

Risk factors for depression in patients with epilepsy

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Abstract

Purpose. Symptoms of depression are present in 40 to 60 percent of patients with epilepsy. Prior research indicated significant correlation between the incidence and frequency of focal seizures and clinical depression, especially in patients with temporal lobe epilepsy. Anticonvulsive drugs and psychosocial factors contribute to the occurrence of depression as well. The aim of the study was to determine the major depression risk factors in patients with epilepsy.

Methods. The research was conducted on 203 patients with epilepsy (117 females and 86 males), aged 18 to 50 years, with total time of illness ranging from 60 to 580 months. All subjects underwent the same research protocol, which was applied interictally. Interictal depression was diagnosed according to ICD-10 diagnostic criteria for affective and delusional disorders. The diagnosis was supported by Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D) and Montgomery-Åsberg Depression Rating Scale (MADRS). Statistical analysis included χ^2 test, Fisher's exact test and stepwise logical regression model analysis.

Results. In our study 100 patients with epilepsy out of 203 suffered from concurrent depression (49.2%); 76 of them had severe depression (37.4%) and 24 patients had mild depression (11.8%). Complex partial seizures and absence of secondary generalized tonic-clonic seizures were found to be the risk factors for depression. Treatment with clonazepam, frequent hospitalizations (drug-resistancy) and lack of occupational activity were revealed to be additional significant contributing factors.

Conclusions. Depression in patients with epilepsy is a serious medical and social problem since it afflicts almost one half of all patients treated in epilepsy referral centers. It seems to be correlated with certain types of epileptic seizures, with high frequency of seizures, sub-optimal pharmacologic treatment and lack of occupational and social activity.

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1. Introduction

Numerous recent studies confirm that the high occurrence (40–60% percent) of depressive symptoms in patients with epilepsy causes severe diagnostic, therapeutic, and social problems [1,2]. Some authors underline the correlation between epileptic focus and depression, particularly in patients with an epileptic focus localized in the temporal lobe of the dominant hemisphere; however the role of epileptic seizures in the development of depressive symptomatology has not been fully explained [3,4]. Other authors

point out the clear influence of high seizure frequency and drug resistance on depressed mood [5,6] and the direct negative impact of certain anticonvulsive drugs on mood as well [7,8]. Moreover, some less specific factors, like those typical of chronic diseases in general (i.e., feeling of isolation and social withdrawal) and individual susceptibility to depression, have been found to act on mood in patients with epilepsy [9]. Because of the higher incidence of depression in patients with epilepsy, it is possible that the epileptic process predisposes to occurrence of depression, but this correlation has not been proven [10–12]. Emotional states of high intensity evoke changes in neurotransmission, and inversely, changes in neurotransmission evoked by seizures, localized in specific brain regions, predispose to intensification of emotional disturbances. A role for kindling, the

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well-known epileptogenetic phenomenon, in occurrence of depression in patients with epilepsy has not yet been proven [13–17].

The notably increased predisposition for depression is also suggested by the frequent occurrence of severe depressive syndromes requiring hospitalization and the elevated risk for suicide in patients with epilepsy. Both significantly exceed the risks observed in other somatic and neurological diseases [18,19].

According to Boylan and colleagues, 54% of patients with epilepsy have depression, and 19% have severe depression with suicidal thoughts. Nonetheless most of them (37%) are not diagnosed as depressive, and only 17% receive appropriate antidepressive treatment [2]. In summary all these facts urge further investigation of depression risk factors in epilepsy.

The aim of the study was to find possible risk factors for the development of depression in subjects with epilepsy that may further delineate the group of patients who require special clinical attention and monitoring so that they may receive early pharmacologic intervention.

