Psychiatric disturbances in idiopathic epilepsy

Troubles psychiatriques dans l'épilepsie idiopathique

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Abstract

Background: The relationship between epilepsy and psychiatric disorders has been highlighted for a long time. Idiopathic epilepsy is known to have a benign course in most cases. However, the association of psychiatric disturbances could worsen the disease outcome.
Objective: we aimed to study the frequency of psychiatric symptoms in patients with idiopathic epilepsy and to assess the determinant factors in the patient group with these manifestations.
Methods: In one-year prospective study, consecutive patients diagnosed with idiopathic epilepsy were included. Those with a known psychiatric follow-up or with post ictal psychiatric disturbances were excluded. Psychiatric symptoms were evaluated with the Neurological Disorders Depression Inventory for Epilepsy, the Generalized Anxiety Disorder - 7 and the Neuropsychiatric Inventory Scale. Demographic and clinical data were collected and analyzed.
Results: Among 101 consecutive patients with idiopathic epilepsy, psychiatric symptoms were diagnosed in 61% of them. Anxiety (36.6%), psychotic features (21%) and depression (15.8 %) were the most commonly found psychiatric manifestations. Female gender ($p < 10\text{-}3$) and longer duration of epilepsy ($p = 0.046$) were significantly associated with occurrence of psychiatric disturbances. Patients under Carbamazepine and Valproic acid showed a lower frequency of depression (respectively $p = 0.018$ and $p = 0.003$).
Conclusions: Occurrence of psychiatric disturbances was frequent in idiopathic epilepsy, with psychotic manifestations and anxiety being the most common of them. Female gender and long disease course were the main determining factors of psychiatric manifestations and should be considered in management of idiopathic epilepsy.

Key words: epilepsy, idiopathic, psychosis, anxiety, depression, Tunisians

Résumé

Background: L'épilepsie idiopathique est connue pour avoir une évolution bénigne dans la plupart des cas. Cependant, l'association avec des troubles psychiatriques pourrait aggraver l'évolution de la maladie.
Objectif: Nous avons étudié la prévalence des symptoms psychiatriques chez les patients atteints d'épilepsie idiopathique et évalué les facteurs prédictifs de survenue de ces manifestations.
Méthodes: Nous avons mené une étude prospective incluant de façon consécutive des patients diagnostiqués avec une épilepsie idiopathique. Nous avons exclu ceux avec un diagnostic psychiatrique connu ou avec des troubles psychiatriques post-ictaux. Nous avons évalué les symptômes psychiatriques via le Neurological Disorders Depression Inventory for Epilepsy, le Generalized Anxiety Disorder - 7 et le Neuropsychiatric Inventory Scale.
Résultats: Parmi 101 patients attaints d'épilepsie idiopathique, des symptoms psychiatriques ont été diagnostiqués chez 61 % d'entre eux. Une anxiété (36,6 %), des symptômes psychotiques (21 %) et une dépression (15,8 %) étaient les manifestations psychiatriques les plus fréquentes. Le sexe féminin ($p = 0,000$) et une durée plus longue de l'épilepsie ($p = 0,046$) étaient significativement associés aux troubles psychiatriques. Les patients sous carbamazépine et acide valproïque avaient une fréquence de dépression plus faible (respectivement $p = 0,018$ et $p = 0,003$).
Conclusions: Les troubles psychiatriques sont fréquents dans l'épilepsie idiopathique dominés par les manifestations psychotiques et l'anxiété. Le sexe féminin et la longue évolution de la maladie étaient les principaux facteurs prédictifs des manifestations psychiatriques et doivent être pris en compte dans la prise en charge de l'épilepsie idiopathique.

Mots clés: épilepsie, idiopathique , psychose, anxiété, dépression , Tunisiens

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INTRODUCTION

For a long time, epilepsy was considered as a disorder of the central nervous system manifested only by the occurrence of epileptic seizures. Clinical analysis and investigations focused on the characterization of seizure semiology, epilepsy etiology, and impact of the epileptic disorder on patient's health and quality of life. Treatments of epilepsy aimed to achieve a seizure-free state.

