Tropical Journal of Pharmaceutical Research November 2021; 20 (11): 2381-2386
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i11.21

Original Research Article

Prevalence and predictors of seizure in patients with Alzheimer's disease at a tertiary care center in Riyadh, Saudi Arabia

Mohammed Alessa[1]*, Shaden Alsugheir[2,3], Nouf Almutairi[2,3], Abdulaziz Alqahtani[2,3], Lina Alhumaid[2,3], Rahaf Alqahtani[2,4], Mohamed Eldigire Ahmed[5]

[1]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, [2]King Abdullah International Medical Research Center, Ministry of the National Guard-Health Affairs, [3]College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, [4]College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [5]Applied Statistics and Demography, University of Gezira, Wad Madani, Sudan

For correspondence: **Email: AlessaM@ksu.edu.sa; **Tel:** 00966-504106182*

Sent for review: 23 December 2020 *Revised accepted: 22 October 2021*

Abstract

Purpose: *To assess the prevalence and predictors of seizures in patients with Alzheimer's disease (AD) at a Saudi tertiary hospital.*
Methods: *A retrospective, matched case-control study was conducted using the electronic medical records of patients with AD who had an unprovoked seizure, from October 2015 to May 2018.*
Results: *Nineteen cases and 195 controls were identified. Statistically significant risk factors for an unprovoked seizure in patients diagnosed with AD were hypertension (p = 0.001), autoimmune disease, stroke and TIA (p = 0.001). The multivariate logistic regression analysis identified hypertension (OR = 2.89; p = 0.009) and autoimmune disease (OR = 19.6; p = 0.045) as predictors of unprovoked seizure in AD patients.*
Conclusion: *The occurrence of unprovoked seizures is more likely in severe cases of AD. In addition, the risk of seizure in patients with AD increases with two co-morbid conditions, hypertension, and autoimmune disease. However, further studies are required to determine the underlying mechanism of the association between the two risk factors and AD.*

Keywords: *Alzheimer's disease, Seizure, Incidence, Predictors, Risk factor*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders known among older patients [1]. In the United States, AD is considered the sixth leading cause of mortality and 4.5 million patients are currently living with the disease [1]. In Saudi Arabia, there are no official statistics related to the prevalence of AD, but according to the Saudi Ministry of Health, the estimated number of AD cases are at least 50,000, most of whom are women [2].

Several risk factors have been linked to AD which include aging, smoking, cardiovascular diseases, stroke/transient ischemic attack (TIA),

depression and family history of AD. In general, the clinical manifestations and symptoms of AD develop slowly and are progressive [1]. The most prevalent clinical manifestations of AD include memory loss, confusion, impaired judgment, language disturbance and agitation, while some other clinical manifestations are unusual which include seizures and Parkinsonian features [1].

Some previous studies have linked the late stages of AD with unprovoked seizures [3,4]. It is estimated that the prevalence of seizures in AD patients can reach up to 64 % [5]. While the predictors of an unprovoked seizure in AD patients include a younger age, severe dementia, focal epileptiform findings from an electroencephalogram (EEG) and an African American ethnicity [6]. Amatniek *et al* found that the risk of developing unprovoked seizure was 87-fold higher in younger patients, while it was more than 3-fold higher in the older group compared to the known AD age group [6]. In addition, there is a reported relationship between AD and seizure disorders. Hauser *et al* found that patients with AD are at higher risk of developing seizures and epilepsy [4].

The aim of this study was to determine the prevalence and predictors of seizures in AD patients at King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia.

METHODS

Study setting and participants

A case-control study was conducted retrospectively among AD patients who had seizures from October 2015 to May 2018 and were seen in the neurology clinic at KAMC, Ministry of National Guard-Health Affairs (MNGHA), in Riyadh, Saudi Arabia. Patients with the diagnosis of AD and older than 18 years, either males or females, were included in the study. Patients who had a seizure provoked by medications, hypoglycemia or electrolyte imbalance were excluded from the study. Institutional Review Board (IRB) approval (no. H01R005) was obtained from King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia. In addition, the STROBE guidelines were followed in this study [7].

