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Targeted Review

Late-onset unexplained epilepsy: What are we missing?

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ABSTRACT

With the aging of the US population, the incidence of epilepsy will increase, with 25 to 50% of new cases with no identifiable etiology diagnosed as late-onset unexplained epilepsy (LOUE). In the current targeted review, we discuss the possible role of cerebral small vessel ischemic disease, accumulation of amyloidβ and hyperphosphorylated tau, and sleep apnea as potential pathophysiologic mechanisms explaining LOUE. We highlight the impact of these processes on cognition and avenues for diagnosis and treatment.

Key questions

1. What evidence is there to suggest that cerebral small vessel disease can cause epilepsy?
2. What evidence is there to suggest that accumulation of abnormal proteins such as amyloidβ and hyperphosphorylated tau (p-tau) can cause epilepsy?
3. What evidence is there to suggest that sleep apnea can cause epilepsy?
4. How do these processes interact with each other?
5. What are future diagnostic and treatment strategies for late-onset unexplained epilepsy?

1. Introduction

The incidence of epilepsy is best represented as a U-shaped curve with the highest incidence later in life starting at the age of 50 years [1–3]. The incidence for ages ranging between 65 and 69 is 55/100,000 person years and increases to 88 for the ages 70–74 years and then 111 for the ages 75–79 years [3]. The prevalence of epilepsy by the age of 75 years is 1.5%, twice the rate of younger adults [4], and prevalence rates can reach as high as 7.7% in nursing home residents [5]. Epilepsy in the elderly is also associated with a 2 times increase in mortality [6]. From a cognitive perspective, a cross-sectional study of patients with new-onset focal epilepsy after the age of 60, the majority without an identifiable cause, showed that patients performed worse than age-matched controls across a number of cognitive tests involving memory and executive function [7].

With the aging of the United States population in the coming decades, the incidence and prevalence of epilepsy in the elderly will increase, and so will its psychosocial and financial burden on patients and caregivers and its financial burden on the healthcare system.

The most common identifiable etiologies of epilepsy in the elderly include cerebrovascular disease, tumors, and neurodegenerative diseases; however, a significant proportion do not have an identifiable cause and are given the diagnoses of late-onset unexplained epilepsy (LOUE) [8]. Lüdorf et al. followed 151 patients with new-onset epilepsy after the age of 60 years and could not find an identifiable cause in 25% of their cohort [9]. In a population-based study in Rochester Minnesota, up to 50% of elderly patients with epilepsy or unprovoked seizures were found to be unexplained [10]. After diagnosis, patients with late-onset epilepsy (LOE) tend to require higher healthcare resources and have more frequent medical and psychiatric hospital admissions compared with matched controls without epilepsy [11]. In the current targeted review, we discuss potential pathophysiological mechanisms related to aging that could lead to LOUE specifically the evidence related to cerebral small vessel disease (CSVD), accumulation of amyloidβ and hyperphosphorylated tau (p-tau), and sleep apnea. We also discuss the influence of these pathologies on cognition and ongoing research efforts focusing on treatment.

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2. What evidence is there to suggest that cerebral small vessel disease can cause epilepsy?

Stroke is the most common identifiable etiology of LOE, and occult cerebrovascular disease is suspected to be the main culprit behind LOUE [12–14]. Age-related changes to the cerebral small vessels include arteriolosclerosis characterized by loss of smooth muscle cells, luminal narrowing and wall thickening usually with a strong association with hypertension. Another manifestation of CSVD is cerebral amyloid angiopathy characterized by the deposition of amyloid protein in the small-to-medium size arteries and arterioles [15]. A complex cascade follows the development of CSVD involving chronic and acute ischemia, blood–brain barrier disruption, demyelination, axonal damage, and inflammation ultimately leading to heterogeneous radiographic changes of leukoariosis, lacunar infarcts, microbleeds, and cortical atrophy [15–17]. Network-level changes also occur and are associated with cognitive impairment [18]. Neuropsychological profiles typically demonstrate deficits in information processing speed, attention/executive functioning, and memory [19,20]. Cerebral small vessel disease is very common in the aging population with prevalence rates of white matter hyperintensities (WMH) in around 90% in cohorts older than 65 years (>30% of people >75 years old have a severe load) [21,22], silent lacunar infarcts in 10% [23], and microbleeds in 5% [24]. Total CSVD burden has also been associated with rate of incident dementia in certain populations [25].

