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Potential Similarities in Temporal Lobe Epilepsy and Alzheimer's Disease: From Clinic to Pathology

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Abstract

Alzheimer's disease (AD) is clinically characterized by insidious onset of memory and cognitive impairments, which are also presented in patients with temporal lobe epilepsy (TLE). Many studies have shown that seizures occur in some patients with AD, and AD is a risk factor for epilepsy, mainly complex partial and secondary generalized seizure. Here, we focus on the relationship between TLE and AD in clinical and pathological aspects, as they are having similar comorbidities and mechanisms. In this study, we first reviewed the clinical observations that showed concomitant AD and TLE. Then, we picked up common genetic and pathological changes in both the diseases from neurobiological researches. Although both the diseases have delicate differences in many aspects, their common characteristics intrigue more detailed research to be done by newer technology.

Keywords

Alzheimer's disease, temporal lobe, epilepsy, memory impairment

Introduction

Temporal lobe epilepsy (TLE), the most common partial epilepsy syndrome, has an adverse effect on memory in elder adults.[1] Temporal lobe epilepsy is categorized according to seizure location: mesial TLE (mTLE) for activity arising from the hippocampus, parahippocampal gyrus, and amygdala and lateral TLE for activity from the neocortex on the outer surface of the temporal lobe. Large proportion of patients with TLE have memory dysfunction, including verbal deficits that can be commonly seen with dominant hemisphere involvement and visuospatial deficits with nondominant involvement.[2] As TLE and Alzheimer's disease (AD) share similar pathological changes in mesial temporal structures and clinical manifestations, the diagnosis of TLE is not always easy in patients with AD since it may be overlapped with primary cognitive disorders and vice versa. Meanwhile, AD and TLE need to be considered for differential diagnosis of patients with cognitive impairment.

Besides, it has been widely reported that patients with AD have an increased risk of developing seizures, with rates ranging from 8% to 64%.[3-11] However, it is still controversial whether AD is a risk factor for TLE.

We will first review clinical studies about the incidence of seizures in patients with AD and AD or dementia in patients with TLE and further discuss the clinical and pathological links between TLE and AD. We will also discuss strategies to further explore the association between TLE and AD in clinical research and neuroscience.

Presence of Seizures in AD

As early as 1958, retrospective electroencephalogram (EEG) observations had been done in 17 patients with early-onset AD (31-60 years old). Interictal discharges were found in 7 (42%) patients with AD, while the locations of discharge and seizure types were not elucidated.[12] In other early studies about the prevalence of unprovoked seizures in AD, 8% to 64% of patients with AD had seizures.[3-11] However, all these studies vary in patients' age, types of seizures, and other methodological issues. Electroencephalogram results have not been stated in some studies and some of them even did not apply EEG.[3,5,6] Various seizure types had been observed in patients with AD, and there was controversy to the prominent type. Early surveys showed that most of them were generalized tonic–clonic seizures, followed by complex partial seizures,[8] while recent studies suggest generalized tonic–clonic seizures secondary to partial/focal seizures[13] or complex partial seizures.[14] With refinement of AD diagnosis criteria and wide use of EEG in

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neurology and psychiatry, recent studies have explored the association between seizures and AD more intensively.

A detailed retrospective chart review was performed to analyze seizure types in neurodegenerative disorders associated with cognitive impairment. Of the 1738 patients, 39 had both dementia and recurrent seizures. Among them, 28 (72%) patients had recurrent complex partial seizures and 15 (52%) patients had generalized tonic–clonic seizures.[14] A similar retrospective study in outpatients found 9.7% patients with AD had a history of complex partial or generalized seizures or both.[15] A recent longitude observational study has recorded the clinical data and EEGs of patients with a diagnosis of amnesic mild cognitive impairment (aMCI) and AD from 2007 to 2012. Patients with aMCI or AD developed cognitive decline earlier if they also had epilepsy. More than half of the epilepsies were nonconvulsive symptoms, and epileptic foci were unilateral and temporal.[16]

Amatniek et al prospectively examined the age-specific incidence of a first unprovoked seizure in probable patients with AD. They have adopted the questions to address the occurrence of a seizure by 2 neurologists independently, and nearly 60% of the patients had taken EEGs before or at the baseline visit. After 5.99-year follow-up in average, unprovoked seizure incidence was 0.87% higher than expected in the general population. Younger age and EEG focal epileptiform findings were predictive for unprovoked seizures.[17] A larger multicenter study had used standardized checklist to review the events of 453 patients who diagnosed as "probable AD" from early stage to up to 14 years. Approximately only 1.5% had epileptic events over the course of a mean of 3.7 years of follow-up. No associations between seizures and estimated disease duration or cognitive performance were detected.[18] A recent study pooled patient-level data of 10 AD cooperative clinical trials from 1995 to 2010. The overall incidence rate was 484 (0.048%) per 100 000 person-years. Moreover, younger age was associated with higher incidence of seizures, and dementia severity at baseline was strongly associated with increased risk of seizure.[19]

