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Seizure in Alzheimer's Disease: An Underestimated Phenomenon

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Abstract

Alzheimer's disease (AD) is considered as a potential risk factor for the development of seizure due to neurodegeneration and imbalance between stimulatory and inhibitory circuits in the brain. Seizure could occur in any point during the course of AD, and its presentation varies from fluctuation in cognitive domains to more typical seizures. The clinical diagnosis of seizure in patients with dementia may be challenging due to difficulty in history taking and clinical assessment. No paraclinic methods other than electroencephalogram (EEG) could provide arguments for the diagnosis of AD-related seizures (neither imaging modalities nor cerebrospinal fluid biomarkers). Standard 30-minute EEG may not be sufficiently sensitive to detect epileptiform discharges. In the present study, we aim to review different aspects of seizure in AD, including seizure prevalence, risk factors, underlying mechanisms, electroencephalographic findings, clinical presentations, impact of seizures on AD, and treatment options.

Keywords

seizure, Alzheimer's disease, dementia, cognitive impairment

Introduction

Alzheimer's disease (AD) is the most common cause of memory impairment in elderly individuals, accounting for 46.8 million cases of dementia in 2015, which is predicted to reach 131.5 million in 2050.[1] Aging is a potential risk factor for the development of both dementia and seizure. Seizure, especially in the later stages of AD, could increase the mortality and morbidity and cost of AD care. Fluctuation in cognitive functions could be the only presentation of seizure in patients with AD; as a result, the diagnosis of seizure in these patients could be challenging. Even electroencephalographic (EEG) findings could be noninformative or misleading. There is a question whether seizure could be a manifestation of AD or is a concomitant condition. Emerging clinical evidences revealed comorbidity of epilepsy and AD, particularly when AD is associated with mutations in the amyloid precursor protein (APP)/amyloid beta (Aβ) gene pathway.[2] A considerable group of antiepileptic drugs (AEDs) could deteriorate the cognitive function or have undesirable effects on patient's other medical conditions. Selection and dose adjustment of AEDs in the elderly population with dementia needs careful consideration.

Prevalence and Incidence of Seizure in AD

All types of dementia are associated with an increased risk of seizure in comparison to age-matched general population, but it seems that dementia of Alzheimer type is more commonly associated with seizure than non-Alzheimer dementias (hazard ratio = 5.31).[3,4]

Assessment of the real prevalence of seizures in AD could be challenging. In some cases, the differential diagnosis of AD and other types of dementias is difficult without histological confirmation. If the population of studies are selected from pathologically proven cases, the reported frequency may be more than studies based on clinical diagnosis.[5] History taking in moderate to advanced stages of AD is another problem due to cognitive decline and unreliable history, especially in describing the aura and onset of the seizure.[6] Nonepileptic events mimicking epileptic seizures, such as syncope, and some alterations of behavior in the course of AD may be erroneously diagnosed as seizure, especially in the later stages of AD. According to these limitations, incidence and prevalence of seizure varies among different studies. Based on various studies on different populations of patients with AD, reported lifetime prevalence of seizure is between 1.5% and 64%.[7,8] Even in pathologically proven cases, the prevalence of seizures varies from 10% to 64%.[8-10]

The annual incidence rate of seizure in AD is low, about 2.4 per year as reported by McAreavey et al.[11] In many cases, seizure did not recur. Hauser et al, in their retrospective study on 83 pathologically proven cases of AD, reported that 9.6% of

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their patients had new-onset unprovoked seizure, with 6% having recurrent seizures. In other words, in more than one-third of their cases, seizure did not recur.[9]

Risk Factors for Seizure in AD

Some of the potential risk factors for developing seizure in AD include age of dementia onset, severity of cognitive impairment, Down syndrome (DS), epileptiform discharges in EEG, and medications.[12]

