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Brief Communication

Interictal dysphoric disorder of epilepsy: A continuing diagnostic challenge

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ABSTRACT

Objective: The interictal dysphoric disorder (IDD) is a proposed epilepsy-specific mood disorder characterized by a cluster of symptoms such as depressed mood, irritability, euphoria, and anxiety. Since its introduction, the concept of IDD has been a matter of debate. This study aimed to evaluate the frequency of the IDD and the association between psychiatric disorders and IDD. We also analyzed potential associations between IDD symptoms and epilepsy-related variables.

Methods: A consecutive group of 118 outpatients with epilepsy were screened. Ninety-six patients met inclusion criteria and examined by a trained psychiatrist using Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders fourth edition Text Revision (DSM-IV-TR) (SCID-I). In order to diagnose IDD, all participants completed the self-rating questionnaire consisting of a set of questions aimed to assess the eight key symptoms of IDD. On completion of the questionnaire, the psychiatrist reviewed all the data for completeness and accuracy with the patient.

Results: In our group with epilepsy, we observed IDD in 49.0% (47 of 96) of people with epilepsy (PWE) with substantial overlap (85%) of IDD with depressive and anxiety disorders. The frequency of depressive mood, anergia, and irritability was significantly higher in patients with IDD diagnosis. Older age at epilepsy onset was associated with IDD.

Study limitations: The cross-sectional study design, a consecutive sample of patients presenting to a tertiary referral center, a small sample size of the population, and applied methodology could have affected the results.

Conclusions: The present study indicates that IDD occurs in high frequency in PWE with a substantial overlap of IDD with depressive and anxiety disorders. The study highlights the importance of the observer-based systematic approach for diagnosing IDD and the usage of operationalized diagnostic criteria for psychiatric comorbidities in PWE. Future research should be directed at validating whether IDD is nosologically independent of other psychiatric conditions.

1. Introduction

The existence of a peculiar psychopathological syndrome specific for epilepsy is still a matter of debate. In psychiatric literature, a condition characterized by affective symptoms including low mood, irritability, and euphoria in people with epilepsy (PWE) has long been described [1,2]. Blumer et al. [3] coined the term interictal dysphoric disorder (IDD) as a condition characterized by eight symptoms grouped into labile depressive symptoms (anergia, depressed mood, insomnia, and pain), labile affective symptoms (anxiety and fear), and specific symptoms (euphoric moods and paroxysmal irritability). Euphoria and outbursts of irritability were regarded as the most distinctive symptoms in terms of differentiating IDD from common psychiatric disorders.

There is only limited data on the prevalence of IDD ranging between 19% of outpatient populations [4–8] and up to 57% of inpatients of tertiary referral centers [9].

The majority of studies suggest high comorbidity of IDD with other psychiatric disorders especially depression and anxiety disorders in PWE [4,6,7,10]. Moreover, some studies challenge whether IDD is a condition specific only to epilepsy [4,5,7,11]. It appears that IDD also occurs frequently in patients with migraine [4] and patients with functional nonepileptic events [7]. In the literature, on the psychiatric aspects of epilepsy, there is still a disagreement as to the position of IDD as an independent nosological entity specific for PWE. Several methodologic issues arise in determining the prevalence of psychiatric disorders in PWE, including differences in study populations and psychometric tools employed. Furthermore, many authors agree that up to 50% of PWE with atypical psychiatric symptomatology are not captured by standardized classificatory systems such as DSM or International Classification of Diseases (ICD) [12].

A study in a defined cohort of consecutive PWE from the tertiary reference outpatient epilepsy clinic was designed to address these

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factors. Here, we investigate the frequency of IDD and comorbidity with psychiatric disorders. We also evaluate the occurrence of IDD core symptoms and potential associations between IDD and epilepsy-related variables.

