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REVIEW

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Seizures and Epilepsy in Alzheimer's Disease

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SUMMARY

Many studies have shown that patients with Alzheimer's disease (AD) are at increased risk for developing seizures and epilepsy. However, reported prevalence and incidence of seizures and relationship of seizures to disease measures such as severity, outcome, and progression vary widely between studies. We performed a literature review of the available clinical and epidemiological data on the topic of seizures in patients with AD. We review seizure rates and types, risk factors for seizures, electroencephalogram (EEG) studies, and treatment responses. Finally, we consider limitations and methodological issues. There is considerable variability in the reported prevalence and incidence of seizures in patients with AD– with reported lifetime prevalence rates of 1.5–64%. More recent, prospective, and larger studies in general report lower rates. Some, but not all, studies have noted increased seizure risk with increasing dementia severity or with younger age of AD onset. Generalized convulsive seizures are the most commonly reported type, but often historical information is the only basis used to determine seizure type and the manifestation of seizures may be difficult to distinguish from other behaviors common in demented patients. EEG has infrequently been performed and reported. Data on treatment of seizures in AD are extremely limited. Similarly, the relationship between seizures and cognitive impairment in AD is unclear. We conclude that the literature on seizures and epilepsy in AD, including diagnosis, risk factors, and response to treatment suffers from methodological limitations and gaps.

Introduction

Both epilepsy and Alzheimer's disease (AD) are relatively common neurological disorders whose incidence increases with age [1,2]. There is growing evidence that there is an interaction between these two disorders. Patients with AD have an increased risk of developing seizures and epilepsy, and thus AD may be an important cause of epilepsy in the elderly. In older population studies, neurodegenerative conditions, including but not limited to AD, were the presumed etiology for ~6% of all incident and ~4% of all prevalent cases of epilepsy [3,4]. In patients older than 65, neurodegenerative conditions accounted for approximately 10% of all presumed causes of new-onset epilepsy [3]. There is emerging evidence from animal models of AD that the disorder can lead to pathological excitability in neuronal circuits involved in temporal lobe epilepsy [5]. In this review, we will discuss the links between AD, seizures, epilepsy, and epileptiform electroencephalogram (EEG) abnormalities. We will review the clinical studies as well as some recent findings from animal models that suggest the possibility of a shared pathophysiology between the two disorders. We will also discuss strategies to further explore the impact of epilepsy and abnormal excitatory brain activity to the clinical manifestations of AD and on the progression of the disease.

Risk of Seizures and Epilepsy in Sporadic AD

It has been known for decades that a significant minority of patients with AD will develop clinical seizures during the course of their illness [6]. In prospective and retrospective studies, summarized in Table 1, the proportion of AD patients with at least one unprovoked seizure was between 1.5–64% [7–19]. More recent, larger, prospective studies generally suggest lower proportions. In a study of all first unprovoked seizures in patients older than age 55 in Rochester, MN, between 1955 and 1984, Hesdorffer et al. [14] found that individuals with clinically diagnosed AD were at higher risk for having a first seizure than nondemented patients with an odds ratio of ~6. In a retrospective study of 83 pathologically confirmed cases of AD,

