REVIEW ARTICLE

Seizure susceptibility in Alzheimer's disease

Authors
Karen E. Reyes-Marin[a*], Jonathan A. Zegarra-Valdivia[b,c*] , Angel Nuñez[a]

Affiliations
[a]Departamento de Anatomía, Histología y Neurociencia, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain
[b]Achucarro Basque Center for Neuroscience, Leioa, Spain
[c]Universidad Nacional de San Agustín de Arequipa, Perú

* Both authors should be considered as first author

Correspondence:
Angel Nuñez[a]
Email: angel.nunez@uam.es

Abstract

Epileptic seizures in Alzheimer's disease (AD) patients are rare but still approximately 8 times more common than in the general age-matched population. Experimental and clinical studies have suggested the epileptogenic potential of Aβ, which might represent a principal responsible for the epileptic-like discharges and cognitive decline observed in AD. In addition, an increase in cortical excitability has been demonstrated in AD animal models that may be due to an imbalance of excitatory/inhibitory synaptic transmission. Cortical hyperexcitability has also been demonstrated in the human EEG by the presence of a high proportion of fast oscillatory activities. This review tries to show the mechanisms involved in the generation of the epileptic seizures observed in AD and have been widely studied in animal models. Unfortunately, the EEG analysis in AD is not a standard procedure in clinical practice. Nevertheless, seizures and other electroencephalographic abnormalities are commonly found in AD patients. We suggest that EEG studies in these patients could help to an early diagnosis and inform about the evolution of this disease and their possible cognitive deterioration.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, or loss of intellectual function, among people aged 65 and older. Diseases that cause dementia are often not diagnosed in the early stages and symptoms are often misdiagnosed or ignored. An early and accurate diagnosis would be beneficial for these patients because starting treatment early in the disease process can help preserve daily activity function for some time, even though the underlying Alzheimer's process cannot be stopped or reversed. Besides, an early diagnosis would reduce the economic cost of treating these patients. Numerous studies have shown that the socioeconomic costs are enormous.

Currently, the total cost of dementia is estimated to cost the US economy $305bn a year or £34.7bn for the UK economy [1, 2]. Nonetheless, recent projections indicate that the prevalence in low-and-middle income countries increases between 47-71% over the 15 following years, compared to 23% in Europe and 41% in the US [3]. Considering the economic cost, a recent systematic review study points out that the cost in low-middle income countries borders $20k per patient [4]. Thus, a quick tool for diagnosis of AD would have numerous advantages worldwide, and precisely, in low-middle income countries. In this review, we show signs in the EEG recordings that could aid in the diagnosis of these patients quickly and at a meager cost compared to image analysis methods, so its use should be generalized. In fact, the initiative to use EEG as an early tool for AD diagnosis was made by the associations of AD and epilepsy [5].

AD is characterized clinically by severe cognitive deficits and pathologically by amyloid plaques, neuronal loss, and neurofibrillary tangles [6-8]. Disease progression before diagnosis lasts for decades representing a valuable window for therapeutic intervention before irreversible neurodegenerative changes and consequent cognitive loss occur [9]. The progressive accumulation of amyloid-β (Aβ) in brain regions is suggested to contribute to the cognitive decline in AD. Excessive Aβ can affect the expression of synapse-related proteins, decrease dendritic spine density, inhibit excitatory synaptic transmission, affect synaptic plasticity, and cause cognitive impairments both in AD patients and animal models of this disease [10-13]. AD pathogenesis is also associated with significant cholinergic neurotransmitter system dysfunction, including changes in the levels of neurotransmitters [14-16]. The basal forebrain is the main origin of cholinergic cortical projections [17, 18], which undergoes severe atrophy in AD patients and reduces cholinergic inputs to the cortex [19, 20]. Although there are abundant studies about this pathogenesis, the molecular mechanisms underlying the cognitive deficits seen in AD are unclear, and there remains no effective treatment to slow or halt its progression.

The EEG analysis in AD is not a standard procedure in clinical practice. Nevertheless, seizures and other

electroencephalographic abnormalities are commonly found in AD patients that may contribute to the development of cognitive deficits [21-23]. People with AD are ten times more likely to develop epilepsy than the age-matched general population [8, 21, 22, 24, 25]. Epileptiform-activity in AD usually displays a non-motor presentation what could explain misdiagnosis [26]. Subclinical epileptiform activity was identified in 42% of AD patients but only in 11% of age-matched control subjects. These patients with epileptiform activity had a faster decline of their cognitive abilities [26, 27]. EEG abnormalities in AD patients can also include diffuse slowing, excessive delta-waves, triphasic waves, and/or sharp waves [8, 28]. Late-onset sporadic AD is associated with a threefold increase in seizure incidence compared with the general population, whereas early-onset familial AD is linked to an 87-fold rise [24]. These findings support the notion that seizures can be a part of the natural history of AD patients [11] and raise the question of whether this kind of 'silent' epileptic activity needs to be medically treated.