The International League Against Epilepsy has recognized these epileptic syndromes as idiopathic or genetic: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), epilepsy with generalized tonic-clonic seizures (GTCS) only, rolandic epilepsy, temporal lobe epilepsy, etc. Although all having a presumed genetic or idiopathic origin, they have different epidemiological characteristics and pathophysiological pathways and mechanisms. Age at onset differs between these syndromes starting from childhood to extend to adulthood. The understanding of genetic basis knew several steps from the channelopathy pattern usually with monogenic inheritance to spill over into the complex epilepsies with the identification of the susceptibility genes (1).

In the last few decades, there is a growing interest in psychiatric disturbances in epileptic patients. They were found to be more frequent in patients with epilepsy compared to the general population (1). Moreover, epilepsy and psychiatric disorders may have a much more complex interplay than expected. In fact, patients with epilepsy are at a higher risk of developing psychiatric disturbances, and those with a primary psychiatric illness could develop epileptic seizures for many reasons. Hence, previous studies have suggested a "bidirectional" relation between epilepsy and several psychiatric disorders including psychosis, mood disturbances, and anxiety disorders (2).

In this study, our aim was to determine the prevalence and the type of psychiatric symptoms in patients with idiopathic epilepsy and to investigate the predictive factors of their occurrence.

METHODS

A hospital-based, cross-sectional, and prospective study was conducted at the Neurology Department Razi University Hospital, a tertiary referral center in Tunisia, over a period of 12 months from January to December 2019.

Study Population:

Consecutive patients with a documented history of idiopathic epilepsy and who gave verbal consent prior to data collection were included. The diagnosis of idiopathic epilepsy was based on the 2014 International League Against Epilepsy (ILAE) definition of epilepsy and the 2017 classification of epilepsy etiologies (4). All patients who presented a seizure in the last seven days were excluded to avoid considering any post-ictal psychiatric disturbances (5). Those who already had a diagnosis of a psychiatric disorder or had a history of cognitive impairment were not included in the present study.

Clinical and Neuropsychological Assessment:

All patients were interviewed by neurologists specialized in epileptic disorders using a pre-established structured questionnaire, including socio-demographic data (age, sex, marital status, educational level, occupation), family and personal medical history, clinical history, and outcome of epilepsy (seizures semiology, disease duration, follow-up duration, seizures' frequency), electroencephalography, and administered antiseizure medications (ASM).

Previously-validated psychiatric tools in evaluating epileptic patients were used. They included the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), the Generalized Anxiety Disorder - 7 (GAD-7), and the Neuropsychiatric Inventory scale (NPI) (6–9). Caregivers were needed to answer to the questions related to NPI items. After assessment, data were reviewed by psychiatrists experienced in managing epileptic patients.

The NDDI-E is a six-item questionnaire that allows the rapid identification of major depression in patients with epilepsy. It was approved by the Harris County Hospital District's Patient Education Committee in November 2007. An NDDI-E score greater than 15 was considered positive for depression. This score has a specificity of 90% and sensitivity of 81% (9).

Generalized Anxiety Disorder-7 (GAD-7) is the only screening tool for GAD that has been validated in patients with epilepsy. It's a self-rated scale, developed by Spitzer and colleagues in 2006, as a screening tool and severity indicator for GAD. This test includes seven items, is rapid, and can be completed in less than three minutes with a sensitivity and specificity exceeding 80% (10).

