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Cerebrovascular disease burden in late-onset non-lesional focal epilepsy

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ABSTRACT

Purpose: Late-onset non-lesional focal epilepsy, defined as new-onset seizures in patients older than 60 years, is diagnosed increasingly more often in relation to aging of the population. It has been attributed mainly to occult cerebral small vessel disease (SVD), although high levels of evidence to support this notion are lacking. This study aimed to evaluate the burden of leukoaraiosis, a marker of cerebral SVD, and hippocampal atrophy in patients with late-onset epilepsy (LOE).

Methods: Brain magnetic resonance imaging (MRI) studies were retrospectively analyzed by two blinded radiologists. The Fazekas and Scheltens scales were used to assess the degree of leukoaraiosis and hippocampal atrophy in 33 patients with non-lesional LOE, 41 patients with clinical signs of SVD (eg, recent history of transient ischemic attack [TIA] or lacunar stroke), and 26 healthy controls, all > 60 years of age.

Results: Mean age in epilepsy patients was 70.9 (± 6.6) years; 57.6% were men. The history of vascular risk factors was similar in all groups. Median (interquartile range) Fazekas score was 1 (0–1) in the epilepsy group, 1 (0–2) in TIA/lacunar stroke patients, and 0 (0–1) in the healthy group. Degree of leukoaraiosis was milder in epilepsy patients compared to the TIA/lacunar stroke group ($p = 0.004$), and similar to that of healthy controls ($p = 0.593$). Hippocampal atrophy was significantly greater in patients with epilepsy ($p < 0.005$).

Conclusion: These findings suggest that the etiology of LOE is not exclusively related to cerebrovascular disease. Hippocampal atrophy may contribute to the origin of the seizures.

1. Introduction

The overall incidence of epilepsy is approximately 37.4 cases per 100,000 population per year and is increasing in older individuals [1,2]. New epilepsy diagnoses in the elderly population have increased by 3.5 cases per 100,000 over the last 25 years, and are now situated at 30 cases per 100,000 per year [2,3].

Late-onset epilepsy (LOE) usually refers to the development of epilepsy at the age of 60 years or older [4], with cerebrovascular disease and dementia being the main etiological explanations [5]. Although the number of patients with an identifiable cause of epilepsy increases with age [6], nearly 40% remain with an unknown etiology [7]. In the absence of a consistent etiology for this condition, occult cerebrovascular disease detected on magnetic resonance imaging (MRI) has been proposed as a feasible underlying explanation [4,8–10].

Small vessel diseases (SVD) are mainly systemic disorders, often related to arteriolosclerosis and affecting various organs and areas of the body. SVD of the brain can affect the small arteries, arterioles, capillaries, and veins. SVDs produce several MRI signatures, one of which is leukoaraiosis; that is, deep white matter hyperintensities. It is a mainly age-related feature and is particularly associated with hypertension and diabetes [11]. The relationship between LOE and occult cerebrovascular disease has not been well established as there is limited supporting clinical evidence [4,8–10]. In the absence of a manifest stroke, some authors have put forth the theory that epilepsy may be associated with leukoaraiosis; however, there is no consensus on the epileptogenic role of this abnormality [9,10,12,13].

The lack of consistent pathophysiological explanations for LOE has raised several additional hypotheses to explain the epileptogenic process. Some authors believe that occult cortical microinfarcts may be present in these patients [14–16], whereas others have proposed that subcortical epileptogenesis or cognitive decline secondary to lacunar

Abbreviations: LOE, Late onset epilepsy; SVD, cerebral small vessel disease

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stroke may be involved in development of the seizures [12,13,17,18].

LOE patients commonly have temporal lobe seizures with interictal temporal lobe slow waves on electroencephalography (EEG). However, the EEG pattern can also be normal due to a deep origin of the seizures [9,19,20].

Based on the hypothesis that occult cerebrovascular disease may be involved in the origin of LOE, we aimed to determine whether the SVD burden in patients with this condition is similar to that of minor stroke patients. Furthermore, as the mesial temporal lobe is a common site of origin of LOE, we sought to define the degree of hippocampal atrophy in LOE patients as compared to a healthy population.

