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Interictal dysphoric disorder: Further doubts about its epilepsy-specificity and its independency from common psychiatric disorders

Kirsten Labudda[a,b,*], Dominik Illies[a,b], Christian G. Bien[b], Frank Neuner[a]

[a] Bielefeld University, Department of Psychology, Bielefeld, Germany
[b] Epilepsy Center Bethel, Mara Hospital, Bielefeld, Germany

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ABSTRACT

Purpose: The interictal dysphoric disorder (IDD) is a proposed epilepsy-specific psychiatric condition characterized by a conglomerate of symptoms such as depression, irritability, euphoria, and anxiety. However, there are doubts about IDD as an independent entity and about its presumed epilepsy-specific nature.

Methods: Here, we investigated the association between psychiatric disorders and IDD in 120 patients with epilepsy, also analyzing potential associations between IDD symptoms and epilepsy-related variables. To test the epilepsy-specificity of IDD, we also studied IDD rates in 28 patients with pure psychogenic non-epileptic seizures.

For the assessment of psychopathology, we used a structured clinical interview to determine the presence and nature of Axis I disorders and clinical questionnaires to assess psychopathological symptoms (anxiety, depression and severity of global distress). In accordance with most previous studies, we used the Interictal Dysphoric Disorder Inventory to assess IDD symptoms.

Results: In our epilepsy group, we observed an IDD in 33% (42 of 120) of the patients. We diagnosed IDD in 39% (11 of 28) of the patients with psychogenic non-epileptic seizures without epilepsy. The majority of the patients with epilepsy with IDD have or had a psychiatric disorder (33 with a current, 6 with a past Axis I diagnosis). Patients with epilepsy with IDD had higher scores on all psychopathology questionnaires compared to the epilepsy patients without IDD.

Conclusion: Our findings suggest that IDD is not epilepsy-specific in nature, but occurs with the same frequency and the same pattern of symptoms in a purely psychiatric sample. We found a large overlap of IDD and common psychiatric comorbidities, mainly depression and anxiety disorders. This result calls the presumed nosological independency of IDD into question.

1. Introduction

Referring to Kraepelin's description of an epilepsy-related "Verstimmungszustand" (Kraepelin, 1923), Blumer et al. (1995) redefined a pleomorphic affective disorder in patients with epilepsy (PWE), termed interictal dysphoric disorder (IDD). The concept of IDD was initially based on observations of a frequent atypical affective disorder symptomatology that specifically seemed to occur in PWE. Later, Blumer et al. (2004) defined eight affective-somatoform symptoms that characterize IDD: depressive moods, anergia, pain, insomnia, paroxysmal irritability with explosive affect, euphoric moods, fear, and anxiety (see also Krishnamoorthy et al., 2007). The diagnosis should be made when at least three symptoms are present over a period of 12 months. Symptoms were assumed to occur periodically with a duration of a few hours up to several days. Some of the symptoms might be present steadily at a baseline level but fluctuate in their intensity. Mula et al. (2008) developed a self-rating questionnaire for the assessment of the IDD symptoms, called Interictal Dysphoric Disorder Inventory (IDDI, see also Mula and Trimble, 2008 and method section) that was used in several studies. Prevalence rates of IDD in different studies usually were about 19% in outpatient populations of PWE (Amiri and Hansen, 2015; Suda et al., 2016), and up to 57% in inpatients of tertiary referral centers (Blumer et al., 1998).

However, the existence of IDD as an independent nosological entity that specifically occurs in PWE is under debate. Although a very recent study suggests that IDD can be found often without "common" psychiatric disorders (de Araújo Filho et al., 2017), the majority of studies suggests that IDD most frequently occurs accompanied by psychiatric comorbidities, such as depression and anxiety disorders. In the first systematic study using the IDDI, Mula et al. (2008) showed that the diagnosis of a depressive disorder was correlated with the IDD diagnosis and anxiety disorders also occurred frequently (51%) in those PWE with

* Corresponding author at: Bielefeld University, Department of Psychology, Clinical Neuropsychology and Epilepsy Research, PO Box 10031, D-33615 Bielefeld, Germany.
E-mail address: kirsten.labudda@uni-bielefeld.de (K. Labudda).

