Original Article

Frequency of Seizure Clusters and Their Associated Risk Factors in Adult Patients with Epilepsy Referred to Epilepsy Center of Kashani Hospital in Isfahan from 2011 to 2016

Abstract

Background: Epilepsy is a chronic neurologic condition and affects people of all ages. Seizure clusters are generally referred to seizures that occur at close intervals with complete recovery between attacks. Various studies have reported a variety of frequencies and risk factors for this condition. **Methods:** We designed a study to determine the frequency of seizure cluster and their associated risk factors in Iranian population for the first time. **Results:** Among 40 variables analyzed, 18 of them were significantly associated with seizure clustering. Risk factors including educational level, age of onset, number of drugs, seizure types, perinatal complication, developmental delay, other illnesses, parental consanguinity, systemic diseases, number of drugs used, mentation, motor signs, sensory signs, cranial nerves signs, cerebellar signs, seizure duration, existence of magnetic resonance imaging (MRI) lesion, and type of MRI pathology are significantly associated with clustering of seizures. When associated risk factors were analyzed with multivariate analysis, age of onset of seizures, number of antiepileptic drugs currently used, lack of seizure-free periods, seizure frequency, and type of MRI pathology are significantly defining for anticipating clustering of seizures. **Conclusions:** Seizure cluster has a significant negative impact on the quality of life of patients. Important risk factors that are found to be associated are age of onset, parental consanguinity, frequency of seizure, lack of have seizure-free period or periods, pathologies in neurological examination, and MRI findings.

Keywords: *Epilepsy, predictors, risk factors, seizure freedom*

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Introduction

Epilepsy is a chronic neurologic condition and affects peoples of all ages and is the most common neurologic disorder in the elder people after cerebrovascular disease and dementia.[1] Aging is one of the most important risk factors for developing epilepsy. Epidemiological studies have shown that incidence and frequency of seizures increase after age 60 years.[2,3] The prevalence of epilepsy in the United States is estimated to be about 1% of the adult population.[4] About 1 in 26 Americans suffer from epilepsy throughout their lives, and 150,000 Americans are diagnosed with epilepsy every year.[5] Seizure clusters, also called acute repetitive seizure, are generally referred to seizures that occur at close intervals in patients with epilepsy. The seizure cluster significantly diminishes the quality of life of patients with epilepsy and also creates many problems for them. Seizure clusters, if not managed, can be transformed into status epilepticus, which is more severe and threatens patients' life.[6]

Despite the high importance of seizure clusters, there is no precise definition for it. Some studies define it based on the absolute number and duration of seizures without relation to patients' baseline, and others define it based on the baseline of seizure condition of patients. The frequency of seizure clusters was reported in different studies all over the world in the range of 3%, and most in patients with epilepsy (76%). The wide range in estimation of frequency is due to the lack of a precise definition for seizure clusters, difference in the type of study, difference in the population studied, and different methodology for collecting information.[7]

Various studies have reported a variety of risk factors for this condition. In addition, numerous studies in different parts of the world have reported a different frequency

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of 3%–76% for seizure clusters. According to the importance of seizure clusters in the occurrence of various life-threatening conditions including status epilepticus and their impact on quality of life of patients, and due to lack of studies estimating the frequency and risk factors of cluster seizures in Iran and the varying frequency of it in different parts of the world, we designed a study to determine the frequency of seizure cluster and their associated risk factors.

Materials and Methods

Our study is a cross-sectional study. This descriptive analytic study evaluates the frequency of seizure cluster and their associated risk factors in adult patients with epilepsy referred to epilepsy center of Kashani hospital, Isfahan, from 2011 to 2016. We prospectively reviewed recorded medical documents of 902 adults (>18 years), outpatients with epilepsy from 2011 until 2016. Patients who have not been diagnosed with definite epilepsy are excluded. Patients are considered to have cluster of seizure when (1) patients self-reported at least three seizures in 24 h with complete recovery between episodes and/or (2) there was closely group/series of seizure attacks, which was noted and identified as a seizure cluster by the patients' neurologist.

We began our study after the approval of our research project by the research council of the university. Patients' information including demographic information, seizure details, drug history, age of onset of seizure, and risk factors for epilepsy were assessed using their medical files.