Identification of cases

The KAIMRC database was used to identify the cases that will be matching the inclusion criteria at the neurology clinic. Using an electronic chart review approach, all AD patients diagnosed with seizures from October 2015 to May 2018 were included (n = 214). Of the 214 identified AD patients, only 19 patients matched our inclusion criteria. For each case, the electronic medical record was reviewed to ensure that the case is eligible for inclusion. Cases were matched to controls based on predictors of seizure.

Seizure's predictors in AD Patients

Seizure's predictors assessed based on published findings, seizure's epidemiological knowledge, and patient's characteristics. The evaluated potential predictors are listed in Table 1.

Table 1: Potential predictors based on previous studies [3,4,8-10]

Demographic data	• Age • Age at diagnosis of AD • Age at onset of seizure • Gender
Disease duration	
Seizure type	• Simple • Generalized
Severity of AD	• Mild • Moderate • Severe
Co-morbidity	• Hypertension • Congestive heart failure • Autoimmune diseases (systemic lupus erythematosus, celiac disease, myasthenia gravis, rheumatoid arthritis, psoriasis, Hashimoto's encephalopathy, neuromyelitis optica, multiple sclerosis, and bullous pemphigoid) • Depression • Stroke • CNS infection • Mental illness
Medications	• Anti-depressant medication
Addiction	• Alcohol • Drugs

CNS: Central nervous system

Data collection and handling

The data was retrieved from the Best-Care System, an electronic medical records system used in Ministry of National Guard - Health Affairs (MNGHA), under the supervision of a neurology consultant and a statistician. Medical record information was collected using a prepared data collection form. The data collectors used the approved data collection form to ensure consistency of coding. The supervisors

reviewed the data collected by the data collectors to ensure the accuracy of the data.

Statistical analysis

Data cleaning

The raw data was audited and cleaned prior to the statistical analysis. In order to accomplish this task, all interval variables were checked and summarized in terms of maximum and minimum values. Minimum and maximum values were checked and compared against a possible maximum and minimum value of each variable and variables with implausible values were flagged. A similar process was done to the categorical variables to identify any potential anomalies (miscodes) using a frequency analysis.

Data analysis

Descriptive statistical analyses were performed. Continuous variables were summarized as mean ± SD and median (range). Proportions were used for categorical variables. In addition, demographic and clinical information were summarized in frequency tables. The 95% confidence interval (CI) was used. The binary logistic regression model was used to estimate the regression equation between the outcome variable (AD) and selected significant explanatory variables, namely hypertension and auto-immune disease. The binary logistic regression model takes the formula:

A *P* value of less than 5 % was considered as statistically significant. All statistical analyses were performed using SPSS 21.0 (Release 21.0.0.0, IBM, USA).

RESULTS

The total number of identified AD patients was 214 patients. Patients' age ranged from 56 years to 111 years. Almost half of the sample (46 %, n = 98) were males. In addition, majority of the patients (98 %) were Saudis.

Prevalence of seizures

Out of 214 patients, 19 (8.9 %) of AD patients developed an unprovoked seizure (95 % CI, 8.2 - 9.5). Males constituted 47.4 % (n = 9). The mean age at diagnosis of AD was 73.2 ± 8.8 years (range = 53 to 88 years), and the mean age at seizure onset was 74.3 ± 13.8 years (range = 57 - 91years). The mean duration from the AD diagnosis to the occurrence of the seizure was 19 ± 12.8 months (range = 6 - 60 months). Generalized tonic-clonic seizure was the most prevalent type of seizure accounting for 94.7 % (n = 18) of the patients, and one patient (5.2 %) had a focal seizure.

Table 2: Characteristics of AD patients with and without unprovoked seizures

Characteristics	AD with seizures (n = 19)	AD without seizure (n = 195)	*P*-value
Male	9	89	0.885
Mean age years (SD)	78.2 + 8.8	75.1 ± 8.9	0.140
Mean age at diagnosis of AD (SD)	73.2 ± 8.8	73.1 ± 9.5	0.098
Mean duration of AD months (SD)	19 ± 12.8	18.2 ± 10.6	0.444
Severity of AD			
Mild	0	25	
Moderate	3	31	0.001
Severe	16	42	
Unknown	0	97	
Risk factors			
Head Trauma	5	3	0.155
History of Epilepsy	1	3	0.717
Hypertension	15	80	0.001
Congestive Heart Disease	2	15	0.776
Auto-immune Disease	1	11	0.040
Use Anti-depressant	3	14	0.060
Mental Disease	6	29	0.710
Stroke	9	28	0.001