2. Methods

2.1. Study population

This study used data collected as part of more extensive research reported elsewhere [MSW]. Briefly, 118 consecutive PWE from a tertiary epilepsy center were screened, with 96 patients enrolled. Subjects who received a diagnosis of active epilepsy according to the International League Against Epilepsy criteria [13] receiving stable antiepileptic treatment in the past two months and aged 18–65 years were included. The exclusion criteria selected to reduce the impact of periictal and ictal psychiatric symptoms were last seizure within 24 h of examination and more than ten seizures in the previous month. The exclusion criteria also included a history of severe traumatic brain injury with midline shift as determined with neuroimaging, neurosurgery, unstable disease, or severe neurological disorder. Further exclusion criteria were the identification of psychogenic nonepileptic seizures (pseudoseizures), mental retardation, alcohol and/or drug dependence or abuse in the past six months, and borderline, antisocial personality disorder as determined by psychiatric interview, as the psychiatric symptomatology manifested in those psychopathologic domains may confound estimates of morbidity rates across IDD.

The study was performed in agreement with the Declaration of Helsinki following the approval of the Research Ethics Committee of the Institution. For each study participant, written informed consent was obtained.

2.2. Evaluation

All subjects were assessed at a single study visit by the same investigator (MSW) and diagnosed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) [14]. The structured interview was used to obtain information on disease history and sociodemographic status of patients, including gender, age, economic situation, marital status, the age at seizure onset, duration of epilepsy, seizure frequency, seizure type, an experience of auras and duration of treatment, existence of lesions, and psychiatric history.

The last section of the interview consisted of a set of questions from the Seizure Questionnaire (SQ) [3,8,9] aimed to assess the eight key symptoms of IDD (depressive mood, anergia, irritable explosive affect, euphoric mood, pain, insomnia, fear, anxiety) during the last 12 months. Following the original description of the diagnostic process by Blumer et al. [9], after completing the self-rating questionnaire, the psychiatrist (MSW) reviewed the data for completeness, accuracy, and clinical significance of each key symptom with the patient. Interictal dysphoric disorder was diagnosed when at least three of the eight core symptoms were confirmed clinically significant. As the Polish version of the questionnaire was not available for us, we translated the original version into Polish. This version was then back-translated by a bilingual speaker (English and Polish). Of note, for the identification of IDD, we did not use the Interictal Dysphoric Disorder Inventory (IDDI), which is a self-questionnaire created by Mula et al. [4] used in most of the studies. We followed the exact methodology described by Blumer et al. [3,8,9] instead. The main difference is that initially, after completing the self-rated SQ, examiner reviewed all the data for completeness whereas IDDI relies solemnly on self-evaluation.

None of the patients had been diagnosed with a psychiatric disorder before entering the study. Drug-resistant epilepsy was defined as two consecutive failures of suitably selected and applied and tolerated by the patient's antiepileptic treatments in mono- or polytherapy [15]. Computed tomography/magnetic resonance imaging, electroencephalogram, and laboratory test results were available for the majority of subjects. Data were corroborated by referral source records from the epileptologist.

2.3. Statistics

Frequencies and descriptive statistics were analyzed for each variable. Comparisons between patients with current IDD and patients without IDD were made using Student's t-tests for normally distributed continuous data, Mann–Whitney's U-test for non-normally distributed data, and Fisher's exact test for categorical data. To explore the influence of factors on the occurrence of IDD, we used the logistic regression model. A value of $p < 0.05$ was considered statistically significant.

3. Results

The study group characteristics are presented in Table 1, with the detailed analysis of demographic and clinical variables described elsewhere [16,17]. The antiepileptic drugs (AEDs) used in the study group were carbamazepine (34.2%), sodium valproate (21%), lamotrigine (15.7%), and topiramate (8.5%). Patients in the study group have not received any other neurological/psychiatric medication apart from AEDs.