Table 1 Summary of clinical studies of seizures and AD

Study	Study type	N	Age	Follow-up	N (%) Szs	EEG	Seizure type	Treatment	Risk factors and relationship to dementia stage	Pathology	Methodological issues
Sjorgren et al. 1952 [20]	Retrospective autopsy study of patients with AD and Pick's disease	18	53.0 ± 5.0	n/a	4 (22%)	n/r	n/r	n/r	All during late stage of dementia	Yes	Small sample size, limited clinical information available, Sz diagnosis uncertain
Letemendia et al. 1958 [70]	Retrospective autopsy series of patients with AD and EEGs	17	31–60	n/a	7 (41%)	EEGs in all pts with Szs 3 (42%) had IEDs	n/r	n/r	n/r	Yes	Small sample size, early onset patients.
Sulkava et al. [7]	Cross-sectional study of hospitalized AD patients at one center in Finland	71	35 AD onset before age 65	n/a	6 (8%)	All had 8 channel EEG IEDs not reported	n/r	n/r	n/r	No	Diagnosis of epilepsy not well characterized, EEG findings not described; not assessed for other potential causes of Sz
Hauser et al. 1986 [8]	Retrospective autopsy series of AD patients in Rochester, MN	83	n/r	n/a	8 (9.6%) 5/8 had epilepsy	n/r	"convulsive" Szs (other Sz types not assessed)	n/r	Mean latency to first Sz was 6.5 from dementia onset	Yes	Retrospective, criteria for Sz diagnosis unclear, assessed only convulsive Szs
Heyman et al. 1987 [27]	Prospective cohort study of early onset probable AD patients at a single center	92	62 (51–74)	1–6.8 yrs	13 (14%)	n/r	n/r	n/r	Szs occurred late in course of dementia	Yes for 14	Diagnosis of epilepsy not well characterized; EEG findings not described; limited pathological confirmation
Romanelli et al. 1990 [10]	Prospective case-control study of patients with mild AD	44 (58 controls)	71.5 ± 4.9	90 months	7 (16%) (vs. 0 in control group)	EEG in 2 pts only; IEDs seen in both	All had "GTC" 2 (29%) pts noted to have focal features (Todd's)	PHT	All had advanced dementia at time of Sz	Yes for 3	EEG not performed; Sz diagnosis is clinical/historical, limited pathological confirmation
Risse et al. 1990 [9]	Prospective cohort study of hospitalized male suspected AD patients who had autopsy	28	51–83	n/a	14 (64%)	n/r	n/r	"most" patients treated	12 (86%) had Szs noted in last 1/2 of illness	Yes	EEG not noted, Sz diagnosis not specified, duration of follow-up not stated, male only

Table 1 *continued*

Study	Study type	N	Age	Follow-up	N (%) Szs	EEG	Seizure type	Treatment	Risk factors and relationship to dementia stage	Pathology	Methodological issues
Forstl et al. 1992 [21]	Prospective autopsy series	56	75.4 ± 7.4	n/a	6 (10%)	n/r	"generalized motor seizures" in all	n/r	Szs in late stage of disease	Yes. Patients with Szs had cell loss in parietal lobe and in parahip-pocampal gyrus but not in CA1	Limited details on Sz diagnosis; assessment via historical information, older onset group
McAreavey et al. 1992 [11]	Cross- sectional retrospective study of hospitalized patients with dementia in Scotland	208	58–94	n/a	19 (9.1%)	n/r	82 total Sz reported, 59 (72%) 2nd GTCs, 18 (22%) CPS, 5 (6%) unclassified	8 (42%) of pts with Szs on AEDs (PHT, CBZ, or PB)	Sz patients younger more impaired on CAPE informa-tion/orientation score, trend toward lower MMSE scores	No	Inpatients likely represent more severe disease type, no clear criteria for making AD diagnosis, ascertainment of epilepsy/Sz not clearly defined
Mendez et al. 1994 [12]	Retrospective autopsy series from a brain bank	446	64.1 ± 8.8 (Sz group) 67.0 ± 9.8 (no Sz group)	n/a	77 (17%)	52 (67%) total EEGs 39 (75%) with focal slowing; 15 (29%) with IEDs	69 (89%) GTC; 9 (11%) partial	65 (84%) were on AED	Younger age of onset of AD compared to age-/sex-matched non-Sz AD patients; mod-advanced AD;	Yes. No neuropath-ological differences between pts with and without Szs	Not matched for AD severity at time of Sz (only age of onset/duration of illness). Sz ascertainment based on historical information, family questionnaire
Volicer et al. 1995 [13]	Cross-sectional study of hospitalized patients with probable AD	75	70.6 ± 4.4	n/a	27 (36%)	No discussion of IEDs in patients who had EEGs (number not stated)	n/r	23 pts (85%) treated	Szs were associated with worsening in language function	Yes for 17 (63%)	No clear criteria for diagnosing epilepsy; variable disease severity at onset, incomplete pathological confirmation