2. Subjects and methods

The subjects ($N = 203$) comprised 117 females (57.6%) and 86 males (42.4%), with a mean age of 33.3 (range = 18–50 years). All patients analyzed in this trial were under ambulatory care in the Referred Epileptic Outpatient Clinic of the Department for Neurology and Epileptology, Medical Centre for Postgraduate Education, Warsaw, or were hospitalized in the Department of Neurology and Epileptology, Medical Centre for Postgraduate Education. All subjects had a confirmed diagnosis of epilepsy, based on documented clinical data and prolonged video/EEG monitoring, with simple and/or complex partial seizures with or without secondary generalization lasting at least 5 years. The duration of epilepsy ranged from 60 to 580 months (mean = 215.4 months). No patients were being treated with any drugs having influence on the central nervous system (except antiepileptic drugs). There were no patients with symptoms of mania, bipolar affective disorder, or posttraumatic stress disorder in both groups of patients analyzed. None of them had a prior diagnosis of depression or prior antidepressive treatment. Patients with active neurological disease, mental retardation (moderate to severe), or terminal disease were excluded. All patients signed an informed consent according to ethical committee regulations.

In the interictal period, at least 24 hours after the last epileptic seizure, all patients underwent the same research protocol, which included patient's history, physical and neurological examination, standard laboratory tests (blood, liver functions), MRI, and standard EEG. Interictal depression was diagnosed according to ICD-10 diagnostic criteria for affective and delusional disorders, in patients with coexisting symptoms of decreased mood and psychomotor activity, suicidal thoughts, anxiety, and somatic complaints (e.g., insomnia, loss of appetite) [20]. Confirmation and severity assessment of the diagnosis were supported by the Polish version of the Beck Depression Inventory (BDI) [21], Hamilton Depression Rating Scale (HAM-D) [22], and Montgomery–Åsberg Depression Rating Scale (MARDS) [23]. The BDI was validated in Polish clinical psychiatric samples [24]. The HAM-D and MARDS scales were not validated in Polish populations. In our study we used translations of both tools prepared at the Institute of Psychiatry and Neurology (regional WHO Centre) for clinical purposes. This is possible in cases of investigator-scored instruments (Institute of Psychiatry and Neurology, Warsaw, 1997, unpublished manuscript). Because of the lack of Polish norms for HAM-D and MARDS, we decided to use norms from original studies and Polish norms for the BDI. Mild depression, moderate depression,

and severe depression groups were determined on the basis of the BDI scores. Investigator-scored tools were used as secondary measurements. Severe depression was diagnosed in patients who scored more than 30 points on the BDI and more than 30 points on the HAM-D or MADRS. Mild depression was diagnosed in patients scoring 15 to 30 points on the BDI and 15 to 30 points on the HAM-D or MADRS. Patients who scored below 15 points on the BDI or on the clinician-administered scales (HAM-D and MADRS) were qualified as not depressed [24,25]. There were no discrepancies between self-reported symptoms and clinicians' assessments.

2.1. Statistical analysis

Initially, the statistical significance of cross-break analysis of the data was tested with χ^2 test and Fisher's exact test. Statistical significance of differences between means was assessed with the nonparametric Mann–Whitney test. To explore the influence of factors on the occurrence of depression, the stepwise logistic regression model was used and Wald statistics were calculated.

A logistic regression model was used for dichotomous variables, and a linear regression model was applied for other types of variables. The statistical significance level was set at $P < 0.05$.

3. Results

Data analysis revealed that 100 of 203 patients with epilepsy (49.2%) were in a depressive episode; severe mood disturbances (severe depression) were detected in 76 patients (37.4%) and a less serious condition (mild depression) in 24 patients (11.8%). The nondepressed group and both depressed groups were compared with respect to family, social, and epileptologic factors, treatment, and laboratory findings. Detailed results are summarized in Table 1.

3.1. Family history and social factors

The groups of patients with epilepsy with and without concurrent depression were similar with respect to sex distribution, mean age, and educational level. No differences in family history of neurological disorders and depression were revealed. Patients with epilepsy and depression were significantly less active professionally and educationally when compared with patients with epilepsy without depression ($P < 0.01$, χ^2) (Table 1, section a).

