

Risks of suicidality in adult patients with epilepsy

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Abstract

AIM: To determine the prevalence and risks of suicidality in a group of patients with epilepsy.

METHODS: Included were 200 adult patients and 100 matched healthy subjects. The clinical interview using The Diagnostic and Statistical Manual of Mental Disorders (4th edition), Beck Depression Inventory (2nd edition) (BDI-II), Hamilton Anxiety Rating Scale (HAM-A), Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Eysenck Personality Questionnaire-Revised Rating Scale testings were used for diagnosis and assessment of severity of psychiatric symptoms. Blood concentrations of serotonin, catecholamines and dopamine were also measured.

RESULTS: Suicidality was reported in 35% (compared to 9% for controls), of them 80%, 72.86%, 55.71% and 52.9% had depression, anxiety, obsession and aggression respectively. Patients with suicidality had higher scores of BDI-II ($P = 0.0001$), HAM-A ($P = 0.0001$), and Y-BOCS ($P = 0.037$) and lower scores of psychotic ($P = 0.0001$) and extroversion ($P = 0.025$) personality traits. Regardless the presence or absence of suicidality, patients with epilepsy had low serotonin ($P = 0.006$), noradrenaline ($P = 0.019$) and adrenaline ($P = 0.0001$) levels. With suicidality, significant correlations were identified between: (1) age and scores of BDI-II ($r = 0.235$, $P = 0.0001$) and HAM-A ($r = 0.241$, $P = 0.046$); (2) age at onset and concentrations of noradrenaline ($r = -0.502$, $P = 0.024$); (3) duration of illness and scores of BDI-II ($r = 0.247$, $P = 0.041$), Y-BOCS ($r = 0.270$, $P = 0.025$) and neurotic personality trait ($r = -0.284$, $P = 0.018$); and (4) doses of antiepileptic drugs and scores of psychotic personality traits ($r = -0.495$, $P = 0.006$ for carbamazepine; $r = -0.508$, $P = 0.0001$ for valproate).

CONCLUSION: This is the first study which systematically estimated the prevalence and risks of suicidality in a homogenous group of patients with epilepsy. This study emphasizes the importance of epilepsy itself as a risk for suicidality and not its treatment.

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Key words: Epilepsy; Anti-epileptic drugs; Psychosocial variables; Serotonin; Catecholamines; Dopamine

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INTRODUCTION

Epilepsy is one of the most important and common chronic medical problems with prevalence rate of 8.2-12.9 per 1000 in general population^[1]. Fortunately 70% of patients with epilepsy become seizure free on antiepileptic drugs (AEDs) while the remaining had medically refractory seizures (intractable epilepsy). In such patients, resection of the region of the brain causing seizures is one approach of treatment^[2]. The research literature indicates that people with epilepsy are at higher risk for suicide and suicidality (suicidal thoughts and attempts) with an estimated lifetime prevalence rate that varies between 3.3% and 14.3% or even up to 32.5%. This rate has been reported to be 6 to 25 times higher with temporal lobe epilepsy (TLE)^[3,4] compared to 1.4%-6.9% in general population^[5] and even higher for those who had temporal lobectomy^[2]. Suicide accounts for > 10% of deaths with epilepsy compared with 1.4% in general population^[6].

Suicidality in patients with epilepsy has complex and multifactorial aetiologies. Several factors have been identified as risks which include: male sex^[6], early age at onset^[7,8], TLE, high frequency of primary generalized seizures, polymorphic seizures combination, severe epilepsy, lateralization of the epileptic focus, recent control of seizures, absence of seizures for a long time especially after being very frequent, cognitive deterioration and hypofrontality and psychiatric comorbidity^[6-9]. Retrospective studies indicate that the majority (81%-100%) of suicides occurs in subjects with psychiatric illnesses of which depression is the most common with a risk of 15%-18.9%, and even as high as 50 times than of general population. Others include anxiety, mood disorders and epileptoid personality and past or family histories of psychiatric disorders^[6-9].

Recently, AEDs have been suggested as a risk of suicide with epilepsy^[10,11]. The mechanisms of the negative psychotropic effects of AEDs are complex and vary dramatically between patients. It has been suggested to be related to the direct (i.e., anticonvulsant action) and indirect mechanisms of the drug action, particularly with rapid dose titration, slow drug metabolism, polypharmacy, drug-drug interactions, drug toxicity, drug withdrawal and metabolic derangements (as folate deficiency)^[12]. Also non-pharmacological treatments as surgery^[2] and vagus nerve stimulation^[13] have been suggested to increase the risk of suicide up to 5-folds higher than pharmacological therapy. The concept of forced normalization (or alternative psychosis) in which a good control of seizures regardless control of EEG changes by pharmacological and non-pharmacological therapy results in appearance of behavioral abnormalities or psychosis, has been suggested as a cause of behavioral adverse effects or even

suicid, although the exact mechanisms are not fully understood^[14].

Despite the above information, the prevalence of suicidality and the spectrum of comorbid psychiatric disorders with epilepsy tended to range greatly from one study to another. This reflects the heterogeneity of epilepsy and the differences in study designs and studied populations.

Early recognition and possible modification of clinical and psychosocial variables will have significant impact on the medical management and quality of life of patients with epilepsy.

To our knowledge, this is the first study in our population which aimed to estimate the prevalence and risks of suicidality in a homogenous group of patients with epilepsy.