Age at Dementia Onset

Epileptic seizure can occur in any point in the course of AD[9], from the early to late stages.[5,13,14] Prevalence of seizures is higher in older ages[7,15] and advanced stages of dementia[8,13,14] and has a reverse correlation with the age of AD onset.[16] The greatest cumulative incidence of seizure in AD is reported in the early-onset AD (EOAD), defined as those that begin under the age of 65. Reported prevalence of seizure in EOAD varies between different studies from 11% to 45%. In a study by Sulkava, the epileptic seizures were nearly 2-fold more common in EOAD than "senile" AD (11% vs 6%).[16] In Samson et al's study, 45% of their 198 patients with EOAD had seizure.[17] One possible explanation is that seizure could hasten onset of cognitive decline and lead to earlier AD diagnosis.[18] Some authors proposed that the higher risk of seizure in EOAD might relate to the underlying genetic mutations. Seizures may be a feature of AD associated with presenilin-1 mutations.[5] Zarea et al reported that seizures are a common feature of EOAD, especially in cases with APP duplication.[19] However, some other studies have different results. For instance, 2 studies claimed that there was no correlation between the age of dementia onset and development of seizures.[3,9]

Early-onset AD may be familial (EOFAD) which is characterized by positive family history of dementia. Common pathogenic pathway of AD is excessive production of Aβ. Mutation in 3 genes, including presenilins (PS1 and PS2),and APP, have been recognized in EOFAD. Seizures have been described in 37% to 58% of patients with the PS1 E280A mutation,[20] 30% of patients with PS2 mutation,[21] and 57% of patients with APP duplication.[22,23]

Severity of Cognitive Decline

Most of the previous studies support the higher incidence of seizures in the later stages of AD, on average 3.4 to 6.8 years after disease onset.[17,18,24] Even in the early stages of AD, worse cognitive performance predicts later development of unprovoked seizures.[25] Moreover, prospective studies showed that most of the patients with AD progress to the more severe stages of dementia by the time of their first seizure.[8,24] According to the 1984 NINCDS-ADRDA criteria for clinical diagnosis of AD, seizures at the onset or very early in the course of the illness makes the diagnosis of probable AD uncertain or unlikely, but seizure in advanced disease is consistent with the diagnosis of probable AD.[26] However, it has been established that all stages of dementia from mild cognitive impairment (MCI) to severe dementia could increase the risk of seizure.[5,27-29] In a study on 177 patients with probable AD, 6.8% of them had seizure at the time of AD diagnosis, and in half of the cases, AD was the sole explanation for new-onset seizures.[5] The authors concluded that AD should be considered as the differential diagnosis of cognitive decline in patients with seizures, and seizure in early stages of dementia does not exclude AD as the possible diagnosis.

Down Syndrome

The gene for the Aβ-protein is located on chromosome 21, and patients with DS (trisomy 21) may develop AD by the age of 40 years.[30] It was shown that Alzheimer's type pathological abnormalities could be detected in patients with DS, both demented and nondemented.[23] More than half of patients with DS above 50 years may develop AD.[31] According to previous studies on patients with DS who developed dementia, the frequency of seizure was up to 84% and most commonly occurred in the fourth decade of life.[23,32]

Epileptiform Discharges in EEG

Result of studies regarding the prognostic value of epileptiform discharges in EEG varies widely; some researchers claimed that it has a strong predictor value for development of seizure,[27] while others consider it has a less predictive factor.[33] It should be considered that standard 30-minute EEG does not provide sufficient sensitivity for detecting epileptiform discharges in AD, as will be discussed later in this article.

Medications

Some routinely prescribed drugs in AD could lower the seizure threshold, including acetylcholinesterase inhibitors and memantine.[34,35] In an experimental study, combination of memantine with donepezil could increase the risk of seizure more than each one alone.[36] Memantine, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, has demonstrated to have both pro- and anticonvulsant effects in animal models with unknown clinical significance.[37]

Neuroleptics and antidepressants have been associated with 0.1% to 9% increased risk of seizure in large series.[38] Two neuroleptics associated with the higher risk of seizure induction are clozapine and chlorpromazine, which seldom used in patients with AD.[38]

Other Risk Factors

Myoclonus is another potential risk factor for the development of seizure in AD. In the presence of myoclonus, seizure is nearly 8-fold more common.[8,17] In few studies, male gender was considered as a probable risk factor for developing AD-related seizures.[8,39]

