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Original Article

Psychosis of Epilepsy: A 10-Year Iranian Clinical Survey

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Abstract

Objective: Psychoses of epilepsy usually have an acute onset, accompanied by brief symptom duration and a risk of recurrence. Managing these conditions can be challenging due to the potential for seizures associated with certain antipsychotic medications, as well as exacerbating psychosis resulting from some antiepileptic medications. Our objective in this study was to assess the occurrence of psychosis among patients with epilepsy, as well as identify the factors linked to the presence and severity of psychosis in this population.
Method: In this study, we included a total of 514 subjects diagnosed with epilepsy referring to our neuropsychiatry clinic affiliated with Tehran University of Medical Sciences from April 2011 to December 2021, among whom 57 patients showed psychotic presentations. We compared baseline and clinical characteristics between patients with psychosis of epilepsy and non-psychosis patients who also had epilepsy.
Results: Marital status was the sole demographic factor that displayed a statistically significant difference between the psychosis and non-psychosis groups ($P = 0.019$). There was no significant difference observed between the two groups regarding family history of epilepsy and age at the onset of the epilepsy. Patients with psychosis experienced significantly more frequent seizures and generalized type ($P < 0.001$). Participants were matched for demographics and other clinical factors between the refractory and controlled psychosis groups, except for the psychosis frequency ($P = 0.007$). The type of epilepsy was significantly associated with psychosis when adjusted for the covariates ($P < 0.001$).
Conclusion: Patients with psychosis of epilepsy experienced more episodes of epilepsy than non-psychotics. We identified generalized epilepsy as an independent risk factor for the development of psychosis. Additional cohorts are warranted to explore the factors associated with epilepsy-related psychosis across diverse populations.

Key words: *Epilepsy; Generalized Epilepsy; Health Survey; Partial Epilepsy; Psychotic Disorders*

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As a chronic neurological disorder, epilepsy is specified by the presence of recurring epileptic seizures (1). Globally, nearly 50 million individuals have epilepsy with almost 80% being in developing countries (2). The prevalence of epilepsy exhibits significant variation across countries due to differences in the distribution of risk factors, etiology, and diagnostic criteria (3). Based on a meta-analysis, the estimated prevalence of epilepsy in the general population was found to be 7.60 per 1000 individuals. Notably, this rate was higher in developing countries, with a prevalence of 8.75 per 1000, compared to high-income nations, where the prevalence was 5.18 per 1000 (4). The Global Burden of Epilepsy Report reveals that epilepsy accounts for an estimated 13 million disability-adjusted life years (DALYs) annually, representing approximately 0.5% of the total burden of diseases (5, 6).

Psychotic manifestations can be due to underlying psychiatric disorders or a secondary manifestation of neurological disorders, such as epilepsy (7). The plausible link between epilepsy and psychosis has captivated the interest of psychiatrists for nearly a century (8). While previous studies have reported a prevalence rate of about 3% for psychotic disorders in the general population, some reports have suggested that psychosis develops in 7% to 10% of individuals with epilepsy (9). A meta-analysis demonstrated that approximately 6% of patients with epilepsy also experience a form of psychotic illness, suggesting a nearly eight times higher rate of psychosis in patients with epilepsy compared to the general population (8). Notably, another research showed that individuals diagnosed with schizophrenia are also more likely to have epilepsy compared to the general population (10). Therefore, based on epidemiological studies, it seems that there is a mutual connection between epilepsy and psychosis, which might be independent of other influencing factors (11).

Several factors could contribute to psychosis in epilepsy. The involvement of dopaminergic pathways in the development of both epilepsy and schizophrenia has been well-documented. Notably, altered dopamine activity in the prefrontal cortex appears to be a shared factor in these two conditions. This alteration in dopamine activity may result in irregularities in the mesiotemporal dopamine circuitry, which could potentially promote either seizures or psychosis (7). Neuroimaging studies have revealed significant alterations in patients who have both epilepsy and psychosis. These changes may include variations in the size of the hippocampal and amygdala structures, which are related to the mesolimbic architecture (12, 13). Another study indicated increased cerebral blood flow in the posterior cingulate gyrus in individuals with psychosis of epilepsy (14). Psychosis induced by antiepileptic medications is also a common condition, which could occur after either consumption or withdrawal (15). Some trials have shown that the prevalence of psychosis induced by antiepileptic medications varies from 1% to 8% (16).

