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Determination the Proportion of Refractory Epilepsy and Some Associated Factors in Epileptic Patients in the North East of Iran

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ABSTRACT

Background: Epilepsy is the second common neurologic disorder. Although many antiepileptic drugs have been formulated to control the seizures, but not all seizures have been controlled by them. Uncontrolled epilepsy can actually reduce the patients' quality of life.
Objectives: Identifying the proportion of adult intractable epilepsy among epileptic patients in an area in the North East of Iran
Materials and Methods: All epileptic patients who admitted to neurology clinic of a teaching hospital associated with Islamic Azad University of Mashhad in 2014 that were eligible for inclusion criteria enrolled this cross-sectional study. After fulfilling the informed consent, interview, examination and EEG were done. The data was expressed and analyzed by using Mean±Standard deviation and the Likelihood Ratio Chi-Square test in SPSS software version 22. Significance level was considered as less than 0.05%.
Results: From 171 patients, 59 patients with epilepsy (34.5%) met the criteria for intractable epilepsy (37.5% male, 31.3% female) with mean age of 28.2±8.5 years. The mean duration of disease was 14.5±8.4 and 11±8.8 years in patients with refractory epilepsy and controlled epilepsy respectively (t-test=2.5 and p=0.013). The seizure frequency was significantly higher in pharmacoresistant patients than pharmacoresponsive ones (7.15±8.4 *vs.* 0.29±7 per month p=0.0001). Also taking Carbamazepin and Clobazam and Primidone were associated with intractable epilepsy (p<0.05).
Conclusions: Our results accounted that about one-third of patients with epilepsy are categorized in refractory epilepsy with higher duration of disease.

Key Words: Epilepsy; Prevalence

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Introduction

Epilepsy is the second common neurologic disorder after stroke. Epilepsy affects about 0.5% to 1% of the world's population and about 700 thousand people have been diagnosed in Iran. Epilepsy can occur in all age groups, ethnicities and genders. The age adjusted annual epilepsy rate is 29-53 per 100,000. The highest age-specific incidence rates of epilepsy pertain to children and the elderly. About 50% of all the epilepsy cases emerge during childhood or early adolescence. The

incidence rates of this condition are slightly higher in men than in women (1-3). Epilepsy is a condition defined as transient nervous signs caused by abnormal synchronous and paroxysmal neuronal electrical activity in the cerebral cortex, leading to a variety of clinical states. The occurrence of each of these signs depends on the brain damage focus and the epileptic discharge depletion site (4). It is caused by an extensive list of idiopathic, symptomatic and cryptogenic etiologies. In the idiopathic type, causes are genetic and begin during childhood. The symptomatic type is the result of a specific brain damage. The cryptogenic type is still lacking a cause (2). The definition proposed by the International League Against Epilepsy (ILAE) for refractory epilepsy is "the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic schedule drugs selected as the antiepileptic medication therapy of choice (whether as mono or in combination) to achieve sustainable seizure freedom" (3). When no curable causes can be found for resistant seizures, and the seizures are not progressive due to any neurodegenerative diseases and cannot be controlled despite two years of medication therapy either, the patient should be assessed for the helpfulness of surgical operations (1).

The majority of refractory epilepsies are caused by a temporal lobe sclerosis (75% of the cases) and the Lennox-Gastaut syndrome (50% of the cases). Resistance may reach 90% in patients with hippocampal sclerosis accompanied with focal dysgenesis or other abnormal disorders (5). The prognostic factors of refractory epilepsy include: (1) high density of seizures (the number of seizures experienced each time) before beginning the treatment (2), prolonged history of poor seizure control (3), early onset of seizures (4), having more than one type of seizure, (5) frequent seizures after beginning the treatment (6), previous causes (such as head trauma and infection) (7), particular structural disorders (such as cortical dysplasia and hippocampal sclerosis) (8), special EEG abnormalities, (9) mental retardation (10), accompanying psychiatric disorders (11), abnormal neurological examination results (12) and history of permanent epilepsy (6). Epileptic patients suffer from problems such as isolation, dependence, psychiatric disorders, celibacy, unemployment and a poor quality of life. Although antiepileptic medications (especially new ones) have relatively controlled seizures, their side-effects cause serious problems and occasionally exacerbate the seizures as well (5).

