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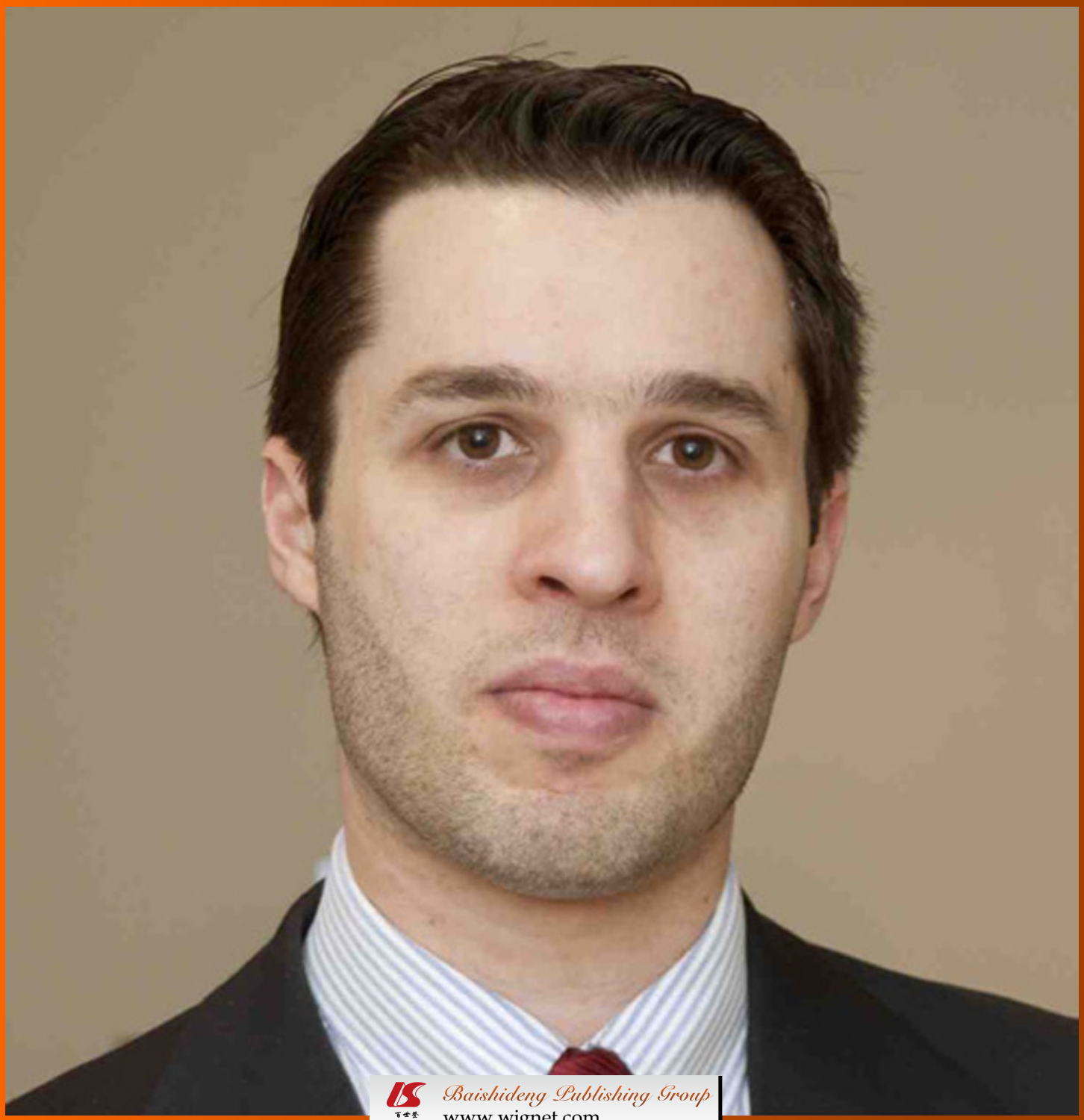

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ORIGINAL ARTICLE

Depression in adults with epilepsy: Relationship to psychobiological variables

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Abstract

AIM: To characterize the relationship between depression and epilepsy-related seizures, treatment, hormonal and biological variables.

METHODS: Included were 200 Egyptian adults (male = 100, female = 100) with epilepsy (mean age: 30.87 ± 7.88 years; duration of illness: 13.89 ± 7.64 years) and 100 healthy matched subjects for comparison. Psychiatric interview, Beck Depression Inventory (BDI-II) and Hamilton Anxiety Rating Scale (HAM-A) were used to assess depression and anxiety. Blood levels of free testosterone, sex hormone binding globulin, prolactin, free thyroxin and thyroid stimulating hormone, serotonin, noradrenaline and adrenaline neurotransmitters were measured to assess endocrine and biological states.

RESULTS: Patients had higher rates of depressive disorder (25.5% or 51/200), mostly intermixed with anxiety (47.06%), psychotic features (19.61%), aggression (40%) and suicide (55%). Compared to controls, higher scores on the BDI-II were observed with right-sided epileptic foci (P = 0.011), polytherapy (P = 0.001) and lack of control on antiepileptic drugs (AEDs) (P = 0.0001). Patients had lower levels of serotonin (P= 0.001) [marked with depression (P = 0.012)] and adrenaline (P = 0.0001), while noradrenaline was lower with temporal lobe epilepsy (P = 0.039), left-sided foci (P = 0.047) and lack of control on AEDs (P = 0.017). Negative correlations were observed between levels of serotonin and BDI-II (P = 0.048) and HAM-A (P = 0.009) scores, but not with AEDs dose or drug level.

CONCLUSION: Comorbid depressive disorder with epilepsy appears to be closely related to seizure type, focus, side, intractability to medications and neurotransmitter changes. Thus, optimizing seizure control and early recognition and management of depression is necessary to improve patients' quality of life.