MATERIALS AND METHODS

The out-patient epilepsy clinic of Assiut University Hospital manages patients with epilepsy who were not covered by insurance service and all families were of low-income. The number patients of epilepsy of unknown etiology (idiopathic epilepsy) attending the clinic monthly for follow up is 601 (adults = 474 and children = 127). Clinical psychiatric interviewing was the primary method for examining the patients and in addition by applying the criteria for diagnosis of Diagnostic and Statistical Manual of Mental Health Disorders (4th edition) (DSM-IV)^[15]. Accordingly, patients were divided into two groups: (1) those with no psychiatric symptoms ($n = 107$); and (2) those without psychiatric symptoms ($n = 367$). Also 100 healthy subjects matched for age, sex, educational level and socioeconomic states were included as controls for statistical comparisons. Healthy subjects were recruited from the general population. The patient's seizure type was diagnosed according to Berg *et al*^[16] Revised terminology and concepts for organization of seizures and epilepsies: report of The International League Against Epilepsy Commission on Classification and Terminology, 2005-2009". Excluded were subjects with: (1) intelligence quotient < 70 as assessed by the Arabic version of Wechsler Adult Intelligence Scale Revised^[17,18]; (2) other neurologic, systemic or medical diseases that result in psychiatric abnormalities; (3) psychiatric disorder prior to the onset of epilepsy; (4) regular medication(s) in addition to AEDs; and (5) alcoholism or substance abuse. The study protocol was approved by the ethical committee of The Faculty of Medicine of Assiut University and all participants gave their informed consent to participate in the study.

Neurological evaluation included information regarding seizure variables (as age at onset, precipitating factors, duration of illness, type and frequency of seizures, type of utilized AED(s), duration of treatment, degree of control on AEDs and family history of psychiatric illness. The frequencies of seizures were defined as described before^[19] as follow: (1) very frequent: occurring several

times a day or at intervals shorter than 7 d; (2) frequent: occurring at intervals longer than 7 d but shorter than 30 d; (3) occasional: occurring at intervals longer than 30 d but shorter than 1 year; and (4) rare: occurring at intervals longer than 1 year. Regarding the degree of control on AEDs, patients were considered controlled when seizure free for ≥ 1 year, partially controlled when seizure were occasional or rare and uncontrolled when seizures were frequent or very frequent.

Patients were divided into two groups according to the presence or absence of suicidality. The following Arabic translated questionnaires and scales were used for screening and assessment of severity of psychiatric symptoms and disorders: (1) Beck Depression Inventory (2nd edition) (BDI-II)^[20,21]; (2) Hamilton Anxiety Rating Scale (HAM-A)^[22,23]; (3) Yale-Brown Obsessive Compulsive Scale (Y-BOCS)^[24,25]; and (4) Eysenck Personality Questionnaire-Revised Rating Scale (EPQ-R)^[26,27].

BDI-II consists of 21 items and each corresponds to a symptom of depression is summed to give a single score. Accordingly, subjects were divided into: (1) those with no or minimal symptoms (scoring: 0-13); (2) those with mild symptoms (scoring: 14-19); (3) those with moderate symptoms (scoring: 20-28); and (4) those with severe symptoms (scoring: 29-63). HAM-A consists of 14 items, each is scored on a 5-point scale, ranging from 0 (not present) to 4 (severe). Accordingly, subjects were divided into: (1) those with no anxiety symptoms (scoring: 0-13); (2) those with mild symptoms (scoring: 14-17); (3) those with moderate symptoms (scoring: 18-20); and (4) those with severe symptoms (scoring: 25-30). Y-BOCS is formed of two subscales: obsessions and compulsions. Each subscale consists of 5-items: (1) time spent in the symptoms; (2) subjective distress; (3) interference from symptoms; (4) resistance from symptoms; and (5) control over symptoms. Each item is scored from 0 (no symptoms) to 4 (extreme symptoms). The total Y-BOCS score ranges from a minimum of 0 to a maximum of 40. Accordingly, subjects are divided into: (1) those with no OCSs (scoring: 0-7); (2) those with mild symptoms (scoring: 8-15); (3) those with moderate symptoms (scoring: 16-23); (4) those with severe symptoms (scoring: 24-31); and (5) those with extreme symptoms (scoring: 32-40). EPQ-R consists of 4 scales: (1) Extroversion (E) which is formed of 23 items; (2) Neuroticism (N) which is formed of 24 items; (3) Psychoticism (P) which is formed of 32 items; and (4) social desirability or Lie (L) which is formed 21 items. Each scale is measured and has a dichotomous response format (yes or no).

Laboratory investigations: Subjects included in this study were controlled for timing of blood samples which were drawn at (8.00-10.00 am) after an overnight fast and patients were seizure free for at least 72 h (as any post-ictal central neurochemical dysfunction, is recognized to reverse within hours). The following laboratory tests were done: (1) Standardized which included: measurements of complete blood count and levels of creatinine, liver enzymes and fasting blood glucose; and (2) Specific

which included: measurements of serum levels of serotonin and plasma levels of catecholamines (adrenaline and noradrenaline) and dopamine. The levels of serotonin, catecholamines and dopamine were measured by enzyme immunoassay method kits (IBL international GMBH, Hamburg, Germany). For confirmation, levels were assessed twice at two different days and combined with the cross sectional assessment while clinical evaluation and interviewing of included subjects. The serum levels of AEDs were measured as part of the investigation in batched assays in The Therapeutic Drug Monitoring laboratory of Assiut University hospital, Assiut, Egypt using Fluorescence Polarization Immunoassay System of Abbott, TDxFLX apparatus (Abbott Lab, Wiesbaden, Germany). The approximated reference therapeutic serum level of carbamazepine (CBZ) was 4-10 $\mu\text{g/mL}$ and 50-100 $\mu\text{g/mL}$ for valproate (VPA)^[19].