The Neuropsychiatric Inventory (NPI) is a validated informant-based interview, developed by Cummings et al in 1994. Initially, it was designed to target demented populations. It evaluates 12 psychiatric disturbances: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, appetite and eating abnormalities. Later, the scale was validated to evaluate neurological disorders such as epilepsy (11). The NPI was originally validated by Krishnamoorthy as a caregiver rated-measure including 4 main groups of symptoms or factors as mentioned in the original article (11):

- The psychosis factor characterized by delusions, hallucinations, and aberrant motor behavior and sleep behavior.
- The interictal dysphoric disorder factor characterized by agitation, apathy, disinhibition, and irritability.
- The depression factor including both appetite change and sleep disorder with depressive mood.
- The anxiety factor characterized by anxiety and euphoria.

NPI has good content validity, internal consistency, and reliability to epileptic patients. The severity and occurrence of each neuropsychiatric symptom from each category are rated on the basis of scripted questions administered to the patient's caregiver (11). The elaboration of the questionnaire and the choice of the used psychiatric tools were made by neurologists and psychiatrists who used to deal with patients with epilepsy from two departments of neurology and psychiatry in our hospital mainly specialized in psychiatry and mental health in Tunis-Tunisia.

Statistical Analysis:

Data were analyzed using IBM-Statistical Package for the Social Sciences (SPSS) version 25. Categorical variables were characterized using frequencies and percentages. Means, medians, and standard deviations were specified for quantitative variables. Significance was assessed using Pearson's chi-square test for categorical variables. Fisher exact test was applied for corrections wherever applicable. A statistically significant difference was retained if $p < 0.05$.

RESULTS

Study Population Characteristics:

A total of 101 consecutive participants (50 males, 51 females) were included. The mean age was 37.4 years ± 18.5 Standard deviation (SD) [18-85 years]. Personal history of febrile seizures was reported in 5.9% of cases. Family history of neurological diseases was noted in 40.6%: epilepsy in 25.7% and psychiatric illness in 11.9%. Sociodemographic data, lifestyle behaviors, and main features of epileptic syndromes were summarized in Table 1.

Table 1. Demographic and clinical characteristics of the studied population

Age	37.4 years (Standard Deviation= 18.5)
Age at onset	17.9 years (Standard Deviation = 14.6)
Gender : Male/ Female	50 (49.5%) / 51 (50.5%)
Marital Status	
- Single	47 (48.5%)
- Married	44 (45.4%)
- Widower	5 (5.2%)
- Divorced	1 (0.9%)
Education	
- Illiterate	12 (11.9%)
- Primary School level	45 (44.6%)
- Secondary School level	33 (32.7%)
- Graduation and above	11 (10.9%)
Socio-economic level	
- Low	40.6 (41 %)
- Middle	51.5 (52 %)
- High	7.9 (8 %)
Occupation :	
Employed/ Unemployed	50 (49.5%) / 51 (50.5%)
Lifestyle behaviours	
- Tobacco	23 (22.8%)
- Alcohol	7 (6.9%)
- Psychoactive substance use	1 (1%)
Epilepsy syndromes	- Generalized tonic-clonic epilepsy (52 patients, 51.4%)
	- Juvenile myoclonic epilepsy (8 patients, 7.9 %)
	- Childhood absence epilepsy (5 patients, 4.9%)
	- Temporal lobe epilepsy (25 patients, 24.7%)
	- Frontal lobe epilepsy (6 patients, 5.9%)
	- Rolandic epilepsy (5 patients, 4.9 %)

Clinical Characteristics of the Studied Population:

The mean duration of the disease in our patients was 19.45 years, with extremes ranging between three months to 68 years. Seizures were with generalized onset (64.2%) and focal onset (35.8%). Epilepsy was generalized in 64.2% and focal in 35.8% of our patients. All patients were receiving ASM: monotherapy (79.2%) and polytherapy (20.8%). Prescribed ASM is summarized in figure 1. About fifteen Patients (14.8%) were seizure-free five years before the study inclusion. Drug resistance was diagnosed in only three percent of our patients.

