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SEIZURES IN ALZHEIMER'S DISEASE

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Abstract—Alzheimer's disease (AD) increases the risk for late-onset seizures and neuronal network abnormalities. An elevated co-occurrence of AD and seizures has been established in the more prevalent sporadic form of AD. Recent evidence suggests that nonconvulsive network abnormalities, including seizures and other electroencephalographic abnormalities, may be more commonly found in patients than previously thought. Patients with familial AD are at an even greater risk for seizures, which have been found in patients with mutations in *PSEN1*, *PSEN2*, or *APP*, as well as with *APP* duplication. This review also provides an overview of seizure and electroencephalography studies in AD mouse models. The amyloid-β (Aβ) peptide has been identified as a possible link between AD and seizures, and while Aβ is known to affect neuronal activity, the full-length amyloid precursor protein (APP) and other APP cleavage products may be important for the development and maintenance of cortical network hyperexcitability. Nonconvulsive epileptiform activity, such as seizures or network abnormalities that are shorter in duration but may occur with higher frequency, may contribute to cognitive impairments characteristic of AD, such as amnestic wandering. Finally, the review discusses recent studies using antiepileptic drugs to rescue cognitive deficits in AD mouse models and human patients. Understanding the mechanistic link between epileptiform activity and AD is a research area of growing interest. Further understanding of the connection between neuronal hyperexcitability and Alzheimer's as well as the potential role of epileptiform activity in the progression of AD will be beneficial for improving treatment strategies.

Key words: Alzheimer's disease, seizures, mouse models, amyloid precursor protein, amyloid β, antiepileptic therapy.

Contents

Introduction 251
Co-morbidity of AD and seizures suggests common pathological mechanisms 251
Dominant familial AD often presents with seizure or myoclonus co-morbidity 253
Abnormal network activity in mouse models of AD 255
APP and Aβ contribute to electrical imbalances 256
Targeting cognitive dysfunction in AD with antiepileptic drugs 258
Conclusions 259
Acknowledgements 260
References 260

INTRODUCTION

Seizures and neuronal network imbalances have recently been implicated in the development of cognitive deficits in a subset of Alzheimer's disease (AD) patients (Rabinowicz et al., 2000; Palop and Mucke, 2009). Understanding the contribution of seizure-driven neuronal network dysfunction to AD may provide new insight for therapeutic strategies (Scharfman, 2012; Chin and Scharfman, 2013). Work linking amyloid precursor protein (APP), a protein important in the development of AD pathology, to epileptiform activity suggests these two diseases may be more tightly connected than previously assumed (Cabrejo et al., 2006; Born et al., 2014). This review focuses on findings from human patient and mouse model studies that examine the connection between seizures and AD and explores the possibility of treating AD patients with anti-epileptic drugs.

CO-MORBIDITY OF AD AND SEIZURES SUGGESTS COMMON PATHOLOGICAL MECHANISMS

AD affects an estimated 5.2 million Americans, is currently the sixth leading cause of death, and may contribute to almost as many deaths as caused by cancer (Thies and Bleiler, 2013; James et al., 2014).

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Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer's disease; AICD, APP intracellular domain; APP, Amyloid precursor protein; CAA, Cerebral amyloid angiopathy; CTFα, α C-terminal fragment; CTFβ, β C-terminal fragment; DS, Down syndrome; EEG, Electroencephalography; EOFAD, early-onset familial AD; fMRI, functional magnetic resonance imaging; LEV, levetiracetam; LTG, lamotrigine; MCI, mild cognitive impairment; MMSE, mini-mental state examination; PSEN1, presenilin 1; PSEN2, presenilin 2; PTZ, pentylenetetrazol; sAPPα, soluble APPα; sAPPβ, soluble APPβ; SWD, sharp wave discharges; VPA, valproic acid.

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Age is the greatest risk factor for AD, with the majority of patients having a late-onset, sporadic form of the disease (Thies and Bleiler, 2013). AD is characterized by cognitive impairment and memory loss that typically begins with difficulty recalling recent events (Thies and Bleiler, 2013). These symptoms become progressively worse and eventually AD patients are no longer able to function independently (Thies and Bleiler, 2013). In addition to the increased risk for AD, individuals over the age of 50 are also at increased risk for unprovoked seizures, and this risk sharply increases after a person passes 60 years of age (Cloyd et al., 2006). Seizures and epilepsy in the elderly are often triggered by traumatic events such as stroke, head injury, and neurodegenerative disorders (Cloyd et al., 2006). One of the more behaviorally striking types of seizures is generalized convulsive tonic–clonic events. In addition to generalized convulsive seizures, AD patients can develop dyscognitive focal seizures, previously referred to as complex partial seizures, which may be convulsive or nonconvulsive and often result in the patient experiencing altered consciousness, amnestic periods, confusion, and difficulties in speaking as well as other problems (Belcastro et al., 2007; Vossel et al., 2013). Myoclonus, a brief involuntary muscle spasm that is often found in epileptic patients, is a complication that can occur in conjunction with a number of neurological diseases, including Alzheimer's (Caviness and Brown, 2004).

