Chapter

EEG Biomarker for Alzheimer's Disease

Demet Ilhan Algin, Demet Ozbabalık Adapinar and Oguz Osman Erdinc

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that accounts for nearly 70% of the more than 50 million dementia cases estimated worldwide. There is no cure for AD. Currently, AD diagnosis is carried out using neuropsychological tests, neuroimaging scans, and laboratory tests. In the early stages of AD, brain computed tomography (CT) and magnetic resonance imaging (MRI) findings may be normal, but in late periods, diffuse cortical atrophy can be detected more prominently in the temporal and frontal regions. Electroencephalogram (EEG) is a test that records the electrical signals of the brain by using electrodes that directly reflects cortical neuronal functioning. In addition, EEG is noninvasive and widely available at low cost, has high resolution, and provides access to neuronal signals, unlike functional MR or PET which indirectly detects metabolic signals. Accurate, specific, and cost-effective biomarkers are needed to track the early diagnosis, progression, and treatment response of AD. The findings of EEG in AD are now identified as biomarkers. In this chapter, we reviewed studies that used EEG or event-related potential (ERP) indices as a biomarker of AD.

Keywords: Alzheimer's disease, biomarker, EEG, quantitative EEG, neurodegeneration

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that accounts for about 70% of the estimated 46 million dementia cases worldwide. Although there is no definitive treatment for AD, early diagnosis and correct follow-up to stop disease progression can improve the quality of life for the AD patients and caregivers [1].

Amnesia, aphasia, apraxia, and agnosia are the leading clinical signs of AD. The first symptom in AD is often the loss of the ability to learn new information (amnesia). Loss of episodic memory is the main symptom of AD. Episodic memory is particularly concerned with the hippocampus. In the beginning, the patient becomes forgetful, repeats the same things, and loses his things. Semantic memory is about social events and general knowledge. It is not destroyed as markedly as episodic memory in the early stages of AD. As the disease progresses, destruction starts in semantic memory [2–4].

According to the symptomatology, AD is divided into three stages: (1) preclinical, (2) mild cognitive impairment (MCI), and (3) AD-related dementia. (1) Preclinical AD: changes in brain, blood, and cerebrospinal fluid associated with AD begin to occur, but the patient does not show any symptoms. This stage may start years

or decades before the first clinical symptoms of dementia [5]. (2) Mild cognitive impairment (MCI): MCI describes the clinical situation between normal aging and Alzheimer's disease. In 1999, the information that memory impairment differs according to age, as well as educational level, was added to the definition made on MCI. MCI usually manifests itself with subjective complaints such as forgetting the names and not being able to remember where the items were placed. However, it has been observed that 30% of cases diagnosed with MCI do not progress to AD soon [6]. (3) Alzheimer's dementia: Typically, the symptoms of the disease begin with mild memory difficulties and cognitive impairment develops into dysfunctions in complex daily activities and some other aspects of cognition. When AD is diagnosed clinically, neuron loss and neuropathological lesions occur in many brain regions [7]. However, there is no ideal biomarker to identify AD, and a definitive diagnosis can only be made by autopsy or biopsy. Therefore, the diagnosis of AD can be made by medical history, laboratory tests, neuroimaging, and neuropsychological methods. These clinical assessments are not specific and costly. As a result, an accurate, universal, specific, and cost-effective biomarker is needed for early diagnosis and to monitor disease progression and treatment response [8].

The National Institute on Aging-Alzheimer's Association (NIA-AA) has developed new study criteria to use a panel of prognostic fluids and imaging biomarkers to determine the probability of AD pathology and preclinical AD staging and prodromal and later progression to clinical AD. These are cerebrospinal fluid (CSF) amyloid-β (Aβ) 42, amyloid positron emission tomography (PET), CSF total tau, threonine 181 (T181) phospho-tau, magnetic resonance imaging (MRI) mesial temporal lobe (MTL) atrophy, 18F-fluorodeoxyglucose (FDG)-PET temporoparietal/precuneus hypometabolism, or hypoperfusion [9]. Today, standard neuropsychological tests are used to diagnose AD and are widely supported by expensive neuroimaging methods and invasive laboratory tests. In recent years, electroencephalography (EEG) has emerged as an alternative noninvasive technique compared to more expensive neuroimaging methods such as MRI and PET [10, 11].