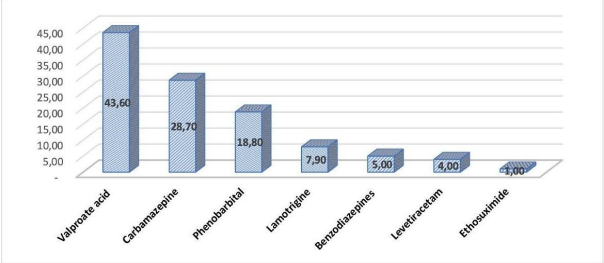

Figure 1. Prescribed antiseizure medications in our cohort (%)

Psychiatric Manifestations:

Psychiatric manifestations were identified in 61% of our patients. Anxiety and depression were found respectively in 36.6% and 15.8%. Psychotic manifestations were found in 21%. Hallucinations and delirium were respectively reported in 21% and 14% of our patients. Other psychiatric features were identified: irritability (53.6%), insomnia (26.7%), anorexia (21.7%), and euphoria (11.8%). Behavioral disturbances (agitation, aggressiveness) were noted in 40%.

Risk Factors of Psychiatric Disturbances:

Psychiatric disturbances were significantly associated with female gender and a duration of epilepsy more than 20 years as shown in table 2. There were no significant correlations between psychiatric symptoms and consanguinity, familial or personal medical history, educational level, socio-economic level, lifestyle behaviors, seizure type, medication status, and drug resistance ($p \geq 0.05$). The relationship between psychiatric manifestations such as anxiety, depression, and psychotic symptoms and age, gender, prescribed antiepileptic treatment, and drug resistance are detailed in table 3. A significant correlation was found between female gender and anxiety ($p = 0.003$) and psychotic symptoms ($p = 0.000$). Moreover, we found a significant correlation between the type of prescribed ASM and depressive symptoms (table 3). In fact, depression was less frequent in patients under carbamazepine or valproic acid (respectively $p = 0.018$ and $p = 0.003$).

Table 2. Predictive factors of psychiatric disturbances in our cohort of patients with idiopathic epilepsy

	Presence of psychiatric comorbidity (n)	Absence of psychiatric comorbidity (n)	p value
Gender			
Male	19	30	0.000
Female	40	11	
Education			
Illiterate	10	2	
Primary School level	49	40	0.05
Secondary School level	-	-	
Graduation and above	-	-	
Socio-economic level			
Low	10	2	
Middle/High	49	40	0.05
Occupation			
Employed	33	17	0.126
Unemployed	26	25	
Lifestyle behaviours			
Tobacco	12	11	0.5
Alcohol	4	3	1
Psychoactive substance use	1	0	1
Types of seizure			
Generalized seizures	34	29	0.24
Focal Seizures	25	13	
Medication status			
Monotherapy	43	37	0.06
Polytherapy	15	6	
Drug resistance			
No	57	41	1
Yes	2	1	
Duration of epilepsy			
0-20 years	29	29	0.046
>20 years	30	13	

Table 3. Predictive factors of anxiety, depression and psychotic features in patients with idiopathic epilepsy

Psychiatric symptoms	Anxiety			Depression			Psychosis		
	Present	Absent	Significance (p< 0.05)	Present	Absent	Significance (p < 0.05)	Present	Absent	Significance (p< 0.05)
Gender									
Male	11	39	p=0.003	7	43	p=0.62	19	31	p=0.000
Female	26	25		9	42		40	11	
Anti-epileptic drugs									
Carbamazepine	14	15	p=0.083	9	20	p=0.018	19	10	p=0.29
Phenobarbital	5	14	p=0.35	6	13	p=0.081	12	7	p=0.56
Valproic acid	12	32	p=0.12	2	42	p=0.003	22	22	p=0.18
Levetiracetam	3	1	p=0.12	1	3	p=0.52	4	0	p=0.13
Lamotrigine	4	4	p=0.45	3	5	p=0.126	5	3	p=1
Ehosuximide	0	1	p=1	0	1	p=1	1	0	p=1
Benzodiazepine	3	2	p=0.34	0	5	p=0.6	5	0	p=0.07
Drug resistance									
No	35	63	p=0.55	15	83	p=0.4	57	41	p=1
Yes	2	1		1	2		2	1	
AED									
Monotherapy	28	52	p=0.56	10	70	p=0.3	43	37	p=0.2
Polytherapy	10	11		6	15		15	6	

DISCUSSION

Idiopathic epilepsies are a heterogeneous group representing up to 47% of all epilepsies and are assumed to be mainly of genetic origin. Most of them are believed to be with polygenic or complex inheritance (12). The diagnosis of idiopathic epilepsies is based on suggestive clinic and electroencephalographic features and normal brain imaging.