For patients who were diagnosed as "probable AD," Lozsadi et al investigated whether seizures accompany the onset of AD. They identified 12 in 177 patients with seizures. Six patients had partial seizures related to AD onset.[20] As a result, epileptic seizures may be symptomatic of AD, perhaps reflecting a shared pathogenesis.

In early-onset familial AD (EOFAD), the incidence of seizures in patients with the presenilin 1 (PSEN1) mutations, which is the most common cause of EOFAD, is 37% to 58%.[21] Epilepsy was also reported in 31% of patients with presenilin 2 (PSEN2) mutations[22] and 57% of patients with amyloid precursor protein (APP) duplication.[23]

However, in all of these studies, EEGs were available for a small proportion of patients, and localizations of epileptiform discharges were not fully documented or analyzed. Thus, neuropathological substrates for concurrence of AD and seizures remained to be clarified by more clinical studies.

Although the diagnosis of TLE could not be made due to lack of detailed EEGs results, unilateral temporal epileptic discharges have been reported in memory clinic cohorts[24] or in patients with a diagnosis of aMCI or AD.[16] There is a study that has also identified frequent interictal EEG abnormalities, which are the common features in TLE, in patients with AD having seizures by scalp EEGs.[15]

Features of Dementia in Patients With TLE

Temporal lobe epilepsy is characterized by hippocampal or mesial temporal sclerosis. Febrile seizures, trauma, and hypoxia are the common causes. The onset of mTLE mainly occurs in the age ranging from 4 to 16 years.[25] However, late-onset TLE has also been reported in patients with memory impairment and reduced mental activity, resembling AD or other dementia.[26-29] In the cases of epileptic amnesic syndrome, memory disturbances, CSF biomarkers, and brain MR were compatible with AD pathological changes.[30] In some cases of epilepsy-derived progressive memory disturbance, it had mainly affected recent memory as well as constructive ability and delayed recall. Persistent and progressive mental deterioration in some patients with TLE may indicate the underlying degenerative disorder.[27]

Common Mechanisms of TLE and AD

Alzheimer's disease and chronic TLE were once classified as 2 distinct disorders according to their major manifestations and pathologic changes. From the above-mentioned clinical studies, it is suggested that they may share similar pathological features. Recent researches in genetics, molecular, cellular, pathological, and animal models demonstrated possible underlying associations between AD and TLE.

Genetics

We have mentioned that younger patients with AD are more susceptible to epileptic seizures. A list of genetic mutations, especially PSEN1 gene on chromosome 14, was mostly concerned when studies tended to reveal the contribution of genetics to epilepsy or even TLE in early-onset AD. More than 100 PSEN1 mutations have been described, and their clinical phenotypes have been discussed in other review.[21] For patients with familial AD (FAD) bearing PSEN1 E280A, a study evaluated the number of neurons in the hippocampus CA1 area. Of the 8 patients bearing the mutation with epileptic seizures, 5 showed CA1 neuronal depopulation, suggesting hippocampal neuronal loss in patients with FAD having epileptic seizures.[31] Mutations of APP gene on chromosome 21 are predisposing factors of EOFAD as well. An APP T174I mutation has been reported in an African American family with AD and prominent seizures.[32]

Besides FAD, in a sporadic case of late-onset AD associated with seizures, PSEN1 R377W mutation in exon 8 was detected, resulting in a substitution from arginine to tryptophan.[33]

It is controversial for apolipoprotein E (ApoE) ε 4 gene in AD and TLE. Apolipoprotein E ε 4 is a predisposing factor

of late-onset AD. A study found that it was not associated with significant hippocampal, hemispheric, or whole brain atrophy in patients with medically intractable TLE.[34] However, a meta-analysis revealed that patients with ApoE ε 4 had epilepsy onset 5.15 years earlier than noncarriers on average.[35]