Key words: Adrenaline; Antiepileptic drugs; Depression; Epilepsy; Noradrenaline; Serotonin

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INTRODUCTION

Epilepsy is one of the most common and important chronic medical problems. The prevalence of epilepsy in the general population is approximately 8.2 per 1000[1]. While epilepsy is defined by the presence of recurrent seizures due to sudden electrical misfiring of neurons or nerve cells in the epileptic brain, it is complicated by a high rate of inter-ictal behavioral or psychiatric comorbid symptoms and disorders which include: depression, anxiety, psychosis, obsessive-compulsive disorder, attention-deficit and personality disorders, aggression and suicide[2-10]. Although inter-ictal behavioral manifestations are frequently mild and reversible, some patients with intractable epilepsy may have enduring manifestations that impair their quality of life. Depression is the most frequent psychiatric disorder in patients with epilepsy, with a prevalence of 20%-80%[9,10] compared to 1.5%-19% in the general population[11]. Depression in epilepsy may manifest as: (1) major depressive disorder which meets the Diagnostic and Statistical Manual, 4th edition (DSM-IV)[12]; (2) atypical depression with a fluctuating course and a pleomorphic presentation such as depressive intermixed with euphoric moods, irritability, fear, symptoms of anxiety, insomnia, psychotic features (including hallucinations, paranoia, delusions or bizarre behavior), aggression and suicidal thoughts or even suicide attempts in severe form; and (3) a dysthymic-like disorder that is milder than those of major depression[9,10,13].

The comorbidity of depression and epilepsy have been found to be correlated with a number of variables including psychosocial (such as stigma, learning problems, unemployment, inability to obtain a driving license)[14,15], demographic-, clinical- and epilepsy-related variables (such as age, gender, age at onset, type of seizures, site and side of structural brain lesion, seizure frequency, severity and duration of epilepsy)[16] and iatrogenic variables or adverse effects due to antiepileptic medications (AEDs)[17]. Recent evidence indicated that it seems to be a bidirectional relationship between epilepsy and depression indicating that both disorders share the same common neuroanatomical or structural and biological mechanisms (i.e., neurotransmitters), which include: (1) dysfunctions of the limbic system, frontal-limbic-subcortical circuits, frontal-striatal systems, limbic-brainstem connections or amygdale and its connections (e.g., amygdale-hypothalamic, amygdale-locus ceruleus)[16,18,19]; and (2) dysfunction of cerebral g-amino butyric acid (GABA), catecholamines, dopaminergic, nonadrenergic, and serotonergic systems[20]. In addition, it has been observed that some AEDs are associated with negative psychotropic effects with higher risk reported with phenobarbital (PB)[21], while low risks were associated with phenytoin (PHT)[22], carbamazepine (CBZ)[23], and valproate (VPA)[24]. The mechanisms of negative psychotropic effects with AEDs are complex and may vary dramatically between patients. They seem to be related to the direct and indirect mechanisms of drug action. They are commonly associated with rapid dose titration, slow drug metabolism, polypharmacy and drug-drug interactions, drug toxicity, drug withdrawal and electrolyte and other metabolic derangements (such as folate deficiency)[17,25]. Early recognition of comorbid depression and other psychiatric disorders with epilepsy will have a significant impact on the medical management and quality of life of patients with epilepsy.

This study aimed to determine the frequency of depression in adult patients with epilepsy. This study also aimed to determine the risk variables and correlates of comorbid depression with epilepsy which include: demographic-, clinical-, seizure-, treatment-, hormonal- and biological- (i.e., neurotransmitters) related variables. The relationship between depression and different related variables were determined.

MATERIALS AND METHODS

Ethics

The study protocol was approved by the ethical committee of the Faculty of Medicine of Assiut University and all patients and control subjects gave their informed consent to participate in this study.

Patient tissue

The original sample consisted of 200 adult patients with epilepsy (males = 100; females = 100), aged between 20 years and 48 years with a mean age of 30.87 ± 7.88 years and total time of illness ranging from 3 to 35 years. The patients' seizure types were diagnosed according to the International League Against Epilepsy (ILAE) criteria[26]. All patients were treated with conventional AEDs (CBZ, VPA or combined therapy (CBZ+VPA) for at least 6 months before participation in our study. Patients were recruited from the out-patient epilepsy clinic of the Department of Neurology and Psychiatry of Assuit University Hospital, Assuit, Egypt. One hundred healthy subjects matched for age- (range: 20-48; mean: 31.63 ± 8.55), sex (male = 50; female = 50), educational level and socioeconomic status, were included in the study for statistical comparisons. Control subjects were chosen from the general population. A standardized psychiatric interview was chosen as the primary method for obtaining data from the participants (patients and controls) in the study. Standardized psychiatric interviews were carried out by applying the Diagnostic and Statistical Manual of Mental Health Disorders, fourth edition (DSM–IV) criteria for the diagnosis of depression[12]. Excluded from the study were subjects (patients and controls) with: (1)

intelligence quotient (IQ) < 70 as assessed by the Arabic version[27] of Wechsler Adult Intelligence Scale revised (WAIS-R)[28]; (2) patients with neurologic (other than epilepsy), systemic or medical diseases that may result in psychiatric abnormalities; (3) patients with epilepsy and their psychiatric interview suggested a diagnosis other than depression (e.g., psychosis, anxiety alone, obsessive-compulsive and attention deficit hyperactive disorders; (4) use of any regular medication(s) in addition to AEDs; and (5) alcoholism or diagnosed substance abuse and/or previous hospitalization for substance abuse.

Methods

All patients and healthy control subjects underwent the same research protocol which included following:

Medical and neurological history and examinations: Seizure variables included age at onset, precipitating factors, duration of illness, type, frequency, family history of epilepsy, type of utilized AED(s) (monotherapy or polytherapy), duration of treatment, degree of patients' control on AED(s) and side effects from medications. The frequency of seizures was defined as described previously[29] into: (1) very frequent (occurring several times a day or at intervals shorter than 7 d; (2) frequent (at intervals longer than 7 d but shorter than 30 d); (3) occasional (at intervals longer than 30 d but shorter than one year; and (4) rare (at intervals longer than one year. Regarding the degree of control on AEDs, patients were considered controlled on AEDs treatment, when seizure free for ⩾ 1 year, partially controlled when seizure frequency was occasional or rare and uncontrolled when seizures were frequent or very frequent.