Vascular risk factors have already been linked to the development of LOE; in the Rotterdam study, hyperlipidemia and left ventricular hypertrophy were predictors of LOE after excluding patients with a known stroke [12]. In a case control study of 227 patients with unprovoked seizures, hypertension was found to be an independent risk predictor of epilepsy [26], while in another longitudinal study, diabetes, hypertension, and smoking during midlife were found to be associated with LOE [27]. Patients with LOUE without a history of stroke are also at higher risk to subsequently develop stroke and myocardial infarction [28].

Animal models linking hypertension to late-onset seizures also exist; in the amygdala kindling model for temporal lobe epilepsy, hypertensive rats developed more severe seizures faster than control rats, and pretreatment with the antihypertensive medication enalapril prevented this effect [29]. Neuroimaging studies investigating the association between CSVD and LOE have been sparse; in a case–control study of 105 patients who underwent computed tomography (CT) or magnetic resonance imaging (MRI) with new-onset seizures or epilepsy, higher and more severe rates of CSVD were found in patients with epilepsy [30]. In another investigation of 16 patients with LOE using MRI volumetric analysis and cerebral perfusion imaging, patients with epilepsy were found to have lower whole brain volumes, a greater burden of WMH and increased arterial arrival time in the frontal and temporal lobes [31]. Conversely, in a retrospective review of the MRI scans of 33 participants with LOUE vs. 41 participants with a history of Transient ischemic attack (TIA)/lacunar stroke vs. 26 healthy controls, the participants with LOUE had the same burden of white matter disease as the healthy controls and less than the TIA/lacunar group, but the participants with LOUE did have more evidence of hippocampal atrophy [32]. Hypotheses regarding the pathophysiological link between seizures and CSVD include impaired neurovascular coupling, reduced cerebral perfusion, neuroinflammation, and blood–brain barrier dysfunction [13].

3. What evidence is there to suggest that accumulation of abnormal proteins such as amyloidβ and hyperphosphorylated tau can cause epilepsy?

As the human brain ages, there is a variable accumulation of the pathological proteins amyloidβ_{42} ($A\beta_{42}$) and p-tau. This pathology can be seen in more than half of cognitively normal older adults and has been associated with attention, executive functioning, and episodic memory difficulties [33–36] with higher burden of pathologies noted in mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia. The cooccurrence of Aβ and neurodegeneration on imaging has been shown to accelerate cognitive decline in cognitively normal individuals [37]. The medial temporal lobe is one of the structures impacted the earliest by these pathologies. More specifically, neurofibrillary tangles containing p-tau first aggregate in the transentorhinal and entorhinal cortices. Amyloid plaques first start in the neocortical areas connected to these structures and then accumulate in the hippocampus and entorhinal cortex during the second stage of disease progression [38,39]. In addition, hippocampal sclerosis can also develop de novo in aging and has been associated with accumulation of TAR-DNA binding protein of 43 kDa (TDP-43) especially in individuals older than 90 years [40]. Given that temporal lobe epilepsy is the most common epilepsy and is the most prevalent in older adults [41], there is compelling data highlighting the role of these pathologies in causing seizures. Animal models have consistently shown that these pathological changes lead to network hyperexcitability, and amyloid-based animal models of AD have been shown to produce spontaneous epileptiform abnormalities, a lower threshold for seizure induction, and spontaneous seizures [42,43]. Animal models with reduced or absent tau show a reduction in hyperexcitability and an increased seizure threshold [44,45].

