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Neurodegeneration and Epileptic Seizure: Earlier Than We Think

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Abstract

Objective: The purpose of this study is to compare demographical and cognitive features of patients who have neurodegenerative diseases with or without seizures.

Methods: This descriptive retrospective study included a total of 16 348 participants, 479 with seizures and 15 869 without seizures. Independent samples *t*-test and chi-square tests were used to compare age, education, Mini Mental State Examination, and gender of groups.

Results: There was a significant difference between patients with seizures and without seizures in age [$t(3764) = 2.815$, $P = .005$]. It is found that patients with seizures ($M = 67.51$, standard deviation = 9.69) were significantly younger than patients without seizures ($M = 70.37$, standard deviation = 9.51).

Conclusion: In all neurodegenerative diseases, especially Alzheimer's disease, at an early age and regardless of cognitive status, diagnosis of seizures at the first admission and subsequent follow-ups is of great importance in terms of the patient's quality of life, prognosis of the disease, and treatment options.

Keywords: Cognition, dementia, epilepsy, neurodegeneration, neurology, seizure.

INTRODUCTION

Neurodegenerative diseases is the second cause of epileptic seizures in the elderly after stroke, and the cause of approximately 50% of epileptic seizures in the elderly is unknown.[1] The most common degenerative diseases in the elderly can be listed as Alzheimer's disease (AD), Lewy bodies dementia (LBD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and multisystem atrophy (MSA).[2] Many comorbidities have been associated with dementia, and recent studies have reported that one or more seizures may be associated with dementia.[3] Temporary worsening of cognitive symptoms is common in patients with dementia, particularly AD. This deterioration is often described by loss of response and blank stares.

Caregivers report that the patient is occasionally "missed" or appears more sluggish and unresponsive on some days than others. It is thought that this may be a result of the silent seizures seen in dementia. In a study, it was found that the incidence of having at least 1 seizure in individuals with AD was higher than that in cognitively unimpaired elderly people.[4] In addition, it has been reported that patients with dementia are at 5 to 10 times more risk for epilepsy compared to healthy controls of the same age.[5] According to the evidence from longitudinal studies, the early age of onset, the severity of cognitive impairment, and the use of antipsychotics increase this risk in neurodegenerative diseases.[4] In previous studies, it has been reported that seizures are more common in patients with advanced stages of dementia. The first studies in this area were mostly conducted with patients with severe AD. However, in mouse models of Alzheimer's,[6] studies on seizures seen in the early stages of the disease were emphasized since it was shown that seizures and epileptiform activity can occur before amyloid β plaque deposition. It is known that abnormal synchronization in corticothalamic connections is associated with non-convulsive seizures characterized by momentary loss of consciousness and pauses in movements. Observation of similar seizures in AD patients suggests that the underlying mechanism is similar. It is thought that amyloid β plaques, which are also seen to accumulate in subcortical structures such as the thalamus in AD, cause degeneration and lead to deterioration of thalamocortical inhibition, and the resulting cortical hyperexcitability causes seizures.[7] An increasing number of studies show that seizures, which are possible results of hyperexcitability in the cortex, can occur in the early stages of all dementias, especially AD, and may cause an increase in the severity of cognitive impairment.[8-10] However, some studies have noted an increased risk of seizures with increasing dementia severity or early onset of AD.[11] It is thought that not only cortical but also subcortical structures (cholinergic nuclei and locus coeruleus) are involved in the pathogenesis; also, glutamate/gamma-aminobutyric acid imbalance at the cellular level and inflammation play a role in this situation.[12]

In the longitudinal follow-up of patients before dementia diagnosis, it was reported that seizures may be a precursor to AD or may occur simultaneously with the onset of cognitive impairment.[13]

Seizures can accelerate cognitive decline in patients with dementia.[14] In addition, seizures and myoclonus have been associated with reduced survival rate in patients with Alzheimer's.[15] It is essential to recognize and intervene beforehand, as the frequency of seizures will worsen the current cognitive status and reduce the patient's quality of life.

The aim of this study is to compare the demographical and cognitive characteristics of patients who have neurodegenerative diseases with and without seizures in order to understand the effects of seizures on cognition or factors that affect seizure occurrence.

METHODS

Participants

Data of 16 348 participants from 29 different AD centers were included in the study retrospectively. This data were obtained from the American National Alzheimer's Coordination Center Data Set supported by the National Institute on Aging. The primary etiological diagnoses of the participants included AD, LBD, MSA, PSP, CBD, FTLD, and vascular dementia (VD). Of the participants included in the study, 55.6% had primary etiological diagnoses of AD, 5.5% of LCD, 1% of PSP, 1.1% of CBD, 8.8% of FTDL, and 2.7% of VD. Primary etiological diagnosis information could not be reached in 25.3% of the participants. During the diagnosis of neurodegenerative disease, the history of seizures was questioned; the cases with a history of seizures requiring treatment in the last year were recorded as active, and the cases without seizures in the last year but requiring treatment before were recorded as remote seizures. In all the cases included in the study, neurodegenerative prognoses were proven by autopsy, while 479 participants had a history of seizures, 15 869 participants did not have a history of seizures.