Seizures or myoclonic activity have been reported in patients affected by mutations in the amyloid precursor protein (APP) or presenilin 1 (PSEN1) genes that result in Aβ peptide overproduction and lead to early-onset AD (onset between 40 and 65 years of age) [29, 30]. They show seizure rates ranging between 15% and 67% and myoclonus rates between 9% and 31%, being highest in PS1 mutation carriers [26, 27]. For this reason, a careful EEG study could help clinical physicians to find early epileptic-like activity in AD patients so that they could initiate treatment earlier and delay cognitive impairment.

Recent studies suggest that an excitatory-inhibitory imbalance in cortical neurons can be responsible for the EEG abnormalities and may contribute to the cognitive deficits in AD [11]. In the temporal cortex of AD patients, significantly lower levels of γ-aminobutyric acid (GABA) and glutamate neurotransmitters were observed, indicating a deficient synaptic function [31]. Furthermore, a decreased GABA neurotransmitter levels have been also observed in the cerebrospinal liquid of AD patients [32, 33]. Immunohistochemistry studies indicated that the α1 and γ subunits of the postsynaptic $GABA_A$ receptor were upregulated in human AD subjects [34, 35]. Diminished perisomatic GABAergic terminals were also observed in brain sections from both AD patients and in an animal model of AD, transgenic APP/PS1 mice, especially on cortical neurons adjacent to the Aβ plaques (see also below), indicating a decrease of GABAergic transmission in AD that may contribute to the generation of epileptiform activity [36].

These findings strongly suggest that there is an important alteration of synaptic transmission in AD. For these reasons, eyes-closed resting state EEG shows a reduced power in the posterior alpha (8-12 Hz) rhythm and topographically widespread increases in delta (< 4 Hz) and theta (4-8 Hz) rhythms in AD and MCI patients [37]. Furthermore, when spectral EEG analysis was combined with the

study of "microstate complexity" it is possible to classify AD patients with a sensitivity > 80%, and could predict progression from MCI to AD [38].

Epileptic seizures in AD animal models

Animal models of AD have been widely used lately because they allow the study of the mechanisms that generate this disease. Accumulation of Aβ peptide has been extensively studied in transgenic APP/PS1 mice that overexpress mutant human genes for APP and PS1 [39]. Spontaneous seizures and/or epileptiform EEG activities have been also described in these transgenic mice carrying multiple human APP mutations while they are seldom seen in their wild-type (WT) littermates [11, 40-42]. Seizures and epileptiform-activity facilitate Aβ production, promoting negative feedback between Aβ and synaptic dysfunction, which could accelerate or worsen AD [43]. Although neurodegeneration and age-related co-factors may contribute to the development of seizures in AD, recent data obtained from transgenic mice expressing human APP in neurons have indicated that high levels of the Aβ peptide are sufficient to elicit epileptiform activity and seizures even in the early stages of the disease process, and in the absence of evident neuronal loss [10]. Palop et al. (2007) reported that transgenic overexpression of Aβ peptide causes epileptiform activity within the entorhinal-hippocampal circuitry, suggesting that epileptiform activity may contribute to dysfunction of the neuronal network that underlies memory formation. The Tg2576 mice exhibit many behavioral and pathological features of AD, including elevated production of Aβ peptides. Tg2576 mice had significantly lower afterdischarge threshold when electrical stimulation was applied to the amygdala to induce kindling [44]. Notably, experimental manipulations that prevented seizure activity in hAPP mice have also prevented cognitive deficits in these animal models [45]. Taken together these findings suggest that neural network excitability and neuronal discharge synchronization are enhanced in AD.

We have studied the appearance of epileptic-like activity in APP/PS1 mice [40]. The EEG of the APP/PS1 mice revealed a higher incidence of epileptiform-like discharges than in WT animals. They appeared spontaneously as interictal spikes, spike-waves, or polyspikes [40, 46](Figure 1A). Furthermore, these mice showed decreased threshold for seizure induction [10, 41, 47]. APP/PS1 mice were more susceptible to discharge seizures when the GABA inhibitor pentylenetetrazole (PTZ; 60 mg/kg body weight) was injected. The onset latency (the time from the PTZ injection to the beginning of tonic seizure discharges) was significantly lower in the APP/PS1 mice than in WT mice (74.1 ± 15.7 s vs. 140.0 ± 6.8 s, respectively), suggesting that APP/PS1 show hyperexcitability [40]. However, the mechanism of generation of epileptiform-like discharges is not well known.

