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Association between Risk Factors and New-Onse Seizures in Old Age Population

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Authors' contributions

This work was carried out in collaboration among all authors. The concept of study, data analysis, drafting and finalizing of the results were done by author SJ. The article was critically reviewed and finally drafted by author MZJ Finally reviewed and approved by authors SF and DA. All authors read and approved the final manuscript.

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ABSTRACT

Background: Seizures are one of the most common diseases of the nervous system in the elderly especially late-onset seizures significantly impact the quality of life of older people. A recent epidemiological study showed that the average annual incidence of seizures in the elderly aged 65 years and above is up to 240 per 100,000. Nearly 25% of people newly diagnosed with seizures. With increasing age, the prevalence and incidence of epilepsy and seizures increases correspondingly. The existence of some special causes may contribute to the high incidence of epilepsy and seizures in the elderly. It is reported that the causes of seizures for example (stroke, cns infections, electrolyte imbalance, metabolic disorders, and neurodegenerative diseases) can be found in nearly 50% of elderly patients. Younger patients with epilepsy and seizures often show a genetic cause. However, new-onset seizures in the elderly are mainly the consequence of accumulated injuries to the brain and other secondary factors.
Objective: To determine the association between risk factors and new-onset seizures in old age population at a tertiary care hospital, Karachi.
Methods: A case control study on old age patients of > 60 years visited emergency department (ED) either with new onset seizure or without seizure were conducted at ED of Ziauddin University

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Hospital Karachi. 154 consecutive old age patients were distributed into two groups i.e., case group (77 old age patients of new onset seizure) and control group (77 old age patients without seizure). Risk factors including stroke, dementia, head trauma, metabolic causes, brain tumor, and infection of central nervous system (CNS), depression and anxiety were evaluated.

Conclusion: New-onset seizures are significantly associated with age, diabetes mellitus, hypertension, ischemic heart disease, brain tumor and CNS infection.

Keywords: Seizures; stroke; dementia; infection; depression.

ABBREVIATIONS

ED : Emergency Department
CNS : Central Nervous System
GTCS : Generalized Tonic–Clonic Seizure
DM : Diabetes Mellitus
HTN : Hypertension
IHD : Ischemic Heart Disease
ES : Epileptic Seizures
AD : Alzheimer's disease
QOL : Quality of Life
CNS : Central Nervous System
TBI : Traumatic Brain Injury
CVD : Cerebrovascular Disease
CAA : Cerebral Amyloid Angiopathy
PRES : Posterior Reversible Encephalopathy syndrome
RCVS : Reversible cerebral Vasoconstriction Syndrome
AVMs : Arteriovenous Malformations
CADASIL : Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
MELAS : Mitochondrial Encephalopathy with Lactic Acidosis and Stoke Like Episodes
SE : Status Epilepticus
ECG : Electrocardiogram
EEG : Electroencephalography
MRI : Magnetic resonance imaging
CT : Computed tomography
SPSS : Statistical Package for Social Sciences

1. INTRODUCTION

Seizures are one of the most common diseases of the nervous system in the elderly, second to dementia and stroke [1]. Geriatric seizures include;

1) Pre-elderly (< 60 years old) epilepsy continuing to old age stage.
2) New-onset seizures in the elderly.

Seizures, especially late-onset seizures significantly impact the quality of life of older people and increases the health care resource burden on our society [2].

A recent epidemiological study showed that the average annual incidence of seizures in the elderly aged 65 years and above is up to 240 per 100,000 [3]. Nearly 25% of people newly diagnosed with seizures are underage of 20 and the same proportion of newly diagnosed patients is over the age of 60 [4]. Old age stage is a peak period for developing epilepsy and seizures [5]. The incidence of epilepsy and seizures is higher in the elderly (≥ 60 years old) than in other age groups [6-7]. It has been estimated that the annual incidence is 85 per 100,000 for people aged 65–69 years, 159 per 100,000 for people aged over 80 years, and 80.8 per 100,000 people in the over all age groups [8].

With increasing age, the prevalence and incidence of epilepsy and seizures increases correspondingly [9]. The existence of some special causes may contribute to the high incidence of epilepsy and seizures in the elderly [10-21]. It is reported that an underlying etiology

can be found in nearly 50% of elderly patients [22]. Younger patients with epilepsy and seizures often show a genetic cause [23-29]. However, new-onset seizures in the elderly is mainly the consequence of accumulated injuries to the brain and other secondary factors [30-33].