All patients underwent standard electroencephalography (EEG) and neuroimaging [such as computed tomography (CT) or magnetic resonance imaging (MRI)].

Psychiatric evaluation: A differentiation between behavioral disorders and behavioral symptoms was made throughout the psychiatric interview. In patients with coexisting depressive or mixed depressive and anxiety symptoms, confirmation and severity assessment of the diagnosis was undertaken using the Arabic translated versions of the Beck Depression Inventory (2nd edition) (BDI-Ⅱ)[30,31] and Hamilton Anxiety Rating Scale (HAM-A)[32,33]. BDI-Ⅱ is the revised version of the original BDI (1st edition)[34]. In BDI-Ⅱ, the items reflecting somatic disease and consequences of a medical illness which overlap with depressive symptoms were eliminated (such as fatigue, work disability, weight loss, loss of energy, sleep loss, appetite loss, changes in body image, and somatic preoccupation). The BDI-Ⅱ consists of 21 items to assess the intensity of depression. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-Ⅱ. According to the summation of scores from all 21 parameters, a total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe. The HAM-A consists of 14 items to measure the severity of anxiety. Each of the 14 items is scored on a 5-point scale, ranging from 0 = not present to 4 = severe. According to the summation of scores from all 14 parameters, a total score of 14-17 is considered mild in range, 18-24 is moderate, while 25-30 is severe. The BDI-Ⅱ and HAM-A test both take about 15-20 min to complete the interview and score the result.

Laboratory investigations: Standard laboratory tests included: complete blood count (CBC), measurement of serum creatinine, liver enzymes and fasting blood glucose level. For analysis of serum free testosterone, prolactin, free thyroxin (FT4), thyroid stimulating hormone (TSH) and sex hormone binding globulin (SHBG), serotonin, and plasma levels of catecholamines (adrenaline and noradrenaline) blood samples were drawn at (8.00-10.00 am) after an overnight fast and patients were seizure free for at least 72 h, as any postictal central hormonal dysfunction is recognized to reverse within hours. Assessment protocols were carried out according to the recommendations of the manufacturers. The concentrations of serum prolactin, FT4 and TSH were measured by IMMULITE reproductive hormone assays from Diagnostic Product Cooperation (Los Angeles, United States). The concentrations of free testosterone were measured by enzyme immunoassay (ELISA) (BioSource Europe S.A. Rue de I`Industrie, 8-B-1400 Nivelles-Belgium) and SHBG, serotonin, adrenaline and noradrenaline concentrations were measured by ELISA kits (IBL International GMBH, Hamburg, Germany). For confirmation, the levels of hormones and neurotransmitters were obtained and assessed twice on two different days. The levels of hormones and neurotransmitters were combined with the cross-sectional assessment while clinically evaluating and interviewing the patients and control subjects.

Compliance to antiepileptic medications was confirmed by assessment of the serum drug level at least once during the period of study. The serum levels of AEDs were determined in the Therapeutic Drug Monitoring (TDM) lab, Assiut University Hospital, Assiut, Egypt, using the fluorescence polarization immunoassay system of Abbott (EPIA), TDxFLX apparatus (Abbott Lab, Wiesbaden, Germany) as described previously[35]. The serum levels of AEDs were measured as part of the investigation in batched assays. The approximated therapeutic serum level of CBZ was 4-10 μg/mL and that of VPA was 50-100 μg/mL.

Statistical analysis

Calculations were carried out using the statistical package SPSS, version 12.0. Data were presented as mean ± SD (standard deviation) when normally distributed and mean (quartiles) when not normally distributed (e.g., scores of BDI-Ⅱ for depression and HAM-A for anxiety, serum levels of free testosterone, SHBG and serotonin and plasma levels of noradrenaline and adrena-

line). The Kolmogorov-Simirnov test was used to test the distribution of the parameters. Unpaired two-sided Student's *t* test was used for the comparison of means of normally distributed parameters. In all other cases the Mann-Whitney *U* test was used for comparison. Correlations were assessed using Pearson's test for normally distributed data and Spearman's methods for non-normally distributed data. For all tests, values of $P < 0.05$ were considered statistically significant.

RESULTS

The frequency of comorbid depression in the population with epilepsy was 25.5% (51/200) (male = 20 or 39.22%; female = 31 or 60.78%) compared to 20% (20/100) (male = 7 or 35%; female = 13 or 65%) in healthy control subjects. Based on the psychiatric interview, 95 patients with epilepsy and 32 healthy control subjects had manifestations suggesting a diagnosis other than depression and were thus excluded from the final statistical analysis. The final statistical analysis included 105 patients (male = 51; female = 54) with epilepsy and 68 healthy control subjects (males = 13; female = 55). Patients included in this study ($n = 105$) had a mean age of 30.87 ± 7.88 years (mean age of control subjects: 31.63 ± 8.55 years; $P = 0.559$) and mean duration of illness of 13.89 ± 7.64 years (range: 3-35 years). The majority of patients ($n = 66$; 62.86%) had focal epilepsy (complex partial or partial epilepsy with secondary generalization), while 39 (37.14%) had generalized tonic-clonic convulsions. Twenty six (24.76%) had frontal lobe epilepsy with secondary generalization, 36 (34.29% or 36/105) had temporal lobe epilepsy with secondary generalization and 4 (3.81% or 4/105) had parietal lobe epilepsy with secondary generalization. Thirty seven patients (35.24%) had left-sided foci of epileptic activity, while 29 (27.62%) had right-sided foci. Patients were treated with one or more AED(s) [CBZ ($n = 55$ or 52.38%), VPA ($n = 28$ or 26.67%) and polytherapy ($n = 22$ or 20.95%)] for 2-30 years (mean duration of treatment: 9.08 ± 4.13 years). The majority of patients ($n = 54$ or 51.83%) were uncontrolled on AEDs (had frequent or very frequent seizures), 23 (21.90%) were partially controlled (had occasional or rare frequency for seizures) and 28 (26.67%) were controlled on treatment or seizure free for ⩾ 1 year. Table 1 presents the demographic and clinical features of the patients with epilepsy, patients with comorbid depression and patients without comorbid behavioral disorders.