The potential role of hyperlipidemia and hypertension on the incidence of seizure in AD needs further studies. There are few reports in favor of increased incidence of seizure in

patients with AD having hyperlipidemia,[40] protective effect of controlled hypertension,[25] and aggravating effect of uncontrolled hypertension on developing seizure in AD.[3]

Common Types of AD-Related Seizures

Generalized Convulsive Seizures

Generalized convulsive seizures (GCS) have been reported as a common type of seizure in patients with AD.[9,10,13,24,41] In Mendez et al's study, 446 patients with pathologically proven AD were included; 17% of their patients developed seizure in the course of disease, which about 89% of them was GCS type.[14]

Focal Seizures

Some previous studies reported focal seizures with impaired awareness as the most common seizure type in AD.[5,7,27] Focal seizures are difficult to identify in the elderly population because several other etiologies can result in transient loss of awareness. In a study by Vossel et al conducted on a population of patients in a tertiary memory clinic, the most common seizure type was dyscognitive focal seizures.[27] In their study, more than half of the patients had nonconvulsive seizure type.[27] Rao et al reported focal seizure with impaired awareness as the most common seizure type in AD.[7] They believed that the higher rate of focal seizures could be due to the studied population in which above 50% of their cases were in the stage of MCI.[7] The impaired cognitive function in the advanced stages of dementia may lead to reduced reports of focal seizures in this population.

Cretin et al in their study reported a peculiar variant of sporadic AD, called the "epileptic variant of AD." It was defined as drug-responsive, nonconvulsive temporal or temporofrontal lobe epilepsy that starts around the age of 60 and remains isolated for 1 to 10 years.[42] They claimed that AD could present as an epileptic variant.

Transient Epileptic Amnesia

Patients with AD may show significant fluctuation of cognitive functions especially in the early stages. Alternations in the neural networks activity could result in such a rapid fluctuation.[43] The possibility of epileptic events as the underlying cause of transient deterioration of cognitive function should be considered in this clinical setting.

Transient epileptic amnesia (TEA; also called epileptic amnestic syndrome) is a specific type of temporal lobe seizure involving the hippocampus and parahippocampal gyrus. Transient epileptic amnesia could last from a few minutes to an hour, consciousness is preserved, ongoing activity continues, and the patient seems slightly worried about amnestic attack. Amnesia can be retrograde, antegrade, or both. The defect in the memory resolves gradually and sometimes incompletely. The proposed criteria for TEA are as follows[44,45]:

(1) History of recurrent witnessed episodes of transient amnesia.
(2) Intact cognitive functions other than memory as judged by a reliable witness.
(3) At least one of the following evidences for the diagnosis of epilepsy:
    (a) EEG shows epileptiform discharges.
    (b) Co-occurrence of other seizure types.
    (c) Response to anticonvulsant therapy.

The etiology of TEA is still under debate and probably multifactorial. Proposed causes are structural lesions, cerebral microvascular diseases, and neurodegenerative process.[28]

There are case reports of TEA as the possible explanation for episodic wandering of patients with AD. For instance, in an interesting case report, the authors present 2 patients with dementia with recurrent transient episodes of amnestic wandering and disorientation characterized by getting lost in familiar environments with no recall of the events. The authors suggest that transient wandering of this type may be caused by ictal events or postictal confusional states. The EEG findings of interictal epileptiform discharges in these patients further supported this claim.[46]

Myoclonic Seizures

Myoclonic seizure can occur in patients with AD, with the prevalence of 7% to 10% and a cumulative risk of 80% in the advanced stages of disease.[18] In atypical cases of AD with more neocortical involvement, the rate of myoclonus might be higher. In a study on patients with corticobasal syndrome who had AD pathology at autopsy, the prevalence of myoclonus was reported about 33%.[47,48] According to 1 study, myoclonus at any point during the course of AD increased the risk of mortality significantly.[17]

The incidence of seizures and myoclonus varies in the 3 most common types of dementia: AD, dementia of Lewy body (DLB), and frontotemporal dementia. Overall, the seizure propensity is highest when Aβ or α-synuclein pathology is present (eg, AD, DLB), whereas myoclonus propensity is higher in primary tauopathies (eg, Corticobasal degeneration(CBD)).[49]