Studies have shown that seizures affect approximately 1 to 2% of the elderly population, and the incidence increases progressively with the advance in age [34-45]. These cases of epilepsy can occur due to an acute cerebral seizure or have no apparent precipitator [46].

On the other hand regarding diagnosis, there is consensus in the literature that epileptic seizures (ES) are more difficult to diagnose in the elderly for various reasons such as the difficulty in obtaining an accurate clinical history [47-53], a frequently atypical ictal presentation, difficulty in making a differential diagnosis between an epileptic and non-epileptic event [54] and due the occurrence of comorbidities [55].

Seizures are considered to be one of the commonest neurological affections in the elderly and considering the fact that the population of the elderly is on the rise, remedial public health measures to address this issue becomes mandatory which is unfortunately abysmal in developing countries [56-60]. No national publication was found which should address this entity and on the contrary only a few international publications on epilepsy in this age range were found including one important Brazilian study.

New-onset seizures in elderly people often has an underlying etiology, including cerebrovascular diseases, primary neuron degenerative disorders, intracerebral tumors and traumatic head injury [5]. Stroke and other cerebrovascular diseases are the most important risk factors for new-onset epilepsy and seizures in the elderly, which account for 30%–50% in all identified etiologies [61-63]. Stroke is an important cause of epilepsy and seizures [64]. Primary neurodegenerative disorders like Alzheimer's disease (AD) account for around 10%–20% of all identified causes in older people [65].

The rationale of the study: is to measure the association between risk factors and new-onset seizures in old age population, it is clinically plausible to identify association between risk factors & new onset seizures in our population and surprisingly there have been no local studies published during last 5 years in this regard [66-74]. As a large number of the Pakistani population belongs to the rural areas and poor socio economic strata, therefore most of our patients report very late due to lack of easy access to medical facilities and financial constraints as compared to other developed countries.

It is important to investigate the status of new onset epilepsy in the elderly patients of our country, so that an accurate clinical diagnosis is made and also treatment of such patients could be streamlined in an appropriate direction to prevent further delay and complications.

2. MATERIALS AND METHODS

2.1 Study Setting

The study was performed at Dr Ziauddin University Hospital North Nazimabad Campus, Karachi.

2.2 Study Design

Case control study.

2.3 Duration of Study

Six Months From 02-05-2019 TO 01-11-2019.

2.4 Sample Size

2.4.1 Software: Open epi

- Patient or informants not giving informed consent**.**

Sample Size: 154

- Case group: 77 Old age patients of new onset seizure
- Control Group: 77 Old age patients without seizure

Study Technique:

Non-Probability Consecutive Sampling.

Sample Selection for Case Group

Inclusion Criteria:

- Age > 60 Years
- Either Gender
- Patients with new onset seizures during last 6 month.

Exclusion Criteria:

- Age < 60 Years**.**
- Patients who have been diagnosed as epileptics for more than 6 months.

Sample Selection for Control Group
Inclusion Criteria:

- Age > 60 years
- Either gender
- Healthy population with risk of seizures..

Exclusion Criteria:

- Age < 60 years.
- Patient or Informants not giving informed consent.

3. DATA COLLECTION PROCEDURE

Patients meeting the inclusion criteria attending outpatient department (OPD) and emergency room (ER) were enrolled in the study. Prior to inclusion patients or informants were explained about benefits of the study and informed written consent was taken.

An approval from the institutional ethics committee was taken prior to commencement of this study. Brief history regarding duration of seizures, co-morbidity (diabetes mellitus, hypertension and ischemic heart disease) history of trauma was taken, and detailed clinical examination was done. Patients were divided into two group case and control as per operational definition. EEG (For Clinical Documentation) and brain imaging (CT scan and/or mri) were done to identify the risk factors of new onset seizures and association between risk factors and new onset seizures.

Blood workup like random blood sugar (RBS), urea/creatinine/electrolytes (UCES), liver function tests (LFTS), prothrombin time (PT), international normalization ratio (inr), serum albumin, calcium and magnesium were performed. This information along with demographics was entered in the proforma attached as annexure. Exclusion criteria was followed strictly to avoid confounding variables.