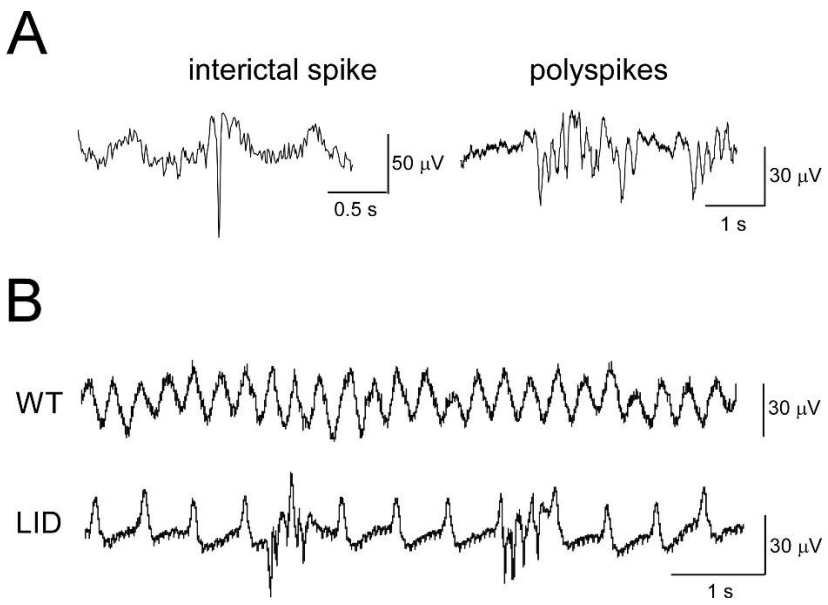

Figure 1. Seizure characteristics in the EEG of APP/PS1 or LID anesthetized mice. A, representative activity observed spontaneously in an APP/PS1 mouse (9 month-old). Epileptiform-like discharges consisted in interictal spikes or polyspikes. B, epileptiform-like discharges recorded spontaneously in wild type (WT) and LID mice. They showed similar characteristics to APP/PS1 mice. Note the slow delta activity in the EEG recording that was due to the anesthetic (isoflurane). Data from Reyes-Marin and Nuñez, 2017 (33) and Zegarra-Valdivia et al., 2019 (45).

The implication of Aβ plaques in the generation of epileptiform-like has been also suggested in a mouse model of serum IGF-I deficiency (the LID mouse), which show reduced brain IGF-I input [48]. This animal model reveals AD-like pathology such as tau-hyperphosphorylation, higher brain Aβ concentration and cognitive loss [48-50]. Although LID mice do not show plaques or tangles, they show diffuse Aβ deposits and intracellular tangle-like phospho-tau staining [51]. In addition, LID mice show a higher incidence of epileptiform-like discharge (Figure 1B) that could be related to an increase in cortical hyperexcitability since fast frequencies in the EEG (beta and gamma frequency bands) were increased [52].

Neuronal hyperexcitability has also been linked to structural degeneration of dendrites. The dendritic structure is known to determine the electrical properties of neurons, therefore, when dendritic integrity is impaired neuronal function is aberrant [36, 53]. In agreement with that, an increase in the mean firing rate and synchrony of hippocampal pyramidal neurons has been observed by patch-clamp recordings *in vivo* in APP/PS1 mice that may be due to structural changes in the dendritic tree and synapse loss [53]. Neuronal hyperexcitability

has also been related to changes in intrinsic neuronal properties. For example, hippocampal neurons show increased excitability in the 3xTg-AD animal model due to altered Kv2.1 potassium channel function [54]. In addition, Aβ evokes a sustained increase in presynaptic Ca^{2+} concentration, increasing neurotransmitter vesicle release probability at hippocampal synapses [55]. Together, these studies suggest that the alteration of neuronal properties in AD could explain the increased in neuronal excitability observed in these patients or animal models.