In humans, LOUE is now recognized as a presentation of a number of neurodegenerative diseases, especially AD [46–51]. In a cohort of 47 patients with amnestic MCI or AD dementia and seizures, seizures preceded or coincided with the diagnosis of MCI or AD dementia in 83% of the patients [46]. In a cohort of 77 patients with different dementias, seizures preceded or occurred within 1 year of cognitive symptom onset in 13% of the patients [47]. Cretin et al. described a cohort of 13 patients with pharmacosensitive LOUE of temporal lobe origin, who were ultimately diagnosed with AD dementia [49]. The advent of cerebrospinal fluid (CSF) biomarkers has allowed the identification of patients with AD biomarkers namely low $A\beta_{42}$ levels suggestive of cortical amyloid deposition, and high p-tau levels reflecting cortical tangle formation [52]. In a prospective case–control study of 40 patients with LOUE, 36.5% already had evidence of low $A\beta_{42}$ levels in the CSF while 10% had elevated p-tau levels as compared to 2.3% and 2.3% of the controls, respectively. The presence of the abnormal CSF findings (low $A\beta_{42}$, elevated p-tau) conferred a higher risk of progressing to dementia during the follow-up duration of 3 years [53]. The same group showed that the $A\beta_{42}$ oligomers isolated from the CSF of patients with LOUE enhanced epileptiform abnormalities in mice [54]. These studies demonstrate that a subset of patients with LOUE may have an underlying neurodegenerative condition with epilepsy as their presenting symptom.

4. What evidence is there to suggest that sleep apnea can cause epilepsy?

There is a high prevalence of sleep apnea in older adults with approximately 50% having at least mild sleep apnea and 20% having at least moderate sleep apnea [55]. Obstructive sleep apnea (OSA) in healthy older adults can impact overall cognitive efficiency, with more prominent effects in the domains of memory and processing speed [56,57]. Higher rates have also been noted in patients with epilepsy as compared to controls [58], while patients with sleep apnea were 1.5 times more likely to subsequently develop epilepsy [59]. In a study of adults older than 50 years with a new unprovoked seizure or seizure worsening and no associated neurologic diagnosis, a higher apnea-hypopnea index of 23.2 (≥5 = mild OSA, ≥15 = moderate OSA) was noted in the 11 patients as compared to a control group [60]. In another study of new-onset unexplained epilepsy in patients older than 50 years, 90% of the sample had at least mild OSA, 25.9% moderate, and 29.6% severe [61]. Treatment of OSA in epilepsy has been shown to reduce interictal epileptiform discharges and seizure frequency [62,63]. Sleep apnea causes a cycle of ischemia, reperfusion leading to

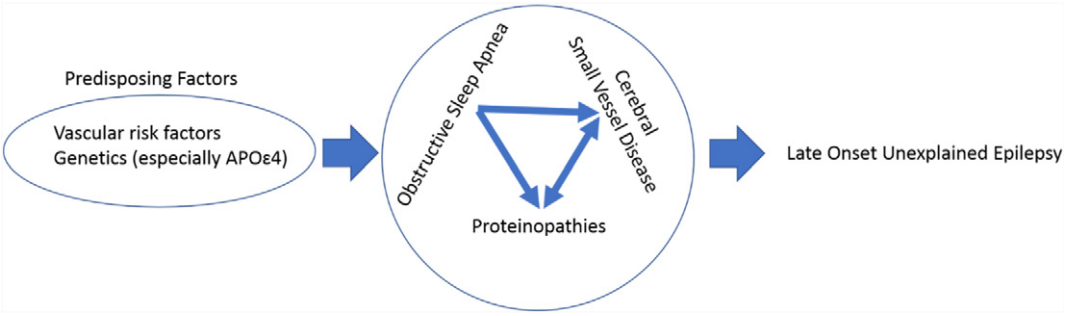

Fig. 1. Schematic representation of the interaction of obstructive sleep apnea, cerebral small vessel disease, and proteinopathies.

increased reactive oxygen species, inflammation and endothelial dysfunction [64]. Untreated sleep apnea has been linked to widespread cortical and subcortical atrophy including left hippocampal and right parahippocampal atrophy, but these changes seemed to be reversible with treatment with Continuous Positive Airway Pressure (CPAP) and attributed to compensatory neurogenesis in the setting of diminished oxidative stress [65].

5. How do these processes interact with each other?

Obstructive sleep apnea, CSVD, and proteinopathies do not often occur in isolation given the complex interactions between each other and similar risk factors. (See Fig. 1.)