Sample Size for Unmatched Case-Control Study

For:

Two-sided confidence level(1-alpha)	95
Power (% chance of detecting)	80
Ratio of Controls to Cases	1
Hypothetical proportion of controls with exposure	40
Hypothetical proportion of cases with exposure:	62.5
Least extreme Odds Ratio to be detected:	2.50

	Kelsey	Fleiss	Fleiss with CC
Sample Size - Cases	78	77	85
Sample Size - Controls	78	77	85
Total sample size:	156	154	170

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19

CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.

Results from OpenEpi, Version 3, open source calculator--SSCC

Print from the browser with ctrl-P

or select text to copy and paste to other programs.

4. RESULTS

A total of 154 old age patients visited ed were selected for study on the basis of inclusion and exclusion criteria. Consecutive old age patients were distributed into two groups i.e., Case group (77 Old age patients of new onset seizure) and control group (77 old age patients without seizure).

Mean age of old age patients in case group (new onset seizure group) was 69.7 ± 7.6 (61-90) years and in control group (without seizure group) was 66.8 ± 6.0 (61-82) years.

Mean duration of disease in old age patients in case group (new onset seizure group) was 3.4 ± 1.6 (1-6) months and in control group (without seizure group) no duration of disease due to absence of seizure.

Gender of old age patients in case group (new onset seizure group) was male 32 (41.6%) and female 45 (58.4%) and in control group (without seizure group) was 40 (51.9%) and female 37 (48.1%). Pearson correlation coefficient was applied that shows p-value of 0.1.

Age distribution of old age patients in case group (new onset seizure group) was 61-70 years with 48 (62.3%) patients, 71-80 years with 22 (28.6%) patients and 81-90 years with 7 (9.1%) patients and in control group (without seizure group) was 61-70 years with 58 (75.3%) patients, 71-80 years with 17 (22.1%) patients and 81-90 years with 2 (2.6%) patients. Pearson correlation coefficient was applied that shows p-value of 0.04*.

Duration of disease distribution in old age patients in case group (new onset seizure group) was 1-3 months with 45 (59.2%) patients and 4-6 months with 31 (40.8%) patients and in control group (without seizure group) no duration of disease due to absence of seizure. Pearson correlation coefficient was not computable.

Type of seizure in old age patients in case group (new onset seizure group) was generalized tonic–clonic seizure (gtcs) in 51 (66.2%) patients and focal seizure in 26 (33.8%) patients and in control group (without seizure group) no type of seizure due to absence of seizure. Pearson correlation coefficient was not computable.

Diabetes mellitus in old age patients in case group (new onset seizure group) was present in 76 (98.7%) patients and absent in 1 (1.3%) patients and in control group (without seizure group) was present in 59 (76.6%) patients and absent in 18 (23.4%) patients. Pearson correlation coefficient was applied that shows p-value of 0.001*.

Hypertension in old age patients in case group (new onset seizure group) was present in 72 (93.5%) patients and absent in 5 (6.5%) patients and in control group (without seizure group) was present in 63 (81.8%) patients and absent in 14 (18.2%) patients. Pearson correlation coefficient was applied that shows p-value of 0.02*.

Ischemic heart disease (ihd) in old age patients in case group (new onset seizure group) was present in 39 (50.6%) patients and absent in 38 (49.4%) patients and in control group (without seizure group) was present in 25 (32.5%) patients and absent in 52 (67.5%) patients. Pearson correlation coefficient was applied that shows p-value of 0.02*.

Stroke in old age patients in case group (new onset seizure group) was present in 23 (29.9%) patients and absent in 54 (70.1%) patients and in control group (without seizure group) was present in 16 (20.8%) patients and absent in 61 (79.2%) patients. Pearson correlation coefficient was applied that shows p-value of 0.1**.**

Dementia in old age patients in case group (new onset seizure group) was present in 3 (3.9%) patients and absent in 74 (96.1%) patients and in control group (without seizure group) was present in 0 (0.0%) patients and absent in 77 (100.0%) patients. Pearson correlation coefficient was applied that shows p-value of 0.08.

Head trauma in old age patients in case group (new onset seizure group) was present in 0 (0.0%) patients and absent in 77 (100.0%) patients and in control group (without seizure group) was present in 33 (42.9%) patients and absent in 44 (57.1%) patients. Pearson correlation coefficient was applied that shows p-value of 0.001*.