In this study sample, IDD was diagnosed in 49% of PWE. The rates of psychiatric diagnoses were described elsewhere [15,16] and are presented in Table 2 for the reference. The frequency of IDD in the study group in the correspondence to other psychiatric diagnoses is presented in Table 2. There was a high cooccurrence of IDD and DSM-IV-TR psychiatric disorders: 40 from 47 (85%) patients with IDD had also other psychiatric comorbidity, and 40 from 46 (87%) patients with DSM-IV-TR psychiatric disorder also suffered from IDD; psychiatric diagnoses (IDD or DSM-IV-TR diagnoses) did not overlap only in 13 patients ($Chi^2 = 51.03$, $df = 1$, $p = 0.0000$).

The frequency of depressive mood, anergia, and irritability was significantly higher in patients with IDD than without IDD (Fig. 1). The

Table 1
General characteristics of analyzed groups.

	All patients	IDD (+)	IDD (−)	p
N	96	47	49	
Demographic characteristics				
Male sex (%)	31 (32.3)	17 (36.2)	14 (28.6)	>0.05
Age, in years (SD - standard deviation)	36.6 (12.0)	38.0 (11.7)	35.2 (12.3)	>0.05
Education, in years	11.5 (2.5)	11.1 (2.3)	11.7 (2.6)	>0.05
Employment status				>0.05
Employed (%)	32 (33.3)	12(25.5)	20 (40.8)	
Unemployed (%)	64 (67,7)	35 (74.5)	29 (59.2)	
Partner relationship				>0.05
Stable	70 (72.9)	36 (76.6)	34 (69.4)	
Single/divorced	26 (27.1)	11 (23.4)	15 (30.6)	
Epilepsy-related characteristics				
Age at epilepsy onset (SD)	19.5 (11.6)	22.2 (12.0)	16.0 (10.5)	**0.0214***
Duration of epilepsy (SD)	17.0 (11.8)	15.9 (12.0)	18.1 (11.5)	>0.05
Number of seizures/last month — median (IQR - Interquartile range)				
All	3 (2, 5)	3 (2, 5)	3 (2, 5)	>0.05
Simple partial	3 (2, 5)	4 (3, 6)	2 (1, 2)	>0.05
Complex partial	3 (2, 4)	2 (2, 3)	3 (2, 4)	>0.05
Partial evolving to secondary general	0 (0, 1)	0 (0, 0)	0 (0, 1)	>0.05
Tonic–clonic	0 (0, 1)	0 (0, 2)	0 (0, 0)	>0.05
Absence	0 (0, 0)	0 (0, 0)	0 (0, 0)	>0.05
Myoclonic	0 (0, 0)	0 (0.0)	0 (0.0)	>0.05
Atonic	0 (0, 0)	0 (0, 0)	0 (0.0)	>0.05
Drug resistant (%)	70 (72.9)	34 (72.3)	36 (73.5)	>0.05
Polytherapy (%)	46 (47.9)	23 (48.9)	23 (46.9)	>0.05

* $df = 94$, $t = 2{,}3402$, diff = 6.2 (0.8–9.9) t-student.

Table 2
Psychiatric characteristics of the study population.
(Modified from [16,17]).

DSM-IV-TR diagnosis	All (n = 96)	IDD (+) (n = 47)	IDD (−) (n = 49)	p[d]
Any anxiety disorders[a]	16 (16.7%)	13 (27.7%)	3 (6.1%)	0.005
Panic disorder	13 (13.5%)	11 (23.4%)	2 (4.1%)	0.006
Agoraphobia	2 (2.1)	2 (4.3%)	0 (0.0%)	0.145
Generalized anxiety disorder	1 (1.0%)	0 (0.0%)	1 (2.0%)	0.325
Any depressive disorder[b]	40 (41.7%)	38 (80.9%)	2 (4.1%)	<0.0001
Major depressive disorder	21 (21.9)	21 (44.7%)	0 (0.0%)	<0.0001
Single episode	17 (17.7%)	17 (36.2%)	0 (0.0%)	<0.0001
Dysthymic disorder	7 (7.3%)	6 (12.8%)	1 (2.0%)	0.043
Brief recurrent depressive disorder	5 (5.2%)	5 (10.6%)	0 (0.0%)	0.019
Minor depressive disorder	5 (5.2%)	4 (8.5%)	1 (2.0%)	0.154
"Mixed" episode[c]	4 (4.2%)	4 (8.5%)	0 (0.0%)	0.037
Others	2 (2.1%)	2 (4.3%)	0 (0.0%)	0.1445
Any psychiatric diagnosis	46 (47.9%)	41 (87.2%)	5 (10.2%)	<0.0001
No psychiatric diagnosis	50 (52.1%)	6 (12.8%)	44 (89.8%)	<0.0001