2. Material and methods

2.1. Study design and populations

From a database including 2225 epilepsy outpatients attended in a tertiary center, we retrospectively selected patients with epilepsy onset at 60 years of age and older with a history of more than one unprovoked seizure, brain MRI showing no evidence of potential epileptogenic lesions, and no other causal explanations for the seizures. Patients with psychogenic seizures, neurodegenerative diseases (ie, those with cognitive decline interfering with daily activities), and coexisting non-vascular lesions were excluded. The local ethics committee authorized the study, which did not require informed consent from the patients or controls.

Two control groups ≥60 years of age were recruited: 41 patients with symptomatic SVD, consisting of a history of transient ischemic attack (TIA) or lacunar stroke with no signs of cortical lesions on brain MRI, and 26 healthy persons who underwent brain MRI due to headache. The following data were recorded in all participants: history of smoking and alcohol consumption, vascular risk factors, cognitive impairment, and age at the MRI acquisition (≥60 years in all cases). Hypertension and cognitive impairment were detected based on clinical history diagnosis. In the epilepsy group, we also recorded the patient's age at the onset of the disease, the type of seizures, whether the EEG yielded an interictal or ictal pattern, and the anti-epileptic drug treatment received.

Epilepsy was defined based on the 2005 ILAE criteria [21] as occurrence of two unprovoked seizures, spaced more than 24 h apart. TIA was defined as a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting < 1 h and showing no lesions related to the clinical symptoms on brain MRI [22]. Lacunar stroke was defined as a neurological deficit with no cortical symptoms, confirmed by a round or ovoid subcortical fluid-filled cavity 3 mm–15 mm in diameter in the territory of one perforating arteriole on MRI [23].

2.2. Imaging protocol

All patients were examined with a 1.5 T or 3 T magnet. All MRI studies included axial and coronal T2-weighted sequences, and axial and coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences.

On axial T2-weighted images, leukoaraiosis was defined as irregular hyperintensities extending into the deep white matter, and its severity was estimated using a modification of the age-related white matter change rating scale (Fazekas scale) [24]. This scale is scored from 0 to 3 as follows: (0) *Absent*, absence of periventricular or subcortical lesions (a single punctate hyperintensity less than 5 mm in size within the subcortical and periventricular white matter was considered normal); (1) *Slight,* continuous periventricular lines less than 5 mm in length and/or various non-confluent subcortical white matter foci less than 5 mm in size; (2) *Moderate*: continuous periventricular lines 5 to 10 mm long and/or subcortical white matter foci 5 to 10 mm in size beginning to merge; and (3) severe: periventricular stripes more than 10 mm long and/or irregular confluent lesions more than 10 mm in size. For one of the study analyses, we divided patients into two severity groups according to the Fazekas scale: mild (0–1) and moderate-severe (2–3).

The degree of medial temporal lobe atrophy was evaluated on coronal T2-weighted images using the Scheltens visual rating scale [25], which scores from 0 to 4 based on the size of the hippocampal gyrus, width of the choroid fissure, and width of the lateral ventricle temporal horn. Values ≥2 were grouped as moderate-severe atrophy. This scale was used independently for each temporal lobe, as previously reported [26,27].

All images were analyzed by a fellowship-trained radiologist and a neuroradiologist with 17 years of experience (LLG, SS). The readers, who were blinded to the clinical information, evaluated the degree of leukoaraiosis and the degree of hippocampal atrophy by consensus.

2.3. Statistical analysis

Descriptive and frequency statistics were obtained and comparisons were made using the IBM SPSS Statistics software, version 22.0. Statistical significance for intergroup differences was assessed by Pearson's chi-square or Fisher's exact-test for categorical variables and Student's *t*-test for continuous variables. Between-group comparisons of the Fazekas and Scheltens scores were carried out with the chi-square test for linear trend. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics and baseline characteristics

Three groups were analyzed: 33 patients with LOE, 41 with a TIA or lacunar stroke, and 26 healthy individuals.