Table 1 Demographic and clinical features of the patients with epilepsy, patients with comorbid depression and patients without comorbid behavioral disorders

Demographic and clinical features	Patients (total) ($n = 105$)	Patients with epilepsy and comorbid depression ($n = 51$)	Patients with epilepsy and without comorbid psychiatric disorders ($n = 54$)	*P*-value
Male/female	52/53	20/31	32/22	-
Age; yr	20-48 (30.87 ± 7.88)	20-48 (30.37 ± 7.68)	20-45 (31.40 ± 8.14)	0.511
Age at onset of disease; yr	1-40 (16.70 ± 8.68)	1-35 (14.69 ± 7.90)	3-40 (18.78 ± 9.05)	0.02
Duration of illness; yr	3-35 (13.89 ± 7.64)	4-31 (15.31 ± 7.20)	3-35 (12.42 ± 7.88)	0.57
Family history of epilepsy (positive)	17 (16.19%)	10 (19.61%)	7 (12.96%)	-
Type of epilepsy:				
GTC	39 (37.14%)	21 (41.18%)	18 (33.33%)	-
Complex partial/ partial epilepsy with secondary generalization:	66 (62.86%)	30 (58.52%)	36 (66.67%)	-
Frontal	26 (24.76%)	11 (21.57%)	15 (27.78%)	
Temporal	36 (34.29%)	16 (31.37%)	20 (37.04%)	-
Parietal	4 (3.81%)	3 (5.88%)	1 (1.85%)	-
Side of epileptic foci:				
Right	29 (27.62%)	15 (29.41%)	14 (25.93%)	-
Left	37 (35.24%)	15 (29.41%)	22 (40.74%)	-
AED(s) utilized				
CBZ	55 (52.38%)	25 (49.02%)	30 (54.7%)	-
VPA	28 (22.87%)	11 (21.57%)	17 (31.48%)	-
Polytherapy	22 (20.95%)	15 (29.41%)	7 (12.96%)	-
Dose of AED(s) utilized; mg/d				
CBZ	400-1200 (764.62±342.6)	400-1200 (735.34±358.5)	400-1200 (722.34 ± 377.9)	0.437
VPA	200-1400 (783.27 ±425.5)	200-1400 (777.27 ±400.2)	200-1400 (750.28 ± 452.7)	0.436
Duration of treatment; yr	2-30 (9.08 ± 4.13)	2-30 (9.12 ± 4.48)	3-20 (9.04 ± 3.80)	0.212
Serum drug level; μg/mL				
CBZ	3.50-12.80 (9.05 ± 3.3)	3.50-12.80 (9.12 ± 4.5)	3.50-11.9 (8.14 ± 3.6)	0.924
VPA	30.04-115.40 (85.88 ± 35.0)	60.54-115.40 (80.64 ± 45.0)	30.04-102.60 (70.74 ± 35.0)	0.875
Degree of control on AED(s)				
Controlled	28 (26.67%)	12 (23.53%)	16 (29.63%)	-
Partially controlled	23 (21.90%)	10 (19.61%)	13 (24.07%)	-
Uncontrolled	54 (51.43%)	29 (56.86%)	25 (46.30%)	-

Values are expressed as mean ± SD and number (%). Controlled: Seizure free for ⩾ 1 year; partially controlled: occasional or rare in frequency; uncontrolled: very frequent or frequent in frequency. GTC: Generalized tonic-clonic; AEDs: Antiepileptic drugs; CBZ: Carbamazepine; VPA: Valproate; PHT: Phenytoin.

Psychometric testing

Compared to healthy control subjects ($n = 68$), the mean scores of BDI-Ⅱ for depression was 28.08 *vs* 12.59 for control subjects ($P = 0.031$). In patients with depression, the risk was higher in females ($n = 31$ or 60.78%) than males ($n = 20$ or 39.22%). Seventeen patients with depressive manifestations (33.33%) fulfilled the Diagnostic and Statistical Manual, 4th edition (DSM-Ⅳ) criteria of major depressive disorder while the majority of patients had depression and anxiety ($n = 24$ or 47.06%) or with psychotic features ($n = 10$ or 19.61%). A moderate/severe degree of depression was reported in 78.43% ($n =$

Table 2 Significance between patients and control subjects in scores of depression, hormones and neurotransmitters in relation to epilepsy related and treatment related variables