Few studies have so far investigated the clinical characteristics of individuals with epilepsy-related psychosis compared to those without psychosis. Several factors including female gender, age at epilepsy onset, type of seizure, and frequency of seizures, may contribute to the development of epilepsy-related psychosis (17, 18). However, these findings are still controversial and further studies are warranted to confirm them. The occurrence of psychosis among Iranian patients with epilepsy has not been previously investigated. Therefore, we aimed to investigate the prevalence and characteristics of psychosis symptoms in individuals with epilepsy who sought treatment at our neuropsychiatry clinic. Additionally, our aim was to explore the differences in epilepsy characteristics between patients with and without psychosis, as well as identify the factors associated with refractory psychosis.

Materials and Methods

Design and Participants

This study initially included all patients diagnosed with epilepsy who sought treatment at our neuropsychiatry clinic affiliated with Tehran University of Medical Sciences from April 2011 to December 2021. Exclusions were made for patients with any other neurologic or psychiatric disorders, as well as those with incomplete data records. We enrolled 514 eligible patients, among which 57 patients exhibited psychotic symptoms.

Measurements and Definitions

Hospital records were used to extract the demographic data of all participants. Additionally, information regarding family history of epilepsy, age at the first epileptic seizure episode, type of epilepsy, and the incidence and frequency of seizures within the past year were collected. The diagnosis and evaluation of epilepsy were conducted by expert neurologists using the criteria and classification for epilepsy set forth by the International League Against Epilepsy (ILAE). Moreover, the manifestation of psychosis symptoms was confirmed by experienced psychiatrists utilizing the Structural Clinical Interview for DSM-V (SCID).

Ethical Considerations

All participants signed written informed consent, and their anonymity was maintained throughout the study. Personal information was recorded confidentially and securely. The study was approved by the research and ethics committee of Tehran University of Medical Sciences, following the ethics code IR.TUMS.MEDICINE.REC.1399.275. The protocol adheres to the principles outlined in the Declaration of Helsinki 2013.

Statistical Analysis

We used R (version 4.1.2) within RStudio statistical software for statistical analysis. A significance level of P-value < 0.05 was considered statistically significant.

Continuous variables were presented as mean with standard deviation, while categorical variables were presented as numbers and percentages. To compare categorical variables, Pearson chi-square or Fisher's exact test was employed, while independent samples t-test or Mann-Whitney U test was utilized to compare continuous variables, depending on the distribution of the variables. Binary logistic regression models were conducted to explore the association between psychosis and the type of epilepsy and frequency, as well as the association between refractory psychosis and psychosis frequency. Age, gender, and marital status were considered confounding variables.

Results

The mean age of the patients in the psychosis group was 34.75 ± 10.75, while it was 34.39 ± 13.91 in the non-psychosis group (P = 0.619). The two groups were matched for gender (P = 0.591) and education years (P = 0.280). However, the psychosis group had a higher proportion of married individuals compared to the non-psychosis group (P = 0.019). Furthermore, no significant difference was found between the two groups regarding their family history of epilepsy (P = 0.159), age at the first epileptic seizure episode (P = 0.137), and type of care (inpatients vs outpatient) (P = 0.586). The psychosis group showed a tendency to be more frequent (P < 0.001) and generalized in terms of the type of epilepsy (P < 0.001). The use of various antiepileptic medications was also compared between the psychosis and non-psychosis groups, indicating significantly higher use of valproate among patients with psychosis of epilepsy (P < 0.001). However, other medications did not show significant differences between these groups. Table 1 presents a comparison of the demographics and clinical characteristics among the psychosis and non-psychosis groups.

Table 1. Demographics and Clinical Characteristics in Psychosis and Non-Psychosis Groups

		Psychosis	Non-psychosis[1]	P-value
Number		53 (10.4%)	457 (89.6%)	
Age (Years)		34.75 ± 10.75	34.39 ± 13.91	0.619
Gender	Male	26 (49.1%)	242 (53.0%)	0.591
	Female	27 (50.9%)	215 (47.0%)	
Education (Years)		8.66 ± 3.67	7.98 ± 5.01	0.280
Marital status	Single	23 (43.4%)	247 (60.2%)	0.019
	Married	30 (56.6%)	163 (39.8%)	
Age at the first seizure episode (Year)		16.60 ± 10.95	15.07 ± 12.73	0.137
Family history of epilepsy	No	44 (83.0%)	298 (74.1%)	0.159
	Yes	9 (17.0%)	104 (25.9%)	
Type of care	Outpatient	44 (83.0%)	365 (80.0%)	0.586
	Inpatient	9 (17.0%)	92 (20.0%)	
Type of epilepsy	Generalized	34 (64.1%)	146 (31.9%)	< 0.001
	Focal	19 (35.9%)	311 (68.1%)	
Epilepsy frequency (during last year)	< 1	7 (13.2%)	172 (41.3%)	< 0.001
	1	13 (24.5%)	95 (22.8%)	
	2	13 (24.5%)	0	
	3	12 (22.6%)	0	
	4 and > 4	8 (15.2%)	149 (35.9%)	
Carbamazepine		20 (37.7%)	180 (39.4%)	0.882
Valproate		35 (66.0%)	162 (35.4%)	< 0.001
Lamotrigine		10 (18.9%)	94 (20.6%)	0.859
Levetiracetam		16 (30.19%)	96 (21.0%)	0.159
Topiramate		4 (7.5%)	15 (3.3%)	0.124
Phenytoin		2 (3.8%)	9 (2.0%)	0.320
Phenobarbital		5 (9.4%)	31 (6.8%)	0.406
Gabapentin		1 (1.9%)	11 (2.4%)	1.000

