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Original Article

The correlation between cluster seizures and findings of magnetic resonance imaging in drug refractory epilepsy patients

Jafar Mehvari Habibabadi[1], Mohamad Zare[1], Seyed-Navid Naghibi[1], Nasim Tabrizi[2], Seyed Nader Naghibi[3]

[1]Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Department of Neurology, School of Medical, Isfahan University of Medical Science, Isfahan, Iran; [2]Department of Neurology, Mazandaran University of Medical Sciences, Sari, Iran; [3]Department of Emergency, Abadan University of Medical Science, Abadan, Iran

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Abstract: Background: Epilepsy is a chronic neurologic condition and affects peoples at 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. Method: We designed a study to determine the frequency of seizure cluster and to determine neuroimaging findings in these patients and also to evaluate the Correlation between Cluster Seizures and Findings of Magnetic Resonance Imaging in Drug Refractory Epilepsy patients. Results: After analyzing data from 568 refractory epilepsy patients, we found that the prevalence of cluster seizure variant is 14.43%. 29.26% of patients with a history of cluster seizure had no obvious abnormal MRI findings whereas 14.40 % of patients without history of cluster seizure had no obvious abnormal MRI findings (*P*-value <0.05). Compared to Drug Refractory Epilepsy patients without history of seizure clusters, patients with a history of seizure clusters had less abnormal MRI findings, less Mesial Temporal Sclerosis, and more Focal Cortical Dysplasia in Magnetic Resonance Imaging (*p* value <0.05). Conclusions: Seizure cluster has a significant negative impact on the quality of life of patients. According to results of this study it seems that brain MRI findings of drug refractory epilepsy patients with a history of seizure clusters are different from brain MRI findings of drug refractory epilepsy patients without a history of seizure clusters. mesial temporal sclerosis is less frequent and focal cortical dysplasia is more frequent in brain MRI of drug refractory epilepsy patients with a history of seizure clusters compared to drug refractory epilepsy patients without a history of seizure clusters.

Keywords: Cluster seizure, frequency, magnetic resonance imaging

Introduction

Epilepsy is a chronic neurologic condition and affects peoples at all ages and is the most common neurologic disorder in the elderly after cerebrovascular disease and dementia [1, 2]. Aging is one of the most important risk factors for developing epilepsy. Epidemiological studies have shown that the incidence and frequency of seizures increases after age 60 [3-6]. The prevalence of epilepsy in the United States is estimated about 1% of the adult population [7, 8]. About one in 26 Americans suffer from epilepsy throughout their lives, and 150,000 Americans are diagnosed with epilepsy every year [9]. Seizure clusters, also called acute repetitive seizure (ARS), are generally referred to seizures that occur at close intervals in patients with epilepsy. The seizure cluster significantly diminished quality of life of epileptic patients and also make many problems for them. Seizure Clusters, if not managed, can be transformed into status epilepticus, which is more severe and threatens the patient's life [10].

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 the

patient's 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 76% of patients with epilepsy. The wide range in estimation of frequency are 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 [11].

Various studies have reported a variety of risk factors for this condition. Also, numerous studies in different parts of the world have reported a different frequency of 3 to 76 percent 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 estimate the frequency and neuroimaging findings 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 to determine neuroimaging findings in these patients and also to evaluate the Correlation between Cluster Seizures and Findings of Magnetic Resonance Imaging in Drug Refractory Epilepsy patients.

Material and methods

Our study is a cross-sectional study. This descriptive-analytic study evaluates the frequency of seizure cluster and their brain MRI findings in adult patients with epilepsy referred to epilepsy center of Kashani hospital, Isfahan from 2011 to 2016. We prospectively reviewed recorded medical documents of 568 adults (>18 years) outpatients with epilepsy from 2011 until 2016. Patient considered to have cluster of seizure when: 1) patient self-reported at least 3 seizures in a 24-hourwith 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. Patients who have not been diagnosed with definite epilepsy are excluded. All of the patients should had a brain MRI imaging with epilepsy protocol and with a same 1.5 T MRI machine. patients who had not brain MRI with mentioned criteria exclude from the study.

We began our study after the approval of our research project by the research council of the university. Patient's demographic information includes age, gender, marital status, occupation, level of education and type of labor they born with and also brain MRI information including existence of brain MRI abnormality, side of MRI abnormality and type of brain MRI pathology were assessed using their medical files. Brain MRI pathologies include: tumor, gliosis and atrophy, mesial temporal sclerosis (MTS), polymicrogyria (PMG), vascular malformation, porencephaly, cortical scar, heterotopia, focal cortical dysplasia (FCD), pachygyria and other pathologies.