2. Alzheimer's disease and its pathophysiology

Data obtained with AD have shown the presence of amyloid plaques and neurofibrillary tangles in the pathology of the disease and that these pathological aggregates have a specific distribution pattern and density [12, 13].

Molecular studies have shown that the main component of amyloid plaques is amyloid beta (Aβ), and neurofibrillary tangles are tau protein. In AD patients, the pathway that forms the Aβ peptide is more active or is thought to be a defect in the mechanism of Aβ clearance. There are mature fibrils in the structure of amyloid plaques. In pathology studies in AD patients, amyloid plaques are indispensable pathological findings and Aβ formation in the pathogenesis of the disease is thought to initiate the pathogenesis of the disease. This hypothesis is defined as the "amyloid cascade hypothesis" [14]. In the pathogenesis of AD, tau hyperphosphorylation is known to impair microtubule stability and function, as well as to gain toxic function, for instance, tau aggregates induce apoptosis. However, like Aβ, it is thought that the tau oligomers they form are associated with neurodegeneration and memory impairment rather than the aggregates formed by the tau protein [15].

3. Alzheimer's disease and EEG

The source of routine EEG activity recorded from the scalp is the postsynaptic potentials of cortical pyramidal cells. According to the synaptic activity being

excitatory and inhibitory, the postsynaptic membrane becomes depolarized or hyperpolarized. The total electrical current generated by these excitatory and inhibitory postsynaptic potentials from millions of neurons creates superficial EEG activity. Adeli and Ghosh-Dastidar developed the wavelet-chaos method for the analysis of delta, theta, alpha, and beta (**Table 1**) subbands of EEG to identify potential markers in Alzheimer's disease.

To evaluate the effect of visual warning and attention, evaluation is done with eyes open and eyes closed. EEGs from different loci in the brain are used to explore the responsible areas of the brain and directly measure the functioning of synapses in real time [16, 17].

In AD, a significant decrease in cortical alpha frequency (8–10.5 Hz) was observed, especially in the limbic, temporal, parietal, and central areas [6]. However, it has been reported that the age of onset of AD can change this criterion, and that focal and diffuse EEG abnormalities are more common in early onset AD patients than in late-age AD patients. In the first studies, an increase in theta activity in EEG was considered as one of the earliest changes in Alzheimer's dementia, while alpha activity was found to decrease during or after the disease [18].

EEG markers showing the progression of the disease in MCI cases include an increase in delta and theta power and a decrease in beta or alpha power in the temporal and occipital regions [19]. Osipova et al. showed that alpha rhythm shifts from the parieto-occipital region to temporal regions in AD [20]. In other spontaneous EEG studies, it was found that frontal delta and occipital theta sources were higher in MCI patients than healthy ones, and frontal delta sources and the Mini-Mental State Examination (MMSE) showed negative correlations [21, 22].

The cortical cholinergic system has an important role in controlling many different functions such as cerebral blood flow, cortical activity, sleep/wake cycle, modulation of cortical plasticity, and cognitive performance and learning-memory processes. The presence of cholinergic neurons in the basal forebrain was first reported by Shute and Lewis in 1967. ACh deficiency is observed in the brains of individuals with AD in the entire cortex, especially the temporoparietal cortex [23, 24]. Also, one of the possible mechanisms underlying the observed relationship between Aβ42 and increased slow EEG activity is Aβ and cholinergic deficiencies in the brain in AD. Cholinergic therapy has different effects on delta and theta oscillation responses. Theta oscillations were similar in controls to those receiving cholinergic therapy in the AD patients, regardless of treatment. In other words, theta oscillation responses are affected by cholinergic therapy in AD patients, while the amplitudes of delta oscillation responses are not affected by cholinergic therapy [25].