In addition to alterations in neuronal excitability, impaired synaptic transmission is also a common feature of AD as deficits in long-term potentiation (LTP) occur in many mouse models of this disease. High Aβ concentrations inhibit LTP, which is essential for the normal development of cognitive functions such as learning and memory, whilst enhance long-term depression (LTD) [11, 56, 57]. Numerous studies in mouse models of AD demonstrate deficits in γ-aminobutyric acid (GABA) pathways. GABA is an important inhibitory neurotransmitter that control neural excitability and is ubiquitously expressed in brains of mammals including humans. Imbalanced GABAergic and glutamatergic transmission has been shown to impair neuronal activity and to induce hyperexcitability [31, 58]. Indeed, reduced GABAergic inhibitory synaptic activity may lead to epileptic-like phenomena. As indicated above, a diminution of GABAergic terminals occurs close to Aβ plaques [36]. Thus, the GABAergic system might be affected by the presence of Aβ plaques and could explain the correlation between epileptiform-like discharges and the number of plaques. Consequently, we have shown a correlation between the number of Aβ plaques in the primary somatosensory cortex and the frequency of seizure events in APP/PS1 mice (Figure 2). Furthermore, the induction of Aβ plaques with N-(2-chloroethyl)-N-ethylbromo-benzylamine (DSP4), which induces locus coeruleus degeneration and noradrenaline deficiency, also evoked epileptiform-like discharges in the WT mice [40]. In contrast to this hypothesis, it has been reported that a mouse overexpressing APP displayed frequent sharp-wave discharges independently of the Aβ plaque load [59]. These authors conclude that APP overexpression, and not Aβ overproduction, is responsible for the EEG abnormalities. Thus, more studies are required to decipher the influence of Aβ peptide on synapse function.

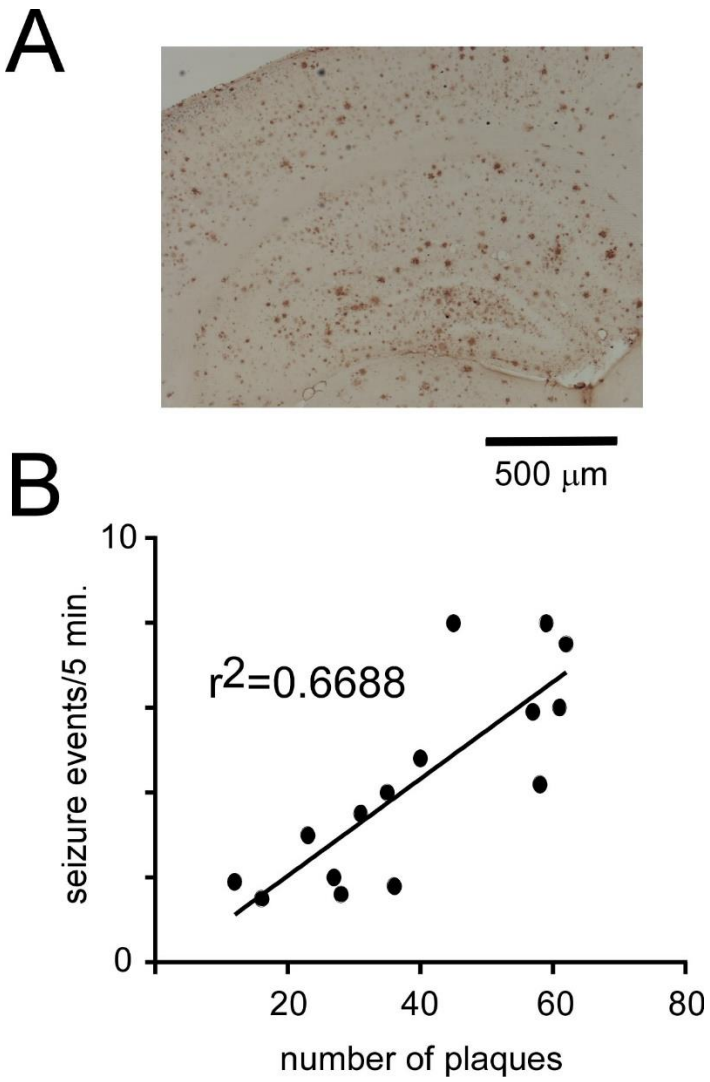

Figure 2. Correlation of seizure events and the number of Aβ plaques. A, representative microphotograph showing Aβ plaques in APP/PS1 mice of 9 month-old. B, the scatterplot shows the correlation of spontaneous epileptiform-like discharges and plaque number in 15 APP/PS1 mice (4–9 month-old mice). The line indicates the best fit (r2 = 0.6688). Data suggest that the possible lesion induced by the Aβ plaques may evoke the generation of seizure events in APP/PS1 mice. Data from Reyes-Marin and Nuñez, 2017 (33).