[a] 10 patients with depressive comorbidity.
[b] 4 patients with "double depression", 10 patients' comorbidity with anxiety disorder.
[c] 4 patients with symptoms of depression and mania but did not fulfill DSM-IV-TR mixed episode criteria.
[d] Two independent proportions test.

Table 3
Presence of irritability in relation to IDD and psychiatric comorbidity.

Diagnosis	Irritability		Total sum
	(+)	(−)	
No IDD AND DSM-IV-TR diagnosis {1}*	1 (2.3%)	43 (97.7%)	44
IDD all {2}	39 (83.0%)	8 (17.0%)	47
IDD only {3}**	6 (100%)	0 (0.0%)	6
AD AND/OR DD only {4}***	2 (33.3%)	4 (66.7%)	6
IDD AND [AD AND/OR DD] {5}	33 (82.5%)	7 (17.5%)	40
All patients	42 (43.8%)	54 (56.2%)	96

IDD — interictal dysphoric disorder, DD — depressive disorder, AD — anxiety disorder.
* vs {2}: $p < 0.0001$; vs {3}: $p < 0.0001$; vs {4}: $p = 0.018$; vs {5}: $p < 0.0001$ (two independent proportions test).
** vs {4}: $p = 0.030$; vs {5}: $p = 0.304$ (two independent proportions test).
*** vs {5}: $p = 0.0123$ (two independent proportions test).

presence of irritability in relation to IDD and psychiatric comorbidity is presented in Table 3. The presence of euphoria was higher only in patients with IDD and other depressive disorders (26.3%, $p < 0.05$).

4. Discussion

The findings from the present study indicated that almost one-half of participants were diagnosed with IDD. We also found a substantial overlap of IDD and common psychiatric comorbidities, namely depressive and anxiety disorders. According to the symptom patterns, depressive mood, anergia, and irritability were the most frequently occurring features of IDD in the study group.

Originally, Blumer et al. [3,8,9,18] reported on the frequency of IDD ranging from 34% of outpatients admitted for neurodiagnostic monitoring [8] to 57% of inpatients evaluated for surgical treatment of epilepsy [9]. Recent data show that the frequency of IDD is mostly consistent across the studies that applied the same methodology, namely the IDDI [19]. Prevalence rates of IDD across these studies oscillated between 17% and 34% [4–8,20] with only one exception of 50.7% [21]. The relatively larger proportion of patients with IDD diagnosis (49%) in our sample compared with other studies may be explained by the use of different methodologies.

In accordance with previous studies [4,6,7,10], our findings further indicate that IDD is strongly associated with psychiatric disorders listed

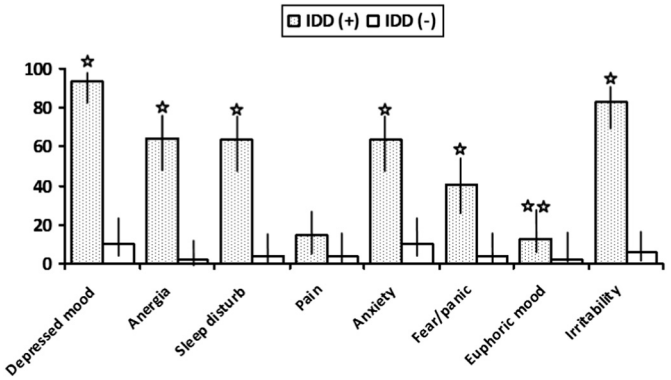

Fig. 1. Frequency (%) (plus 95% Confidence Interval (CI)) of IDD items: comparison of IDD (+) and IDD (−) groups. (⋆$p < 0.0001$, ⋆⋆$p = 0.031$; z test for independent proportion).