Electroencephalogram Findings in AD

Electroencephalogram is reported as normal in a significant proportion of patients with AD. According to previous studies, 14.3% to 57.1% of patients with AD have been reported to have normal EEG findings.[40,50,51] Obviously, EEG findings depend on the stage of AD and the presence of comorbid epilepsy. The EEG abnormalities can be 2-fold more common in patients with AD with a history of seizure than seizure-free group.[44] Abnormal EEG changes varies from focal to diffuse abnormalities, including epileptiform discharges and slowing.[52,53]

According to a study by Scarmeas et al, EEG was completely normal in 38%, showed diffuse slowing in 38%, focal

slowing in 20%, and epileptiform activity in 16% of patients with AD.[13]

In one study, mesial temporal lobe activity was assessed directly using intracranial foramen ovale electrodes in 2 patients with AD without a history or scalp EEG evidences of seizures. Clinically, silent hippocampal seizures and epileptiform spikes were detected during sleep. They concluded that early development of occult hippocampal hyperexcitability may contribute to the pathogenesis of AD.[54]

There are several limitations in the interpretation of EEG in elderly patients with dementia. Some normal but confusing findings are more prevalent in this age-group and may be misdiagnosed as abnormal. Among these findings, wicket spikes, small sharp spikes, and subclinical rhythmic EEG discharge of adults and temporal slow-wave transients are of particular importance.[53]

Probably, a standard 30-minute EEG is not sufficiently sensitive to detect epileptiform discharges in patients with AD. The odds of detection of epileptiform discharges by standard scalp EEG is about 2% to 16%[13,18,52] and in the setting of established seizure varies from 38% to 62%.[18] In a study by Vossel et al, the role of serial EEG or long-term EEG monitoring (LTM) in detecting epileptiform discharges in AD was evaluated. In their study, the rate of detecting epileptiform discharges was 62.5% by LTM and serial EEG versus 29.2% by standard EEG.[27] Video EEG monitoring could increase the chance of epileptiform discharge detection. In patients with dementia, poor compliance of hospitalization could be a potential problem. A recent study suggested that 8 hours awake EEG or 1-hour sleep EEG is sufficiently sensitive in detecting epileptiform discharges in AD.[55]

It was reported that only 10% of patients with AD and epileptiform discharges in interictal EEG may develop future seizure.[52] Therefore, detection of epileptiform discharges in interictal EEG is not necessarily equal to development of future seizure.[29]

Effects of Seizure on Cognitive Function in AD

Chronic epilepsy is associated with impairment in general IQ and specific cognitive functions including memory,[56,57] and drug-resistant epilepsy may lead to progressive cognitive decline.[45] Patients with a history of chronic epilepsy have higher risk of developing dementia and AD.[6] It is reported that temporal lobe epilepsy may hasten the development of senile plaques[39,58,59] and accelerate the course of MCI and AD.[7,51,60] Comorbid epilepsy was associated with 6.8 years earlier development of cognitive decline in AD and 5.5 years for MCI.[27] However, there are studies which propose that AD and seizure are 2 independent disorders.[61,62]

Proposed Mechanisms of Seizure in AD

Some possible mechanisms for the development of seizure in dementia of Alzheimer type are as follows.

Neuronal Loss

Selective loss of GABAergic inhibitory neurons has been proposed as a possible mechanism of seizure in AD.[10,51,63,64] Another possible mechanism is disproportionate neuronal degeneration in different brain areas, which may lead to imbalance between stimulatory and inhibitory circuits and susceptibility to development of seizure. In a clinicopathologic study, selective loss of large pyramidal cells in parietal cortex (area 7) and parahippocampal gyrus and scarring of temporal lobe was reported in patients with AD who developed seizure.[63] Scarring of temporal lobe is suggested to be the cause of seizure in AD, but hippocampal sclerosis (HS), which is diagnosed pathologically by severe neuronal loss and gliosis in hippocampus, should be considered as a possible confounding factor. Some studies suggested that HS is a potential cause of dementia.[65-67]