Table 1 *continued*

Study	Study type	N	Age	Follow-up	N (%) Szs	EEG	Seizure type	Treatment	Risk factors and relationship to dementia stage	Pathology	Methodological issues
Hesdorffer et al. 1996 [14]	Population-based case-control study in Rochester, MN, of patients >55 yrs with 1st unprovoked Sz; compared to 2 age-matched controls without Szs at time of diagnosis	145	55–94	n/a	17 (11%) of patients with Sz had AD	n/r	6 (35%) AD pts partial onset Sz 11 (65%) AD pts generalized onset Sz	n/r	Szs occurred 3.3 (0.4–9.3) yrs from AD onset	No	Sz diagnosis based on historical data
Samson et al. 1996 [35]	Cross-sectional population study of patients with probable early onset AD	198	36–64	n/a	13 (7%) at time of initial AD diagnosis; 94 (45%) over course of AD	n/r	n/r	n/r	Presence of myoclonus was associated with a 7.7 RR of having Szs.	No	Retrospective, Sz diagnosis made from chart only, criteria for epilepsy diagnosis is not clearly delineated
Lozsadi and Larner 2006 [16]	Retrospective cohort study, single outpatient dementia clinic with clinical AD diagnosis	177	49–84	n/a	12 (6.8%) total; half had Szs felt to be temporally related to AD onset	n/r	All 6 (100%) with epilepsy after AD onset had CPS, 1 (17%) with 2nd GTC	n/r	n/r	No	Clinical diagnosis, retrospective, small size, criteria for epilepsy diagnosis is not clearly delineated
Amatniek et al. 2006 [15]	Prospective cohort study of mild probable AD patients from 3 centers	233	n/r	5.99 yrs (0–8.95)	12 (7.75%).	135 (58%) had EEG Focal IEDs in all Sz subset (9 Sz pts had EEGs)	n/r	n/r	Sz more common in younger, African American, more severely demented	No	EEGs not performed on all patients. Sz diagnosis by history, chart review, clinical impression; incomplete information on many patients; no age-matched control cohort (Sz rates in controls estimated from literature)

Table 1 *continued*

Study	Study type	N	Age	Follow-up	N (%) Szs	EEG	Seizure type	Treatment	Risk factors and relationship to dementia stage	Pathology	Methodological issues
Scarmeas et al. 2009 [18]	Prospective cohort study of mild probable AD from 3 centers	453	74.4 ± 8.9 yrs	3.9 yrs	7 (1.5%); 3 (0.7%) with epilepsy	21 pts (5%) had EEGs; 3 of these (16%) had epileptiform activity	GTC in 6 (86%)	Only 4 treated	Sz more common in younger patients	Yes for 15	EEGs not performed on all patients. Sz diagnosis made by review of chart–patients; incomplete information on many patients. No age-matched control cohort (Sz rates in controls estimated from literature)
Rao et al. 2009 [17]	Retrospective cohort study of dementia and MCI outpatients in single center AD registry	1738	50–100	n/a	61 (3.6%) had epilepsy (sufficient records on 31 [1.7%])	29 (72%) had EEGs 15 (51%) had IEDs	44 (72%) had CPS 22 (36%) had probable remote symptomatic cause for their epilepsy	AEDs used: PHT, VPA, CBZ, GBP, PB, CLZ; 79% "excellent" response	n/r	No	Retrospective, included MCI and patients with remote symptomatic causes of epilepsy predating onset of cognitive impairment. Not controlled for disease severity. Limited, incomplete clinical information
Bernardi *et al*. 2010 [19]	Retrospective cohort study of probable AD patients at single center	145	51–91	n/a	14 (9.7%) with Sz; 10 (6.9%) had epilepsy	Incomplete EEGs in non-Szs cohort; in Sz cohort 37.5% had IEDs	13 (93%) had CPS with secondary generalization	n/r	Nonsignificant trend for Sz occurring in more severe dementia	No	Retrospective, Sz diagnosis based on chart review

n/a, not applicable; n/r, not reported; AD, Alzheimer's disease; IED, interictal discharges; CPS, complex partial seizure; GTC, generalized tonic-clonic seizure; MCI, mild cognitive impairment; MID, multi-infarct dementia; 2nd GTC, secondarily generalized tonic-clonic seizure; Sz, seizure; PHT, phenytoin; CBZ, carbamazepine; CLZ, clonazepam; GPB, gabapentin; VPA, valproic acid; PB, phenobarbital.

Hauser et al. [8] found that 9.6% of patients had unprovoked seizures after dementia onset with 6% having recurrent seizures, that is, epilepsy. The incidence of convulsive seizures in this study was estimated to be 10-fold higher in AD patients than expected in the age-matched general population. Other autopsy series have reported rates of seizures of 10–22% [12,20,21], with most patients having single seizures, and fewer having epilepsy [12].