in DSM-IV-TR. Amiri and Hansen [5] estimated the prevalence of IDD to be 19% and found that 57% of patients with IDD had also had additional psychiatric comorbidity, mainly depression, occurring in 27% of patients. Suda et al. [6] demonstrated that there were no patients with epilepsy with IDD but without any psychiatric comorbidity [6]. Finally, in a recent study on the subject, the majority of outpatients with IDD had a comorbid current psychiatric disorder (78%): 27% of patients were diagnosed with current depressive disorder, 36% of patients had a current anxiety disorder, and 33% of patients suffered from both [7]. Our study also revealed a high cooccurrence (85%) of IDD and DSM-IV-TR-defined mood and anxiety disorders (Table 2). Current major depressive disorder was the leading diagnostic category correlated with IDD with frequency (44%) matching those reported by Mula et al. (40%) [4]. Moreover, in a subgroup of PWE with a diagnosed psychiatric problem (IDD or DSM-IV-TR diagnosis), only 24.5% (13/53) of the diagnoses did not overlap.

Given the substantial overlap of IDD with other depressive and anxiety disorders and the fact that these psychiatric disorders and IDD have many symptoms in common, it could be speculated whether IDD is a specific disorder [5,7]. However, Blumer et al. [8] found euphoria and irritability, beyond depressive mood and anergia, to be very frequent symptoms in PWE. He assumed these two symptoms to be distinctive for IDD. Mula et al. [4] also argue that IDD is qualitatively different from depression. Contrarily, to what was initially observed and hypothesized, the results from two recent studies found a very low rate of euphoria and a low rate of irritability in IDD with and without comorbid psychiatric disorder [5,7]. The findings from these studies also indicated that euphoria and irritability are not specifically prominent among PWE (with and without IDD) and occur with psychiatric comorbidity more generally [5,7]. Analogously to those studies, a rate of euphoria in IDD with a comorbid psychiatric disorder was generally low, except for the four cases with IDD and mixed features (Fig. 1, Table 2). This observation suggests that a high rate of euphoria in PWE is more closely associated with bipolar disorder comorbidity, although it has already been accepted that isolated hypomanic/manic symptoms also occur in PWE [22]. Also, in line with other studies, paroxysmal irritability was found in a higher frequency in patients with IDD and additional psychiatric disorders compared with PWE without IDD or any other comorbid psychiatric disorder. In contrast to these studies, however, we found that irritability is connected with IDD specifically (Table 3), hence, our results may support Blumer's hypothesis. Still, this observation has limited value because of the small sample size and cannot be generalized.

Although we did not find any significant correlation related to AEDs and IDD symptoms or mood disorders [15] in our study population, it should be noted that AEDs could have a negative effect on psychiatric symptomatology in PWE. Antiepileptic drug-induced dysphoria has been reported [23,24], and some AEDs have negative psychotropic actions that reduce the quality of life for patients with epilepsy [25]. Suda et al. [6] found that patients with IDD were more likely to report adverse events associated with AEDs. In our study, irritability occurred in PWE

almost exclusively in the presence of IDD or psychiatric comorbidity; therefore, it is unlikely that IDD symptoms were related to adverse events induced by AEDs.

Surprisingly, our results indicated that IDD is associated with a slightly later age at epilepsy onset. This unexpected finding should be interpreted with caution because other studies found no statistical significance in none of the directions, and one study indicated that IDD is associated with younger age at epilepsy onset [6,7].