Metabolic causes in old age patients in case group (new onset seizure group) was present in 27 (35.1%) patients and absent in 50 (64.9%) patients and in control group (without seizure group) was present in 27 (35.1%) patients and absent in 50 (64.9%) patients. Pearson correlation coefficient was applied that shows p-value of 1.0.

Types of metabolic causes in old age patients in case group (new onset seizure group) were hypoglycemia in 12 (44.4%) patients, hyponatremia in 9 (33.3%) patients, hypernatremia in 1 (3.7%) patients, hypocalcemia in 1 (3.7%) patients, hepatic encephalopathy in 3 (11.1%) patients and uremic encephalopathy in 1 (3.7%) patients and in control group (without seizure group) were hypoglycemia in 6 (22.2%) patients, hyperglycemia in 4 (14.8%) patients, hyponatremia in 11 (40.7%) patients, hypocalcemia in 1 (3.7%) patients, hepatic encephalopathy in 3 (11.1%) patients and uremic encephalopathy in 2 (7.4%) patients. Pearson correlation coefficient was applied that shows p-value of 0.4**.**

Brain tumor in old age patients in case group (new onset seizure group) was present in 6 (7.8%) patients and absent in 71 (92.2%) patients and in control group (without seizure group) was present in 0 (0.0%) patients and absent in 77 (100.0%) patients. Pearson correlation coefficient was applied that shows p-value of 0.01*.

Types of brain tumor in old age patients in case group (new onset seizure group) were primary brain tumor in 2 (33.3%) patients and secondary brain tumor in 4 (66.7%) patients and in control group (without seizure group) no type of brain tumor due to absence of brain tumor. Pearson correlation coefficient was not computable.

Infection of central nervous system (CNS) in old age patients in case group (new onset seizure group) was present in 17 (22.1%) patients and absent in 60 (77.9%) patients and in control group (without seizure group) was present in 1 (1.3%) patients and absent in 76 (98.7%) patients. Pearson correlation coefficient was applied that shows p-value of 0.001*.

Depression in old age patients in case group (new onset seizure group) was present in 2 (2.6%) patients and absent in 75 (97.4%) patients and in control group (without seizure group) was present in 0 (0.0%) patients and absent in 77 (100.0%) patients. Pearson correlation coefficient was applied that shows p-value of 0.1.

5. DISCUSSION

Elder population is most rapidly growing throughout the world and exposed to different chronic diseases and neurological disorder. Incidence as well as prevalence of epilepsy is much higher in elder population as compared to youngers. A large population of elders with epilepsy always remain undiagnosed due to failure in obtaining clinical history, absence of eye witness, atypical presentation of seizure and difficulty in differentiation between epileptic and non-epileptic events [1,75-76].

Globally, diagnosis of epilepsy in elder is always a big challenge for physicians for provide optimal health care and enhanced the quality of life of elders. Therefore, identification of comorbidities and risk factors is very important for early and accurate diagnosis of epilepsy in elders. Therefore, current research was designed in tertiary care hospital of karachi for determining the association between risk factors and new-onset seizures in old age population.

In current study, 154 older age patients were selected and distributed into two groups i.e., case group (77 old age patients of new onset seizure) and control group (77 old age patients without seizure). Most of them were female 45 (58.4%) diagnosed with new onset seizure as compared to male 32 (41.6%). Mean age of patients in new onset seizure group was high 69.7 ± 7.6 (61-90) years. Age is always an important factor in elders, as the age increased risk of developing epilepsy also increased. All the studies on elder population confirms the higher mean age of elders suffering from epilepsy such as; shariff em, et al. And phabphal k, et al. Reports the 70.12 ± 8.72 and 73.07 ± 9.97 years as mean age of epileptic patients [77-78].