Cerebrovascular Events

The most common cause of new-onset seizure in the elderly population is stroke.[68] Although most cases of new-onset seizure in elderly individuals is due to occult vascular lesions, this is not the etiology of all seizures in this age-group.[10] Bernardi et al showed that in patients with AD there was no association between radiological abnormalities and the development of seizure.[40] Moreover, vascular abnormalities such as multiple lacunar infarcts or leukoaraiosis did not appear to be a risk factor for the development of seizure. This finding provides further support to the hypothesis that the underlying mechanism of seizure in AD differs from poststroke epilepsy.[40]

Amyloid Plaques

Senile plaques can be found in nondemented old individuals, probably as an age-related change in brain parenchyma. However, toxic aggregation of Aβ peptides could cause dementia. This aggregation is probably due to imbalance between the production and clearance of Aβ peptides.[69] Deposition of Aβ is more severe in carriers of APOE4 than noncarriers.[70-72] Some studies showed that abnormal accumulation of Aβ may trigger aberrant patterns of neuronal circuit activity which result in epileptiform discharges at neuronal network.[73,74] Amyloid β-induced dysfunction of inhibitory interneurons likely increases synchrony among excitatory principal cells and contributes to the destabilization of neuronal networks.

In a pathology-based study, β-APP messenger RNA and protein levels were examined in temporal lobe and hippocampal tissue of 36 patients with refractory epilepsy. They reported significantly increased levels of these proteins and suggested that β-APP may contribute to the pathogenesis of refractory epilepsy.[62]

Chemically Induced Epileptic Susceptibility

Seizures could result from a chemically induced epileptic susceptibility caused by reduction in choline acetyl transferase,

alterations in dopaminergic or inhibitory transmitters, or other neuroendocrine and neuromodulator alternations.[10]

Treatment of Seizure in AD

Antiepileptic Drug Indications

Aside from usual indications of AED administration in general population, there are other possible indications for AED therapy in the setting of cognitive decline. Høgh et al, based on their case reports of three patients with epileptic amnesia, recommended a trial of AED in patients with progressive memory deficit in the presence of temporal lobe epileptiform discharges.[15] This claim is supported by other studies that proposed the epileptic seizure as a possible cause of unexplained cognitive deterioration in patients with dementia.[75]

Selection and Administration of AEDs

Selection of AED in the elderly population depends on comorbidities, potential drug interactions, and clearance route. Elimination of drug in the elderly individuals is 20% to 40% slower than younger age groups.[75] Drugs with renal clearance are preferred because renal function can be easily monitored. Starting dosage should be low with a slow titration schedule. Adverse effects of AEDs, especially sedation, imbalance, and cognitive problems, are more common and can occur with the lower doses.[76-80] In patients with epileptiform activity in EEG but no witnessed seizures, the decision to treat with AEDs is controversial and should be based on the clinician's judgment. Empirical treatment with AEDs is not recommended for patients without clinical or EEG evidences of seizure.

Preferable AEDs in the elderly individuals include lamotrigine and levetiracetam.[80,81] Levetiracetam and lamotrigine can reduce excessive glutamate release from excitatory neurons, which may play a role in epileptogenesis of AD.[82] Furthermore, levetiracetam has an interesting effect on cognition, with little improvement in Mini-Mental State Examination (MMSE) scores after 1 year of treatment.[83] In a study, administration of low doses of levetiracetam (250 mg/d) in patients with MCI had positive effects on memory with reducing hippocampal activity in functional MRI protocols.[84]

There are diverse reports in regard to comparison between different AEDs in the setting of AD. According to a multicenter randomized double-blind study on 593 elderly cases with newly diagnosed seizure, lamotrigine and gabapentin were better tolerated than carbamazepine.[76] In agreement with this study, Brodie et al showed that lamotrigine is superior to carbamazepine in both effectiveness and tolerability,[78] but another study, using sustained release formulation of carbamazepine, showed comparable effectiveness for both.[77] Arif et al showed that among several AEDs (including lamotrigine, levetiracetam, carbamazepine, gabapentin, oxcarbazepine, phenytoin, and topiramate), lamotrigine and levetiracetam are the most effective and best tolerated AEDs in the elderly individuals.[82] Levetiracetam should be used with caution in patients with advanced dementia and behavioral disturbances because it can exacerbate agitation.