Statistical analysis

Calculations were done with the statistical package SPSS, version 12.0. Kolmogorov-Smirnov test was used to test the parameter distributed. Data were presented as mean \pm SD when normally distributed and mean (quartiles) if did not normally distributed (e.g., scores of BDI-II and HAM-A and blood levels of serotonin, catecholamines and dopamine). Student's *t* test was used for comparison of means of normally distributed parameters while Mann-Whitney *U* test was used for comparison of non-normally distributed parameters. Correlations were assessed using Pearson's test for normally distributed data and Spearman's coefficient for non-normally distributed data. For all tests, values of $P < 0.05$ were considered statistically significant.

RESULTS

This study included 200 adults (males = 100; females = 100) with epilepsy psychiatric symptoms. Their ages ranged between 20 to 48 years (mean: 30.47 ± 7.56 vs 29.14 ± 6.90 for control subjects; $P = 0.229$) and duration of illness ranged from 3 to 35 years (mean: 13.94 ± 7.24). The majority (62%) had complex partial or partial epilepsy with secondary generalization, while 38% had generalized tonic-clonic convulsions (GTC). Sixty patients (32.2%), 58 (46.77%) and 5 (4.03%) had frontal, temporal (TLE) and parietal lobe epilepsies. Seventy four (59.68%) had left sided foci of epileptic activity while 50 (40.32%) had right sided foci. The majority of patients were treated with CBZ (57%, $n = 114$ and/or VPA 19%, $n = 38$ and 24%, $n = 48$, respectively) for 2-30 years (mean: 9.28 ± 4.02). The majority of patients (54.0%, $n = 108$) were uncontrolled on AEDs, 23.5% ($n = 47$) were partially controlled and 22.5% ($n = 45$) were controlled.

Suicidality was reported in 35% (suicidal attempts = 23, 32.9%, suicidal thoughts = 47, 67.1%; male = 34, 17%; female = 36, 18%) compared to 9% of healthy subjects (suicidal thoughts = 9, 100%; male = 4, 4%; female = 5, 5%, Table 1). The majority of patients with

Table 1 Demographic and clinical features of the studied group of epilepsy (mean \pm SD) *n* (%)

Demographic and clinical features	Patients (<i>n</i> = 200)	Patients with history of suicidality (<i>n</i> = 70)	Patients without history of suicidality (<i>n</i> = 130)
Male/female	100/100	34/36	66/64
Age (yr)	20-48 (30.47 \pm 7.56)	20-48 (29.33 \pm 7.60)	20-48 (31.08 \pm 7.50)
Age at onset of disease (yr)	1-40 (16.24 \pm 8.40)	1-39 (15.46 \pm 8.66)	1-40 (16.66 \pm 8.26)
Duration of illness (yr)	3-35 (13.94 \pm 7.24)	3-31 (13.77 \pm 6.93)	3-35 (14.04 \pm 7.42)
Type of epilepsy			
GTC	76 (38.0)	23 (32.9)	53 (40.8)
Complex partial/partial epilepsy with secondary generalization	124 (62.0)	47 (67.1)	77 (59.2)
Frontal	60 (48.39)	22 (46.81)	38 (49.35)
Temporal	58 (46.77)	23 (48.94)	35 (45.45)
Parietal	5 (4.03)	1 (2.13)	4 (5.19)
Occipital	1 (0.80)	1 (2.13)	0
Side of epileptic activity			
Right	50 (40.32)	22 (46.81)	28 (36.36)
Left	74 (59.68)	25 (53.19)	49 (63.63)
AED(s) utilized			
CBZ	114 (57.0)	31 (44.3)	83 (63.8)
VPA	48 (24.0)	21 (30.0)	27 (20.8)
Polytherapy	38 (19.0)	18 (25.7)	20 (15.4)
Dose of AED(s) (mg/d)			
CBZ	400-1200 (750.54 \pm 350.5)	400-1200 (700.24 \pm 320.25)	400-1200 (760.25 \pm 300.25)
VPA	200-1400 (850.50 \pm 345.7)	200-1400 (840.30 \pm 305.75)	200-1400 (730.50 \pm 255.7)
Duration of treatment (yr)	2-30 (9.28 \pm 4.02)	2-30 (9.28 \pm 4.02)	2-30 (9.38 \pm 4.39)
Serum drug level (μ g/mL)			
CBZ	4.30-12.80 (9.56 \pm 4.5)	4.30-12.80 (9.56 \pm 4.5)	4.30-12.80 (9.56 \pm 4.5)
VPA	35.54-120.45 (80.50 \pm 30.0)	35.54-120.4 (100.50 \pm 30.0)	35.54-120.4 (85.50 \pm 25.0)
Degree of control on AED(s)			
Controlled	45 (22.5)	9 (12.9)	24 (26.2)
Partially controlled	47 (23.5)	14 (20.0)	3 (25.4)
Uncontrolled	108 (54.0)	47 (67.1)	63 (48.5)