Refractory epilepsy entails numerous complications for the patients and their families. Patients who do not respond to or who respond only partially to antiepileptic medications experience debilitating seizures leading to neurological, psychological and social complications with a subsequent reduced quality of life and increased disability and mortality (6). Nasehi *et al.* (2010) conducted a study in Mofid hospital of Tehran in order to assess the factors affecting the response to treatment in children with refractory epilepsy and concluded that a refractory epilepsy that is secondary to an underlying disease clearly affects the patients' response to treatment and increases the likelihood of not responding to the medical treatments at all (7). A study conducted by Shnayder *et al.* in 2008-2010 in in Russia aimed to assess cases of refractory epilepsy with different severities, the exact number of drug-resistant samples hardly reached one

third of the total sample population after the modification of the treatment (26.6%). The proper method of reducing refractory cases among these samples was therefore to use a dedicated approach for the treatment of each patient (8). In a study conducted by French *et al.* (2007) in the Hospital of the University of Pennsylvania in Philadelphia entitled "Refractory epilepsy: A clinical review", the results obtained showed that despite the abundance of new antiepileptic medications introduced to the market over the past 10 years, refractory epilepsy is still highly prevalent, and according to the available epidemiological data, the condition becomes refractory in 20% to 40% of newly diagnosed epilepsy patients. Prognostic factors of epilepsy include the type of epilepsy, associated syndromes, etiology, frequency history and the frequency and concentration of seizures. Environmental factors (such as trauma) and genetic factors may also affect the response to treatment with antiepileptic medications. Resistance to treatment is therefore a multi-factorial phenomenon (9). The present study was therefore conducted to assess the prevalence of refractory epilepsy and examine its associated factors so as to collect a basic set of data that can be used for making decisions about evidence-based treatment approaches and the appropriate management of epileptic patients with the ultimate aim of improving quality of life in these patients.

Materials and Methods

The present observational, descriptive-analytic, cross-sectional study was conducted on the entire population of epilepsy patients admitted to a teaching hospital associated with Islamic Azad University of Mashhad in the North East of Iran in 2014 collected through simple, purposive and non-random sampling. A checklist was designed to register the personal details of participants, including their gender, age, duration of the disease, type of epilepsy, medications used and the monthly frequency of seizures. Since the study aimed to examine refractory epilepsy, the type of epilepsy (*i.e.* refractory or non-refractory) was identified. Patients who experienced more than one seizure per month despite their use of two medications at the right dose for a period of one year were considered as the cases of refractory epilepsy. Also the accompanying symptoms were then recorded in the checklist. The study inclusion criteria consisted of being older than fifteen in age (in children under 15, epilepsy is classified as pediatric), having epilepsy based on the criteria proposed by the ILAE. The exclusion criteria consisted of having acute symptomatic seizures (caused by acute conditions such as hypoglycemia and tramadol poisoning, and *etc.* which are different from seizures secondary to underlying diseases such as vascular malformation or space-occupying lesions and abscesses), having psychogenic epilepsy. Eligible patients were briefed on the study objectives and then submitted their informed consent. Participants were then interviewed and examined by a neurologist and underwent imaging and EEG. Patients diagnosed with pseudo-seizures using diagnostic and statistical manual of mental/behavioral disorders as cases of conversion disorder were excluded (10).

Tables and appropriate statistical indicators such as the Mean±Standard deviation were used in describing the data and the Likelihood Ratio Chi-Square test was used to analyze the nominal scale data. In cases where more than 20% of the expected

frequencies of the tables were below 5 (Cochran), Fisher's Exact test was used. The one-sample Kolmogorov-Smirnov (the revised Lilliefors version) test was used to ensure the normality of the data (where the data were discrete or qualitative or the sample size was below 30). Appropriate parametric tests such as the student T-test were used when the normality of the data was confirmed, and if it was not confirmed, the Mann-Whitney U test was used instead. Analysis was performed in SPSS software version 22. The significance level was considered as $p<0.05$. (The values less than 0.05 identified with an asterisk (*) and values less than 0.01 with a double-asterisk (**).

Results

The present study was conducted on 171 epileptic patients. Patients were in the age range of 16 to 58 and had a mean age of 28±9 years. As for the gender distribution of the patients, 88 (37.5%) participants were men and 83 (31.3%) women. A total of 59 patients (34.5%) had refractory epilepsy. The statistical tests showed that refractory epilepsy was not significantly related to the patients' age (t-test=0.06 and p=0.947) or gender (likelihood ratio=0.72 and p=0.424). According to the results obtained, the mean duration of disease in patients with refractory epilepsy was 14.5±8.4 years, which was significantly greater compared to in patients with controlled epilepsy (11±8.8 years; t-test=2.5 and p*=0.013). There was a significant difference between two groups in terms of the monthly frequency of seizures, which was 7.15±8.4 in the refractory group and 0.29±7 in the controlled group (t-test=6.3 and p**=0.0001). Table 1 shows the frequency of refractory epilepsy in each type of seizure. In each seizure type group there wasn't any significant difference in the frequency of controlled and uncontrolled epilepsy except for mixed epilepsy in which, controlled seizure was more prevalent (p=0.04).