Table 3: Positive risk factors by seizure status

Factor	AD with seizures n=19 n (%)	AD without seizure n=195 n (%)	OR (95% CI)
History of epilepsy	5 (26.3)	3 (1.5)	22.8 (4.9-105.6)
Head Trauma	1 (5.3)	3 (1.5)	3.5 (0.35-35.9)
Hypertension	15 (78.9)	80 (41.0)	5.4 (1.7-16.8)
Congestive heart disease	2 (10.5)	15 (7.9)	1.4 (0.29-6.7)
Auto-immune disease	1 (5.3)	1 (0.51)	10.8 (0.65-179.7)
Use anti-depressant	3 (15.8)	14 (7.2)	2.4 (0.63-9.3)
Mental disease	6 (31.6)	29 (14.9)	2.7 (0.92-7.5)
Stroke	9 (47.4)	28 (14.4)	0.4 (2.0-14.4)

Table 4: Binary logistic regression of seizure predictors

Variable	β	*P*-value	OR
Hypertension	-1.061	0.009	2.89
Auto-immune disease	2.983	0.045	19.6

The analysis included 19 patients with AD and an incidental diagnosis of seizures, and 195 patients with AD diagnosis but without seizures. Characteristics of matched cases reported in Table 2. The majority of the patients (84.0 %, n = 16) had severe AD, and 3 patients (15.8 %) were classified as moderate AD, suggesting that the risk of a seizure is more likely to occur in severe cases of the disease.

The potential risks of developing a seizure in AD patients include hypertension, stroke or transient ischemic attack (TIA), head injury, current use of psychotropic medications, congestive heart disease and auto-immune disease. The confounders were analyzed using bi-variant analysis. Statistically significant risk factors of developing a seizure in AD patients were hypertension *(p* = 0.001), autoimmune disease (*p* = 0.040) as well as stroke and TIA (*p* = 0.001) (Table 3).

The multivariate logistic regression analysis indicated hypertension (OR = 2.89; *p* = 0.009) and autoimmune disease (OR = 19.6; *p* = 0.045) as predictors of seizure in AD patients (Table 4).

DISCUSSION

Earlier studies reported a higher risk of unprovoked seizures among patients with AD [4-6]. In the current study, unprovoked seizure was reported in 19 of 214 AD patients with an incidence rate of 8.9 %. McAreavey *et al* conducted a study among AD patients, and found that out of 208 AD patients, unprovoked seizures were reported among 19 of them (9.1 %) [11]. In addition, Cheng et al reported that 44 of 937 AD patients (4.7 %) developed unprovoked seizures during the 10 - year follow-up period [12].

In terms of the type of seizure, different types are reported in literature [4,6]. In the current study, the majority (94.7 %, n = 18) were classified as generalized seizures. Similarly, Mendez *et al* reported generalized seizures in majority of AD cases (90 %) [13]. In contrast, Rao *et al* reported that 72 % of the seizures were complex partial seizures [9]. In addition, Mendez *et al* indicated that the onset of the seizures tends to occur during the later stages of the disease, on average 6.8 years after the diagnosis of AD [13]. In contrast, in the current study, the average seizure onset was 1.5 years after the diagnosis of the disease.

Furthermore, many studies suggested that the severe form of AD had a higher risk of seizure with frequencies ranging from 9 % to 64 % [13 - 15]. In our study, 84 % of AD patients with seizure had a severe type of AD. In addition, hypertension also indicated an increased risk of seizure in AD patients. However, Bernardi *et al* did not find hypertension as a predictor of seizure in AD patients but considered it as a protective factor against seizure occurrence [16].

In addition, many studies have reported that a younger age at diagnosis of AD was a significant risk factor for developing seizures [6,8-18]. However, in the current study, younger age was not a risk factor for developing seizure in AD patients. This could be attributed to the lack of proper documentation as many of the files lacked the date of the initial diagnosis.