On the other hand, we focused on mutations that have potential pathogenic consequences on hippocampus in TLE. Genetic susceptibility factors for TLE include polymorphisms in γ-aminobutyric acid receptors,[36] interleukin receptor antagonists,[37] serotonin transporter gene,[38] and especially calcium homeostasis modulator 1 (CALHM1). Calcium homeostasis, influenced by CALHM1, contributes to long-term potentiation in hippocampus. In addition, amyloid-β (Aβ) peptide has found to be relevant with CALHM1. Our group found CALHM1 P86L polymorphism (rs2986017) as genetic risk factors for AD.[39] Lv et al screened 5 single-nucleotide polymorphisms (SNPs) of CALHM1 in 560 patients with TLE and 401 healthy controls. A positive association between rs11191692 and TLE was found (odds ratio = 1.35, 95% confidence interval = 1.10-1.65), while rs2986017 showed negative results with TLE.[40] Although TLE and AD were found to be associated with different SNPs in CALHM1, the contribution of CALHM1 dysfunction to both diseases needs to be further investigated.

Amyloid and τ Pathology

Amyloid and τ are the classic pathologic changes in AD, but they have also been reported in TLE. The specimens from 101 patients with TLE after surgery showed plaques in 10 of them, and the age-related incidence of plaques was greater in patients with TLE than the normal population.[41] This suggested that TLE may also have a positive influence on the formation of amyloid plaques.

Human APP (hAPP) transgenic mice provides strong evidence as the hAPP mice with high levels Aβ peptides in the brain developed AD-like abnormalities and also had spontaneous nonconvulsive seizure activity in cortical and hippocampal networks.[42] Changes in sodium channel provide possible explanation. β-Site APP-cleaving enzyme 1, which cleaves APP to produce the Aβ peptides, also cleaves the β2-subunit of voltage-gated sodium channels (Navβ2). Enhanced cleavage of Navβ2 occurs in APP transgenic mice, and it was associated with aberrant EEG activity and cognitive deficits.[43]

Abramov et al has examined the acute effects of endogenously released Aβ peptides on synaptic connections in rodent hippocampal cultures and slices. Increasing extracellular Aβ enhanced ongoing activity in the hippocampal network, suggesting that Aβ also acts as a positive regulator at the presynaptic level.[44] However, higher concentration of Aβ worked oppositely and caused synaptic depression.[45] In a previous review, the author implied that abnormal synaptic activity could result in network instability and promote synchrony, which predispose to epileptiform activity.[46]

Moreover, in an animal model of epilepsy,[47] tauopathy or phosphorylated τ (p-τ) overexpression has also been detected. Nagaishi et al has examined 14 clinical cases of seizure-associated glioneuronal lesions, and they found τaccumulation in 37% of cases.[48] Triple transgenic model of AD mice with pilocarpine-induced chronic epilepsy had more neuritic plaque formation and altered intraneuronal p-τ expression in temporal lobe structures, with elevated β-secretase 1 and Aβ immunoreactivity.[49]

Hippocampal Sclerosis

Sclerosis of the hippocampus, the hallmark pathology in TLE, progresses over time as both a consequence and a cause of seizures.[50] However, it is not only a characteristic of TLE but also a relatively common pathologic condition occurring in elderly individuals including those who were diagnosed with AD.[51,52]

The neuronal loss areas in hippocampal sclerosis (HS) include CA1, CA3, and the hilus, with sparing of the dentate gyrus granule cells and area CA2 pyramidal cells. In AD, the diagnosis of HS is warranted when the extent of neuronal loss outweighs the density of extracellular neurofibrillary tangles in that region as described in a relevant study.[53]

Autopsy from brain bank in 1 study showed that 21.7% of patients with AD indicated HS. Among them, HS was presented in 9% of autosomal dominant familial forms of AD, 16% of patients with early-onset AD, and 29% of patients with late-onset AD. Hippocampal sclerosis was also associated more with an amnesic presentation, probably mediated by DNA-binding protein 43.[54]

Neurons Loss and Sprouting

Although epilepsy is not considered as a neurodegenerative disorder, TLE is associated with neuronal loss in layers II and III of the entorhinal cortex. In early AD or MCI, entorhinal cortical volume is reduced compared to normal population,[55] with a loss of layer II[56] or layer V[57] neurons primarily. Although the entorhinal cortex is also vulnerable in TLE, layer III is the area where most neurons are lost.[58] Despite this mild difference, the networks from entorhinal cortex to hippocampus are greatly affected in TLE and late AD in pathological conditions.