Vascular risk factors such as hypertension and obesity have been linked with both OSA and CSVD [55], and moderate to severe OSA is associated with higher rates of moderate to severe WMH representing CSVD but not microbleeds or lacunar infarcts [66]. Similarly, an elderly cohort at high risk of OSA was found to have larger volumes of WMH on MRI and impaired verbal episodic memory [67]. In an animal model of CSVD, induction of OSA led to exacerbation of hypertension, blood–brain barrier disruption, and microglial activation [68].

Elevated serum levels of $A\beta_{42}$ and p-tau181 were also seen in patients with OSA and levels of $A\beta_{42}$ correlated with OSA severity [69], although serum $A\beta_{42}$ has not been clearly established as an AD biomarker. Obstructive sleep apnea has also been linked with lower levels of $A\beta_{42}$ and higher levels of p-tau in the CSF; in a cohort of 25 patients with untreated OSA, 32% had elevated p-tau and 64% had decreased $A\beta_{42}$ in the CSF, while a separate group of treated OSA had rates of 20% and 0%, respectively [70]. In another study with longitudinal follow-up of a cohort of cognitively normal participants, those with OSA had decreases in CSF $A\beta_{42}$ and a trend toward increases in cortical Pittsburgh Compound B positron emission tomography (PET), which measures amyloid burden [71]. Several explanations have been hypothesized for this correlation; hypoxia and hypoperfusion due to OSA lead to upregulation of amyloid precursor protein (APP), increased APP cleavage, hypoglycemia induced tau phosphorylation, oxidative stress, and inflammation [72]. Another possibility is that OSA disrupts slow wave activity, which is when the release of $A\beta_{42}$ is at its nadir, and the glymphatic system is most efficient in clearing $A\beta_{42}$ [73]. It should be noted however that the correlation between OSA and abnormal CSF profiles has not been consistent across studies, as some studies have documented low levels of both $A\beta_{42}$ and p-tau. This was attributed to impaired interactions and decreased clearance of the proteins from the interstitial fluid to the CSF [73,74]. Increasingly, reports suggest that OSA is not only a frequent diagnosis in patients with AD but also raises the risk of developing MCI and AD [70,75–77].

Cerebral small vessel disease and Aβ are also linked; lower CSF $A\beta_{42}$ has been noted in patients with microbleeds, WMH, and lacunes, especially in Apolipoprotein E ε4 carriers [78]. Elevated levels of serum Aβ have also been associated with CSVD cross-sectionally and longitudinally [79,80]; however, these findings have not been consistent [81].

Unifying mechanisms that arise from the review of the literature linking all three risk factors together include neuroinflammation, disruption of the neurovascular unit, and oxidative stress. Studies looking specifically at poststroke epilepsy and stroke outcomes have already highlighted a comorbidity interactome, and the interaction of genetic polymorphisms and their influence on clinical outcomes; APP seemed to be a prominent node in these interactions [82].

Looking at these risk factors from another angle, one can view them as representing a "hit" in the process of epileptogenesis in aging. A common model of acquired epilepsy is the second hit model in which there is an initial insult or predisposing factors (e.g., genetics) lowering the seizure threshold and then a second insult causing the expression of seizures/epilepsy [83,84]. Clinically, this can manifest as someone with underlying AD pathology developing seizures after mild head trauma, or seizure recurrence in someone with a history of epilepsy as they age.

6. What are future diagnostic and treatment strategies for late-onset unexplained epilepsy?

To adequately address LOUE, advances in diagnosis, prevention and treatment are required. Ambulatory electroencephalograms (EEGs) and epilepsy monitoring unit admissions currently play a role and provide great utility in establishing the correct diagnosis and the burden of interictal and ictal abnormalities [85]. One of the diagnostic challenges in the field is that seizures arising from the neuroanatomical area of interest (the hippocampus) may not have a surface EEG signature; in an analysis of 2 patients with surgically implanted foramen ovale electrodes with simultaneous scalp EEG, hippocampal seizures and epileptiform discharges did not have a scalp correlate [86] suggesting that LOUE might be underdiagnosed. Advances in serum biomarkers such as serum tau and amyloid [87], and multimodal PET imaging [88] will provide measures of pathologies of interest and will likely become available for diagnostic work ups in the near future. From a research perspective, applying a multimodal biomarker approach using available technologies may lead to a better understanding of LOUE.