3.2. Epileptologic factors

The groups did not differ significantly with respect to mean duration of epilepsy, age at epilepsy onset, etiology of epilepsy, history of status epilepticus, and cluster seizures. When seizure types were compared, it was found that patients with epilepsy and depression were more frequently diagnosed as having complex partial seizures than those not depressed ($P < 0.01$, χ^2). Nondepressed patients with epilepsy more commonly had secondary generalized tonic–clonic seizures in contrast to those with epilepsy and depression ($P < 0.01$, χ^2). No difference between groups in frequency of simple partial seizures was inferred. Depressed patients with epilepsy had a higher mean monthly frequency of complex partial seizures than nondepressed patients ($P < 0.05$, χ^2). Differences in the mean fre-

Table 1

Social status, epileptic factors, treatment, and laboratory findings in epileptic patients with severe depression, those with mild depression, and depression-free patients ($N = 203$)

Variable	Severe depression ($n = 76$)	Mild depression ($n = 24$)	No depression ($n = 103$)	Statistical significance
(a) Occupational activity (students and/or working)	20/76 (19.4%) ^a	9/24 (37.5%)	57/103 (55.3%)	$P < 0.01^b$
(b) Seizure type				
Simple partial	12/76 (15.8%)	4/24 (16.7%)	19/103 (18.4%)	NS ^b
Complex partial	62/76 (81.6%)	18/24 (75.0%)	39/103 (37.9%)	$P < 0.01^b$
Secondary generalized tonic–clonic	2/76 (2.6%)	2/24 (8.3%)	45/103 (43.7%)	$P < 0.01^c$
(c) Monthly seizure frequency				
Complex partial	34.2 (1–34) ^d	28.7 (1–40)	22.1 (1–33)	$P < 0.05^e$
Simple and complex partial	25.3 (1–34)	22.8 (1–38)	21.8 (1–34)	NS ^e
Secondary generalized tonic–clonic	4.0 (1–7)	4.0 (1–10)	4.0 (1–9)	NS ^e

^a Number (%).

^b χ^2 test. NS, not statistically significant.

^c Fisher's exact test.

^d Mean (range).

^e Mann–Whitney test.

quency of other types of seizures (simple partial seizures and secondary generalized tonic–clonic seizures) were not statistically significant (Table 1, sections b and c).

3.3. Treatment factors

The groups did not differ significantly with respect to number of anticonvulsive drugs taken, both currently and in the past, and also with respect to other types of medication taken.

Patients with comorbid epilepsy and depression more often required hospitalization than nondepressed patients, but the difference was not significant (χ^2).

In the group of patients with epilepsy and depression (vs nondepressed), clonazepam, tiagabine, and vigabatrin were more common in current treatment ($P < 0.05$, Fisher's exact test) (Fig. 1), and of this group, clonazepam was more frequently used in past anticonvulsive treatment, in 30% of patients versus 13% of nondepressed patients ($P < 0.05$, χ^2) (Fig. 2).

3.4. Physical examination and laboratory tests

There were no significant between-group differences in physical and neurological examinations, MRI findings, and laboratory test abnormalities. However, compared with nondepressed patients, those with both epileptic seizures and depression more frequently exhibited theta waves in the left temporal lobe and left or right frontal lobe on standard EEGs (Fig. 3).