In the LOE group, mean age was 70.9 ± 6.6 years and 19 patients were men (57.6%). The most common vascular risk factor was hypertension (n = 24, 72.7%). Five patients (15.2%) had mild cognitive impairment, and none were diagnosed with dementia or impairment in

Table 1
Demographics and clinical characteristics of each study group.

	Late-onset epilepsy (n = 33)	TIA/Lacunar stroke (n = 41)	p	Healthy individuals (n = 26)	p
Age mean ± sd	70.9 ± 6.6	73.2 ± 6.4	0.133	68 ± 5.7	0.080
Sex, n (%)	14 (42.4)	18 (43.9)	0.898	15 (57.7)	0.244
Hypertension, n (%)	24 (72.7)	34 (82.9)	0.289	16 (61.5)	0.361
Diabetes mellitus, n (%)	14 (42.4%)	12 (29.3)	0.239	4 (15.4)	0.025
Dyslipidemia, n (%)	18 (54.5)	22 (53.7)	0.939	10 (38.5)	0.219
Ischemic cardiopathy, n (%)	2 (6.1)	3 (7.3)	1.000	2 (7.7)	1.000
Atrial fibrillation, n (%)	2 (6.1)	0	0.195	1 (3.8)	1.000
History of TIA, n (%)	1 (3.0)	9 (22.0)	0.036	0 (0.0)	1.000
Cognitive decline, n (%)	5 (15.2)	2 (4.9)	0.231	0	0.061
Depression, n (%)	4(12.1)	3 (33.3)	0.693	2 (22.3)	0.685

Table 2
Seizure and EEG characteristics in the late-onset epilepsy group.

Type of seizures, n (%)	Focal awareness preserved	10 (30.3)
	Focal impaired awareness	18 (54.4)
	Focal to bilateral tonic-clonic	17 (51.5)
EEG Epileptiform activity, n (%)	Temporal	7 (21.2)
	Frontotemporal	7 (21.2)
	No epileptiform activity	19 (57.6)
EEG Non-epileptiform activity, n (%)	Normal	5 (15.2)
	Focal fronto-temporal or temporal slowing	26 (78.8)
	Diffuse slowing	2 (6)

daily activities. The main baseline characteristics of these patients and the control groups are shown in Table 1.

The most commonly reported seizure types were focal impaired awareness seizures consisting in epigastric aura followed by unresponsiveness in most patients (54.4%). EEG showed no epileptiform activity in 57.5% of patients. Seizures were controlled with one epileptic drug in 93.3% (Table 2).

Mean age was 73.2 (± 6.4) years in patients with TIA/lacunar events and 68 (± 5.7) years in the healthy individuals. Hypertension was the most frequent vascular risk factor in both groups (82.9% and 61.5%, respectively). The prevalence of vascular risk factors in the three groups was similar, with the exception of diabetes mellitus, which was higher in epilepsy patients compared to healthy controls.

3 T MRI were obtained in 21.2% (n = 7) of epilepsy patients, 12.2% (n = 5) of TIA/lacunar stroke group and 11.5% (n = 3) of healthy subjects, the remaining scans were performed with 1.5 T MRI.

3.2. Burden of leukoaraiosis

The median (interquartile range) Fazekas score was 1 (0–1) in the epilepsy group, 1 (0–2) in TIA/lacunar, and 0 (0–1) in healthy individuals. TIA/lacunar patients showed a higher degree of leukoaraiosis than epilepsy patients (p = 0.004) or healthy controls (p = 0.003). There were no significant differences in the leukoaraiosis burden between the epilepsy and healthy control group (p = 0.593) (Fig. 1).

Differences were more significantly noticeable when the Fazekas score was subdivided into two severity levels: mild (0–1) and moderate-severe (2–3). The Fazekas score was moderate-severe in 42.3% of TIA/lacunar patients versus 9.1% of epilepsy patients, and 7.7% of healthy controls (p < 0.001).