Epilepsy-related variables	BDI-Ⅱ	HAM-A	Free testosterone	SHBG	Serotoni (*n*)	Noradrenaline	Adrenaline
Type of epilepsy							
Generalized (*n* = 39)							
P1	0.016	0.538	0.347	0.476	0.001	0.169	0.008
Focal (*n* = 66)							
P1	0.102	0.458	0.816	0.125	0.01	0.049	0.004
P2	0.364	0.861	0.212	0.65	0.093	0.563	0.505
Focal epilepsies							
Frontal (*n* = 26)							
P1	0.076	0.8	0.567	0.255	0.019	0.253	0.065
Temporal (*n* = 36)							
P1	0.33	0.494	0.75	0.231	0.008	0.039	0.014
P3	0.387	0.77	0.053	1	0.884	0.683	0.456
Parietal (*n* = 4)							
P1	0.065	0.658	0.325	0.467	0.822	0.385	0.184
P3	0.483	0.668	0.095	0.564	0.567	0.655	1
P4	0.168	0.635	0.538	0.229	0.112	1	0.596
Side of epileptic activity							
Right (*n* = 29)							
P1	0.011	0.896	0.631	0.202	0.027	0.127	0.023
Left (*n* = 37)							
P1	0.474	0.388	0.95	0.282	0.012	0.047	0.017
P5	0.149	0.518	0.197	0.248	0.754	0.685	0.779
CBZ (*n* = 55)							
P1	0.07	0.069	0.512	0.61	0.011	0.085	0.028
P6	0.725	0.224	0.457	0.205	0.196	0.713	0.304
P7	0.03	0.006	0.334	1	0.293	0.465	0.237
VPA (*n* = 28)							
P1	0.443	0.784	0.451	0.129	0.001	0.044	0.007
P7	0.032	0.069	0.432	0.813	0.859	0.391	0.609
Polytherapy (*n* = 22)							
P1	0.001	0.084	0.936	1	0.017	0.349	0.02
Controlled (*n* = 28)							
P1	0.11	0.001	0.873	0.873	0.013	0.805	0.042
P8	0.01	0.026	0.024	0.462	0.658	0.047	0.094
P9	0.0001	0.0001	0.067	0.564	0.534	0.086	0.659
Partially uncontrolled (*n* = 23)							
P1	0.06	0.6	0.352	0.265	0.014	0.068	0.005
P9	0.3	0.173	0.873	0.624	0.567	0.951	0.164
Uncontrolled (*n* = 54)							
P1	0.000	0.253	0.254	0.79	0.004	0.017	0.012

CBZ: Carbamazepine; VPA: Valproate; BDI-Ⅱ: Beck depression inventory – 2nd Edition; HAM-A: Hamilton anxiety rating scale; SHBG: Sex hormone binding globulin; P1: Patients *vs* controls; P2: Generalized *vs* focal; P3: Versus frontal; P4: Versus temporal; P5: Right *vs* left; P6: CBZ *vs* VPA; P7: Versus polytherapy; P8: Versus partially controlled; P9: Versus uncontrolled.

40 or 40/51). Compared to patients without psychiatric disorders, patients with depression had a high frequency of aggression (*n* = 34 or 66.67% *vs* 14 or 25.93%) and suicidality (thoughts *n* = 21 or 41.18%; attempts *n* = 7 or 13.73% *vs* thoughts *n* = 9 or 16.67%). The risk of suicide (particularly thoughts) was higher in males (*n* = 13 or 65%) than females (*n* = 15; 48.39%), while the risk of aggression was higher in females (*n* = 14 or 45.16%) compared to males (*n* = 6 or 30%).

Compared to control subjects, higher scores of BDI-II for depression were observed with right-sided foci of epileptic activity ($P = 0.011$), polytherapy ($P = 0.001$) and those who lacked control on AEDs ($P = 0.0001$) (Table 2). Compared to patients without comorbid psychiatric disorders, patients with comorbid depression had higher scores of HAM-A for anxiety ($P = 0.0001$) (Table 3).

Hormonal findings

No significant difference in the levels of free testosterone and SHBG between patients with epilepsy and control subjects regardless of the type, focus and side of epilepsy, type of AEDs or the degree of control on AEDs. However, patients with comorbid depression had lower serum levels of free testosterone ($P = 0.054$) and higher levels of SHBG ($P = 0.029$) compared to patients without psychiatric disorders (Table 3). In patients with epilepsy, there were no significant differences in the serum levels of prolactin (8.4 ± 2.5 ng/mL *vs* 8.9 ± 3.2; $P = 0.226$), FT4 (0.48 ± 0.15 ng/dL *vs* 0.54 ± 0.27; $P = 0.645$) or TSH (2.35 ± 1.67 μIU/mL *vs* 2.48 ± 0.88; $P = 0.475$) compared to control subjects.

Table 3 Comparative statistics between patients with epilepsy and comorbid depression, patients without comorbid psychiatric disorders and control subjects in psychosocial-, hormonal- and neurotransmitter-related variables

	BDI-Ⅱ	HAM-A	Free testosterone (pg/mL)	SHBG (nmol/L)	Serotonin (ng/mL)	Noradrenaline (ng/mL)	Adrenaline (ng/mL)
Patients with epilepsy (n = 105)							
Range	3.0-47.0	4.0-44.0	9.0-24.0	118.0-200.0	0.0-74.9	1.1-100.5	0.1-521.4
Mean	28.08	20.63	18.75	159.75	43.39	27.93	65.4
Skewness	0.13	0.2	-1.65	-0.04	-0.36	1.32	2.83
Std. error of skewness	0.33	0.33	1.01	1.01	0.51	0.72	0.75
25th percentiles	22	13	11.75	121.25	24.38	2.45	0.1
50th percentiles	26	22	21	160.5	42.8	4.7	0.1
75th percentiles	33	27	23.5	197.5	64.2	58.45	0.93
Patients with epilepsy and comorbid depression (n = 51)							
Range	3.0-47.0	4.0-44.0	9.0-24.0	118.0-200.0	0.0-64.2	1.1-100.5	0.1-521.4
Mean	28.08	20.65	18.75	159.75	23.67	27.93	65.4
Skewness	0.13	0.2	-1.65	-0.04	0.97	1.32	2.83
Std. error of skewness	0.3	0.3	1.01	1.01	0.58	0.72	0.75
25th percentiles	22	13	11	121.25	6.4	2.45	0.1
50th percentiles	26	22	21	160.5	21.4	4.7	0.1
75th percentiles	33	27	23	197.5	42.8	58.45	0.93
Patients with epilepsy and without comorbid psychiatric disorders (n = 54)							
Range	1.0-19.0	1.0-15.0	5.0-100.0	17.3-185.0	0.0-74.9	4.5-213.4	0.1-1.2
Mean	7.62	6.15	44.73	110.44	43.39	58.13	0.39
Skewness	0.76	0.64	0.66	0.15	-0.36	1.51	1.12
Std. error of skewness	0.33	0.33	0.66	0.64	0.51	0.66	0.69
25th Percentiles	5	3.5	24	76.25	24.38	5	0.1
50th Percentiles	8	7	24	105.50	42.8	31.4	0.1
75th Percentiles	9	8	80	162.50	64.2	98.3	0.95
Control subjects (n = 68)							
Range	1.0-51.0	2.0-48.0	5.0-100.0	80.0-185.0	42.8-107.0	1.5-493.2	0.1-1897.0
Mean	12.59	14	57.14	103.07	74.9	135.42	269.84
Skewness	1.93	1.47	-0.14	2.04	0.18	1.71	2.59
Std. Error of skewness	0.29	0.29	0.6	0.60	0.79	0.62	0.51
25th percentiles	6	6.25	19	83.00	62.2	23.15	3.08
50th percentiles	10.5	10	68	91.00	74.9	128	51.5
75th percentiles	15.75	15.75	95	116.50	96.3	186.8	383.88
Significance							
P1	0.031	0.519	0.717	0.219	0.001	0.028	0.000
P2	0.001	0.000	0.741	0.817	0.007	0.173	0.001
P3	0.000	0.825	0.182	0.008	0.001	0.016	0.014
P4	0.000	0.000	0.054	0.029	0.012	0.128	0.965

