predominance.

One possibility is that the left temporal lobe is more vulnerable in aging. Longitudinal studies have revealed more prominent atrophy in the left temporal lobe over time, especially in patients with amnestic mild cognitive impairment (Yao et al., 2012). The buildup of abnormal proteins in aging including amyloid and tau could be asymmetric in this patient population leading to the expression of a unilateral seizure onset, or the dominant hemisphere might be more prone to become hyperexcitable even with the same burden of pathology. Another possibility is the direction of dipoles in left

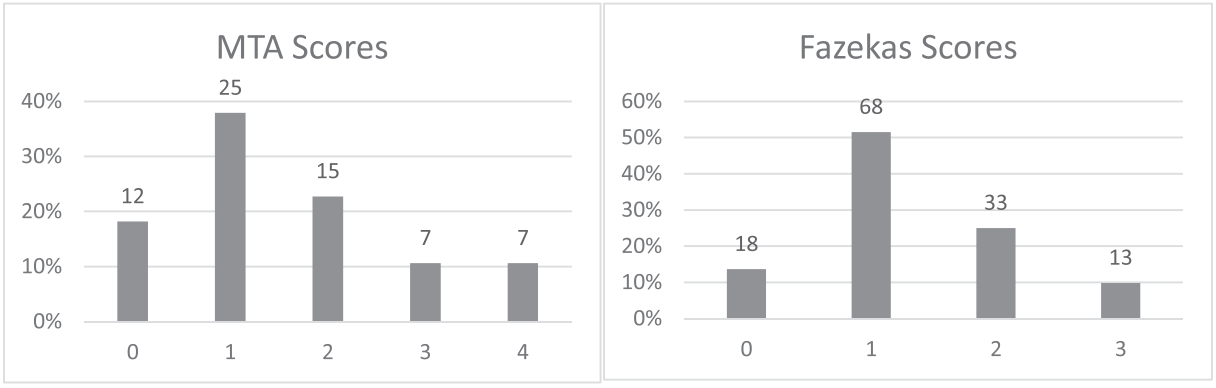

Fig. 2. Neuroimaging findings based on MRI. MTA (mesial temporal atrophy, n = 66): 0: no atrophy, 1: only widening of choroidal fissure, 2: also widening of temporal horn of lateral ventricle, 3: moderate loss of hippocampal volume, 4: severe volume loss of hippocampus. Fazekas scores for white matter hyperintensities (n = 132): 0: none or single lesion 1: multiple punctate lesion, 2: beginning of confluency, 3: large confluent lesions.

vs. right temporal lobe epilepsy; in a prospective study of patients with Alzheimer's disease there was a clear asymmetry with left temporal predominance on EEG but right temporal predominance for discharges detected on magnetoencephalography (Vossel et al., 2016). In the small subset of patients whose seizures were captured in our cohort, this was less striking. Finally, patients might be more likely to present to clinical attention when symptoms are originating from their dominant hemisphere, while right temporal symptoms may be subtle and more difficult to diagnose.

The rates of epileptiform abnormalities are generally lower in the elderly population (Drury and Beydoun, 1998), and the rate of detection can be increased with more prolonged EEGs, especially those which include stage N2 sleep (Tolchin et al., 2017).

4.3. Vascular risk factors

Occult cerebrovascular disease is suspected to be the main etiology behind unexplained seizures (Li et al., 1997). We found patients with LOUE to have higher rates of smoking, treatment with an antihypertensive agent, and sleep apnea. However, they had lower body mass index and systolic blood pressure. We found the Framingham Heart Study general cardiovascular disease risk score to be 7.4% higher in the epilepsy group, but this difference becomes 2.3% when adjusting for age, and the findings need to be interpreted with caution.

Studies have implicated hypertension as risk factors for late onset epilepsy (Ng et al., 1993), and a rat model of hypertension was noted to have more severe seizures as compared to controls (Russo et al., 2017). In a study of mid-life vascular risk factors and the development of epilepsy, hypertension, smoking and diabetes were found to be significantly associated with the development of epilepsy (Johnson et al., 2018). The mechanisms whereby these risk factors may cause seizures is unclear but possibilities include the induction of neuroinflammation, compromise of the neurovascular unit, blood brain barrier disruption, and oxidative stress (Sarkis et al., 2019).

We also found higher rates of anxiety and depression in the LOUE patients, this has been described in temporal lobe epilepsy and there is strong evidence that there is a bidirectional relationship between psychiatric comorbidities and seizures (Pohlmann-Eden et al., 2015).

4.4. Neuroimaging findings

In studies looking at EEG in elderly patients without epilepsy, focal left temporal delta slowing is frequently described and has been linked with cerebral white matter disease (Oken and Kaye, 1992; Inui et al., 2001). We found high rates of left temporal slowing in our cohort, but could not replicate the association with white matter disease. About a third of patients in our study were found to have higher grades of periventricular hyperintensities (Fazekas grade 2–3), in contrast to community based studies with 8–11% in elderly participants (Takami et al., 2012; Wehrberger et al., 2014).

A mesial temporal atrophy score of >1.33 was found to have an 85% sensitivity and 82% specificity for probable Alzheimer's disease (Duara et al., 2008), and in our limited sample with coronal sections, 44% fulfilled this criterion suggesting that in a subpopulation of patients LOUE, Alzheimer's disease pathology may already be prevalent. This is also in line with seizures being a presenting symptom in some patients with Alzheimer's disease (Vossel et al., 2013; Sarkis et al., 2016). Late onset epilepsy has been associated with a 2-fold risk of dementia (Keret et al., 2020), and in our cohort the average time to dementia diagnosis was 6.1 years.

Finally, we found that patients with more severe temporal atrophy were less likely to exhibit epileptiform abnormalities on their first EEG. One possible explanation is the absence of critical hippocampal volume to generate surface EEG epileptiform abnormalities. Certain mesial temporal spike populations may also go undetected on the surface and can only be seen with invasive recordings (Lam et al., 2017). Future studies with volumetric sequences and volumetric analysis of hippocampal volume would be of interest and would help in quantifying the degree of atrophy and its relationship with EEG findings.

4.5. Limitations

Our study has several limitations: it relied on a retrospective chart review based on ICD coding, but we tried to also include broad codes while applying strict criteria for inclusion. There is the possibility of referral bias at a tertiary care center (presence of dedicated cerebrovascular, trauma, and cancer centers).

MRI images were not always available for review, the protocols varied across patients, and coronal sections were only obtained in a subset of patients, thus making it difficult to also determine the frequency of mesial temporal sclerosis. The number of routine and long-term EEGs varied between patients. Our control group consisted of community-dwelling subjects enrolled in the Harvard Aging Brain Study, who enrolled voluntarily and likely have healthier lifestyles, but they were within the same age range and geographic location of our LOUE patients. The HABS cohort may thus represent the "healthiest" comparison group and amplify the differences.

We could not control for educational background and socioeconomic status between groups given the limited data in the LOUE cohort.

5. Conclusion

LOUE is pharmacosensitive and interictal discharges are left temporal predominant. Patients with LOUE have more vascular risk factors as compared to controls and a subset of them have mesial temporal atrophy suggestive of underlying Alzheimer's disease pathology. These findings need to be replicated with larger prospective cohorts.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.08.014.

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