3.5. The influence of risk factors on the occurrence of depression

A logistic regression statistical model (with Wald statistics) was used to assess independently the influence of different potential risk factors on the occurrence of depression. The following independent variables were analyzed: sex, etiology of epilepsy, occurrence of complex partial seizures, occurrence of generalized tonic–clonic seizures, status epilepticus or cluster seizures in the past,

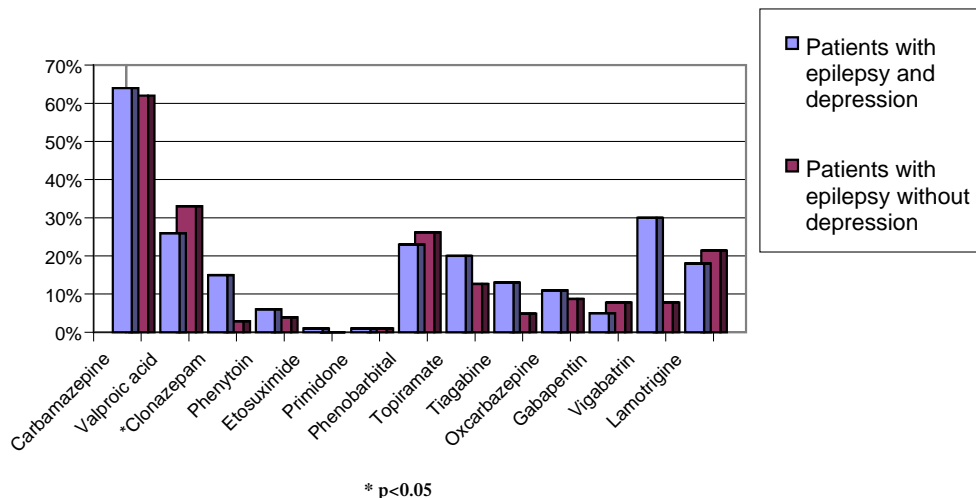


Fig. 1. Effect of antiepileptic drugs on depression in patients with epilepsy (current therapy).

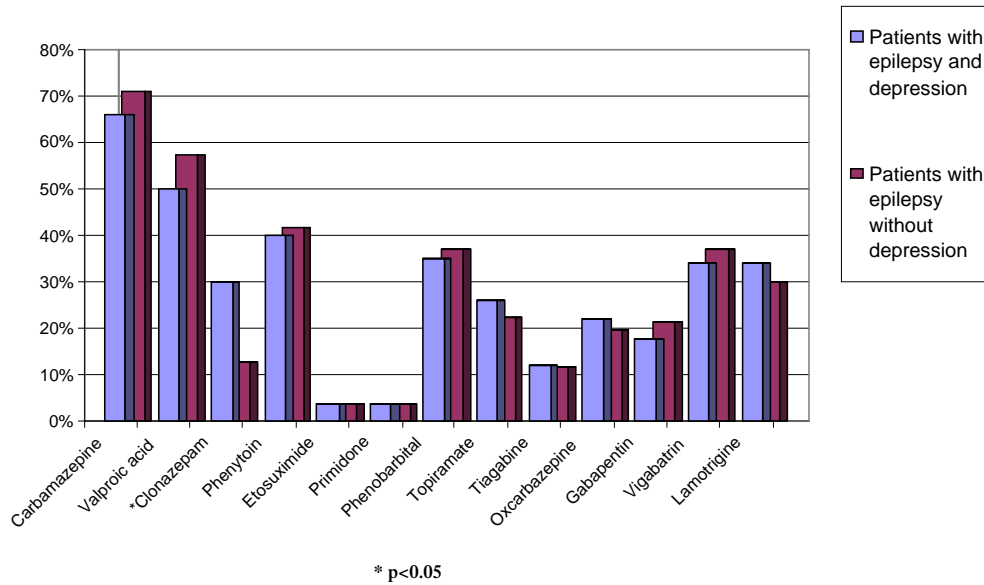


Fig. 2. Effect of antiepileptic drugs on occurrence of depression in patients with epilepsy (past anticonvulsive treatment).