Patients' demographic information includes age, gender, marital status, occupation, level of education, and type of labor they born with. Seizure details include freedom of seizure for at least 1 year, history of aura, seizure classification [focal seizure, generalized seizure, and psychogenic nonepileptic seizures (PNES)], and type of seizures (motor, nonmotor, absence, unclassified). In addition, we reviewed the drug history including the number of antiepileptic drugs used. The risk factors for epilepsy include the following: history of encephalopathy, psychological status (such as history of psychosis, history of suicide), history of central nervous system (CNS) infection, cerebral palsy, dementia, family history of seizures, head trauma, and stroke. Electroclinical syndromes are also recorded. To determine the risk factors for seizure cluster, the patients were examined. Informed, written consent was given from all the patients.

We analyzed data using SPSS software (version 24, IBM, New York, United States) and Kolmogorov–Smirnov *Z*-test to test correlation between each individual variables and occurrence of seizure clustering. The normal distribution of data was checked, and parametric or nonparametric tests were used to analyze quantitative data. Spearman and Pearson's tests were used to evaluate correlation between quantitative variables. Distribution and correlation between qualitative variables are evaluated by Chi-square test. Reporting of numerical variables is done in terms of mean (standard deviation) and non-numerical variables in numbers and percentages. *P* value less than 0.05 is considered meaningful.

Results

In this study, information of 902 patients was reviewed. The mean age was 28.33 ± 10.55. In all, 477 of them were male and 425 of them were female. About 47.2% of them were married and 52.8% were single. About 9.7% of them were left-handed and 90.3% of them were right-handed. Most of them had high school degrees (38.9%). In addition, most of them were employed and did have jobs (54.2%). Finally, the labor type they born was distributed between normal vaginal delivery and cesarean section (86.1% and 13.8%, respectively) [Table 1].

Medical records were assessed for existence of 40 risk factors. Factors include age, sex, marriage, handedness, education, job, labor type, perinatal complications, developmental delay, neonatal icterus, febrile convulsions, head trauma, coma after head trauma, CNS infection, stroke, brain tumor, intracranial surgery, systemic illnesses, having pathologic motor signs, having pathologic sensory signs, having pathologic cranial nerve signs, having pathologic cerebellar signs, electroclinical syndrome, other illnesses, smoking, alcohol abuse, other substances' abuse, parental consanguinity, family history of seizure, mentation, seizures classification, seizures types, magnetic resonance imaging (MRI) lesion, MRI pathology type, side of MRI

Table 1: Demographic specifications

Variable (*n*=902)	Mean or frequency
Age (years)	28.33±10.55
Gender	
Male	477 (52.9)
Female	425 (47.1)
Marriage	
Single	220 (52.8)
Married	197 (47.2)
Handedness	
Right	695 (90.3)
Left	75 (9.7)
Education	
Uneducated	72 (3.4)
Elementary	126 (19.7)
Higher elementary	116 (19.2)
High school	248 (38.9)
University	125 (19.6)
Job	
Unemployed	126 (45.8)
Employed	149 (54.2)
Labor type	
Normal vaginal delivery	733 (86.1)
Cesarean section	118 (13.8)

lesion, frequency of seizures, duration of seizures, existence of seizure free period, age of seizure onset, and number of drugs used for treatment of seizure. First, we assessed variables in multinomial logistic regression analysis, whether they are significantly associated with more risk of seizure clustering occurrence. Among 40 variables analyzed, 18 of them were significantly associated with seizure clustering [Tables 2 and 3].

In initial analysis, we found that frequency of seizure clustering is about 10.4%. About 73.11% of the patients have focal epilepsy, 23.65% generalized epilepsy, and 3.22% of them show PNES. In addition, we found factors including educational level, lack of seizure-free periods (defined as at least 1-year freedom from seizure), seizure frequency, age of onset, number of antiepileptic drugs used, perinatal complication, developmental delay, other illnesses, parental consanguinity, systemic diseases, mentation, motor signs, sensory signs, cranial nerves signs, cerebellar signs, seizure type, abnormal brain MRI, and existence of MRI pathology to be associated with clustering of seizures. We did not find association between age, sex, marriage, handedness and labor type, and occurrence of seizure clusters, and therefore from demographic data, only the level of education makes sensible impact; from which high school educated patients significantly show higher frequency of cluster of seizures. Also, patients who have seizure-free period or periods significantly did have fewer clusters. In addition, more frequent seizures tend more to be cumulate in clusters. About 37.36% of patients have multiple seizures daily, 21.97% daily, 25.27% weekly, 14.28% monthly, 1.09%