Table 1. Age distribution in case and control

Age (years)	CASE		CONTROL	
	N	%	N	%
61-70	48	62.3	58	75.3
71-80	22	28.6	17	22.1
81-90	7	9.1	2	2.6
Total	77	100	77	100.0
Pearson Correlation coefficient				P-Value 0.04*

Table 2. Types of metabolic causes distribution in case and control

Types of metabolic causes	Case		Control	
	N	%	N	%
Hypoglycemia	12	44.4	6	22.2
Hyperglycemia	0	0	4	14.8
Hyponatremia	9	33.3	11	40.7
Hypernatremia	1	3.7	0	0
Hypocalcemia	1	3.7	1	3.7
Hepatic encephalopathy	3	11.1	3	11.1
Uremic encephalopathy	1	3.7	2	7.4
Total	27	100.0	27	100.0
Pearson correlation coefficient			P-Value 0.4	

Table 3. Brain tumor distribution in case and control

Brain tumor	Case		Control	
	N	%	N	%
Yes	6	7.8	0	0.0
No	71	92.2	77	100.0
Total	77	100.0	77	100.0
Pearson correlation coefficient			P-Value 0.4	

Table 4. Gender distibution in case and control

CNS infection	Case		Control	
	N	%	N	%
Male	32	41.6	40	51.9
Female	45	58.4	37	48.1
Total	77	100.0	77	100
Pearson correlation coefficient			P-Value 0.1	

Table 5. Depression distribution in case and control

Depression	Case		Control	
	N	%	N	%
Yes	2	2.6	0	0
No	75	97.4	77	100
Total	77	100.0	77	100.0
Pearson correlation coefficient			P-Value 0.1	

Table 6. Dementia distribution in case and control

Demetia	Case		Control	
	N	%	N	%
Yes	3	3.9	0	0.0
No	74	96.1	77	100
Total	77	100.0	77	100.0
Pearson correlation coefficient			P-Value 0.08	

Table 7. Stroke distribution in case and control

Stoke	Case		Control	
	N	%	N	%
Yes	23	29.9	16	20.8
No	54	70.1	61	79.2
Total	77	100.0	77	100.0
Pearson correlation coefficient			P-Value	
			0.1	

In current study, most of the patients were suffering from generalized tonic–clonic seizure. Commonly reported comorbidities in seizure and non-seizure group were; diabetes mellitus, hypertension and ischemic heart diseases and commonly reported risk factors were; stroke, dementia, head trauma, metabolic causes brain tumor, cns infection and depression. And patients with notable risk factors were metabolic disorder, strok, cns infection followed by brain tumor, dementia and depression.

Different studies reported the different prevalence of different risk factors significantly or non-significantly associated with epilepsy of elders. Shariff em, et al. Reported the stroke as most commonly diagnosed factor in 58% patients, occult cvd in 22.7%, tumors in 16.8% patients and others (infection, trauma, etc.) In 2.5% patients [77]. Another study by guo y, et al. Also reported the stroke as most commonly diagnosed factor in 48.7% patients, brain injury 17.5% patients, tumor in 9.7% patients, dementia in 7.0% patients and cns infection in 3.8% patients [79].

Metabolic disorders are common causes of acute symptomatic seizures in elderly inpatients and in elderly outpatients,and the more rapidly the disorder develops, the more likely it is to induce seizures [80].

Stroke is considered as the most commonly diagnosed risk factor throughout the world responsible for developing epilepsy in elders. Our study finding also stroke is considered as the most commonly diagnosed risk factor throughout the world responsible for developing epilepsy in elders. Our study finding also reported the stroke as second common cause of epilepsy in elders. Cns infection and brain tumors are also the important risk factors behind the epilepsy of elders. Our study finding also confirms that cns infection and brain tumors both are actively playing their role in emerging of new onset seizure in elders.

6. CONCLUSION

New-onset seizures are significantly associated with age, diabetes mellitus, hypertension, ischemic heart disease, brain tumor and cns infection. Most commonly reported risk factors in new onset seizure were metabolic causes, stroke and cns infection followed by brain tumor, dementia and depression.

Potentially modifiable risk factors in midlife and the apoe e4 genotype were positively associated with risk of developing late-onset epilepsy, vascular and life style risk factors were significant even in the absence of stroke or dementia [81].

Our study supports a bidirectional relationship between the first seizure and depression. prevalence rate of depression increased with duration of undiagnosed epilepsy at the time of first clinical assessment [82].

More than three-fifth of newly diagnosed epilepsy cases in elderly patients were confirmed as symptomatic , and stroke and traumatic brain injury were the primary aetiologies in elderly epileptic patients [83].

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CONSENT

As per international standards or university standards, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards, written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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