Our study highlighted the higher prevalence of psychiatric disturbances in our patients with idiopathic epilepsy compared to the most reported rates in the literature (11,13–31). In fact, it differs from one study to another due to the variability of the sensitivity of the used tools to assess psychiatric symptoms in epilepsy and to different methodological designs and epilepsy subtypes (Table 4).

In our study, we used three previously validated tests to screen psychiatric disturbances in epilepsy easy to perform in a follow-up outpatient clinic. In our patients, anxiety disorder, found in 36.6 % of our epileptic subjects, was higher than what was reported in other published studies (five to 25%) (32,33). However, depression was low in our patients (15.8%) compared to most studies in literature (7,25,36–39) (5.2 to 89.6%). Psychotic symptoms had a higher prevalence rate (21%) in our series (0.7 to 18% in previously published studies) (9,30,37). This different trend with a lower prevalence of depression and a higher prevalence of anxiety and psychotic manifestations could be due to a bias of recruitment. Indeed, our department is a tertiary hospital center and a part of a mental health and psychiatric hospital in Tunis where patients' consultations are mainly due to psychological and behavioral problems.

Table 4. Overview of studies on psychiatric disturbances in Epilepsy

Study, Year	Country	Population (n)	Used Tool	Psychiatric comorbidity
Pond et al,1960 (13)	United Kingdom	245	Psychiatric interview	29%
Rutter et al, 1970 (14)	Isle of wight	64	Psychiatric interview	28.6%
Currie et al, 1971(15)	United Kingdom	666	Interview and cases notes	29%
Shukla G et al, 1979 (16)	India	132	DSM-II	62%
Edeh and Toone et al, 1987(17)	United Kingdom	88	Clinical Interview Schedule	48%
Fiordelli E et al,1993 (18)	Italy	100	DSM-II	19%
Manchanda et al, 1996 (19)	Canada	300	Present state examination	29%
Jalava et al, 1996 (20)	Finland	94	Chart review and International Classification of diseases 9 (ICD-9)	24%
Bredkjaer et al, 1998 (21)	Denmark	116	ICD-8	16.8%
Steffansson et al, 1998 (22)	Iceland	241	ICD-9	35.3%
Cyriac et al, 2002 (23)	India	106	ICD-10 symptom checklist ICD-10-DCR	42-45%
Davies et al, 2003 (24)	United Kingdom	67	Psychiatric interview based on DSM-IV	37%
Agoub M et al, 2004 (25)	Morocco	92	ICD-10	18.5%
Gaitatzis et al, 2004 (26)	United Kingdom	5834	ICD-9	41%
Jones JE et al, 2005 (27)	United States of America	174	Mini International Neuropsychiatric Interview (MINI) Mood disorder module Structured Clinical Interview Schedule (SCID)	49%
Krishnamoorthy ES et al,2008 (11)	India	228	NPI, Brief Psychiatric Rating Scale (BPRS)	25.6%
Jacob R et al, 2010 (28)	India	80	Structured Clinical Interview Schedule (SCID), DSM IV Version	28.7%
Desai S et al, 2014 (29)	India	50	MINI	52%
Elghazouani F et al, 2015 (33)	Morocco	89	MINI, Beck Depression Inventory (BDI), Hamilton Rating Scale	74.1%
Rehman S et al ,2016 (30)	India	100	MINI	50%
M'bayoT et al,2017 (31)	Sierra Leone	142	Validated screen by a psychiatric clinical officer using DMS-IV criteria	27.4%
Kuladee S et al,2019 (32)	Thailand	170	DIAGNOSTIC AND STATISTICAL Manual of Mental Disorders, 4th Edition	25.3%
Our study, 2023	**Tunisia**	**101**	**NDDI-E, GAD-7, NPI**	**61%**