Moreover, in studies evaluating the relationship between AD neuropathology, EEG frequencies, and CSF markers, amyloid β42 (Aβ42) showed a significant relationship with slow frequency (delta and theta) activity, while phospho-tau (p-tau) and total tau (t-tau) are associated with activity at only fast frequencies (alpha and beta) (26). Smailovic et al. demonstrated the correlation of qEEG and

Type of wave	Frequency
Beta	>13 Hz
Alpha	8–13 Hz
Theta	4–7 Hz
Delta	1–4 Hz

Table 1.
EEG waves.

CSF abnormalities with the AD profile at different stages of cognitive impairment, which revealed that qEEG can demonstrate neurodegeneration-induced synaptic dysfunction [26].

4. Sensory-stimulated oscillations

Sensory-evoked oscillatory responses are obtained by digital filtering of the frequency bands such as delta, theta, alpha, beta, and gamma of the "evoked potential" that appears with the delivery of the sensory stimulus. Haupt et al. showed that gamma and beta2 bands showed a different distribution compared to both patient groups in the visual-evoked oscillatory responses that they examined in Alzheimer's, MCI and healthy group controls, and the current density distribution followed a movement from the right hemisphere to the left hemisphere in these patient groups. In a visual sensory-evoked oscillatory study, the difference between AD patients and the healthy group was shown to disappear when the stimulus did not contain the cognitive load. Besides, when controlled, the parieto-occipital theta-stimulated oscillatory responses of the untreated Alzheimer's patient group were found to be higher than those of the treated Alzheimer's patient group and the healthy group [27].

5. Sensory-evoked coherencies and event-related coherences

Coherence or phase-locking statistics are the most common methods used to evaluate relationships between neural communities [28, 29]. Hogan et al. investigated memory-related EEG strength and coherence in the temporal and central areas in early stage AD patients and the normal control group and the behavioral performances of mild Alzheimer patients did not differ significantly from the healthy ones while they found a decrease in high alpha coherence between central and right temporal cortex of Alzheimer patients [30]. Rossini et al. measured the spontaneous EEG coherence of healthy control and MCI patients (progressive and constant) and found that the course of disease in patients with high coherence in the delta and gamma frequency bands progressed faster [31]. In another study examining the coherencies related to the event in patients with mild AD using visual sparse stimuli, the authors found higher OI coherence in the "delta," "theta," and "alpha" bands compared to the controls in the AD group that did not receive drug treatment. Alpha OI coherence values are higher in the medicated group compared to the drug-free AD group [32].

6. Conclusion

AD is a progressive neurocognitive disease in the elderly population. This disease is characterized by behavioral problems, cognitive impairment, delirium, and memory loss.

Most studies in AD have been done on frequency changes with EEG reactivity. When eyes are open, theta and alpha reactivity index and alpha/theta index were integrated into this study and were found as a useful approach to evaluate quantitative EEG (qEEG). EEG is advantageous compared to functional MRI or PET, which indirectly detects metabolic signals due to its noninvasive, wide availability, low cost, and direct access to neuronal signaling. Studies reveal that neuritic plaques, nodes, tangles, granulovacuolar degeneration, and the formation of amyloid

angiopathy are some of the pathological variations that cause AD. Neuroprotective and symptomatic approaches such as antioxidants and neurotransmitters are effective in treating AD symptoms and delay their development. No cure can treat AD, but medications that can treat disease symptoms and delay its progression have been developed and will continue to be developed. Therefore, early diagnosis is the key in treating the disease. Advances in neuroimaging technology, cognitive neuroscience, psychopathology, neuropathology, and neurobiology lead to the discovery of AD biomarkers for early detection.

Researchers are also working on improving the accuracy of EEG-based AD diagnosis. New studies are needed to develop an algorithm in the early onset diagnosis of AD, and this will happen sometime in the future.

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Conflict of interest

The authors proclaim that they have no competing interests.

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