Statistical Analysis

Demographic and cognitive characteristics of patients with seizures (active and remote) were compared with individuals without seizures. Statistical Package for the Social Sciences version 24.0. (IBM SPSS Corp.; Armonk, NY, USA) was used in all analyses. Demographic variables were evaluated with independent samples *t*-test for comparisons between groups (age, education, and Mini Mental State Test scores). Gender (female-male) variable was analyzed with chi-square test. The normality distribution of data was evaluated with Shapiro–Wilk Test.

RESULTS

Determining the distribution of the variables was important for choosing an appropriate statistical method. So a Shapiro-Wilk test was performed and did not show evidence of non-normality for MMSE [W(479) = .990; P = .30], age [W(479) = .759; P = .15], and education [W(479) = .402; P = .28].

Independent samples *t*-test showed that there was a statistically significant difference in age between subjects with and without seizures [t(3764) = 2.815, P = .005]. Participants with seizures (M = 67.51, standard deviation (SD) = 9.69) were found to be significantly younger than participants without seizures (M = 70.37, SD = 9.51). Significant difference in education [t(16346) = .577, P = .571], MMSE [t(152)=.179, P=0.774], and gender variables [χ^2 (1, N = 12238) = .176, P =.615.] was not observed (Table 1).

Table 1. Demographic Variables and MMSE Scores in Patients With and Without Seizures With Cognitive Impairment

	With Seizures (N = 479)	Without Seizures (N = 15 869)	*P*
Age[a]	68.86 ± 10.80	72.27 ± 10.10	**<.001**
Education[a]	15.39 ± 9.47	15.64 ± 9.31	.571
Gender (F/M)[b]	240/239	8136/7733	.615
MMSE[a]	24.47 ± 12.32	25.32 ± 13.18	.199

Data are presented as mean ± standard deviation.
[a]Independent samples *t*-test; [b]Chi-square test.
MMSE, Mini Mental State Examination; F, female; M, male.
Statistically significant values are shown in bold type.

DISCUSSION

The findings of our study show that patients with seizures and neurodegenerative disease are younger than those without seizures and with neurodegenerative disease. In our study, MMSE was used as a basis for grading the cognitive status of the participants, and it was observed that there was no difference in MMSE scores in participants with and without seizures.

In previous studies, it has been reported that seizures are seen in the later stages of AD.[16,17] Current studies supported by electrophysiology show that seizure activity precedes the symptoms of the disease in a substantial number of cases.[8] Seizures are 2 times more common in early-onset AD than late-onset AD. As shown in our study, the younger age of patients with seizures may be since seizures are associated with early-onset familial AD. It has been shown that autosomal dominant presenilin I (PSEN1) and/or amyloid precursor protein (APP) gene mutations, which are known to be associated with early-onset AD, are also associated with seizures.[18,19]

Previous studies show that the degree of cognitive deterioration in AD is associated with the risk of seizures. However, this relationship was found by evaluating the severity of cognitive impairment according to the duration of the disease.[20] In our study, the cognitive status of the participants was evaluated with MMSE, and contrary to the general, no difference was found between the MMSE scores of the patients with and without seizures. In the light of this information, it is thought that the presence of seizures should be questioned in the presence of any neurodegenerative disease, regardless of the patient's cognitive status. Short screening tests performed in the clinical setting do not always provide detailed information about the cognitive status, and the presence of seizures may also occur independently from the worsening of the cognitive status or the severity of cognitive symptoms. The difference of our study from the similar ones in the literature is that the sample size is quite large, and the participants consist of cases with different neurodegenerative diseases proven by biomarkers.

Our findings show that seizures should be questioned at an early age, preferably at the first admission and all subsequent follow-ups, not only in AD but also in all degenerative processes with cognitive impairment. In current studies initiated with the increasing importance of therapeutic approaches on the pathophysiology of AD, it has been reported that hyperexcitability may be associated with the underlying pathological protein accumulation. It has been suggested that the inhibitory effect of antiepileptic drugs on hyperexcitability may reduce pathological

MAIN POINTS

- Seizures can occur in the early stages of all dementia syndromes.
- Seizures and epileptiform activity can occur before amyloid β plaque deposition.
- Hyperexcitability accelerates protein accumulation in neurodegenerative diseases.
- The frequency of seizures will worsen the current cognitive status and reduce the patient's quality of life.

Aβ protein accumulation.[21] Controlling possible seizures in patients followed up with a diagnosis of neurodegenerative disease may also provide benefits in terms of reducing the burden of pathological aggregation, along with preventing seizure-related cognitive decline.

In general, it is thought that seizures tend to appear in the later stages of the disease and at an older age. However, studies have reported that the incidence of seizures in the early period is relatively high. For this reason, seizures should be inquired at the first diagnosis and follow-ups. Since the clinical presentation can be very diverse in dementia patients, especially AD, it is not always easy to recognize seizures. Therefore, besides generalized motor seizures, a more detailed seizure query [vacant stare, automatism, temporary confusion, etc.] should be done.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Dokuz Eylul University Faculty of Medicine (Date: October 6, 2021, Decision No: 2021/27-01).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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