Limitations of the study

We acknowledge that our study has some limitations. This is a single center study. The research results may have been more generalizable if it was conducted in multiple centers with a larger population. In addition, due

to the retrospective study design, no follow up data of patients were obtained. Furthermore, the data were collected from electronic medical records with some missing data; for example, the Mini-Mental State Examination scores (MMSE), Clinical Dementia Rating (CDR), Electroencephalogram (EEG), and the classification of AD.

CONCLUSION

The results of this study show that the occurrence of seizure in patients with AD is more likely in severe cases of the disease. In addition, the risk of seizure in patients with AD increases with two co-morbid conditions, namely, hypertension, and autoimmune disease. Further studies are required to determine the underlying mechanism of the association between the risk factors for seizures and AD.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

REFERENCES

1. *Alzheimer disease. National Center for Biotechnology Information (US). Genes and Disease. 1998 [cited 2018 May 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK22170/.*
2. *World Alzheimer's Day. Health Days. 2013 [cited 2018 May 26]. Available at: https://www.moh.gov.sa/en/HealthAwareness/healthDay/2013/Pages/HealthDay-019.aspx.*
3. *Hesdorffer, DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult-onset unprovoked seizures. Neurol 1996; 46(3): 727-730*
4. *Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. Neurol 1986; 36(9): 1226–1230.*
5. *Friedman D, Honig LS, Scarmeas N. Seizures and epilepsy in Alzheimer's disease. CNS Neurosci Ther 2012; 18(4): 285–294.*
6. *Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, Albert M, Brandt J, Stern Y. Incidence and Predictors of Seizures in Patients with Alzheimer's Disease. Epilepsia 2006; 47(5): 867-872.*
7. *Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Clin Epidemiol 2008; 61(4): 344-349*
8. *Daniel FM, Lawrence SH, Nikolaos S. Seizures and Epilepsy in Alzheimer's Disease. CNS Neurosci Ther 2012; 18(4): 285–294.*
9. *Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: Frequency, seizure types, and treatment outcome. Epilepsy Behav 2009; 14(1): 118–120.*
10. *Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, et al. Prevalence of Dementia in the United States: the Aging, Demographics, and Memory Study. Neuroepidemiol 2007; 29(1-2): 125-132.*
11. *McAreavey MJ, Ballinger BR, Fenton GW. Epileptic seizures in elderly patients with dementia. Epilepsia 1992; 33(4): 657–660.*
12. *Cheng CH, Liu CJ, Ou SM, Yeh CM, Chen TJ, Lin YY, Wang SJ. Incidence and risk of seizures in Alzheimer's disease: A nationwide population-based cohort study. Epilepsy Res 2015; 115, 63–66.*
13. *Mendez MF, Catanzaro P, Doss RC, ARguello R, Frey WH II. Seizures in Alzheimer's disease: Clinicopathologic study. J Geriatr Psychiatry Neurol 1994; 7(4): 230–233.*
14. *Yaffe K, Falvey C, Harris TB, Newman A, Satterfield S, Koster A, Ayonayon H, Simonsick E. Effect of Socioeconomic Disparities on Incidence of Dementia among Biracial Older Adults: Prospective Study. BMJ 2013; 347: f7051.*
15. *Risse SC, Lampe TH, Bird TD, Nochlin D, Sumi SM, Keenan T, Cubberley L, Peskind E, Raskind MA. Myoclonus, seizures, and paratonia in Alzheimer disease. Alzheimer Dis Assoc Disord 1990; 4(4): 217–225.*
16. *Bernardi S, Scaldaferri N, Vanacore N, Trebbastoni A, Francia A, D'Amico A, Prencipe M. Seizures in Alzheimer's disease: a retrospective study of a cohort of outpatients. Epileptic Disorders 2010; 12(1): 16–21.*
17. *Volicer L, Smith S, Volicer BJ. Effect of seizures on progression of dementia of the Alzheimer type. Dementia 1995; 6(5): 258–263.*
18. *Jacobs D, Sano M, Marder K, Bell K, Bylsma F, Lafleche G, Albert M, Brandt J, Stern Y. Age at onset of*

Alzheimer's disease: relation to pattern of cognitive dysfunction and rate of decline. Neurol 1994; 44(7): 1215–1220.