GTC: Generalized tonic-clonic; AEDs: Antiepileptic drugs; CBZ: Carbamazepine; VPA: Valproate; Controlled: Seizure free for \geq 1 year; Partially controlled: Occasional or rare in frequency; Uncontrolled: Very frequent or frequent in frequency.

suicidality (regardless of gender) had depression (80%). While anxiety, obsession, extroversion personality traits and aggression were reported in 72.86%, 55.71%, 21.5% and 52.9%, respectively (Tables 2 and 3). In general and regardless to the presence or absence of suicidality, patients with epilepsy had: (1) high scores of BDI-II, HAM-A and psychotic and neurotic personality traits regardless the type and focus and side of epilepsy and type of AEDs; (2) high scores of Y-BOCS particularly with frontal lobe epilepsy ($P = 0.001$) and left foci of epileptic activity ($P = 0.015$) and regardless to the type of AEDs; (3) the lack of control of seizures on AEDs was a risk for high scores of BDI-II ($P = 0.0001$), HAM-A (partially controlled: $P = 0.02$; uncontrolled: $P = 0.0001$) and Y-BOCS (partially controlled: $P = 0.01$; uncontrolled: $P = 0.0001$) (Table 4); (4) low serotonin concentrations particularly with GTC ($P = 0.002$) and TLE ($P = 0.003$) and with VPA ($P = 0.009$) and polytherapy ($P = 0.007$); (5) low catecholamines (noradrenaline and adrenaline) concentrations regardless the type, focus and side of epilepsy and type of AEDs; and (6) low dopamine concentrations particularly with GTC ($P = 0.051$) and lack of seizures control on AEDs ($P = 0.004$) (Table 5).

When patients with and without suicidality were compared, the former group had higher scores of BDI-

Table 2 The frequencies of psychiatric symptoms in the studied group of epilepsy *n* (%)

Psychiatric disorders	Patients (<i>n</i> = 200)	Patients with history of suicidality (<i>n</i> = 70)	Patients without history of suicidality (<i>n</i> = 130)
BDI-II	108 (54)	56 (80.00)	52 (40)
Mild	17 (15.74)	5 (8.93)	12 (23.08)
Moderate	37 (34.26)	18 (32.14)	19 (36.54)
Severe	54 (50)	33 (58.93)	21 (40.38)
HAM-A	96 (48.0)	51 (72.86)	45 (34.62)
Mild	19 (19.79)	7 (13.73)	12 (26.67)
Moderate	30 (31.25)	14 (27.45)	16 (35.56)
Severe	47 (48.96)	30 (58.82)	17 (37.78)
Y-BOCS	102 (52.5)	39 (55.71)	66 (50.77)
Mild	45 (44.12)	13 (33.3)	32 (48.48)
Moderate	27 (26.47)	7 (17.95)	20 (30.30)
Severe	18 (17.65)	11 (28.21)	7 (10.61)
Extreme	15 (14.71)	8 (20.51)	7 (10.61)
EPQ-R			
Psychosis	71 (35.5)	13 (18.4)	58 (44.6)
Neurosis	36 (18.0)	11 (15.7)	25 (19.2)
Extroversion	33 (16.5)	5 (7.1)	28 (21.5)
Lying	0	0	0
Aggression	70 (35)	37 (52.9)	33 (25.4)

BDI-II: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale.

Table 3 Frequencies of psychiatric abnormalities in the studied group of epilepsy in relation to gender *n* (%)

Psychiatric disorders	Males (<i>n</i> = 100)		Females (<i>n</i> = 100)	
	Males with suicide (<i>n</i> = 34)	Males without suicide (<i>n</i> = 66)	Females with suicide (<i>n</i> = 36)	Females without suicide (<i>n</i> = 64)
BDI-II	34 (100)	18 (27.27)	26 (72.22)	34 (53.13)
Mild	3 (8.82)	7 (38.89)	2 (7.69)	5 (14.71)
Moderate	10 (23.26)	5 (27.78)	8 (30.77)	14 (41.18)
Severe	17 (52.94)	6 (33.33)	16 (61.54)	15 (44.12)
HAM-A	27 (79.41)	15 (22.72)	24 (66.67)	30 (46.88)
Mild	4 (14.81)	3 (20)	3 (12.5)	9 (30)
Moderate	9 (33.33)	8 (53.33)	5 (20.83)	8 (26.67)
Severe	14 (51.85)	4 (26.67)	16 (66.67)	13 (43.33)
Y-BOCS	22 (64.71)	27 (40.91)	17 (47.22)	39 (60.94)
Mild	9 (40.91)	13 (48.15)	4 (23.53)	19 (48.72)
Moderate	4 (18.18)	7 (25.93)	3 (17.65)	13 (33.33)
Severe	4 (18.18)	4 (14.81)	7 (41.18)	3 (7.69)
Extreme	5 (22.73)	3 (11.11)	3 (17.65)	4 (10.26)
EPQ-R				
Psychosis	5 (14.7)	29 (43.9)	8 (22.4)	29 (45.3)
Neurosis	4 (11.8)	18 (27.3)	7 (19.4)	7 (19.4)
Extroversion	4 (11.8)	22 (33.3)	1 (2.8)	6 (9.4)
Lying	0	0	0	0
Aggression	20 (58.8)	21 (31.8)	17 (47.2)	12 (18.8)

BDI-II: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale.