BD Ⅰ-Ⅱ: Beck depression inventory-2nd edition; HAM-A: Hamilton anxiety rating scale; SHBG: Sex hormone binding globulin; P1: Patients versus control subjects; P2: Patients with comorbid depression versus control subjects; P3: Patients without comorbid psychiatric disorders versus control subjects; P4: Patients with comorbid depression versus patients without comorbid psychiatric disorders.

Neurotransmitter findings

Compared to healthy control subjects, patients with epilepsy had lower serum levels of serotonin (P = 0.001) regardless of the type, focus of epilepsy or side of epileptic activity, type of AEDs and the degree of control on AEDs. Lower plasma levels of noradrenaline were observed in patients with focal epilepsy (P = 0.049), particularly with temporal lobe epilepsy (P = 0.039), left-sided foci of epileptic activity (P = 0.047), those on VPA (P = 0.044) and those who lacked control on AEDs (P = 0.017). Lower plasma levels of adrenaline (P = 0.0001) were observed in patients with epilepsy regardless of the type, focus of epilepsy or side of epileptic activity, type of AEDs and the degree of control on AEDs (Table 2). Compared to patients without psychiatric disorders, patients with depression had lower serum levels of serotonin (P = 0.012), but not noradrenaline or adrenaline (Table 3).

Correlations between scores of depression, anxiety, hormonal-, neurotransmitters-, demographic- and clinical related-variables, showed that there was a significant positive correlation between the BDI-Ⅱ and HAM-A scores (P = 0.0001) and a negative correlation between the BDI-Ⅱ score and serum levels of serotonin (P = 0.048). Significant negative correlations were observed between the HAM-A score and serotonin (P = 0.009) and noradrenaline (P = 0.032). Significant positive correlations were shown between the levels of serotonin and noradrenaline (P = 0.038) and between the levels of adrenaline and noradrenaline (P = 0.039). For healthy control subjects, a significant positive correlation was observed between the BDI-Ⅱ and HAM-A scores (P = 0.0001). No significant correlations were identified between patient age, age at onset, duration of illness, dose and serum level of AEDs and scores of depression or anxiety, or levels of sex hor-

Table 4 Correlations between scores of depression, anxiety, hormonal- and neurotransmitters related variables

Variables	BDI-Ⅱ	HAM-A	Free testosterone	SHBG	Serotonin	Noradrenaline	Adrenaline
BD Ⅱ	-						
HAM-A	0.69	-					
	0.000						
Free testosterone	0.2	0.4	-				
	0.8	0.6					
SHBG	0.6	0.8	-0.2	-			
	0.4	0.2	0.8				
Serotonin	-0.447	-0.569	-1	-0.274	-		
	0.048	0.009	1	0.389			
Noradrenaline	-0.028	-0.576	-0.113	0.006	-0.632	-	
	0.458	0.032	0.677	0.981	0.038		
Adrenaline	-0.094	0.016	-0.123	-0.196	0	0.733	-
	0.825	0.971	0.628	0.422	1	0.039	
Age	0.077	0	0.106	-0.2	-0.118	-0.143	0.133
	0.59	0.997	0.597	0.8	0.621	0.714	0.753
Age at onset	0.04	0.04	0.3	-0.4	-0.352	0.25	-0.312
	0.778	0.778	0.2	0.6	0.128	0.516	0.452
Duration of illness	-0.007	-0.007	0.238	0.316	0.176	-0.305	-0.078
	0.96	0.96	0.262	0.684	0.458	0.425	0.854
Dose	-0.141	-0.141	0.266	-0.258	0.229	-0.775	-0.084
	0.552	0.552	0.333	0.742	0.289	0.225	0.844
Drug level	-0.073	-0.019	0.23	-0.273	0.008	-0.291	-0.284
	0.54	0.476	0.523	0.417	0.97	0.335	0.397

BDI-Ⅱ: Beck depression inventory – 2nd edition; HAM-A: Hamilton anxiety rating scale; SHBG: Sex hormone binding globulin.

mones and neurotransmitters (Table 4). In patients with suicide and aggression, significant positive correlation was observed between scores of BDI-Ⅱ ($P = 0.0001$ for both) and HAM-A ($P = 0.0001$ for both).