Polysomnography remains the gold standard for the diagnosis of sleep apnea, and advances in wearable technologies will allow the longitudinal monitoring of sleep and the impact of treatment [89]. Primary prevention should also take center stage at the individual and public health level. Vascular risk factors have an adverse impact on aging and likely play a central role in the development of LOUE [27]. Multidomain interventions in at-risk populations have been shown to have a positive impact on cognition with a Finnish study of an intervention of diet, exercise, cognitive training, and vascular risk monitoring being a prime example [90].

With regard to treatment, we are in need of antiepileptic drugs (AEDs) that are well-tolerated in the elderly [91], have minimal drug interactions, and we need to understand how aggressive we should be with interictal epileptiform abnormalities given their association with accelerated cognitive decline [92]. Neuromodulation, already commonly used in refractory epilepsy, may also play a role in this population especially if AEDs are not completely effective at tolerated doses [93]. Targeting the underlying pathologies would be expected to modulate

seizure activity. It is unfortunate that anti-amyloid treatments have not been successful in the field of AD [94], but there has been progress in anti-tau [95] approaches and there might still be a role for targeting amyloid in CVSD. A large number of therapeutic targets for CVSD are either available or in development ranging from antiplatelet therapy to immunosuppressive agents, lipid lowering agents, endothelial modulation, nitric oxide augmentation, and vitamins [96]. Dietary treatments, including the ketogenic diet, are known to be successful in epilepsy and have also been highlighted as a potential treatment in neurodegenerative conditions [97]. Other anti-inflammatory approaches are also of interest given that neuroinflammation seems to be a common link between the diverse pathologies [98]. The current treatment options for OSA with either CPAP or mandibular devices are sometimes not well-tolerated by patients, and pharmacologic options are currently being explored [99].

Finally, as physicians caring for patients with LOUE we should continuously strive to address the "unexplained" aspect of this disease and consider incorporating vascular risk screening, OSA screening, and cognitive screening in our practices.

Summary response to key questions

1. What evidence is there to suggest that cerebral small vessel disease can cause epilepsy?
   Vascular risk factors such as hypertension, diabetes, and smoking have been linked to the development of late-onset epilepsy even in the absence of stroke. Older patients with epilepsy have also been shown to have higher and more severe rates of CVSD, and are at increased of developing stroke.
2. What evidence is there to suggest that accumulation of abnormal proteins such as amyloidβ and hyperphosphorylated tau (p-tau) can cause epilepsy?
   Late-onset epilepsy is now recognized as a presentation of neurodegenerative diseases especially Alzheimer's disease. Patients with late-onset unexplained epilepsy (LOUE) are also more likely to have abnormal levels of amyloidβ $_{42}$ ($A\beta_{42}$) and p-tau in the CSF. Amyloid and tau-based animal models have interictal epileptiform abnormalities, lowered seizure thresholds, and spontaneous seizures.
3. What evidence is there to suggest that sleep apnea can cause epilepsy?
   Patients with sleep apnea are 1.5 times more likely to develop epilepsy, and patients with LOUE have high rates of OSA. The treatment of OSA has been shown to reduce seizure frequency and interictal discharges.
4. How do these processes interact with each other?
   Vascular risk factors predispose to OSA and CVSD, and patients with moderate to severe OSA are more likely to have CVSD. The presence of OSA has also been linked to impaired clearance of $A\beta_{42}$ and p-tau. Finally, patients with CVSD have lower $A\beta_{42}$ in the CSF.
5. What are future diagnostic and treatment strategies for LOUE?
   Treatment of vascular risk factors and obstructive sleep apnea with continuous positive airway pressure are strategies that may lower the risk for LOUE. Advances in neuroimaging and CSF and serum biomarker identification will allow a better understanding of the contribution of different pathologies to the disease. Treatment options already include anti-seizure medications, although better tolerated ones are needed in this age group. Future trials with adjunctive neuromodulation could determine if this is a particularly beneficial strategy in the population with LOUE.

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