Table 1: The frequency distribution of types of seizures in patients with refractory epilepsy

Type of epilepsy	Refractory epilepsy	Yes		No		Total	
		Number	%	Number	%	Number	%
Tonic	Yes	53	32.7	109	67.3	162	100.0
	No	6	66.7	3	33.3	9	100.0
	Statistic test- Probability level	Fisher's Exact Test --- *p-value*=0.065					
Myoclonic	Yes	52	38.0	85	62.0	137	100.0
	No	7	20.6	27	79.4	34	100.0
	Statistic test- Probability level	Likelihood Ratio=3.88 --- *p-value*=0.070					
Tonic- colonic	Yes	26	42.6	35	57.4	61	100.0
	No	33	30.0	77	70.0	110	100.0
	Statistic test- Probability level	Likelihood Ratio=2.73 --- *p-value*=0.130					
Atonic	Yes	57	34.1	110	65.9	167	100.0
	No	2	50.0	2	50.0	4	100.0
	Statistic test- Probability level	Fisher's Exact Test --- *p-value*=0.609					
Mixed	Yes	55	33.1	111	66.9	166	100.0
	No	4	80.0	1	20.0	5	100.0
	Statistic test- Probability level	Fisher's Exact Test --- *p-value*=0.049*					
Absence	Yes	54	34.6	102	65.4	156	100.0
	No	5	33.3	10	66.7	15	100.0
	Statistic test- Probability level	Likelihood Ratio=0.01 --- *p-value*=0.999					
Sensory	Yes	51	33.6	101	66.4	152	100.0
	No	8	42.1	11	57.9	19	100.0
	Statistic test- Probability level	Likelihood Ratio=0.53 --- *p-value*=0.610					
Motor	Yes	44	32.4	92	67.6	136	100.0
	No	15	42.9	20	57.1	35	100.0
	Statistic test- Probability level	Likelihood Ratio=1.33 --- *p-value*=0.319					
Cognitive	Yes	34	30.9	76	69.1	110	100.0
	No	25	41.0	36	59.0	61	100.0
	Statistic test- Probability level	Likelihood Ratio=1.74 --- *p-value*=0.240					

Refractory epilepsy occurred significantly more frequently in patients taking carbamazepine (likelihood ratio=6.1, and *p**=0.021), clobazam (likelihood ratio=6.97 and *p**=0.017) and primidone (Fisher's exact test, *p**=0.013).

Table 2: The frequency distribution of refractory epilepsy by type of antiepileptic medication taken

Type of drug	Refractory epilepsy	Yes		No		Total	
		Number	%	Number	%	Number	%
Valproate	Yes	20	34.5	38	65.5	58	100.0
	No	39	34.5	74	65.5	113	100.0
	Statistic test- Probability level	Likelihood Ratio=0.00 --- *p-value*=1.00					
Carbamazepine	Yes	28	27.2	75	72.8	103	100.0
	No	31	45.6	37	54.4	68	100.0
	Statistic test- Probability level	Likelihood Ratio=6.1 --- *p-value*=0.021*					
Ethosuximide	Yes	56	33.9	109	66.1	165	100.0
	No	3	50.0	3	50.0	6	100.0
	Statistic test- Probability level	Fisher's Exact Test --- *p-value*=0.417					
Topiramate	Yes	46	32.2	97	67.8	143	100.0
	No	13	46.4	15	53.6	28	100.0
	Statistic test- Probability level	Likelihood Ratio=2.04 --- *p-value*=0.192					
Phenobarbital	Yes	50	32.3	105	67.7	155	100.0
	No	9	56.3	7	43.8	16	100.0
	Statistic test- Probability level	Likelihood Ratio=3.5 --- *p-value*=0.094					
Phenytoin	Yes	53	32.7	109	67.3	162	100.0
	No	6	66.7	3	33.3	9	100.0
	Statistic test- Probability level	Fisher's Exact Test --- *p-value*=0.065					
Levetiracetam	Yes	46	31.7	99	68.3	145	100.0
	No	13	50.0	13	50.0	26	100.0
	Statistic test- Probability level	Likelihood Ratio=3.13 --- *p-value*=0.115					
Lamotrigine	Yes	34	30.4	78	69.6	112	100.0
	No	25	42.4	34	57.6	59	100.0
	Statistic test- Probability level	Likelihood Ratio=2.44 --- *p-value*=0.130					
Clonazepam	Yes	51	32.7	105	67.3	156	100.0
	No	8	53.3	7	46.7	15	100.0
	Statistic test- Probability level	Likelihood Ratio=2.45 --- *p-value*=0.153					
Clobazam	Yes	41	29.7	97	70.3	138	100.0
	No	18	54.5	15	45.5	33	100.0
	Statistic test- Probability level	Likelihood Ratio=6.97 --- *p-value*=0.017*					
Primidone	Yes	55	32.9	112	67.1	167	100.0
	No	4	100.0	0	0.0	4	100.0
	Statistic test- Probability level	Fisher's Exact Test --- *p-value*=0.013*					