DISCUSSION

The results of this study confirm that depression is a common comorbid condition with epilepsy with an estimated frequency of 25.5% which is mostly of a moderate/severe degree (78.43%)[6]. Females with epilepsy had a higher frequency of depression compared to males (60.78% *vs* 39.22%)[15]. The majority of patients had depression intermixed with symptoms of anxiety, irritability and insomnia (47.06%) or psychotic features such as hallucinations and delusions (19.61%). Patients with depression also had higher scores of HAM-A for anxiety. In addition, scores of BDI-Ⅱ for depression and HAM-A for anxiety were positively correlated[36]. Nearly 40% of the patients with depression had manifestations of aggression and more than half of the patients with depression (55%) had suicidal thoughts and/or attempts[7,36]. Depression is the most frequent psychiatric disorder in adults with epilepsy, with an estimated prevalence of 20%-80%[6] compared to 1.5%-19% in the general population[11]. Anxiety is the second most common psychiatric disorder in adults with epilepsy with a prevalence estimated to range from 19% to 25% or up to 66%[5] compared to 19.6% in the general population[37]. The coexistence of inter-ictal anxiety and depression is not unusual (73%) in patients with epilepsy[8,36]. The prevalence of aggressive behavior in patients with epilepsy has been estimated to vary between 4.8% and 50%, not taking into account the specific epileptic subsyndromes, specific socio-economic profile, public and family factors and ethnic social vulnerabilities[4]. Suicide and suicidality (suicidal thoughts and attempts) are also frequent in subjects with epilepsy with an estimated risk of about 13%[7,38] compared to 1.4%-6.9% in the general population[39].

Traditionally, psychosocial variables have been strongly implicated as causes of psychiatric manifestations associated with epilepsy. Depression has been considered a manifestation of a negative effect on effort and attitude about his or her abilities, low self-esteem and reduced well-being, which are the results of poor adjustment to seizures, low socio-economic status, financial stress, poor cultural approach to epilepsy, poorer academic achievement, unemployment (with rates up to 50% in developed countries if seizures are not fully controlled and up to 100% in developing countries), inability to drive, marital stresses, diminished sexual desire and responsiveness. These factors result in social isolation, stigmatization, depression and lower quality of life[14,15]. Anxiety has been considered a response to the unpredictability of seizures and fear of the unknown or fear of death which result in restrictions on normal living and activities, stigmatization and social rejection, misinformation about the disorder and low self-esteem[6]. Aggression and suicidality (thoughts and attempts) have been considered a consequence of decreased adaptive abilities, depression, increased emotional problems and anxiety[7,36]. Several studies reported that depression is one of the psychiatric disorders that increases the risk of suicide which reached approximately 15%-18.9%, and in some studies, it may be as high as 50 times that of the

general population[40].

However, the results of this study indicate that not only functional (psychosocial) but also epilepsy itself and its related variables (such as type, focus, side, frequency, severity, intractability to medications and structural brain changes), and epilepsy-associated biological changes (neurotransmitter abnormalities) are important risks which contribute to the comorbidity between epilepsy and depression, depression/anxiety, aggression and suicide. These results also indicated that the risk of epilepsy itself as a cause of psychiatric abnormalities overweighed that of AEDs. Our view is supported by the following: First**,** in this study, higher scores of BDI-II for depression were observed in patients with right-sided foci of epileptic activity (P = 0.011)[41], those who lacked control on AEDs (P = 0.0001) and those on polytherapy (P = 0.001), indicating epilepsy intractability[42,43]. These findings support the fact that epilepsy itself and its related variables (such as type, focus, side, frequency, severity, intractability to medications and structural brain changes) contribute to the comorbidity between epilepsy and depression, depression/anxiety, aggression and suicide. Further supporting evidence includes: the presence of different patterns of psychiatric symptoms and disorders with different seizure types (i.e., generalized *versus* localization-related) and lateralization asymmetry. For example: (1) dysfunctions of the limbic system, frontal–limbic–subcortical circuits, frontal-striatal systems, limbic-brainstem connections or amygdale and its connections (e.g., amygdale-hypothalamic, amygdale-locus ceruleus) are the most important causes of epilepsy and its related comorbidities such as depressive and behavioral symptoms[16,19]; and (2) growing evidence in the literature suggests that hippocampal sclerosis appears to be the main factor associated with the occurrence of depression in patients with epilepsy[42,43]. This may explain why some studies found that the frequency of seizures did not correlate with severity of depression, and a seizure-free state did not protect epileptic patients from developing depression and consequently committing suicide. This was further confirmed by the finding that improvement in behavioral manifestations was associated with the disappearance of seizures after temporal lobectomy[44]; (3) The majority of the studies implicate left-sided foci (2-3-fold higher) rather than right-sided foci as a potential risk factor for depression in epilepsy, particularly left-sided temporal lobe epilepsy (TLE) in association with frontal lobe hypofunction[45,46]. However, and in accordance to our findings, some studies implicate the right hemisphere in the risk of depression in epileptic patients and suggest that this might be attributed to the extensive limbic connections compared with the left hemisphere. A few studies found no effect of lateralization [41]; and (4) reduced activity measured with single photon emission computed tomography (SPECT) in bilateral frontal and right temporal regions was associated with higher scores on the BDI in patients with left TLE[47,48].

Second, in this study, lower levels of serotonin (P = 0.001) (particularly in patients with comorbid depression) (P = 0.012) and adrenaline (P = 0.0001) were reported in patients with epilepsy regardless of epilepsy- and treatment-related variables. A significant negative correlation was observed between serum levels of serotonin and scores of BDI-Ⅱ for depression (P = 0.048) and HAM-A for anxiety (P = 0.009). Lower levels of noradrenaline were observed in patients with focal epilepsy (P = 0.049), particularly with TLE (P = 0.039), left-sided foci of epileptic activity (P = 0.047), and in those who lacked control on AEDs (P = 0.017). These findings indicate that epilepsy-associated biological changes (neurotransmitter abnormalities) are important risks which contribute to the comorbidity between epilepsy and depression, depression/anxiety, aggression and suicide. In support: (1) decreased serotonergic and noradrenergic functions or alterations in dopaminergic activity were identified as pivotal pathogenic mechanisms for comorbid depression in some patients with epilepsy[38]; (2) preclinical and clinical studies suggest that 5-hydroxytryptamine 1A (5-HT1A) receptors play a role in the pathophysiology of both TLE, depression and anxiety disorders[49]; (3) the hypoperfusion (hypo-metabolism) observed in the limbic frontal regions has been found to be related to inter-ictal inhibitory activity, depletion of substrates with decreased levels of neurotransmitters (such as serotonin, catecholamines and dopamine) and increases in the vulnerability to depression[47]; and (4) analysis of the literature has shown that serotonin metabolism disturbances are involved in the pathogenesis of suicidal behavior irrespective of primary diagnosis. Serotonin disturbances also seem to be a common link between depression, suicidality and even epilepsy itself[38].