Topiramate has the potential adverse effect on cognition; up to 10% of patients treated with topiramate may complain of mild to moderate cognitive problems and up to 50% may discontinue it due to cognitive side effects.[85,86] There are reports of cognitive function aggravation[87]and even reversible new-onset dementia following treatment with topiramate.[88] As a result, topiramate is not recommended for treatment of seizure in the elderly individuals.

Phenytoin is poorly tolerated in patients with AD having epilepsy.[27,82] Administration of phenytoin in these patients is associated with rapid cognitive deterioration.[89] Evidence for using phenytoin in patients with AD is mostly limited to observational studies that have reported variability in its efficacy and side effects, including ataxia, delirium, sedation, and accelerated cognitive decline.[89] Lamotrigine, similar to phenytoin, inhibits sodium channels. But it has a higher potency for glutamate inhibition, which makes it a better choice than phenytoin.[82,90] Reports of patients with DS, who develop seizure in younger ages, showed well toleration of phenytoin. Conversely, those who develop AD and epilepsy in the later stages of life may show cognitive function deterioration with phenytoin.[89]

Valproate therapy may lead to sedation, gait disturbance, cognitive decline, parkinsonism, and greater hippocampal atrophy in patients with AD.[91]A multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy of valproic acid in treating agitation in 313 patients with moderate AD without epilepsy.[91,92] Valproic acid treatment did not reduce incidence of agitation or psychosis and was associated with higher rates of somnolence, gait disturbance, tremor, diarrhea, and muscle weakness. Patients who were taking valproic acid also showed greater brain volume loss and faster decline in MMSE than patients in the placebo group. As a result, valproate should be avoided in patients with AD with or without history of seizure.

Long-term use of benzodiazepines (BNZs) is not recommended in the elderly individuals,[93] due to its association with dementia. Although these drugs are highly effective in suppressing seizure and myoclonus, they can induce delirium. Moreover, sudden discontinuation of BNZs can induce withdrawal seizures, even in patients without epilepsy. Furthermore, chronic BNZ use in elderly individuals has been associated with increased risk of developing AD.[93]

Other AEDs, such as oxcarbazepine and lacosamide, have been used successfully as monotherapy to treat seizures in elderly individuals, but limited data are available for their use in patients with AD.[94]

Enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital could be associated with decreased bone density. Therefore, long-term use of AEDs in elderly patients should be accompanied by routine examination of bone density and supplementation with calcium and vitamin D.[94]

According to a study on newly diagnosed patients with epilepsy, elderly individuals are more likely to remain seizure-free on AEDs in comparison to younger patients.[94]

Summary

Alzheimer's disease is a potential risk factor for development of seizures, especially in the early-onset form and later stages of the disease. Proposed mechanisms of seizure in AD are neuronal loss, alternation in neurotransmitters, amyloid plaques formation, and concomitant cerebrovascular events.

The diagnosis of seizure in AD could be challenging. Seizure may present with alternation in cognitive function or unexplained transient amnesia. Even, more typical seizure semiologies may be misinterpreted, as in the advance stages of AD, clinical assessment and history taking may be difficult. Moreover, several other nonepileptic etiologies could result in seizure-mimicking symptoms in old patients with dementia.

A standard scalp EEG does not have enough sensitivity for detecting epileptiform discharges in patients with dementia suspected to have seizure. Eight hours awake EEG or 1-hour sleep EEG could increase the yield of sensitivity. Moreover, the detection of epileptiform discharges is not necessarily equal to the diagnosis of epilepsy and should be interpreted according to clinical setting.

According to previous studies, preferred AEDs in patients with AD are lamotrigine and levetiracetam due to better tolerability, lower risks of drug interactions, and side effects. Moreover, these drugs were not associated with potential cognitive deterioration, sedation, and gait imbalance.

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