The appearance of seizures in AD patients has previously been proposed as a marker of late stage disease resulting from cortical neurodegeneration (Romanelli et al., 1990), although further study has shown the timing of seizure onset is not restricted to late stage AD. Regardless of whether the first seizure occurs a year or a decade after the onset of cognitive impairment, the development of seizures following AD onset suggests that AD pathology contributes to abnormal neuronal network activity in patients that develop both disorders. However, recent studies suggest epileptiform activity accelerates AD onset (Vossel et al., 2013). Studies reporting timing of seizure onset in AD patients show inconsistent results, and seizures may be a highly variable aspect of disease co-occurrence. In one study on patients affected by both AD and seizures, the average seizure onset ranges from 0.4 to 9.3 years after AD onset (Hesdorffer et al., 1996). Alternatively, the differences in seizure onset may be the result of inconsistent data collection and limited number of studies with electroencephalography (EEG) recordings as well as differing criteria for patient inclusion. One observational study on newly diagnosed AD patients found that 3.4% of the total AD cohort showed seizure onset and cognitive decline onset at roughly the same time (Lozsadi and Larner, 2006). Seizures during the early stages of AD may be due to aggressive disease progression and/or to other factors influencing susceptibility to hypersynchronous electrical activity (Amatniek et al., 2006; Irizarry et al., 2012). Alternatively, epileptiform activity may be found in patients with more rapid AD progression because it accelerates the course of AD, but the effect of one disease on the other is difficult to separate. Recent evidence from a sporadic AD patient study shows an association of EEG abnormalities with an earlier onset of AD and faster progression of clinical impairment (Vossel et al., 2013).

Numerous prospective studies on AD patients have also shown an increased risk for seizure incidence in the late-onset population (> 70 years) in comparison to the normal risk for this age group (Sulkava, 1982; Hauser et al., 1986; Romanelli et al., 1990; Amatniek et al., 2006). The reported cumulative incidence of at least one unprovoked seizure throughout the course of AD is in the range of 10–22% (Mendez and Lim, 2003). More recent studies have examined larger AD patient groups and have confirmed an increased risk for unprovoked seizure in AD patients. In one prospective study, unprovoked seizures were identified in seven out of 453 patients (1.5% and incidence rate of 418 per 100,000 person years) (Scarmeas et al., 2009). Similarly, data pooled from multiple clinical trials of mild–moderate AD patients found the incidence rate for seizures to be 18 seizures/3078 patients (incidence rate of 484 per 100,000 person years) (Irizarry et al., 2012). Compared to the seizure-free patient cohort, Irrizary et al. also reported that patients who experienced a seizure event had on average an earlier age of dementia onset (62.9 years vs. 70.3 years) and a lower mini-mental state examination MMSE score (16.7 vs. 20.2). The overall threefold or greater risk for seizures in late-onset AD and lower MMSE score for those with seizure events highlights the detrimental outcomes of the co-morbidity of these conditions (Amatniek et al., 2006; Irizarry et al., 2012).

EEG abnormalities have also been observed in non-epileptic AD patients (Hauser et al., 1986; Rae-Grant et al., 1987; Forsgren et al., 1996; Amatniek et al., 2006; Scarmeas et al., 2009). Nonconvulsive epileptiform activity may underlie episodes of amnestic wandering and memory problems in AD patients (Rabinowicz et al., 2000; Palop and Mucke, 2009). EEG abnormalities in AD patients without documented seizures can include diffuse slowing, excessive δ-wave activity, triphasic waves, and/or sharp waves (Sulkava, 1982; Rae-Grant et al., 1987; Scarmeas et al., 2009). In agreement with previous studies, a recent retrospective study examining EEG recordings from a larger group of mild cognitive impairment (MCI) or AD patients found that patients with either an epilepsy diagnosis or epileptiform EEG activity had an earlier age at onset of cognitive decline and clinical AD diagnosis (Vossel et al., 2013). In this study, the timing of the first unprovoked seizure was clustered near cognitive decline onset, suggesting that seizure activity may be more common in early disease stages than previous studies have found (Vossel et al., 2013). Seizure onset was more than 2 years prior to the onset of cognitive decline in only two out of 47 patients with epilepsy or EEG epileptiform activity, and only four patients showed seizure onset more than 2 years after disease diagnosis (Vossel et al., 2013). The work by Vossel et al. suggests that epileptiform activity may contribute to the development of cognitive decline in AD patients and is not just a marker of end stage of disease. As a result, EEG abnormalities may be present in a larger proportion of AD patients than