Third, in this study, no relationship was identified between the dose and level of AEDs and scores of BDI-II or HAM-A [50]. This indicates that the risk of epilepsy itself as a cause of psychiatric abnormalities overweighed that of AEDs. Although lower levels of noradrenaline were observed in patients on VPA (P = 0.044), however, neither the dose of the drug nor its serum level were correlated with scores of BDI-Ⅱ or HAM-A as well as serum serotonin levels. This is supported by the finding that VPA is associated with increased synaptic secretion of serotonin, has an antidepressant effect and thus is effective as a mood stabilizer[50]. However, some studies reported sedation and infrequently cognitive impairment, irritability, depression, hyperactivity and aggressive behavior with VPA [24]. This may be related to its mechanism of action[17].

CONCLUSION

Depressive or depressive/anxiety manifestations associated with epilepsy appear to be more closely related to seizure type, focus, side, severity and intractability to medications as well as epilepsy-related neurotransmitter changes rather than the effect of treatment-related adverse effects. However, it is possible that the overall function and well-being of the patient, the presence of

negative, depressed or irritable mood, periods of anxiety and stress in combination with negative life events, may increase the frequency of seizures[39,51]. Attention should be paid to optimizing seizure control and the early recognition of depression and its correlates. Regular psychiatric consultation, psychotherapy and medical treatment are sometimes needed. It is also imperative to properly understand the pathophysiologic mechanisms of comorbid depression with epilepsy. This should move the treatment of patients toward a comprehensive biopsychosocial model that focuses on the whole person rather than on the disease process.

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COMMENTS

Background

Epilepsy is one of the most common and important chronic medical problems. Depression with epilepsy has been previously related to psychosocial factors (such as stigma, learning problems, unemployment, and inability to obtain a driving license).

Research frontiers

Recent evidence has indicated that there seems to be a bidirectional relationship between epilepsy and depression, indicating that both disorders share the same common neuroanatomical or structural and biological mechanisms which also correlate with a number of variables including demographic-, clinical- and epilepsy-related variables (such as age, gender, age at onset, type of seizures, site and side of structural brain lesion, seizure frequency, severity and duration of epilepsy) and iatrogenic variables or adverse effects due to antiepileptic medications (AEDs). In this study, the authors demonstrate the frequency of depression in adult patients with epilepsy and the risks correlated to comorbid depression with epilepsy which include: demographic-, clinical-, seizure-, treatment-, hormonal- and biological- (i.e., neurotransmitters) related variables.

Innovations and breakthroughs

Patients had higher rates of depressive disorder (25.5%), mostly intermixed with anxiety (47.06%), psychotic features (19.61%), aggression (40%) and suicide (55%). Higher scores of BDI-Ⅱ were observed with right-sided epileptic foci, polytherapy and lack of control on AEDs. Patients had lower levels of serotonin and adrenaline, while noradrenaline was lower with temporal lobe epilepsy, left-sided foci and lack of control on AEDs. Negative correlations were observed between the level of serotonin and BDI-Ⅱ and HAM-A scores, but not with AEDs dose or drug level.

Applications

Comorbid depressive disorder with epilepsy appears to be closely related to seizure type, focus, side, intractability to medications and neurotransmitter changes. Thus, optimizing seizure control and early recognition and management of depression is necessary to improve patients' quality of life.

Peer review

The paper is very well written and well organized.

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January 27-30, 2012
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Bangalore, Karnataka, India

March 13-27, 2012
Neurology and Pain Management
Sydney, Australia

April 10-14, 2012
14th International Neuroscience Winter Conference
Soelden, Tirol, Austria

May 3-6, 2012
8th International Congress on Mental Dysfunction and Other Non-Motor Features in Parkinsons Disease and Related Disorders
Berlin, Germany

May 9-12, 2012
7th Baltic Congress of Neurology
Tartu, Estonia

May 14-16, 2012
International Conference and Exhibition on Neurology and Therapeutics
Las Vegas, NV, United States

May 16-17, 2012
Tübinger Pflegesymposiums Neurologie/Neurochirurgie
Tübingen, Germany

May 17-20, 2012
2nd Global Congress for Consensus in Pediatrics and Child Health
Moscow, Russia

May 27-June 1, 2012
International Child Neurology Congress 2012 Incorporating The 11th Asian And Oceanian Congress Of Child Neurology 2012
Brisbane, Queensland, Australia

June 4-8, 2012
13th Asian Oceanian Congress of Neurology 2012
Melbourne, Australia

June 6-9, 2012
The 10th European Congress of Neuropathology
Edinburgh, United Kingdom

July 14-18, 2012
8th FENS Forum of Neuroscience
Barcelona, Spain

September 6-9, 2012
10th Meeting of the European Association of Neuro Oncology
Marseille, France

September 8-11, 2012
The 16th Congress of the European Federation of Neurological Societies
Stockholm, Sweden

November 8-10, 2012
2nd International Congress on Neurology and Epidemiology 2012
Nice, France

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GENERAL INFORMATION

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Name of journal

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Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Format

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood

CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
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Editorial: http://www.wjgnet.com/2218-6212/g_info_20100723220145.htm

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