Risk of Seizures and Epilepsy in Familial AD

Early-onset familial AD (EOFAD) is helpful in understanding the pathophysiology of the AD. Like patients with sporadic AD, these patients may develop seizures and epilepsy. Mutations in the presenilin-1 (*PSEN1*) gene are the most common cause of familial EOFAD; seizures have been reported for individuals carrying many, but not all, of the known mutations. For instance, seizures have been described in 37–58% patients with the *PSEN1* E280A mutation [22]. Seizures do not appear to occur in all affected individuals and it is not clear if the incidence of seizures is any higher in familial compared to sporadic cases after accounting for disease duration and severity. Seizures have also been described in cases of familial AD due to presenilin-2 mutations, occurring in 30% of affected patients in one series [23]. Seizures are common in patients with amyloid precursor protein (APP) duplications, occurring in 57% of affected individuals in one study of 5 families [24]. AD-associated epilepsy is common in adult patients with Down's syndrome (who by age 40–55 universally harbor AD-type neuropathological changes and develop dementia), but there may be other etiologies besides AD neurodegeneration. In one prospective study of 96 adults with Down's syndrome, 51% developed dementia and 84% of these patients developed seizures [25]. All but 8% of these patients had their first seizure after dementia onset. In a cross-sectional study of 191 adults age 19–69 with Down's syndrome, 9.4% had epilepsy and the prevalence increased with age; 46% of patients older than 50 had epilepsy [26]. These studies suggest that genetic forms of AD marked by abnormal processing and deposition of amyloid-β (Aβ), a common final pathway in all of these familial causes of AD, may be particularly likely to be associated with seizures (see the section *Mechanisms of seizures in AD* later).

Prognostic Factors for Seizures and Epilepsy in AD

Seizures may relate to disease severity and/or duration of dementia illness. In some studies, seizures noted after the onset of dementia were more likely to occur in later stages of the disease [9,10,21,27]. However, other population studies found that neither disease duration nor age of onset were significant risks for seizures in AD patients [8,14]. One possible explanation is that dementia severity, rather than disease duration, may be associated with risk of seizures. In prospective studies of patients with probable AD of mild severity, seizures occurred in 1.5–16% of patients over 1–8.5 years of follow-up [10,15,18,27] whereas in studies of institutionalized AD patients, most of whom had more severe dementia, higher seizure frequencies of 9–64% have been reported [7,9,11,13]. Dementia severity [15] or worse performance on tests of orientation and information [11] have been reported to be associated with an increased risk of seizures in AD patients. Some studies suggest that younger age of dementia onset is associated with increased seizure risk [12,15,18]. However, some population studies demonstrate no effect of age of onset for seizure risk [8,14].

Seizure Types in AD Patients

Patients with AD have been reported to have either generalized or complex partial seizures. Some studies only assessed generalized seizures or seizures with motor manifestations [3,14]. In studies that reported both convulsive and nonconvulsive seizures, generalized tonic-clonic seizures were more frequent in most [10–12,18], but not all studies [19].

Epileptiform EEG Activity and AD

There is only limited evidence for the presence of epileptiform surface EEG abnormalities in AD patients, with or without seizures. Only some of the observational studies of seizures in AD reported the results of EEG tests and often they were not performed in all patients [15,18,19,28]. In these studies, epileptiform discharges were seen in a minority of patients with seizures and in some patients without seizures. Few studies have systematically examined the incidence of epileptiform discharges in patients with AD or dementia. Liedorp et al. [29] reviewed routine EEGs performed on 1674 patients in a memory disorders clinic. They found epileptiform discharges (spikes or sharp waves) in 3%, 26% of whom had a known diagnosis of epilepsy. Most of the discharges were focal and temporal. Twenty-five percent of the patients with discharges had no clinical evidence of epilepsy. Two patients (17%) in this small group were reported to have had a subsequent seizure in follow-up. Another study examined EEG abnormalities in severe AD patients, nonaffected first-degree relatives, and normal elderly and middle-aged subjects; this study found increased theta and delta activity, and sharp waves, in AD subjects and ApoE4-positive relatives [30]. However, the frequency and localization of epileptiform abnormalities were not described and the authors did not show examples of the observed abnormalities. The infrequent occurrence of epileptiform discharges in the AD and memory clinic population even in those with seizures may be reflective of a tendency for the elderly to be generally less likely to have interictal discharges on routine interictal EEGs [31,32]. In one study of the elderly, such discharges were found in only 36% of patients with new onset epilepsy [33].