3.3. Hippocampal atrophy

In each participant, the right and left hippocampus were examined separately. The epilepsy group showed more marked hippocampal atrophy than healthy individuals (right hippocampus: p = 0.021, left hippocampus: p = 0.037). A nonsignificant trend was observed when comparing the Scheltens scale score between TIA/lacunar patients and the healthy group (right hippocampus: p = 0.263, left hippocampus: p = 0.170). The Scheltens score was ≥2 in nearly 25% of epilepsy patients (right side, 25% [n = 8]; left side, 18% [n = 6]) and a much smaller percentage of TIA/lacunar patients (right side, 9.4% [n = 3]; left side, 3.2 [n = 1]). All healthy controls had a preserved hippocampus (Fig. 2). The presence of mild cognitive decline did not have impact on the results.

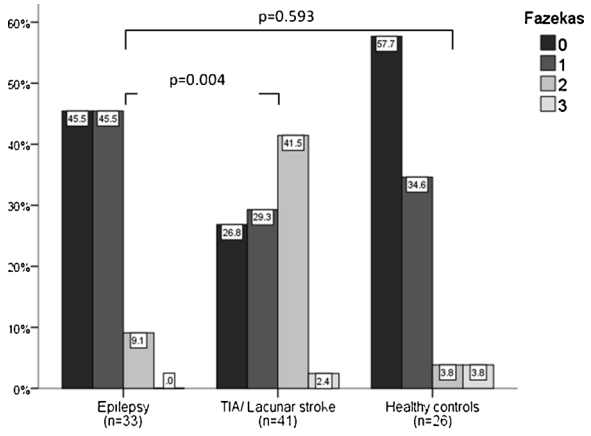

Fig. 1. Degree of leukoaraiosis in all the groups according to the Fazekas scale.

4. Discussion

The pathophysiologic mechanisms leading to LOE are a matter of debate. In this study, brain MRI evaluation in LOE patients and two control populations showed that leukoaraiosis was present to a smaller degree in the epilepsy group than the TIA/lacunar stroke group, and was similar to that seen in healthy individuals. These results suggest that factors other than leukoaraiosis may contribute to the development of epilepsy in elderly patients. Furthermore, LOE patients showed a higher degree of hippocampal atrophy than the other populations, which suggests that neurodegenerative involvement of the medial temporal lobe structures may be implicated in the genesis of their seizures.

The LOE and TIA/lacunar stroke groups had similar cardiovascular risk profiles. Hence, we must ask why patients with TIA/lacunar stroke did not develop seizures even though their leukoaraiosis burden was greater than that of patients with LOE. It could be that LOE patients have a higher underlying predisposition to experience seizures. Neurodegenerative changes in the medial temporal lobe structures could be one such predisposing factor [17].

Our results suggest that cerebral SVD, investigated in terms of leukoaraiosis, does not, in itself, explain the etiology of LOE. Other factors may be involved in the development of epilepsy in these patients, and it is very likely that the coexistence of several factors is responsible for their predisposition to experience seizures.

Most of our patients had focal impaired awareness seizures in line with previous reports in LOE [9,28]. Because of the large variety of seizure presentations and the possibility that epilepsy can be misdiagnosed particularly in elderly persons [29], we selected patients who had experienced at least two seizures. EEGs showing abnormal findings documented focal slowing and no epileptiform activity in most patients.

Only a small number of studies have focused on the clinical and neuroimaging features of patients with LOE [9,13,30]. Gasparini et al reported a higher prevalence of temporal lobe epilepsy in patients with associated leukoaraiosis than in epilepsy associated with a well-defined vascular lesion (post-stroke epilepsy). All patients in the study underwent brain MRI, but it did not include a control group.

Maxwell et al [13] combined CT and MRI data, and found a higher prevalence of leukoaraiosis in patients with LOE than in controls, in contrast to our results. Moreover, they also found a higher prevalence of large vessel disease, as well as all types of small vessel disease. Our study included selected LOE patients, excluding those with large vessel disease or hemorrhage, and all were evaluated with MRI.

In the study by Okroglic et al [30], the presence of parieto-occipital white matter changes and lacunar infarcts was associated with a higher frequency of TIAs, seizures, and incontinence. However, the diagnosis of seizures was established clinically, without EEG examination, which could make the results of this study less robust.

An exploratory study with a small number of patients (n = 16) undergoing 3-Tesla MRI examination reported data consistent with our findings. Grey matter volume in the temporal lobe was smaller in patients with LOE than in healthy controls. However, LOE patients had a higher degree of leukoaraiosis [8].