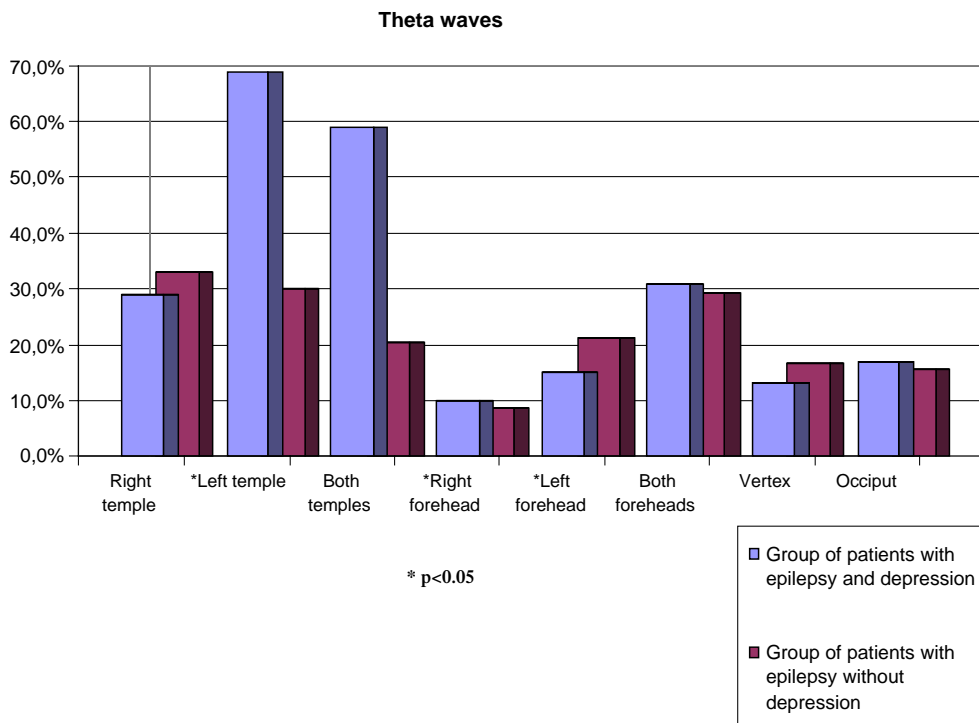


Fig. 3. Comparison of EEG abnormalities in epileptic patients with and without depression.

neuroimaging abnormalities, family history of depression and epilepsy, past hospitalizations, present and past mono- or polytherapy, present and past antiepileptic medications, and occupational activity. The strongest predictor of depression was the lack of occupational activity (odds ratio (OR) = 2.89, $P < 0.004$, $\beta = 1.06$). Past hospitalizations for epilepsy yielded a slightly weaker predictive value (OR = 2.3, $P < 0.05$, $\beta = 0.3$). Another risk factor of weaker association was the absence of generalized tonic-clonic seizures (OR = 1.9, $P < 0.05$, $\beta = 0.14$). Depression was

significantly correlated with past use of clonazepam (OR = 2.3, $P < 0.02$, $\beta = 0.7$) (Fig. 4).

4. Discussion

The analyzed group contained patients hospitalized in the clinical department as well as outpatients. In comparative analysis, there were no differences between outpatients and hospitalized patients with respect to statistical aspects of frequency, examined characteristics, or risk factors. Our