II ($P = 0.0001$), HAM-A ($P = 0.0001$) and Y-BOCS ($P = 0.037$) and lower concentrations of serotonin ($P = 0.006$), noradrenaline ($P = 0.019$) and adrenaline ($P = 0.0001$), while the latter group had lower scores of psychotic ($P = 0.0001$), neurotic ($P = 0.003$) and extroversion ($P = 0.025$) personality traits (Tables 6 and 7).

In presence of suicidality, significant correlations were identified between: (1) age and scores of BDI-II ($r = 0.235$, $P = 0.0001$) and HAM-A ($r = 0.241$, $P = 0.046$); (2) age at onset and concentrations of noradrenaline ($r = -0.502$, $P = 0.024$); (3) duration of illness and scores of BDI-II ($r = 0.247$, $P = 0.041$), Y-BOCS ($r = 0.270$, $P = 0.025$) and neurotic personality trait ($r = -0.284$, $P = 0.018$); and (4) doses of AEDs and scores of psychotic personality traits ($r = -0.495$, $P = 0.006$ for CBZ; $r = -0.508$, $P = 0.0001$ for VPA). In absence of suicidality, significant correlations were identified between: (1) age at onset and scores of BDI-II ($r = 0.350$, $P = 0.043$) and serotonin concentrations ($r = -0.432$, $P = 0.014$); and (2) doses of AEDs and scores of psychotic ($r = -0.271$, $P = 0.020$) and neurotic ($r = -0.348$, $P = 0.003$) personality traits.

DISCUSSION

Several longitudinal and large sample-sized population studies with longer durations of follow-up, have shown that suicide is more frequent with epilepsy than in general population and represents the chief cause of death with epilepsy^[3,4,6]. However, big differences in rates of suicidality have been shown across epilepsy studies. In this study, we reported high prevalence of suicidality (35% *vs* 9% for control subjects). In the literature, the estimated lifetime prevalence of suicide in epileptic population is 3.3%-14.3% or even up to 25%-32.5%^[2,4] compared to

1.4%-6.9% for general population^[5]. In contrast, some investigators did not find excess mortality with epilepsy due to suicide^[28]. These great differences reflect the heterogeneity of epilepsy and epileptic disorders and differences in culture and risk factors across populations.

We and others reported a link between epilepsy, suicidality and comorbid interictal psychiatric abnormalities^[4,9,29]. Depression was the most prevalent (80%) psychiatric comorbidity in patients with suicidality, followed by anxiety (72.86%), obsession (55.71%) and aggression (52.9%). Several studies reported that depression is the most prevalent interictal with epilepsy and frequently associated with emotional instability, poor impulse control, anxiety, obsession and aggression, reaching about 15%-18.9% or even as high as 50 times that of the general population^[9,30,31]. Anxiety is the second most frequent psychiatric comorbidity with epilepsy and commonly associated with depression, inattention, aggression and obsession^[32]. Obsession is the third most frequent psychiatric comorbidity with epilepsy and commonly associated with depression and anxiety, hostility, aggression, paranoid ideation, low intelligence, seizure frequency, duration of education, brain magnetic resonance imaging abnormalities and number of AEDs^[33]. Male sex, increasing age, long duration of illness and lack of control on AEDs were the identified risks for higher scores of depression, anxiety and obsession^[6,30,31]. It was observed that the earlier onset of seizures (< 18 years old), the better quality of life in adulthood. This reflects the more effective coping mechanisms and the adjustment to social and psychological consequences of the disease, while the late onset seizures, the more disruption of patient's life (e.g., due to loss of the ability to drive and unemployment)^[34].

Table 4 Significance between patients and control subjects in scores of BDI-II, HAM-A, Y-BOCS and EPQ-R in relation to epilepsy itself- and its treatment-related variables regardless to the presence or absence of suicidality

Epilepsy itself- and its treatment-related variables	BDI-II	HAM-A	Y-BOCS	EPQ-R			
				Psychosis	Neurosis	Extroversion	Lying
Type of epilepsy							
Generalized							
P1	0.0001	0.296	0.003	0.015	0.0001	0.435	0.0001
Focal							
P1	0.0001	0.214	0.008	0.001	0.0001	0.436	0.0001
P2	0.511	0.958	0.682	0.729	0.521	0.867	0.786
Focal epilepsies							
Frontal							
P1	0.0001	0.182	0.001	0.005	0.0001	0.346	0.0001
Temporal							
P1	0.005	0.259	0.555	0.011	0.0001	0.448	0.0001
P3	0.514	0.607	0.037	0.818	0.656	0.893	0.353
Side of epileptic activity							
Right							
P1	0.0001	0.327	0.068	0.030	0.0001	0.131	0.002
Left							
P1	0.001	0.138	0.015	0.003	0.0001	0.821	0.0001
P4	0.919	0.697	0.805	0.800	0.397	0.189	0.064
CBZ							
P1	0.0001	0.852	0.007	0.0001	0.0001	0.407	0.0001
P5	0.857	0.186	0.900	0.071	0.897	0.682	0.242
P6	0.005	0.004	0.213	0.034	0.160	0.443	0.155
VPA							
P1	0.007	0.074	0.108	0.207	0.0001	0.762	0.0001
P6	0.024	0.112	0.279	0.750	0.299	0.341	0.039
Polytherapy							
P1	0.0001	0.003	0.003	0.380	0.0001	0.199	0.013
Controlled							
P1	0.714	0.001	0.144	0.0001	0.878	0.034	0.0001
P7	0.070	0.020	0.499	0.001	0.001	0.025	0.238
P8	0.0001	0.0001	0.087	0.0001	0.0001	0.0001	0.951
Partially uncontrolled							
P1	0.078	0.917	0.611	0.033	0.0001	0.992	0.0001
P8	0.0001	0.0001	0.010	0.183	0.034	0.017	0.176
Uncontrolled							
P1	0.0001	0.0001	0.0001	0.373	0.0001	0.007	0.0001