We analysis Data using SPSS software (version 24) and the Kolmogorov Smirnov Z-test to test normal distribution of data. The logistic regression test was used to evaluate the correlation between quantitative variables. Cluster group and non-cluster group compared regarding MRI findings using independent t-test. *P*-value less than 0.05 is considered meaningful.

Results

In this study information of 902 patients was reviewed. Mean age was 28.33±10.55. 477 of them were male and 425 of them were female. 47.2% of them were married and 52.8% were single. 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 were distributed between normal vaginal delivery and cesarean section 86.1% and 13.8%, respectively (**Table 1**).

Of these patients 568 patients had a brain MRI with epilepsy protocol and defined MRI criteria as mentioned in section of material and methods; other patients without MRI criteria excluded from study. Medical records were assessed for existence MRI lesion, side of MRI lesion, and MRI pathology type.

In initial analysis we found that Frequency of seizure clustering is about 14.43%. 70.74% of patients with history of cluster seizures had abnormal brain MRI findings whereas 85.6% of patients without history of cluster seizures had abnormal brain MRI findings which was statistically significant (p value <0.05). In cluster group

Table 1. Demographic specifications

Variable (n=902)		
Age		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)

32.39% of patients had right side brain lesions, 28.04% of patients had left side brain lesions and 9.75% had bilateral brain lesions. Whereas in non-cluster group percentages of right side brain lesions, left side brain lesions, bilateral brain lesions was 34.36, 38.27 and 10.75% respectively which was not statistically meaningful. In MRI pathology of patients with history of cluster seizures, 7.31% of patients had Tumor, 19.51% of patients Gliosis atrophy, 12.19% had MTS, 2.43% had polymicrogyria, 0% had vascular anomaly, 2.43% had Porencephaly, 0% had Cortical scar, 3.65% had Hetrotopia, 9.75% had FCD, 1.21% had pachygyria and 9.75% had other types of brain pathology. Abnormal brain MRI pathologies found in Patients without a history of seizure clusters were included: tumor in 9.87% of patients, Gliosis & atrophy in 20.37%, MTS in 27.57% of patients, polymicrogyria in 1.44% of patients, vascular anomaly in 2.56% of patients, porencephaly in 5.14% of patients, Cortical scar in 1.85% of patients, hetrotopia in 3.70% of patients, FCD in 3.90% of patients, pachygyria in 0.61% of patients, and finally other types of brain pathology were seen in 26.83% of patients. among mentioned pathologies only differences between percentage of MTS, FCD and other brain pathologies were statistically significant (*P*-value <0.05) (**Tables 2** and **3**).

Discussion

Seizure clusters largely affect patient's quality of life. We found that Frequency of seizure clustering was about 10.4% among epileptic patients referred to epilepsy center of Kashani hospital in Isfahan from 2011 to 2016; after patient exclusion according to mentioned brain MRI criteria, the frequency of seizure cluster was 14.43% among remained 568 patients. Definition of seizure cluster is important factor in estimating its Frequency. In our study we define it as when 1) patient self-reported at least 3 seizures in a 24-hour 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 patients, three or more occurrence of seizures during a 24-hour period was defined as the cluster epilepsy. The frequency of cluster seizures was about 32% [12]. The study by Silanpa and colleagues 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 hours. The frequency of cluster seizure was 22% [13]. In a cohort study by Martinez and colleagues in 2009, cluster seizures were defined as three-times or more focal or generalized seizures during a period of 24 hours. The frequency of cluster seizure in 21,000 epileptic patients 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 studies published before and there is limited information regarding the epidemiology of seizure clusters in general population.

A study by Haute 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 hours were reported as cluster seizures. In this cross-sectional study, 29% of patients with cluster seizure had Extra temporal epilepsy and head trauma were recognized as the most important risk factors for cluster incidence [14].