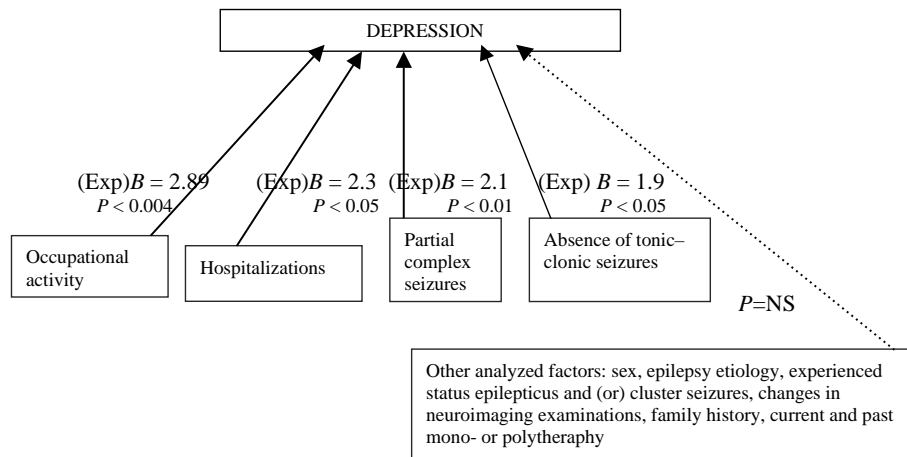


Fig. 4. Influence of analyzed factors on presence of serious depression in patients with epilepsy (logistic regression model). $\chi^2 = 29.73$; $R^2 = 0.184$. NS, no statistical significance.

study revealed a prevalence of depression in patients with epilepsy similar to that reported in previous studies. It was also found that the frequencies of severe depression requiring pharmacological treatment were similar [2,26]. Although it is well established that being female and having a family history of mood disorders are common depression-predisposing factors [17,27,28], our study did not identify any correlation between gender, age, or family history of depression and other neurological disorders and the risk of depression in the patients with epilepsy. Some authors point out that the risk of depression in patients with epilepsy rises with age [6] and may, in part, parallel the elevated risk of depression in the general population over 40 years of age [17,27]. Our survey revealed a relatively low frequency of depression in this age group.

Many research studies have indicated that a large number of patients with depression and epilepsy are unemployed or fail to continue their education. Considering the high prevalence of both disorders, this situation creates a huge social problem [29,30]. It is disputable whether such phenomena are separate from or secondary to depression. Depressive patients quit jobs because of depressed mood, general lack of activity, cognitive disturbances, and changes in biological rhythms that negatively influence their ability to work. Because patients with epilepsy frequently are socially isolated and epilepsy is still perceived in the community as some sort of mental disease, patients have serious problems in continuing education or maintaining employment. In addition to lack of employment (education), we analyzed: type of work, being in a constant relationship with a partner or wife/husband, past divorce, and living with children. Only lack of employment (education) was found to be statistically significantly correlated with depression.

In the study completed at our center there were no statistically significant differences with respect to the level of education in the groups compared, although the nondepressed group included more patients at the college/university educational level. This may confirm the thesis that lack of professional activity contributes to mood

disorders rather than mood disorders contributing to lack of professional activity [4,31].

From our results it seems that type of seizures may be important factor determining the occurrence of depression. The results confirmed the strong correlation between complex partial seizures and depression and the negative correlation between secondary generalized tonic-clonic seizures and the occurrence of mood disorders. Therefore, partial seizures may constitute the main risk factor for depression, especially if we take into account that the high frequency of these types of seizures also predisposes to the occurrence of depression.

Numerous reports in the literature point to the important correlation between the occurrence of mood disorders and the presence of seizures with focal onset [6,32,33]. Our material confirmed the surprisingly rare occurrence of depressive symptoms in patients with secondary generalized tonic-clonic seizures (also of focal onset) that had also been reported in earlier studies. Discharges propagated in secondary generalized seizures spread in different directions of the brain, whereas in partial seizures, the discharge is limited to the original epileptic focus. Additionally, it is worth noting that endorphin production is stimulated during generalized seizures and that such seizures could possibly have mood-elevating properties [31]. In the case of complex partial seizures, the quantity of endorphins is probably too small, and moreover, frequent discharges in the same epileptic focus, in patients with frequent seizures, lead to a decrease in blood flow and cause a noticeable decrease in metabolism in the perifocal area, which clinically may manifest as the patient's distressful sensations [32,34–36]. Subclinical interictal focal discharges, especially those localized in the temporal lobe, may exercise similar influence on mood [37].