CBZ: Carbamazepine; VPA: Valproate; BDI-II: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale; P1: Patients *vs* controls; P2: Generalized *vs* focal; P3: *vs* frontal; P4: Right *vs* left; P5: CBZ *vs* VPA; P6: *vs* polytherapy; P7: *vs* partially controlled; P8: *vs* uncontrolled.

It seems that the increase in the prevalence of suicidality with comorbid depression, anxiety and obsession in patients with epilepsy is due to the followings: (1) poor adjustment to seizures occur as a result of low socio-economic status, financial stress and poor cultural approach to epilepsy, the lower the expectations of parents and teachers, poor academic achievement, unemployment, inability to drive and diminished sexual desire and marital stresses. All result in low self-esteem, social isolation, stigmatization, depression, low quality of life and increase the risk of suicidality with epilepsy^[34]; (2) misinformation about the disorder, results in low self-esteem, stigmatization, restrictions of normal daily activities, depression, obsessions, anxiety and increase the risk of suicidality with epilepsy^[32]; and (3) giving in to obsessions and compulsions, knowing that they are unreal and incapacity to stop them, result in lack of self-confidence, depression, anxiety and even suicide^[33].

We and others^[35] observed no difference in the prevalence of suicidality and scores of psychiatric questionnaires and scales in relation to the dose, drug level and duration of treatment with AEDs. This indicates that the impact of epilepsy itself on suicidality is more significant than its medications. In contrast, suicidality was found in 4.3/1000 patients treated with AEDs in the active arm, compared with 2.2 per 1000 patients in the comparison arm as a result of a meta-analysis done by the Food and Drug Administration (FDA) on 199 randomized clinical trials and encompassed on 43 892 patients treated with different 11 AEDs for epilepsy, psychiatric disorders, pain and others. Which were: CBZ, VPA, felbamate, gabapentin, lamotrigine, levetracitam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide. Thus, in January 2008 and based on this meta-analysis, FDA reported that exposure to AEDs increased the risk of suicidality by 1.80-fold. The FDA issued an alert and decided to insert

Table 5 Significance between patients and control subjects in the concentrations of serotonin, catecholamines and dopamine in relation to epilepsy itself- and its treatment-related variables regardless to the presence or absence of suicidality

Epilepsy-related variables	Serotonin	Noradrenaline	Adrenaline	Dopamine
Type of epilepsy				
Generalized				
P1	0.002	0.016	0.0001	0.051
Focal				
P1	0.017	0.007	0.0001	0.558
P2	0.176	0.305	0.662	0.096
Focal epilepsies				
Frontal				
P1	0.074	0.032	0.0001	0.469
Temporal				
P1	0.003	0.014	0.0001	0.400
P3	0.375	0.575	0.818	0.810
Side of epileptic activity				
Right				
P1	0.031	0.061	0.0001	0.754
Left				
P1	0.017	0.007	0.0001	0.387
P4	0.781	0.392	0.966	0.626
CBZ				
P1	0.068	0.001	0.0001	0.064
P5	0.239	0.546	0.682	0.739
P6	0.051	0.374	0.682	0.528
VPA				
P1	0.009	0.007	0.0001	0.324
P6	0.170	0.628	0.698	0.867
Polytherapy				
P1	0.007	0.243	0.0001	0.806
Controlled				
P1	0.136	0.115	0.0001	0.208
P7	0.189	0.116	0.090	0.056
P8	0.185	0.174	0.528	0.683
Partially uncontrolled				
P1	0.019	0.003	0.0001	0.542
P8	0.903	0.524	0.158	0.034
Uncontrolled				
P1	0.012	0.001	0.0001	0.004

CBZ: Carbamazepine; VPA: Valproate; P1: Patients *vs* controls; P2: Generalized *vs* focal; P3: *vs* frontal; P4: Right *vs* left; P5: CBZ *vs* VPA; P6: *vs* polytherapy; P7: *vs* partially controlled; P8: *vs* uncontrolled.

suicide warnings in the package inserts of all AEDs^[10]. However, the results of FDA meta-analysis must be considered with caution because of the followings^[36]. (1) not all patients with epilepsy but some of them may be more susceptible to negative psychotropic effect of AEDs which may be resulted from the direct (i.e., anticonvulsant mechanisms) and/or the indirect effect of the AEDs as: (a) metabolic adverse effects (folate deficiency); (b) interactions between the AED and the underlying epileptic process; (c) presence of hippocampal sclerosis; (d) forced normalization; (e) polytherapy; and (f) past or family history of psychiatric disorder; and (2) some AEDs (e.g., CBZ, VPA, topiramate and gabapentin) are well known mood stabilizers and are used in treatment of bipolar, impulse-control, borderline personality and episodic dys-control disorders. Thus patients with epilepsy should be closely followed whenever a new AED is introduced.