Discussion

Despite taking antiepileptic medications, seizures are not controlled in more than 30% of the epileptic patients (11). In the present study around one third (34.5%) of the patients had refractory epilepsy. In a study conducted by French *et al.* the prevalence of refractory epilepsy was estimated at 20% to 40% in the newly diagnosed patients (9). In another study, Picot revealed 15.6% of the patients to meet the criteria for a refractory epilepsy diagnosis, with no significant difference in terms of gender (12). However, in a study by Allen Hauser conducted during 1935-1984, the overall incidence of epilepsy was found to be significantly higher among men (13), which is consistent with the results of the present study. In Picot's study, patients' age was taken as an important factor, so that the mean age was 19.6 years in patients with refractory epilepsy and 28.1 years in those who responded to treatments, which is inconsistent with the results of the present

study (12). In a study by Hui *et al.* (2007), of the total of 260 patients with a mean age of 34 (at the age range of 15-79), only 157 patients had total seizure control and the others were uncontrolled (14). In a study conducted in Saudi Arabia, Sinha *et al.* (2011) argued that defining refractory epilepsy is not just because more than 40% of patients are identified as resistant to medications, but also is in order to facilitate the selection and comparison of these patients for research purposes (15). Farghaly *et al.* found the prevalence of refractory epilepsy as 11.4% (16). In 2010, Ashtari *et al.* studied 101 patients in Isfahan University of Medical Sciences and reported their mean age as 26.8 and found the most frequent types of uncontrolled seizure in them to be partial (56.4%), followed by secondary generalized (24.8%) and primary generalized (19.8%) (17).Various factors were discussed in a study by Semah *et al.* with respect to refractory epilepsy, including the type of seizure. A total of 82% of the patients with idiopathic generalized seizure, who had been under treatment, experienced no seizures for over a year, while this figure was 26% in patients with symptomatic generalized seizure. In patients with cryptogenic and symptomatic focal seizures, this figure reached 45% and 35%, respectively (18). Farghaly found focal epilepsy to be significantly more prevalent in patients with refractory epilepsy compared to those with controlled epilepsy (64% *vs.* 26%). The results of analysis show that focal epilepsy is clearly associated with refractory epilepsy (15). In a study conducted in Pennsylvania University on 246 adult patients resistant to antiepileptic medication, 58% were found to experience focal seizures, 11% to have Lennox Gastaut and 6.9% to have generalized primary epilepsy (19). In the present study, in each seizure type group there wasn't any significant difference in the frequency of controlled and uncontrolled epilepsy except for mixed epilepsy in which, controlled seizures were more prevalent than uncontrolled ones which indicates that having mixed seizure type is not associated with to be refractory to the treatment of epilepsy. These figures are in conflict with some other results obtained in the previous study cited. Tripathi *et al.* also conducted a study on 200 patients with refractory epilepsy and found that 83% had partial seizures, 13.5% generalized (7% started with generalized seizures and 6.5% had myoclonic seizures at the onset of their disease) and 3.5% had mixed seizures (20). Despite the availability of more than 20 different types of antiepileptic drugs, 8 of which have been formulated in the past decade, refractory epilepsy is still highly prevalent according to statistics. Many studies have been conducted on these drugs, showing that the use of maximum doses of drugs such as topiramate, oxcarbazepine, levetiracetam, and pregabalin can reduce the frequency of seizures by 50% in only 32% to 37% of patients with refractory epilepsy (21-25). While in the present study, the use of medications such as carbamazepine, clobazam and primidone was significantly associated with refractory epilepsy. Probably these patients have not previously received the some potent drugs such as topiramate, oxcarbazepine, levetiracetam, and pregabalin or have taken but their seizure has not been controlled and they have compulsorily been prescribed the probably more potent drugs such as carbamazepine, clobazam and primidone.

Conclusion

Given the high prevalence of epilepsy among patients of active ages and its adverse effects on their lives, medical approaches should be taken to control this disease. Given its frequency and the involvement of one third of the cases of epilepsy as refractory epilepsy, it is still a serious problem that reduces performance levels in the patients. Some of these patients can benefit from undergoing surgery in case an early diagnosis is made and EEG monitoring is performed. The use of new and more effective antiepileptic medications at the right dose and as an adjunctive treatment can be effective in reducing the frequency of seizures in these patients.

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Conflict of Interest

No conflict of interest.

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