Table 2: Association of assessed factors with clustering of seizures using multinomial logistic regression analysis

Variable	Seizure cluster		Significance	OR (95% CI)
	Yes	No		
Age, years (mean age±SD)	28.6±9.75	28.37±10.646	0.792	0.997 (0.977-1.018)
Sex				
Male	46 (9.7)	427 (90.3)	0.554	1.138 (0.74-1.744)
Female	47 (11.2)	374 (88.8)		
Marriage				
Single	38 (17.3)	182 (82.7)	0.673	1.118 (0.665-1.879)
Married	31 (15.7)	166 (84.3)		
Handedness				
Right	86 (12.4)	609 (87.6)	0.153	1.977 (0.776-5.036)
Left	5 (6.7)	70 (93.3)		
Education			0.015*	
Uneducated	1 (11.08)	21 (88.92)	0.188	0.250 (0.032-1.96)
Elementary	11 (8.7)	115 (91.3)	0.416	0.778 (0.425-1.425)
Guidance school	9 (7.8)	107 (92.2)	0.054	0.442 (0.192-1.014)
High school	32 (12.9)	216 (87.1)	0.084	0.502 (0.23-1.098)
University	20 (16)	105 (84)	0.188	0.25 (0.032-1.966)
Job			0.740	
Employed	23 (15.4)	126 (84.6)	0.399	0.470 (0.368-1.489)
Unemployed	15 (11.9)	111 (88.1)	0.330	0.540 (0.319-0.972)
Labor type				
Normal vaginal delivery	75 (10.2)	658 (89.8)	0.107	1.579 (0.906-2.753)
Cesarean section	18 (15.3)	100 (84.7)		
Seizure-free periods	0 (0)	31 (100)	0.000*	
Multiple daily	34 (23.6)	110 (76.4)	0.000*	1.607E9 (2.159E8-1.196E10)
Daily	20 (15.9)	106 (84.1)	0.000*	9.810E8 (1.292E8-7.450E9)
Weekly	23 (11.9)	171 (88.1)	0.000*	6.993E8 (9.298E7-5.260E9)
Monthly	13 (6.9)	176 (93.1)	0.000*	3.840E8 (4.948E7-2.981E9)
Seasonal	1 (1.04)	95 (98.95)	0.000*	5.473E7 (5.473E7-5.473E7)
Yearly	0 (0.00)	33 (100)	0.000*	6.845E8 (4.893E7-2.107E9)
Seizure duration (min)			0.204	
<1	19 (9)	93 (91)	0.041	1.767 (1.024-3.047)
1–5	60 (14.8)	345 (85.2)	0.817	0.781 (0.097-6.304)
Over 5	1 (7.1)	13 (92.9)	0.130	10540E7 (1.54E7-1.540E7)
Age of onset, years (mean±SD)	8.15±7.83	13±11.07	0.000*	0.944 (0.917-0.972)
Number of currently used antiepileptic drugs (mean±SD)	2.81±1.11	2.47±1.11	0.007*	1.297 (1.075-1.564)

*Statistically significance: *P* value <0.05. OR=Odds ratio, CI=Confidence interval, SD=Standard deviation

Table 3: Association of assessed factors with clustering of seizures using multinomial logistic regression analysis