To summarize, it seems that the comorbidity between suicidality and epilepsy is correlated to epilepsy itself-related clinical, psychosocial and biological variables and

not to its medications (AEDs). This is supported by the findings of this and other studies as follow: (1) the frequency of suicidality was associated with increase in seizures' frequency, severity of seizures and intractability to medications. On the other hand, the frequency of depression and suicidality was associated with the type of epilepsy (e.g., GTC and frontal and temporal lobe epilepsies^[37] and the lateralized foci of epileptic activity^[38]); (2) lower blood concentrations of serotonin and catecholamines were identified in patients regardless to the presence or absence of suicidality^[39,40]; (3) some investigators observed the followings: (a) the absence of a correlation between the severity of seizures and depression; (b) seizure-free state couldn't protect patients from developing depression and consequently suicide; (c) improvement of psychiatric manifestations with disappearance of seizures after temporal lobectomy^[41]; and (d) In fact: (i) some brain areas and their connections are incriminated in generating both epileptic discharges and psychiatric symptoms which include: frontal-limbic-

Table 6 Comparative statistics between patients with and without suicidality and control subjects in relation to psychosocial variables

	BDI-II	HAM-A	Y-BOCS	EPQ-R			
				Psychosis	Neurosis	Extroversion	Lying
Patients with history of suicidality (<i>n</i> = 70)							
Range	3.0-53.0	3.0-44.0	0.0-38.0	3.00-20.00	4.0-21.00	3.0-18.0	3.0-18.0
Mean	27.19	21.30	14.25	8.94	11.56	9.83	11.14
25th Percentiles	18.00	12.75	4.00	6.00	8.00	6.00	8.75
50th Percentiles	26.50	22.00	13.50	9.00	10.50	9.00	11.00
75th Percentiles	37.25	28.25	24.25	11.00	13.25	15.00	13.25
Patients without history of suicidality (<i>n</i> = 130)							
Range	1.0-50.0	1.0-44.0	0.0-40.0	3.0-15.0	4.00-21.00	2.0-18.0	2.0-19.0
Mean	15.88	11.95	10.72	11.65	13.42	11.38	11.00
25th Percentiles	7.00	5.00	2.00	4.00	9.00	17.00	9.00
50th Percentiles	11.00	8.00	9.50	6.00	13.00	13.00	11.00
75th Percentiles	23.25	18.00	16.00	9.00	18.00	16.00	13.00
Control subjects (<i>n</i> = 100)							
Range	1.0-51.0	2.0-48.0	0.0-35.0	2.0-13.0	3.0-22.0	2.0-19.0	3.0-18.0
Mean	11.80	13.20	7.54	6.50	18.08	11.27	8.47
25th Percentiles	7.00	6.00	2.25	4.00	14.00	6.25	7.00
50th Percentiles	10.00	10.50	6.00	7.00	18.00	12.00	9.00
75th Percentiles	14.00	15.00	12.00	9.00	19.75	16.75	10.00
Significance							
P1	0.0001	0.0001	0.0001	0.0001	0.0001	0.050	0.0001
P2	0.031	0.235	0.042	0.0001	0.0001	0.108	0.0001
P3	0.0001	0.0001	0.037	0.750	0.003	0.025	0.911

BDI-II: Beck Depression Inventory (2nd edition); HAM-A: Hamilton Anxiety; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; EPQ-R: Eysenck Personality Questionnaire-Revised Rating Scale; P1: Patients with suicide *vs* control subjects; P2: Patients without suicide *vs* control subjects; P3: Patients with suicide *vs* patients without suicide.

Table 7 Comparative statistics between patients with and without history of suicide and control subjects in relation to concentrations of serotonin, catecholamines and dopamine

	Serotonin (ng/mL)	Noradrenaline (ng/mL)	Adrenaline (ng/mL)	Dopamine (ng/mL)
Patients with history of suicidality (<i>n</i> = 70)				
Range	0.00-96.3	1.1-161.5	0.10-80.2	0.10-165 222
Mean	36.25	40.27	8.60	9133.12
25th Percentiles	10.70	4.13	4.10	14.03
50th Percentiles	21.40	20.90	5.10	51.85
75th Percentiles	64.20	61.25	60.35	837.98
Patients without history of suicidality (<i>n</i> = 130)				
Range	0.0-96.30	2.0-213.4	0.10-521.40	0.10-2145.00
Mean	42.67	57.53	27.71	301.44
25th Percentiles	21.60	4.70	0.10	5.50
50th Percentiles	42.80	30.65	0.10	34.00
75th Percentiles	64.20	104.35	4.08	161.50
Control subjects (<i>n</i> = 100)				
Range	42.8-107.0	1.50-493.20	0.1-1914.00	0.10-5146.0
Mean	71.69	125.35	314.72	235.53
25th Percentiles	50.83	28.30	9.85	20.50
50th Percentiles	69.55	128.00	55.00	56.60
75th Percentiles	96.30	181.50	417.45	6253.80
Significance				
P1	0.031	0.005	0.0001	0.282
P2	0.006	0.019	0.0001	0.077
P3	0.303	0.399	0.719	0.842

P1: Patients with suicide *vs* control subjects; P2: Patients without suicide *vs* control subjects; P3: Patients with suicide *vs* patients without suicide.

subcortical circuits, frontal-striatal systems and limbic-brainstem, amygdale-hypothalamic and amygdale-locus coeruleus connections^[37,38,42-44]; and (ii) disturbances in serotonin metabolism has been found by many investiga-

tors to be involved in the pathogenesis of suicide irrespective of primary diagnosis. Thus Serotonin could be a link between suicidality, epilepsy, depression, anxiety and obsession^[45].