GTC, Generlized Tonic-Clonic Seizure; TLE, Temporal Lobe Epilepsy
Data are presented as mean ± standard deviation or number (frequency)
[1] numbers may not add up to total due to missing

Table 2 illustrates a comparison between the refractory and controlled psychosis groups among those 57 epilepsy patients with an episode of psychosis. No significant differences were observed regarding demographics,

including age, gender, education, and marital status. Furthermore, there were no significant differences observed between the two groups regarding epilepsy-related factors, including the age at the first epileptic seizure episode, family history of epilepsy, type of epilepsy, and epilepsy frequency. The duration of psychosis showed no significant difference (P = 0.625); however, the group with refractory psychosis experienced more frequent episodes of psychosis compared to the controlled group (P = 0.007).

Table 2. Comparison of Demographics and Clinical Characteristics between Controlled and Refractory Psychosis Groups among Patients with Epilepsy

		Refractory	Controlled	P-value
Number		13 (24.5)	40 (75.5%)	
Age (Years)		32.62 ± 10.86	10.76 ± 35.45	0.414
Gender	Male	6 (46.2%)	20 (50.0%)	1.000
	Female	7 (53.8%)	20 (50.0%)	
Education (Years)		9.62 ± 3.45	8.35 ± 3.72	0.264
Marital status	Single	8 (61.5%)	15 (37.5%)	0.198
	Married	5 (38.5%)	25 (62.5%)	
Age of first seizure episode (Year)		17.85 ± 10.10	16.20 ± 11.30	0.605
Family history of epilepsy	No	12 (92.3%)	32 (80.0%)	0.424
	Yes	1 (7.7%)	8 (20.0%)	
Type of epilepsy	GTC	10 (76.9%)	24 (60.0%)	0.334
	TLE	3 (23.1%)	16 (40.0%)	
Epilepsy frequency (during last year)	< 1	2 (15.4%)	5 (12.5%)	0.934
	1	2 (15.4%)	11 (27.5%)	
	2	4 (30.8%)	9 (22.5%)	
	3	3 (23.1%)	9 (22.5%)	
	4 and > 4	2 (15.4%)	6 (15.0%)	
Family history of psychosis	Yes	5 (38.5%)	5 (12.5%)	0.052
	No	8 (61.5%)	35 (87.5%)	
Psychosis duration (Years)		9.46 ± 10.19	9.55 ± 7.95	0.625
Psychosis frequency (during last year)	< 1	0	1 (2.5%)	0.007
	1	0	13 (32.5%)	
	2	3 (23.1%)	16 (40.0%)	
	3	6 (46.2%)	9 (22.5%)	
	4 and > 4	4 (30.8%)	1 (2.5%)	
Temporal relationship with seizures	Ictal	1 (7.7%)	2 (5.0%)	0.890
	Inter ictal	6 (46.2%)	17 (42.5%)	
	Post Ictal	6 (46.2%)	21 (52.5%)	
Delusion	Yes	12 (92.3%)	36 (90.0%)	1.000
	No	1 (7.7%)	4 (10.0%)	
Hallucination	Yes	9 (69.2%)	18 (45.0%)	0.202
	No	4 (30.8%)	22 (55.0%)	
Negative symptoms	Yes	12 (92.3%)	38 (95.5%)	1.000
	No	1 (7.7%)	2 (5.0%)	
Carbamazepine		8 (61.5%)	12 (30.0%)	0.054
Valproate		7 (53.8%)	28 (70.0%)	0.326
Lamotrigine		1 (7.7%)	9 (22.5%)	0.419
Levetiracetam		3 (23.1%)	13 (32.5%)	0.731
Topiramate		3 (23.1%)	1 (2.5%)	0.042
Phenytoin		0	2 (5.0%)	1.000
Phenobarbital		0	5 (12.5%)	0.317
Gabapentin		0	1 (2.5%)	1.000