Variable	Seizure cluster		Significance	OR (95% CI)
	Yes	No		
Perinatal complications	16 (21.6)	76 (9.5)	0.002*	2.615 (1.434–4.771)
Developmental delay	14 (19.2)	77 (9.5)	0.011*	2.253 (1.202–4.222)
Neonatal icterus	6 (16.2)	80 (10.2)	0.247	1.704 (0.691–4.199)
Febrile convulsions	8 (8)	85 (10.6)	0.396	0.72 (0.338–1.536)
Head trauma	22 (11.6)	82 (10.2)	0.583	1.153 (0.694–1.915)
Coma after head trauma	4 (17.4)	82 (10.3)	0.281	1.833 (0.61–5.508)
CNS infection	3 (18.8)	83 (10.4)	0.293	1.982 (0.554–7.088)
Brain tumor	3 (3)	12 (1)	0.870	
Intracranial surgery	2 (8.7)	85 (10.6)	0.77	0.804 (0.185–3.484)
Other illnesses	9 (25.7)	79 (9.9)	0.005*	3.14 (1.424–6.924)
Smoking	2 (2.5)	16 (2)	0.670	
Alcohol abuse	0 (0)	4 (100)	0.999	
Other substances abuse	0 (0)	1 (100)	1	
Parental consanguinity	19 (30.6)	81 (10.1)	0.000*	3.933 (2.174–7.117)
Family history	20 (12.7)	81 (10.1)	0.33	1.3 (0.767–2.204)
Systemic diseases	70 (13.8)	48 (6)	0.000*	2.503 (1.531–4.09)
Mentation	61 (13.1)	63 (7.8)	0.011*	1.785 (1.143–2.787)
Motor signs	66 (13.3)	55 (6.8)	0.002*	2.098 (1.313–3.354)
Sensory signs	71 (14)	46 (5.7)	0.000*	2.686 (1.632–4.42)
Cranial nerves signs	69 (13.9)	48 (6)	0.000*	2.506 (1.543–4.069)
Cerebellar signs	68 (14)	50 (6.2)	0.000*	2.491 (1.543–4.022)
Seizure classification			0.387	
Focal	68 (73.11)	555 (78.27)	0.463	0.469 (0.062–3.544)
Generalized	22 (23.65)	140 (19.74)	0.573	1.55 (0.338–7.101)
PNES	3 (3.22)	14 (1.97)	0.547	1.569 (0.362–6.806)
Seizure type			0.000*	
Motor	77 (91.66)	541 (89.42)	0.998	1.70E+07
Non motor	4 (4.76)	47 (7.76)	0.998	1.19E+08
Absence	2 (2.38)	5 (0.82)	0.998	2.17E+08
Unclassified	1 (1.19)	12 (1. 98)	0.998	4.04E+08
MRI lesion				
Normal	24 (29.26)	70 (14.40)	0.025*	2.7 (1.132–6.442)
Abnormal	58 (70.74)	416 (85.6)	0.001*	2.459 (1.43–4.21)
Side of MRI lesion				
Right	27 (32.39)	167 (34.36)	0.573	1.27 (0.54–2.95)
Left	23 (28.04)	186 (38.27)	0.951	0.974 (0.415–2.28)
Bilateral	8 (9.75)	63 (10.75)	0.375	0.732 (0.211–1.542)
MRI pathology			0.005*	
Tumor	6 (10.71)	48 (9.46)	0.160	0.125 (0.07–2.26)
Gliosis atrophy	16 (28.57)	99 (19.52)	0.189	0.151 (0.09–2.54)
MTS	10 (17.85)	134 (26.42)	0.74	0.07 (0.04–1.28)
Polymicrogyria	2 (3.57)	7 (1.38)	0.44	0.28 (0.012–6.91)
White matter abnormality	0 (0)	13 (2.56)	0.99	6.5 (9E–9)
Porencephaly	2 (3.57)	25 (4.93)	0.11	0.8 (0.04–1.81)
Cortical scar	0 (0)	9 (1.77)	0.99	6.51 (9E–9)
Hetrotopia	3 (5.35)	18 (3.55)	0.24	0.167 (0.08–3.44)
FCD	8 (14.28)	19 (3.74)	0.55	0.421 (0.023–7.59)
Pachygyria	1 (1.78)	3 (0.59)	0.99	6.5 (9E–9)
Others	8 (14.28)	131 (25.83)	0.056	0.061 (0.003–1.069)

*Statistically significance: *P* value <0.05. OR=Odds ratio, CI=Confidence interval, CNS=Central nervous system, PNES=Psychogenic nonepileptic seizures, MRI=Magnetic resonance imaging, MTS=Mesial temporal sclerosis, FCD=Focal Cortical dysplasia

seasonal, and no one had yearly seizure frequency. A total of 23.75% of patients have seizures less than 1 min, 75% 1–5 min, and 1.25% longer than 5 min. Risk of clustering of seizures is positively associated with the mean number

of antiepileptic drugs currently used by patients. Patients showing clusters typically use 0.34 drugs more than patients without clusters. Finally, age of seizure onset is significantly associated with clusters; earlier onset results in more clusters. The mean age of onset in patients showing clusters is 8.15 ± 8.7 years and typically 5 years lower than patients without clusters.