In conclusion, this is the first study in our population which systematically estimated the prevalence and risks of suicidality in a homogenous group of patients with epilepsy. This study emphasizes the importance of epilepsy itself as a risk for suicidality and not its treatment. Thus, early recognition of seizures, optimizing seizure control and managing its comorbid psychiatric symptomatology and disorders are of paramount importance while managing patients with epilepsy (i.e., biopsychosocial model of treatment which focuses on the whole person rather than simply treating convulsions). However and despite the importance of this study, its main limitation is that the majorities of patients had chronic and severe illness and were intractable to medications. This can be explained by the fact that patients were recruited from a University Hospital (a tertiary referral hospital). Thus performing multicenter studies will represent the accurate prevalence of suicidality with epilepsy of different severities.

COMMENTS

Background

Epilepsy is a common chronic medical problem with a prevalence rate of 8.2-12.9 per 1000 in general population. Suicidality with epilepsy (suicidal thoughts and attempts) is a common cause of mortality with epilepsy which accounts for > 10% of deaths from epilepsy compared with 1.4% in general population. Its lifetime prevalence has been estimated to be between 3.3%-32.5% compared to 1.4%-6.9% in general population. The great difference in prevalence of suicidality between studies might reflect the heterogeneity of epilepsy and epileptic disorders and the differences in risks, study designs and studied populations. The risk factors of suicidality with epilepsy are multiple and include: male sex, early age of onset, severe epilepsy, generalized tonic-clonic convulsions, temporal lobe epilepsy, polymorphic seizures combination, lateralization of epileptic activity, absence of seizures for a long time especially after being very frequent, recent control of seizures, cognitive deterioration and psychiatric comorbidity. The majority (81%-100%) of suicides occurs in subjects with psychiatric abnormalities as depression (which is the most common with a risk of 15%-18.9%), anxiety, epileptoid personality, past or family histories of psychiatric disorders and/or suicidal attempts. Recently, antiepileptic drugs (AEDs) have been suggested as a risk of suicide in patients with epilepsy.

Research frontiers

Suicidality (suicidal thoughts and attempts) is a common risk of morbidity and mortality in patients with epilepsy. The research hotspot is to identify the difference in risk variables (e.g., epilepsy itself- and its treatment-related factors) in different populations as there is great difference in the prevalence of suicidality with epilepsy across studies. Early recognition and possible modification of such variables will have a positive impact on medical management and quality of life with epilepsy.

Innovations and breakthroughs

This is the first study which systematically estimated the prevalence and risk variables of suicidality in a homogenous group of patients with epilepsy. A clinical psychiatric interview, a comprehensive battery of psychiatric questionnaires and scales and blood concentrations of serotonin, catecholamines and dopamine (i.e., neurochemicals which link epilepsy, psychiatric abnormalities and suicidality) were used for analyses. In this study, we reported that epilepsy itself and not its medications is incriminated as a risk for suicidality.

Applications

While managing patients with epilepsy, the responsible physicians have to optimize seizure control and manage the comorbid psychiatric symptoms and disorders.

Terminology

A seizure is defined as a clinical phenomena resulting from brief hyperexcitability of the cerebral hemispheric neurons. Epilepsy is a recurrent unprovoked seizures (≥ 2) and manifested according to the disturbed brain area (e.g.,

disturbance of consciousness, behavior, emotion, motor function, sensation or autonomic manifestations). The cause of epilepsy is usually primary (idiopathic) or secondary to severe brain insult (symptomatic epilepsy). AEDs are currently the mainstay for treatment of epilepsy. The known mechanisms of action of AEDs are: (1) sodium, calcium and potassium channels blockades; (2) enhancement of GABAergic activity; (3) decrement in glutamate-mediated excitation; and (4) others. The majority of patients become seizure free after 2-5 years and utilization of AEDs and thus the AEDs can be slowly discontinued. Some types of epilepsy (20%-35%) are difficult to control for a significant period of time even with addition of 2nd or 3rd AED (conventional or new) (medically intractable). The risks of recurrent brief seizures, intractability and the adverse effects from chronic medications may result in medical, metabolic, neuroendocrine, cognitive and psychiatric problems. Sometimes, psychiatric symptoms (e.g., major depression, generalized anxiety disorder, psychosis, obsessive-compulsive disorder, aggression and suicide) are enduring and negatively impact patient's quality of life. The exact mechanisms of comorbid psychiatric abnormalities are complex and poorly understood, however, clinical-, psychosocial- and treatment- related variables are considered as the main risks.

Peer review

The risks of suicidality in adult patients with epilepsy is an interesting original study on the prevalence and clinical correlates of suicidality in patients with epilepsy. The sample size is adequate and the biochemical tests are an added value to the study.

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