Accordingly, data suggest that the lesions induced by the Aβ plaques and/or APP overexpression may evoke the generation of epileptiform-like discharges in APP/PS1 mice and probably in AD patients. This effect may be due to the damaging action of Aβ plaques on dendrites of cortical cells. Indeed, it has been described in the APP/PS1 mice that dendrites in contact or passing through Aβ plaques suffer alterations that include the sprouting of spines on dendrites contacting Aβ plaques, the loss of dendritic spines and the thinning of dendritic shafts passing

through [36, 60]. Aβ can reduce the number and activity of GABA inhibitory interneurons, resulting in abnormal synaptic transmission [11, 61]. Other studies also implicate the Aβ peptide in the increased hyperexcitability observed in AD. Bath application of soluble Aβ in *in vitro* studies has been shown to induce neuronal hyperactivity in wild-type mice [42, 62], and may enhance epileptic activity in hippocampal slices through a mechanism involving increased surface expression of D1 dopamine receptors [63]. Overall these studies show that inhibition is reduced in AD, which combined with hyperactive excitatory neurons shifts neuronal activity toward excess excitation and probably leading to seizures.

EEG studies in AD

The hyperexcitability observed in AD patients and in animal models may favor a reduction of slow-wave oscillations, increasing fast oscillations, and a network hypersynchrony, which may underlie the higher incidence of epileptiform activity in AD. The hyperexcitability observed in AD patients and animal models (APP/PS1, Tg2576 mice) is suggested by a decrease in delta and theta frequencies and a high proportion of fast activities (beta and gamma frequency bands) in the EEG. Also, an increased amplitude of auditory and somatosensory evoked potentials has been observed [64-68]. We have found that an increase in the cortical excitability induced by injection of physostigmine, a reversible cholinesterase inhibitor which increases the ACh level in the brain, increased the frequency of epileptiform-like discharges in APP/PS1 mice [40]. Accordingly, atropine, a muscarinic cholinergic receptor antagonist, significantly decreased epileptiform-like discharge occurrence in APP/PS1 mice [69].

Pathological elevations of Aβ, present either chronically in mouse models of AD or acutely after exogenous administration, lead to a disruption of slow oscillations and their large-scale coherence in the neocortex, thalamus and hippocampus. Slow oscillations and spindling are the most prominent pattern of brain activity during the slow-wave sleep [70, 71]. APP/PS1 animals present an increase in wakefulness and a decrease in the slow-wave sleep [65]. Epileptiform-like discharges are entrained with the spindle oscillation in APP/PS1 mice [46] and its propagation may be favored by the high neuronal synchrony that occur during slow oscillations [70]. Consequently, Aβ may alter network activities supporting cognition and sleep/wakefulness cycle in AD.

Conclusions

Experimental and clinical studies in the last decade have progressively driven the attention towards the epileptogenic potential of Aβ, which might represent a major contributor to the cognitive decline as well to the etiology of late onset epilepsy. Epileptic seizures in AD patients are rare but still approximately 8 times more common than in general age-matched population. Deposited amyloid

and/or overexpression of Aβ may be responsible for the epileptic seizures that may be fundamentally connected to cognitive dysfunction. In addition, an increase in the cortical excitability has been demonstrated in AD animal models that may be due to an imbalance of excitatory/inhibitory synaptic transmission which may be responsible of the epileptic-like discharges. Cortical hyperexcitability has been also observed in the human EEG by a high proportion of fast oscillatory activities. These observations raises the question whether this kind of 'silent' epileptic activity needs to be medically treated. We propose that it is necessary to study the EEG of these patients because the presence of epileptic-like discharges may inform about the evolution of this disease and of the possible cognitive deterioration.

The diagnosis of AD is established by clinical features combined with biomarker evidence for Aβ accumulation in the cerebrospinal fluid, positron emission tomography (PET) or structural magnetic resonance imaging (MRI) in the brain [72]. These diagnostic methods are expensive and imprecise and only allow a diagnosis when the disease is very advanced. Therefore, they only allow the application of treatments that provide symptomatic relief. On the contrary, EEG studies are an innocuous and inexpensive method that allows to use new analysis tools such as spectral analysis or microstate analysis, which may shed light on the early diagnosis and prognosis of AD and other pathologies such as mild cognitive impairment [38, 73, 74].

Recent advances in EEG technology, especially in analysis methods, are improving the accuracy of EEG technique, applicable in dementia and AD diagnosis. Recent advance for example was due by principal component analysis, microstate complexity analysis, multi-task learning and EEG spectral images strategies or machine-learning, functional connectivity, qEEG, or a combination of these methods [38, 73, 75-77]. On the other hand, EEG in MCI, especially in the amnestic subtype, would be benefited patients identifying possible progression to AD [78]. Thus, EEG in AD is complemented with the new EEG analysis tool, and protocols shed light on their early diagnosis and prognosis [74], where all these different approaches of EEG would benefit AD and MCI early diagnosis, especially in low-and middle-income countries, for its easy access in these countries.

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