A similar correlation between simple partial seizures and depression was not established in our study, probably because of the small number of patients with this type of seizure, in both the depressed and nondepressed groups. In addition, we did not find evidence of any influence of

history of status epilepticus or cluster seizures on the occurrence of depression. Further, long duration of epilepsy (assumed as mean time from the onset of disease or early onset of the disease) did not predispose to depression. Finally, patients for whom a cause for epilepsy has been revealed (e.g., brain lesion) and patients exhibiting structural changes on neuroimaging tests or abnormalities on neurological and physical examinations did not have higher rates of depression, although all these conditions are related to a more severe course of epilepsy [33,38].

Frequent hospitalizations due to epilepsy and related problems (drug-resistant seizures, status epilepticus, cluster seizures, iatrogenic anticonvulsive drug intoxication, and self-inflicted drug intoxication), which were not more frequent in the depressed group, tended to contribute significantly to its occurrence in the logistic regression model analysis. This seems to be in line with the observation that a more severe course of epilepsy is partially responsible for emerging depressive symptoms [33].

Polytherapy, indirectly suggesting drug resistance and a more severe course of epilepsy, is usually related to an increased risk of side effects, intoxication, and adverse drug interactions [18,27,28]. Surprisingly, in our analysis, no correlation between polytherapy and depression was found. The mean number of anticonvulsive drugs prescribed in both groups (depressed and nondepressed) was 3; therefore, the effect of the drugs on mood in both groups was not very clear-cut. Further analysis of the influence of particular drugs on mood showed that in depressed patients with epilepsy, clonazepam, vigabatrin, and tiagabine were more frequently used in current therapy and clonazepam had more commonly been part of past treatment. The results showed that it is very important for epileptologists to diagnose depression in their patients and to start treatment as soon as possible if clinical symptoms require treatment.

Chronic treatment with benzodiazepines (e.g., clonazepam) has an inhibitory effect on the GABA system, potentially lowering mood through overinhibition [4,11,38]. Additionally, the same effect may be provoked by repressing the beneficial influence of cholecystokinin (CCK) on hippocampal neurons, which presumably results in strengthening of anxiety and other aversive emotions. GABA-mediated anticonvulsive action in the brain presumably challenges homeostasis mechanisms by inhibiting corticohypothalamic pathways, and promotes the routing of information on negative emotions with clinical sequelae in the form of lowered mood, dysphoria, and anxiety [8,11,39].

Many reports indicate the existence of a firm correlation between temporal lobe epilepsy, especially originating in the dominant (usually left) hemisphere, and the occurrence of depression [4,29,35,36]. In our research, temporal lobe epilepsy was not analyzed and the side of the originating epileptic focus was not determined. However, in the analysis of interictal EEG recordings, aimed at localizing the focus and possibly the side and

their correlation with mood disorders, epileptic patients with depression more commonly exhibited theta waves in the left temporal area, or in both temporal areas concurrently, and increased delta waves in the left or right frontal areas as well.

Increased theta waves in temporal areas are common in nondepressed patients with epilepsy, and are usually ascribed to disturbances in the functioning of subcortical structures [36]. In depressed patients, the more frequent occurrence of focal changes in the left temporal area is highly correlated with clinical exacerbation of mood disturbances [35]. Left hemisphere temporal foci, in parallel to the normal neurophysiologic function of that area, are responsible for disturbances of mood and emotions [11,32]. Now, it is more commonly believed that depression is influenced not only by temporal lobe dysfunction (especially the left temporal lobe), but also by frontal lobe dysfunction [6,36]. This was confirmed in our research by the frequent recording of slow waves in frontal areas (both left and right) in patients with epilepsy and depression. Still we did not find a significant difference in the occurrence of sharp graphoelements in patients with epilepsy with or without depression. Although, compared with nondepressed patients with epilepsy, more patients with epilepsy and depression had sharp waves, mainly in the left temporal area, the difference was not statistically significant. In general, in our research, the percentage of pathologic EEG recordings containing abnormal graphoelements (including sharp waves) was very high, and therefore it was difficult to document conclusive intergroup differences.

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