We have mentioned the high incidence rate of HS in late AD, and hippocampal neuronal loss is also common in both late AD and TLE. The difference between both of them is the loss of hilar neurons, which is mostly preserved in AD.[59] However, the clinical impact of the difference is still unclear because there are numerous cell types in the hilus and the influence of hilar neurons to dentate gyrus granule cells are also needed to be further investigated.

Calbindin D28K, a robust marker of adult granule cell, decreased in granule cells in hAPP mice and mice carrying mutant human APP with Swedish double mutation and PSEN1 with exon 9 deletion genes (APde9 mice),[42,60] as well as postmortem specimens from patients with AD[61] and TLE.[62] In all, 65% of APde9 mice developed at least 1 unprovoked seizure. Among the mice with unprovoked seizures, 46% had multiple seizures and 38% had generalized seizure after Aβ pathogenesis[60] Neuron death and axonal dystrophy in temporal lobe

structures were also apparent in AD mice after status epilepticus induced by pilocarpine.[49] It is suggested earlier that decreased granule cells in AD mice are associated with seizures, indicating the involvement of neural loss in epileptic seizures in AD animal model.

In hAPP and APdE9AD mouse models, mossy fiber sprouting was associated with spontaneous seizures.[42,60] In patients with AD, the terminal zones of sprouting mossy fiber dramatically increases within the supragranular and polymorphic layer of the dentate gyrus.[63]

Noradrenergic Alternations

Alzheimer's disease is characterized by the loss of the cholinergic neurons in the nucleus basalis of Meynert,[64,65] and the use of acetyl cholinesterase inhibitors like donepezil could lower the speed of cognitive decline. In addition to the loss of cholinergic neurons in AD, significant decrease in noradrenergic neurons in the locus coeruleus (LC) has been detected.[66,67]

Cognitive deficit and depression in TLE are expected to be caused by severely disturbed hippocampus. The hippocampus is one of the regions that receive sole noradrenergic innervations from the LC,[68] so the loss of hippocampal neurons in TLE may result in an alteration in noradrenergic function. The majority of data generated in animal models suggested that the noradrenergic nervous system exerted an anticonvulsant effect.[69]

Animal models of FAD demonstrated the importance of the LC in the early stage of AD.[70] Besides, recent studies also indicated that in the early course of AD, even before the onset of cognitive impairment, the loss of LC noradrenergic neurons may have occurred.[71,72] The hippocampus and the noradrenergic nervous system are both involved in depression and cognition as 2 factors in mediating the symptoms in both AD and TLE.

The difference between AD and TLE in noradrenergic impairment is the origin of neuronal loss. In AD, the dominant neuronal loss is in LC. In TLE, an alteration in neuronal loss is mainly in the hippocampus. It is unclear whether the neuron loss in LC like in AD will lead to secondary changes in noradrenalin receptors in hippocampus or they are independent from each other. Future work will be done to establish possible interaction model and to uncover the comorbidities in AD and epilepsy.

Future Perspective

From the clinical observations mentioned previously, AD acts as a risk factor for epilepsy or seizures. However, epilepsy may be present before the onset of AD. Moreover, for patients with cognitive or memory impairment, both diagnoses need to be considered, and EEGs are routinely required. However, the interaction between TLE and AD remains unclear. In future clinical studies, rigid and updated diagnosis criteria for TLE and AD must be adopted and new auxiliary examinations, such as video-EEG monitoring, invasive sphenoid electrodes EEGs, magnetoencephalography (MEG), or resting functional magnetic resonance imaging,[73] can be used to pinpoint the culprit area if possible. If patients with AD share similar lesion areas as in TLE, these patients may be at high risk of TLE and vice versa. The EEG or MEG may also help to clarify the reasons for cognitive deficit in patients with AD. Prospectively, new predictive factors or genotypes for concomitant TLE and AD could also be explored.

Based on the pathologic changes in TLE and AD discussed earlier, there may be similarities in their underlying mechanisms. Not only electrophysiology but also biomarkers or genotypes, which are under investigation in patients with AD, could be explored in epileptic brain.

However, although younger patients with AD are at a greater risk of developing epilepsy, some neurobiology research found HS, the TLE pathological change, in late-onset AD. The dissociation between clinical presentation and pathology requires more detailed and delicate research.

Conclusion

The concomitant of AD and TLE remains unidentified in both clinical and pathological aspects. Plenty of consolidated evidences showed that they share similar cognitive impairments and could be a risk factor for each other. Genetic or cellular researches also indicated the underlying similarities of mechanisms in AD and TLE. Due to the complicated pathogenesis among them, more in-depth comparisons are needed.

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