GTC, Generlized Tonic-Clonic Seizure; TLE, Temporal Lobe Epilepsy

Additionally, we compared the temporal association between psychosis and seizure between the refractory and controlled groups, which yielded statistically insignificant findings (P = 0.890). Among the 53 patients with psychosis, the majority experienced psychosis during postictal and interictal periods (27 patients in postictal, 23 patients in interictal, and only three in ictal periods). There were no statistically significant differences observed between the two groups regarding psychotic symptoms, including delusions, hallucinations, and negative symptoms. Moreover, the comparison of antiepileptic medication usage between the refractory and controlled groups did not reveal any significant differences.

The binary logistic regression model revealed a significant association between the type of epilepsy and the incidence of psychosis in epilepsy, even after controlling for potential confounders such as age, gender, and marital status (P < 0.001). However, the frequency of epilepsy did not exhibit a significant association with psychosis, both before and after adjusting for confounding factors (P = 0.161 and 0.160, respectively) (Table 3). On the other hand, a separate binary logistic regression analetysis demonstrated a significant association between the frequency of psychosis and being refractory, even after controlling for age and gender (P < 0.001).

Table 3. Binary Logistic Regression in Psychosis and Non-Psychosis Groups

		Exp (B)	95% CI		P-value
			Lower	Upper	
Univariate	Type of epilepsy	3.812	2.103	6.910	< 0.001
	Epilepsy frequency	1.122	0.955	1.319	0.161
Multivariate*	Type of epilepsy	4.279	2.321	7.888	< 0.001
	Epilepsy frequency	1.125	0.955	1.326	0.160

*Adjusted for age, gender, and marital status
CI, Confidence Interval

Discussion

We examined the prevalence of epilepsy-related psychosis and the factors precipitating the psychosis and its severity in patients with epilepsy. Our study is the first of its kind to investigate epilepsy-related psychosis in the Iranian population. In contrast to previous studies that primarily focused on patients from neurology clinics, our study was conducted in neuropsychiatry clinics within a psychiatric hospital. This allowed for the inclusion of cases involving chronic psychosis and psycho-affective conditions. This broader inclusion may contribute to the representative nature of our findings among the wider population of patients with epilepsy-related psychosis. These differences in study design and patient selection may account for the contrasting results obtained in our research compared to some previous comparable studies.

Our findings revealed that approximately 10% of the patients with epilepsy experienced epilepsy-related psychosis, which is consistent with previous reports indicating remarkably higher rates of psychosis in individuals with epilepsy (19). A recent meta-analysis suggested that up to 6% of patients with epilepsy can manifest psychosis and have an approximately eight-fold increased risk of developing psychosis compared to the general population (8). Similarly, a three-year longitudinal cohort study conducted in the UK demonstrated a significantly higher incidence rate of psychosis in patients with epilepsy (20). However, it is important to note that some studies have demonstrated that the rate of psychosis of epilepsy can vary from 0.5% (21) to 35% (22). Differences in studied populations and methodological discrepancies such as varying diagnostic classifications, clinical heterogeneity, and sample size differences could have led to these inconsistencies. Other mental health comorbidities such as mood disorders, anxiety disorders, and psychosis spectrum conditions are also shown to be relatively higher in patients with epilepsy (17).

In our study population, patients with epilepsy-related psychosis had a significantly higher number of epileptic seizure episodes per year. This finding is consistent with a systematic review that found a correlation between the prevalence of psychiatric comorbidities in patients with epilepsy and treatment responsiveness. Another systematic review investigating risk factors associated with psychosis in temporal lobe epilepsy (TLE) also suggested that seizure frequency may be a potential risk factor, although this was not consistently reported across all studies included in the review (18). This observation supports the notion that psychosis may contribute to an increased risk of epileptic seizure attacks. Moreover, it is also plausible to suggest that psychosis is more prevalent among patients who experience a higher frequency of epileptic seizure episodes. Notably, epidemiological investigations have proposed a bidirectional relationship between psychosis and epilepsy (7). In this context, a population-based case-control study conducted on 1885 patients with epilepsy registered in the Stockholm Epilepsy Registration system revealed an increased rate of comorbid psychosis both before and after the onset of seizures (23). This finding suggests a bidirectional relationship between psychosis and epilepsy, with

potential shared underlying mechanisms. Similarly, a retrospective cohort study conducted in Taiwan provided evidence for a strong bidirectional association between epilepsy and psychosis, suggesting the presence of common causes for these conditions (11).