Our study was a retrospective study and to best of our knowledge is the first study to this date that include association between different types of brain MRI pathology and seizure cluster and also the frequency of MRI abnormalities in patients with these patients. Importantly these factors have significant association with

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

Variable		Seizure cluster		Significance	OR (95% CI)
		Yes	No		
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 (7.31)	48 (9.87)	0.160	0.125 (0.07-2.26)
	Gliosis atrophy	16 (19.51)	99 (20.37)	0.189	0.151 (0.09-2.54)
	MTS	10 (12.19)	134 (27.57)	0.001*	0.224 (0.021-2.354)
	Polymicrogyria	2 (2.43)	7 (1.44)	0.44	0.28 (0.012-6.91)
	vascular anomaly	0 (0)	13 (2.56)	0.99	6.5 (9E-9)
	Porencephaly	2 (2.43)	25 (5.14)	0.11	0.8 (0.04-1.81)
	Cortical scar	0 (0)	9 (1.85)	0.99	6.51 (9E-9)
	Hetrotopia	3 (3.65)	18 (3.70)	0.24	0.167 (0.08-3.44)
	FCD	8 (9.75)	19 (3.90)	0.003*	1.263 (0.114-14.053)
	Pachygyria	1 (1.21)	3 (0.61)	0.99	6.5 (9E-9)
	Others	8 (9.75)	131 (26.83)	0.005*	0.166 (0.015-1.775)

*statistically significance: *p* value <0.05. Abbreviations: CI: Confidence Interval; FCD: Focal Cortical Dysplasia; MTS: Mesial Temporal Sclerosis; OR: Odds Ratio; SD: Standard Deviation.

clusters and It seems that more focus MRI findings at the time of admission may be helpful in management of these patients. The major limitation of this study is that brain MRI records sometimes is missing in the medical files and due to retrospective method of study they are hardly accessible.

In this study, we found that generally having lesion in MRI images has a negative relationship with higher clusters. In other hand, refractory epilepsy patients with a history of seizure cluster are more likely to have a MRI-negative epilepsy than refractory epilepsy patients without a history of seizure cluster, this result was statically significant (*P*-value <0.05).

From all kinds of epileptogenic brain pathologies that was investigated in Patients' MRI, just two pathologies, from statistical point of view, were important. Focal cortical dysplasia, significantly is more common in the patients with cluster history. In the study done by Chen et al. in 2017 [10], shown that Existence of Cortical dysplasia, is accompanied by increasing in the risk of cluster seizure. According to High frequency of MRI negative epilepsy in patients with FCDs, and also high frequency of FCDs in refractory epilepsy patients with history of seizure clusters, it seems that the reason of higher frequency of MRI negative epilepsy in these patients is due to higher frequency of FCDs. on the other hand, it is presented in our study that MTS in the refractory epilepsy patients that don't have history of cluster seizures is more common that who have. unlike our study, Two papers reported Changes in the white matter of the brain and the presence of temporal mesial sclerosis as two risk factors in MRI, increase the incidence of cluster seizures [12, 15].

As it is mentioned in many studies, extra-temporal seizures are Accompanied by higher risk of cluster seizures and status epileptics. like our study, a study designed by Haute et al. showed that extra-temporal seizures are risk factors for Cluster seizures [14].

However, the results in this field is "more conflicting". Because in the study that was done by Haut, Sin, MTS was the risk factor for Cluster seizures [15].

In this study, Side of Brain lesions, regardless of underlying pathology, evaluated in two groups of refractory epilepsy patients with and

Table 3. 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% Confidence Interval of the Difference	
		F	Sig*	t	Df	Sig (2-tailed)*	Mean difference	Std. Error 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. Abbreviations: Sig: Significance; df: degrees of freedom; std: standard.

without a history of seizure clusters. There was not a meaningful difference, in terms of existence of lesion in the right side, left side or bilateral. As far as we know, according to previous studies, it is the first time that relation between MRI pathology, MRI Side and cluster seizure will be examined and it is necessary to check out more Studies. We suggest to evaluate MRI findings more because of controversial results in different studies.

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 patient's life if it progresses into status epileptics. The number of "MRI negative epilepsy" in patients who suffer from "refractory epilepsy with history of cluster seizures" are more than patients who suffer from "refractory epilepsy without history of cluster seizures".

Side of brain lesions doesn't have any differences in two group of Patients with refractory epilepsy who have cluster history and the patients who have not. Among various epileptogenic pathologies, FCD in refractory epilepsy patients who have cluster history is more common than the patients who have not. MTS in patients without history of cluster seizures is more common than the patients with history of cluster seizures.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Seyed-Navid Naghibi, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98 916 612 2794; E-mail: navidnaghibi.neuro@gmail.com

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