Seizure Treatment in AD

Few studies have examined the treatment of seizures and epilepsy in AD. Rao et al. [17] noted that 79% of the patients in their cohort with epilepsy had an "excellent" response to treatment (>95% reduction in seizure frequency). In other studies, the frequency of seizures in AD patients with epilepsy was low; for instance, McAreavey et al. [11] reported an annual seizure frequency of

2.4 per year. Other studies reported the use of antiepileptic drugs but did not mention the response to treatment [10–12,18]. The limited data available suggest that seizures due to AD are usually responsive to treatment [17,34]. Studies comparing drugs in AD have not been performed, but a large multicenter trial in the elderly population has been performed comparing the effectiveness of two newer antiepileptic drugs, lamotrigine and gabapentin, and the older drug, carbamazepine in new-onset seizures; all drugs reduced seizures at similar rates but the newer drugs were better tolerated [33]. Side-effect profile is likely the most important consideration in choosing an antiepileptic drug in an elderly patient with seizures and AD.

Seizures and AD Course

Seizures do not appear to impact disease duration or mortality in early-onset AD patients [35]. While some studies suggest that seizures are correlated with more severe dementia [11,15], it is not clear if this is a causal relationship or that seizures are a marker of more severe or aggressive disease. In a study of inpatients with AD, Volicer et al. [13] found that the five patients (7%) of their AD cohort who developed seizures following hospitalization had a more significant decline in language function compared to AD patients without seizures matched for age and disease duration prior to seizure onset. However, four of the five patients were treated with phenytoin, which may have negative impact on cognitive function in the elderly [36]. No studies have directly examined if treating epilepsy with antiepileptics changes cognitive function in patients with AD. Several small randomized studies examined the use of valproate for behavioral problems in patients with AD and found no effect on either behavior or cognitive status [37–39]. It is likely that if any of the patients in this study had unrecognized seizures, these would have been effectively treated with the moderate doses of valproate or its derivatives used in these studies (750–1500 mg/day) since seizures in patients with AD are almost always well controlled with monotherapy [17,34].

Seizures and AD Treatment

There is some theoretical risk that the symptomatic treatment of AD may place patients at risk for seizures. For instance, cholinergic activation with pilocarpine is a common laboratory technique to provoke seizures in animal models [40]. While acetylcholinesterase inhibitors have been reported to rarely provoke seizures in some drug registries [41], a small randomized trial of donepezil in patients with epilepsy and memory complaints conducted by our group was not associated with increased seizure frequency [42]. Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated both pro- and anticonvulsant effects in animal models [43] that are of unknown clinical relevance. Neuroleptics and antidepressants, often used to treat behavioral manifestations of dementia, have been associated with a 0.1–9% rate of seizures in larger series [44]; the most frequent seizures occurred with high doses of clozapine and chlorpromazine, two drugs seldom used in patients with AD. Excluding these two drugs, the seizure rate is less than 0.6% and the seizure rates in AD studies, including those which controlled for neuroleptic use [18], were above that which could be attributed to psychotropic drug use.

Methodological Issues in Studies of Seizures in AD

While there is sufficient evidence to suggest that AD increases the risk of seizures and epilepsy, methodological problems in the epidemiological and observational studies have limited the ability to more accurately estimate that risk. Those studies in which there was pathological confirmation of AD, have small numbers of subjects, with a spectrum of disease durations and severities. In most prospective and retrospective studies, the diagnosis of AD was made clinically, usually based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [45]. While these clinical criteria are generally 80–90% accurate for AD diagnosis, using pathology as the gold standard [46], samples may have admixed cases with non-AD dementia, such as vascular dementia or Dementia with Lewy bodies [11,17], or may have included some patients with only mild cognitive impairment [17]. Some studies were performed prior the routine use of brain MRIs and included patients with other symptomatic causes of epilepsy such as stroke or hemorrhage. In a study from the Mayo Clinic [17], 36% of dementia patients with seizures had MRI evidence of prior stroke, and other pathological studies show about one-third of AD patients have infarcts [47]. In addition, some studies have not controlled for medications such as neuroleptics, antidepressants, acetylcholinesterase inhibitors, or stimulants [11] that are often prescribed to patients with dementia and may reduce seizure threshold. These factors as well as selection bias, such as the inclusion of more severely affected patients in hospital-based cohorts, may explain the wide range of reported frequencies for seizures in AD patients, and the variable associations with risk factors.