In addition, neonatal icterus and febrile convulsions did not significantly associate with clusters. History of brain complications such as trauma or infection or stroke, tumor, and intracranial surgery, and its consequent outcomes were not associated. Smoking and using substances such as alcohol and other substances were not significantly associated. Abnormal neurological examination was significantly associated with increased risk of seizure clusters. According to our study, seizure classification (focal, generalized, PNES) was not associated with increased frequency of cluster seizures. We did not find clusters to be occurring more in a certain type of seizure. Around 91.66% of evaluated patients showed motor seizures, and therefore the number of patients showing cluster were higher in this type of seizure, but difference was not significant. Finally, abnormal brain MRI was significantly associated with increased risk of seizure clusters, but side of brain MRI lesion was not correlated with increased risk of seizure clusters. Patients who have lesion in their MRI image significantly have more clusters. About 29.26% of patients have normal MRI, 32.39% of patients have lesions on the right side of their brain, 28.04% have on left, and 9.75% bilaterally have lesions in their brain. In addition, the type of MRI pathology is an important factor in occurrence of cluster seizures, but no certain type of seizure would increase it [Tables 3 and 4].

After multinomial logistic regression analysis, variables that are significantly associated with seizure clustering were analyzed using multivariate analysis. Therefore, education, age of onset, number of drugs, seizure types, perinatal complication, developmental delay, other illnesses, parental consanguinity, systemic diseases, number of drug used, mentation, motor signs, sensory signs, cranial nerves signs, cerebellar signs, seizure duration, and existence of MRI lesion and type of MRI pathology were put into analysis. Significance level is considered 0.05 in this analysis [Table 5].

However, risk factors individually have significant association with clusters; they cannot play a role in a model for forecasting risk of clusters' occurrence. Age of onset of seizures (P = 0.000), number of antiepileptic drugs currently used (P = 0.000), lack of seizure-free periods (P = 0.000), seizure frequency (P = 0.040), systemic diseases (P = 0.001), existence of MRI lesion (P = 0.007), and type of MRI pathology (P = 0.042) are significantly defining for anticipating clustering of seizures [Table 5].

Discussion

Seizure clusters largely affect patient's quality of life. We found that frequency of seizure clustering is about 10.4% in patients with epilepsy referred to epilepsy center of Kashani hospital in Isfahan from 2011 to 2016. Definition of seizure cluster is an important factor in estimating its frequency. In our study, we define it as when (1) patients self-reported at least three seizures in 24 h and/or (2) there was closely group/series of seizure attacks, which was noted and identified as a seizure cluster by the patients' neurologist. In the study conducted by Sinha *et al*. in 2013 to assess the frequency and response to treatment in cluster seizure and status epilepticus patients over 60 years of age, three or more occurrence of seizures during a 24-h period was defined as cluster epilepsy. The frequency of cluster seizures was about 32%.[8] The study by Sillanpää *et al*. was conducted in 2008, in which patients were followed for 37 years. In this study, cluster seizure was defined as three or more episodes of seizure in 24 h. The frequency of cluster seizure was 22%.[9] In a cohort study by Martinez *et al*. in 2009, cluster seizures were defined as three times or more focal or generalized seizures during a period of 24 h. The frequency of cluster seizure in 21,000 patients with epilepsy was 3% (10). Our center is a tertiary epilepsy center with large population of patients referring with refractory epilepsy, so it may lead to overestimation of frequency of seizure clusters and potential associated risk factors. This is a basic limitation in our study similar to many of the studies published before and there is limited information regarding the epidemiology of seizure clusters in general population.

Little information is available on cluster seizure etiology. However, the underlying mechanism of increasing the excitability of the nervous system or impairment of inhibitory mechanisms of nerve stimulation is known as

Table 4: Independent *t*-test between cluster seizure (normal-abnormal)

	Levene's test for equality of variances		*t*-Test for equality of means		*t*-Test for equality of means			95% CI of the difference	
	F	Significance	*t*	df	Significance (two-tailed)	Mean difference	SE difference	Lower	Upper
Cluster seizure normal-abnormal									
Equal variances assumed	36.49	0.00	−3.37	566	0.001	−0.133	0.039	−0.21	−0.56
Equal variances not assumed			−2.79	114.52	0.006	−0.133	0.038	−0.22	−0.39

*Statistically significance: P value <0.05. CI=Confidence interval, df=Degree of freedom, SE=Standard error

Table 5: Multivariate analysis of associated risk factors for clustering of seizures