Our analysis also revealed that among the different types of epilepsy, the generalized type was more prevalent in patients with psychosis compared with those without psychosis. Particularly, in our population, the generalized type emerged as the prominent risk factor associated significantly with psychosis among individuals with epilepsy. The relationship between the types of epilepsy and the development of psychosis remains a topic of debate and controversy. Previous research on the psychosis of epilepsy has shown that focal epilepsy, such as TLE, has a significantly higher prevalence in patients with epilepsy-related psychosis (24). Notably, according to a recent systematic review, TLE has been associated with higher levels of psychiatric comorbidity, including psychosis (17). Furthermore, a meta-analysis has also reported a higher rate of psychosis specifically in patients with TLE (8). Generally, previous research indicates that TLE may be considered a potential risk factor for the occurrence of psychosis in individuals with epilepsy. Given the involvement of the limbic system in regulating behavior and emotions, it is plausible that the high incidence of TLE in patients with psychosis of epilepsy can be attributed to limbic system dysfunction (24).

Consequently, limbic involvement can be considered a potential risk factor for psychosis in these patients (7). Although our study found a higher frequency of generalized epilepsy in patients with psychosis of epilepsy, it is important to consider that these findings may not be applicable to all individuals with epilepsy. It should be acknowledged that making a comparison between studies is challenging due to differences in baseline patient characteristics and study designs that can affect study outcomes. In this regard, our study included subjects from a neuropsychiatry clinic in a psychiatry hospital, whereas previous studies mainly studied patients with epilepsy referred to neurology clinics, which could ultimately affect the results.

Previous studies have also suggested that several factors including early age at onset of epilepsy, history of seizures, a family history of psychosis or mood disorder, hippocampal sclerosis, and neurodevelopmental disorders increase the incidence of psychosis of epilepsy (7, 18). However, in our study, age at onset of epilepsy and family history of epilepsy were not associated with psychosis of epilepsy. Some studies have also reported that marital status (25) and education levels (26) can impact the incidence of psychosis. For example, a cross-sectional comparative study showed that patients at a high risk of psychosis had lower education levels (26). Another study found that single marital status could increase individuals' vulnerability to psychotic disorders such as schizophrenia (25). Interestingly, our study revealed that significantly more individuals with psychosis of epilepsy are married; however, according to previous data, married marital status was expected to be more prevalent in non-psychotic individuals (27, 28). Further research is warranted to validate these findings and assess whether there are notable variations in these statistics across diverse populations.

Recent evidence suggests a potential association between the use of antiepileptic medications in patients with epilepsy and the occurrence of psychosis. By exploring various antiepileptic medications, these studies reported that levetiracetam was associated with psychosis of epilepsy while the use of carbamazepine and lamotrigine were found to be protective in these patients (15, 29). The same pattern was observed in our population as well. In the present study, the use of levetiracetam was more prevalent in the psychosis group, whereas lamotrigine and carbamazepine were more common in the non-psychosis group. Nevertheless, these differences were not statistically significant. This might primarily be attributed to the limited number of subjects in the study, which may have not been sufficient to detect significant differences. Additionally, previous studies have suggested a number of possible risk factors, including female gender, status epilepticus, a history of psychotic symptoms, and temporal lobe involvement, to be associated with antiepileptic drug-induced psychosis (15, 29). Given the limited scope of existing research, further studies are required in this area of research to expand our understanding and confirm the findings.

Limitation

In terms of limitations, it should be noted that our study was conducted retrospectively, which may introduce certain biases and limitations in data collection. Additionally, our relatively low sample size of psychosis in individuals with epilepsy is attributed to the rarity of the condition, making it challenging to analyze the effects of multiple variables on both epilepsy and psychosis. Moreover, this study was conducted in a neuropsychiatry center on the Iranian population, which could impact our observations due to cultural or environmental factors unique to this population. Therefore, larger-scale comparisons of epilepsy and psychosis with a longitudinal design and prospective follow-ups investigating a wider range of variables are warranted.

Conclusion

In conclusion, our findings suggest that patients with psychosis of epilepsy have a higher frequency of seizures. Generalized epilepsy is an independent risk factor for the occurrence of psychosis in this population. The mediating role of various covariates in predicting psychosis in patients with epilepsy remains to be further studied.

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Conflict of Interest

None.

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