Seizure diagnosis in most studies was made by review of clinical records. In some studies, there was insufficient information to confirm the diagnosis of epilepsy or seizures, and it is possible that convulsive syncope was sometimes labeled seizure. Often diagnosis was based on caregiver or primary physician report. Many studies did not specify criteria for making a seizure diagnosis. Whether a paroxysmal event is a seizure can be difficult to determine based on history and often limited clinical information. In most studies, the ultimate diagnosis of whether a patient had a seizure was made by the study clinicians who often did not have specialty training in epilepsy or by a single epileptologist [8,14,17]. In a study in which two epileptologists made the assessments independently, there was moderate, but not perfect, agreement on whether an event was a seizure (kappa = 0.67) [18] suggesting that determining the nature of a spell in this population may be difficult. Finally, many studies did not make explicit distinctions between unprovoked seizures versus provoked seizures, such as those due to alcohol intoxication or withdrawal. The latter would not fulfill the diagnostic criteria for epilepsy though studies explicitly examining unprovoked seizures would not be affected by this limitation [14,15,18]

In many of the reviewed studies, EEG was either not done, or when reported showed epileptiform changes or other

significant electroencephalographic abnormalities in only a minority of patients. A partial explanation may be that the yield of a single typical 30-minute routine EEG for revealing definite epileptiform discharges is only between 29% and 55% in all patients referred to epilepsy centers [48]. Multiple routine EEGs or prolonged recording to include sleep significantly increases the yield. Furthermore, for many patients, interictal discharges, especially if restricted to the basal or medial temporal lobes never are evident on scalp EEG [49]. Over 10 cm^2 of gyral surface must be involved in a discharge to generate a potential recorded at the scalp [50]. Activity in deep areas, distant from the scalp, may not be seen on scalp recordings.

It is possible that many of the observational and population studies underestimate the true incidence of seizures and distribution of seizure types. Complex partial seizures are more common in elderly patients with epilepsy than primary or secondarily generalized seizures [32,51]. In a prospective treatment trial of new onset epilepsy in the elderly, Rowan et al. [33] found that only 25% of the patients had generalized tonic-clonic seizures. Complex partial seizures may be more difficult to ascertain in retrospective studies or studies based on questionnaires or caregiver reporting [52]. Manifestations of complex partial seizures or the postictal state such as inattentiveness, wandering, aggression, delirium, language, or memory disturbance might be confused with symptoms of dementia. However, these symptoms are commonly seen in dementia and generally are not ictal in nature. Clinical features typically associated with complex partial seizures such as aura and oral or manual automatisms are less common in the elderly [33]. Therefore, the increased proportion of convulsive seizures in the previous literature on seizures and AD may be due to the fact that these are more obvious and unequivocal to observers. However, even apparent convulsive activity can be mistakenly attributed to seizures. Other movements such as myoclonus, tremor, or convulsive syncope can be reported as seizure activity by untrained observers. Experienced epileptologists can still have difficulty determining if a patient's paroxysmal spells are seizures, and make use of ictal video-EEG monitoring for definitive diagnosis. In a retrospective review of 94 patients older than 60 admitted to an epilepsy monitoring unit, McBride et al. [51] found that 49% had seizures. Fourteen percent had other physiological causes for their paroxysmal events including transient ischemic attack, syncope, cataplexy, and nocturnal confusion. Therefore, without videoelectrographic recording of the spell in question, ascertainment of the true incidence of epilepsy in AD may be difficult even in prospective studies.