Variable	Significance	OR (95% CI)
Education		
Uneducated	0.160	
	0.120	0.068 (1.821-2.088)
Elementary	0.071	0.028 (1.857-1.968)
Higher elementary	0.045*	0.030 (1.864-1.980)
High school	0.375	0.020 (1.831-1.911)
University	0.223	0.028 (1.784-1.896)
Age of onset	0.000*	0.615 (9.367-11.783)
Number of currently used Antiepileptic drugs	0.000*	0.061 (2.518-2.759)
Seizure free periods	0.000*	0.037 (2.164-2.313)
Seizures frequency	0.040*	0.038 (2.217-2.365)
Multiple daily	0.002*	0.179 (0.196-0.898)
Daily	0.008*	0.181 (0.127-0.840)
Weekly	0.029*	0.179 (0.041-0.744)
Monthly	0.022*	0.181 (0.061-0.772)
Seasonal	0.034*	0.192 (0.032-0.786)
Yearly	0.044*	0.176 (0.042-0.823)
Seizure type	0.615	0.113 (2.061-2.505)
Perinatal complication	0.079	3.354 (0.871-12.914)
Developmental delay	0.695	0.704 (0.122-4.07)
Other illness	0.509	2.036 (0.247-16.795)
Systemic diseases	0.001*	0.018 (1.422-1.492)
Parental consanguinity Systemic diseases	0.739	1.242 (0.348-4.43)
Mentation	0.889	0.9 (0.205-3.948)
Motor signs	0.454	0.213 (0.004-12.216)
Sensory signs	1	1.491
Cranial nerves signs	1	3.30E+08
Cerebellar signs	1	0.000
Existence of MRI lesion	0.007*	0.016 (1.814-1.878)
MRI pathology	0.042*	0.032 (1.823-1.950)
Tumor	0.366	0.153 (−0.163 to 0.440)
Gliosis atrophy	0.462	0.151 (−0.185 to 0.407)
MTS	0.230	0.150 (−0.114 to 0.475)
Polymicrogyria	0.876	0.178 (−0.322 to 0.377)
White matter abnormality	0.140	0.169 (−0.083 to 0.583)
Porencephaly	0.268	0.159 (−0.136 to 0.488)
Cortical scar	0.201	0.150 (−0.103 to 0.487)
Hetrotopia	0.161	0.178 (−0.100 to 0.600)
FCD	0.507	0.162 (−0.210 to 0.265)
Pachygyria	0.771	0.159 (−0.358 to 0.265)
Others	0.450	0.331 (−0.400 to 0.900)

*Statistically significance: *P* value <0.05. OR=Odds ratio, CI=Confidence interval, MRI=Magnetic resonance imaging, MTS=Mesial temporal sclerosis, FCD=Focal cortical dysplasia

part of its pathophysiologic basis. Cluster seizure is shown to be associated with a variety of epilepsy and seizures. Recent articles suggested that patients with symptomatic generalized epilepsy were more likely to report seizure clusters compared with idiopathic generalized epilepsy and focal seizures.[10] However, according to our study, seizure classification (focal, generalized, PNES) was not associated with increased frequency of cluster seizures. On the other hand, type of seizures (such as seizures with aura, motor, absence, or dialeptic) was significantly associated with clusters but we could not find specific kind of seizure that is associated with cluster occurrence. These data have not been analyzed in similar studies yet, and it should be covered in future prospective studies. Although the occurrence of seizure cluster increases the likelihood of developing status epilepticus, there is not any reliable factor that predicts progression of cluster seizures to status epilepticus.[11]

In this study, we found some factors associated with increase in the occurrence of seizure clusters. These factors

include education level, seizure-free periods, seizure frequency, age of onset, number of antiepileptic drugs used, systemic diseases, prenatal complication, developmental delay, other illnesses, parental consanguinity, mentation, motor signs, sensory signs, cranial nerves signs, cerebellar signs, seizure type, existence of MRI lesion, and type of MRI lesion.