The concept of IDD, as a separate psychopathological construct, still remains an open diagnostic challenge, especially in light of recent findings. Although the IDDI is the only self-rating instrument available for the assessment of IDD and is used in almost all studies, the methodological considerations encountered with its use are another relevant issues [26]. Criticism raised by Amiri and Hansen [5] demonstrated that the retest reliability of the Danish version of the IDDI was low and hence concluded that the IDD is a "doubtful condition." However, taking into account the intermittent nature of IDD and the fact that this is something not uncommon in psychological testing, this conclusion should be interpreted cautiously [12]. The authors also concluded "that the inventory testing for IDD is complicated and difficult" [5]. We agree that for many patients with epilepsy, it is quite possible that the inventory might be difficult to fill out. Hence, in our opinion, relying solemnly on a self-rating instrument in the diagnostic process of IDD may be problematic. The use of self-rating instruments may introduce possible disadvantages including tendencies to falsify responses, varying degrees of understanding or interpretation of particular questions, response bias [24]. Irritability is an adequate example of a symptom that could cause potential problems with the self-report measure. In psychiatric literature, irritability is most often defined as a proneness to anger that may reach a pathological extent, yet it is not the same thing as anger or aggression [27,28]. However, in the IDDI, irritability is defined as feeling "irritable, experience bad temper or fly off the handle easily over little things from time to time" which patients may interpret not only as irritable mood but also as an outburst of anger or aggressive behavior [29]. People with epilepsy are often exposed to stigma and social discrimination mainly because of irregular and unpredictable nature of the seizures. Therefore, while self-reporting, they may be prone to conceal any psychiatric symptoms, which they do not control or which are generally perceived as socially undesirable.

In contrast to most of the studies, to gather data, we used the SQ that required verification of all answers with the patient. We can speculate that the active role of the examiner in the diagnostic process of IDD in our study could influence the assessment and the recognition of the key symptoms of IDD. In our opinion, the IDDI is the comprehensive diagnostic tool that shows a good internal consistency, an acceptable sensitivity, and an excellent specificity [12]. There is also still an urgent need for further studies to clarify if IDD exists. Consequently, to address possible discrepancies between clinician and self-report measures, a matched clinician-rated instrument containing identical items as IDDI should be developed. The use of matched clinician and self-rating IDD questionnaires may provide an opportunity to determine whether a self-report can adequately assess IDD symptoms and to compare these two perspectives for each of the symptoms rated and overall total score among PWE. Future studies could aim at evaluation of this methodology and, together with structured psychiatric examination, investigate if such an approach is sufficient for the purpose of comprehensive psychiatric diagnostics in PWE.

5. Study limitations

The key study limitation is that we used a consecutive sample of patients presenting to a tertiary referral center being associated with a risk of a complicated course of epilepsy. The cross-sectional study design and small sample size of the population could have affected the results. We excluded subjects with the last seizure occurring within 24 h of examination and with more than ten seizures in the last month in order to minimize the influence of periictal and ictal psychiatric symptoms on the study measures. Moreover, because SQ does not capture the relationship between seizures and IDD symptoms, the study could not assess whether periictal symptoms had any influence on IDD. Further, none of the study subjects had a history of epilepsy surgery. Thus, the results cannot be generalized to the entire population of PWE. The study's other limitation is that patients did not undergo IDDI self-questionnaire; thus, the results could be related to the different methodologies used. Also, all evaluations were performed during one session by the same investigator (MSW), which could lead to intrarater reliability bias.

6. Conclusions

This study indicates that IDD occurs in 49% of PWE. We found a substantial overlap of IDD and common psychiatric comorbidities, mainly depressive and anxiety disorders. The study highlights the importance of the observer-based systematic approach for diagnosing IDD. Future research should be directed at validating whether IDD is nosologically independent of other psychiatric conditions.

Disclosure of conflicts of interest

No conflicts of interest exist.

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