Mechanisms of Seizures in AD

Both in AD and temporal lobe epilepsy, pathological changes in mesial temporal structures including the CA1, subiculum, and entorhinal cortex are present [53,54]. Models of temporal lobe epilepsy suggest cell loss and reorganization of neuronal circuitry in these regions leads to pathological hyperexcitability [55]. Prominent cell loss and gliosis in CA1 is also occasionally seen in patients with AD and other forms of dementia [56]. There is evidence from some animal models of AD that deposition of Aβ, the constituent of plaques, can lead to hippocampal hyperexcitability and seizures in certain cases. Amyloid-β can affect synaptic transmission via actions on multiple signaling cascades. It has been shown to modulate NMDA receptors, α7 nicotinic ACh receptors, immediate early genes, and calbindin pathways [5]. Del Vecchio et al. [57] found that transgenic mice expressing double-mutant human APP had reduced seizure thresholds compared to wild-type littermates when given an exogenous convulsant. This difference could be seen prior to the evidence of plaque formation. Other authors [58,59] have shown increased susceptibility to chemoconvulsants in other APP mutant mouse strains. Palop et al. [57] also found that these mice had changes in GABAergic hippocampal circuits such as interneuron sprouting, increased neuropeptide Y expression, and increased inhibitory synaptic activity compatible with compensatory changes in response to chronic excitability. They also recorded prolonged video-EEG in a subset of mutant mice and found frequent epileptiform discharges and intermittent nonconvulsive seizures. Minkeviciene et al. [59] examined the EEG of mice expressing two human APP mutations, APPswe and PS1dE9, and also found frequent epileptiform discharges and seizures in 65% of 4.5-month-old mice of this construct, with many mice having convulsive seizures and one dying of status epilepticus. Using patch clamp recording, the authors found hyperexcitability in superficial neocortical pyramidal cells suggesting that epileptogenic potential may not be limited to mesial temporal structures in AD. The relationship between epileptiform activity and seizures, and cognitive dysfunction and disease progression, is uncertain in these transgenic mice. Frequent interictal activity may itself cause impaired cognition that improves when discharges are suppressed [60]. There is evidence from rodent models of temporal lobe epilepsy that even single interictal discharges can transiently disrupt performance on cognitive tasks [61]. It is also possible that increased inhibition in hippocampal circuits in response to epileptiform activity can impair cognition in APP mutant mice [5].

In addition to evidence for the proepileptogenic role of abnormal Aβ deposition in this mouse model, other factors may contribute to the increased seizure risk in AD. The ApoE4 allele is a risk factor for the development of sporadic AD [62], and there is some evidence that ApoE4 also predisposes nondemented carriers for epileptogenesis. In one study, patients with the ApoE4 allele and moderate-severe traumatic brain injury had a 2-fold increased risk of epilepsy compared to patients without the allele [63]. Recent experimental studies suggest that inflammatory cytokines, specifically interleukin 1β, may promote seizures and epileptogenesis [64]. Amyloid plaques are associated with local inflammatory reactions and cytokine production [65] and it is possible that these cytokines facilitate the development of epilepsy in AD patients. Further work elucidating the role of neuroinflammation in seizures in AD may yield new therapeutic targets.

Future Directions

Evidence from population and observational studies shows that AD is associated with an increased risk for seizures and epilepsy. The true incidence of epilepsy in AD is not known and might be underestimated or overestimated, as discussed earlier, due to

methodological problems and the inherent difficulties in making the diagnosis of epilepsy in this population. Further studies should require rigid standards for seizure diagnosis including careful seizure-focused history taking, and possibly use of video-EEG monitoring to characterize suspicious spells. Epilepsy risk and the potential role of interictal epileptiform discharges in cognitive dysfunction in AD could be better assessed by supplementary methods to scalp electrophysiological recordings. Some electrophysiological, pathological, and experimental evidence suggests that mesial temporal structures may be the likely epileptic focus in AD patients with seizures. However, epileptiform activity restricted to this region may not be evident on scalp EEG. Use of subtemporal surface electrodes can increase the ability to detect discharges that are mesial temporal by 50% [66]. The detection performance of these additional scalp electrodes is comparable to more invasive sphenoidal electrodes [67]. Prolonged or multiple recordings could further increase the ability to detect epileptiform discharges. Foramen ovale electrodes placed in the ambient cistern near the mesial temporal structures under fluoroscopic guidance [68] can detect discharges isolated to mesial temporal structures such as the hippocampus and amygdala almost as well as more invasive intraparenchymal electrodes [69]. However, these electrodes can be associated with serious complications, mostly intracranial hemorrhage, at a rate of 1.8% [69].

Careful investigations of patients with spells suspicious for complex partial seizures may also help determine the true incidence of seizures and epilepsy in AD. For instance, patients with fluctuations in cognition or responsiveness could undergo several days of inpatient video-EEG monitoring to determine if these events are epileptic. However, removing demented patients from a familiar environment and constraining them with electrode leads may cause confusion and agitation. This could increase patient and family distress and might require use of sedating medications (with possible confounding effects in clinical interpretations). One possible alternative could be ambulatory EEG systems, which allow video-EEG monitoring to be performed in a familiar home environment, although such monitoring also might not be well tolerated. If clinical studies confirm a high rate of epileptiform abnormalities in patients with AD, more long-term studies will be needed to determine the contribution of this activity to AD progression and cognitive dysfunction. Abnormal excitatory activity might be another therapeutic target for treating AD symptoms and potentially modifying disease progression [5].

Conflict of Interest

The authors have no conflict of interest.

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