Several studies have been conducted to identify the risk factors for cluster seizures. Physiological factors such as fever, hormonal changes (often menstruation), sleep, and stress were identified as a risk factor for cluster seizure in some other studies.[12] As our study results show, increase in the number and frequency of seizures is important for developing cluster seizures. A study by Bayer showed that patients with long seizure duration were at more risk for cluster seizure,[13] but another study did not find a correlation between seizure duration and increased risk of cluster seizure.[14] A study by Haut *et al*.[14] was conducted in 2005 to investigate the risk factors for cluster seizure. In this study, three or more seizure episodes during 24 h were reported as cluster seizures. In this cross-sectional study, 29% of patients with cluster seizure had extratemporal epilepsy, and head trauma was recognized as the most important risk factor for cluster incidence.[14] In a similar study by Chen *et al*. in 2017, 4116 patients with epilepsy older than 16 years were studied. The results of this study showed that cluster seizure was independently associated with lower age of onset of seizure, symptomatic generalized epilepsy, central nervous system infection, cortical dysplasia, status seizure, and lack of 1-year freedom from seizure.[10] In our study using significantly associated variables in multivariate analysis to forecast risk of cluster occurrence, we found that significant risk factors anticipating clusters were the age of onset of seizures, number of antiepileptic drugs currently used, lack of seizure-free periods, seizure frequency, systemic diseases, existence of MRI lesion, and type of MRI pathology.

In our study, we found a significant association between educational level and seizure clusters, but not about job and marital status. Similar to previous studies,[12,14] our data confirmed that age and sex were not associated with clusters. We found that the frequency of seizures is significantly associated with seizure clusters, and patients with more frequent seizures at are greater risk. Our findings are similar to the study by Fisher *et al*.[12] which used an online diary for recording seizures. Consistent with previous studies, patients who have seizure-free period or periods tend to have fewer clusters.[10] According to our findings, patients showing clusters typically use 0.34 drugs more than patients without clusters, and therefore having a drug history is very important which can lead to more accurate evaluation and risk stratification. If we know the type of drugs used in addition to the number of drugs, we can find some association between used drugs and occurrence of clusters.

In addition, patients with parental consanguinity had a greater likelihood of having seizure clusters. To our knowledge, this factor was not evaluated in any other studies. Patients with consanguine parents were at about four times higher risk for occurrence of clusters.

Our study was a retrospective study, and to best of our knowledge this is the first study till date which includes association between various abnormalities of neurological examination and likelihood of development of seizure clusters. This is the first study that evaluates association between different types of brain MRI pathology and seizure cluster and also the frequency of MRI abnormalities in these patients. Importantly, these factors have significant association with clusters, and it appears that more focus on neurological examination (mentation, cranial nerve, sensory and motor, cerebellar) and MRI findings at the time of admission may be helpful in management of these patients. The major limitation of this study is that physical examination records sometimes are missing in the medical files, and due to retrospective method of study they are hardly accessible. Hence, prospective studies are needed to better identify the risk factors of clusters.

Similar to previous studies, we found that having lesions in MRI images are significantly associated with higher clusters. Two articles reported changes in the white matter of the brain and the presence of temporal mesial sclerosis as two risk factors in MRI and increase the incidence of cluster seizures.[8,15] We suggest to evaluate MRI findings more because of controversial results in different studies. Our investigation includes type of brain MRI pathology. These pathologies include tumor, atrophy gliosis, MTS, polymicrogyria, white-matter abnormality, porencephaly, cortical scar, heterotopia, focal cortical dysplasia, atrophy, ventriculomegaly, and pachygyria. We found significant association between pathologies type and clusters, but not any certain type of them.

In addition, we evaluated smoking, alcohol, and other substances' abuse as factors may be associated with seizure clusters, but there is no significant association. It is similar to the results of the study by Fisher *et al*.[12] that estimated alcohol and other nonmedical drugs made 1% of overall effects. A recent study found head trauma as a risk factor for cluster, regardless of the type of seizure.[14] But in our study history of brain complications such as trauma or infection or stroke, tumor, and intracranial surgery, and its consequent outcomes were not associated.

Conclusions

Seizure is one of the most common neurological disorders. Seizure clusters are generally referred to seizures that occur at close intervals with complete recovery between attacks. Seizure cluster has a significant negative impact on the quality of life of patients, and it can threaten patients' life if it progresses into status epilepticus. Several risk factors

are associated with occurrence of clusters. Important risk factors that are found to be associated are educational level, lack of seizure-free periods (defined as at least 1-year freedom from seizure), seizure frequency, age of onset, number of antiepileptic drugs currently used, perinatal complication, developmental delay, other illness, parental consanguinity, systemic diseases, mentation, motor signs, sensory signs, cranial nerves signs, cerebellar signs, seizure type, abnormal brain MRI, and existence of MRI pathology.

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Conflicts of interest

There are no conflicts of interest.

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