Of particular note, hippocampal atrophy was more marked in our patients with epilepsy than in those with TIA or healthy controls, who

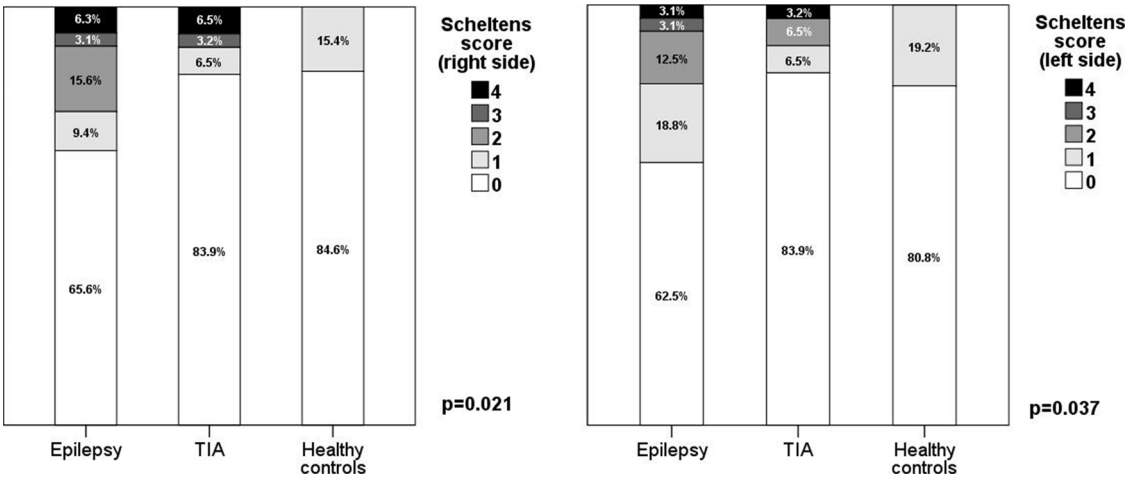

Fig. 2. Hippocampal atrophy in both hippocampi (left and right) according to the Scheltens scale.

showed a completely preserved hippocampus in most cases. These findings suggest that a neurodegenerative process may also be involved in the origin of new-onset seizures in older patients.

De Reuck et al suggested involvement of the cortical structures in the origin of seizures in patients with leukoaraiosis and cognitive impairment. These authors evaluated 292 patients with leukoaraiosis with or without seizures and found a higher percentage of cognitive impairment in seizure patients [17]. In our study, we did not specifically assess the patients' cognitive function. However, the clinical histories showed no baseline differences between the groups. Nevertheless, we assume that the epilepsy patients could have a higher risk of cognitive impairment based on the greater hippocampal atrophy observed in their MRI studies.

The main limitations of this study are its retrospective design and the lack of a standardized MRI protocol. However, all individuals included had at least one axial and/or coronal T2-weighted sequence. The use of other MRI sequences (ie, double inversion recovery) or higher field MRIs such as 7 T [31] would probably have given more reliable data. However, even when a large a number of our patients received 1.5 T scans, we assume that the differences among groups would have remained the same. We are aware of the limitations inherent to assessment of medial temporal lobe atrophy using standard coronal T2-weighted sequences, and the fact that coronal slices were obtained perpendicular to the long axis of the hippocampus only in patients with suspected epilepsy, not in healthy controls or TIA/lacunar patients. As evaluation of medial lobe atrophy was a secondary aim of the study, we believe it reasonable to report these findings as preliminary. Further prospective studies with standardized MRI protocols including volumetric analysis are needed to obtain robust results.

In conclusion, patients with LOE had a smaller prevalence of leukoaraiosis than patients with lacunar strokes or TIAs, whereas hippocampal atrophy was more severe in epilepsy patients. These findings suggest that the etiology LOE may be related not only to the leukoaraiosis features of cerebral SVD; some degree of cortical involvement may also be implicated.

Disclosures

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Conflict of interest

The author(s) declare no potential conflicts of interest.

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