The main risk factors of the occurrence of psychiatric disturbances in our patients were female gender, a prolonged disease course exceeding 20 years, and the type of prescribed ASM. Our results were partly consistent with previously published studies. More frequent psychiatric disturbances in women were also reported in two studies from Morocco and Thailand (32,33). However, this correlation was not confirmed in other published studies (23,30). Hypothesis of sex-dependent psychiatric disturbances was advanced in many studies (34,35). However, results were controversial. A long duration of epilepsy was a predictive factor of psychiatric disease in our series, as well as in the study of Rehman S et al (30) in East India and could be due to the damage in some structures of the brain involved in epileptogenesis and psychiatric disorders. Many authors suggested a bidirectional relationship between anxiety, depression, and psychosis on the one hand and epilepsy on the other hand. Indeed, numerous brain regions may be involved in these disorders (38). The amygdala and the hippocampus play a key role in the neurobiology of both epilepsy and anxiety. In fact, anxiety is not only associated with epilepsy, but it may also precede the onset of epilepsy by years. The amygdala is a determinant structure in emotions such as the experience of fear and its autonomic and endocrine response through the output to the hypothalamus (38). The hippocampus is important in the re-experience of fear. The reduction of an excessive output from fear circuits may improve the clinical picture and suggest similarities with the excessive outburst typical of epileptic neurons, explaining the effects of antiepileptic agents such as benzodiazepines in the treatment of anxiety (38). Moreover, potentiation of the gamma-amino butyric acidergic (GABAergic) inhibition and modulation of calcium channels could represent valuable antiepileptic as well as antianxiety mechanisms (38). Animal models suggested that the association between epilepsy and depression could be explained by deficient arborization of noradrenergic and serotonergic neurons arising from the locus coeruleus and raphe nuclei causing defects in pre- and postsynaptic transmission of both serotonin or 5-hydroxytryptamine (5HT) and norepinephrine (NE) (40). Functional neuroimaging studies with positron emission tomography (PET) targeting the 5HT1A receptor have demonstrated a decreased binding of 5HT1A in common mesial-temporal structures, cingulate gyrus, and raphe nuclei, in both disorders (40). The pathophysiological mechanism of the relationship between epilepsy and psychotic symptoms is not yet fully understood but it is most probably a dysfunction in the thalamus circuit, accumbens nuclei, and prefrontal cortex.

In our series, patients receiving carbamazepine and valproic acid were less depressed than those under other ASM. This could be due to the combined antiepileptic and serotonin mediated effect of these drugs through the inhibition of voltage-gated ion channels and effect on inhibitory neurotransmitter receptors gamma-amino butyric acid (GABA) (40). However, Lamotrigine known as an efficient thymoregulator (Level 1 of evidence in bipolar depression) was not significantly linked to an improvement in depressive symptoms. This finding could be explained by the small sample of patients under Lamotrigine in our study. In contrast with the recently published study of Sager G et al (41), drug resistance was found to have no effect on the risk of occurrence of psychiatric disturbances in our patients with idiopathic epilepsy.

CONCLUSION

Our study highlighted the high prevalence of comorbid psychiatric disturbances in idiopathic epilepsy. Depression, psychosis, and anxiety were the most commonly reported psychiatric symptoms. Female gender and a longer course of epilepsy were the predictive factors of the occurrence of psychiatric manifestations in our patients with idiopathic epilepsy. Thus, awareness is needed especially in women and as the disease progresses. Psychiatric evaluation in epileptic patients is necessary and should be performed by epileptologists during the routine follow-up.

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