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IDD. In a very recent study by Nogueira et al. (2017), 144 patients with temporal lobe epilepsy were assessed according to psychiatric disorders. Only five patients had an IDD without any other psychiatric condition. Suda et al. (2016) found an IDD rate of 19.5% in 128 epilepsy outpatients. All patients who were diagnosed with IDD also suffered from a common psychiatric disorder, suggesting a large overlap between IDD and psychiatric disorders. Although the authors reported a higher psychosocial burden in patients with IDD, it remains questionable whether this is really a result of the IDD or whether the IDD diagnosis simply reflects a stronger severity of psychiatric comorbities.

Another issue under debate is whether IDD is really an epilepsy-specific condition. Some studies found associations between the presence of IDD and epilepsy-related characteristics, such as age of onset (Suda et al., 2016), or intake of more than one AED (de Araújo Filho et al., 2017). However, other studies did not find differences between PWE with and without IDD according to seizure control (Amiri and Hansen, 2015), epilepsy duration and AED intake (Suda et al., 2016). The assumption of the epilepsy-specific nature of IDD is particularly challenged by the finding that IDD occurred with the same frequency in patients without epilepsy but with migraine (Mula et al., 2008).

Here, we investigate the frequency of IDD in PWE and patients with pure PNES to further test the proposed epilepsy-specificity of this disorder. If IDD is an epilepsy-specific condition, it should not be found in patients with pure PNES. Secondly, we aimed at testing the co-occurrence of common psychiatric disorders and IDD hypothesizing that IDD most frequently is diagnosed in PWE who suffer from a psychiatric disorder anyway. We will also focus on the symptom patterns of IDD: Blumer et al. (1995) found euphoria and irritability to be very frequent symptoms in their initial study on IDD. Those symptoms were observed in more than 60% of the PWE. The two symptoms were regarded as most distinctive in terms of differentiating IDD from common psychiatric disorders. Mula et al. (2008) also stressed the significance of these symptoms suggesting similarities between IDD and cyclothymia (rather than unipolar affective disorders). If these symptoms are of differential diagnostic value in terms of being a specific feature of IDD, one would assume that these two symptoms could be found more frequently in those PWE diagnosed with an IDD alone compared to those PWE diagnosed with an IDD and a psychiatric disorder.

2. Material and methods

2.1. Patients

We analyzed the IDDI and psychopathology data of 120 PWE (see also Labudda et al., 2017) and 28 patients with PNES (see Table 1 for demographic and clinical characteristics and Table 2 for the frequencies of psychiatric disorders of both patient groups). All patients were investigated at the Epilepsy Center Bethel, Mara Hospital, Germany, a large tertiary referral center specialized on inpatient treatment of patients with difficult-to-treat epilepsies. Inclusion criteria were age > 18 years, no epilepsy surgery within the last 2 years, no documented intellectual disability (IQ > 70), and fluent German language abilities. In the PWE group, thirty-four patients suffered from temporal lobe epilepsy (TLE), 66 patients had extratemporal focal epilepsies, 12 patients had generalized epilepsies and 8 patients suffered from unclassifiable epilepsies.

From a total sample of 47 patients with PNES, we excluded those with additional (confirmed or suspected) epileptic seizures (n = 17). Two further patients were excluded because PNES seizures were "possible" according to the diagnostic criteria proposed by LaFrance et al. (2013), but were not observed during the hospital stay. In 39.3% (n = 11) of the final pure PNES group, the PNES diagnosis was confirmed by ictal EEG, i.e. no epileptic discharges were observed during a prototypical seizure episode. In the remaining 17 patients, PNES diagnosis was considered "probable" according to LaFrance et al. (2013), i.e. an experienced clinician observed a seizure, evaluated the seizure as non-epileptic with respect to semiology and there was never any epileptiform activity observed during an EEG investigation. In two patients there were unspecific brain lesions (one patient with suspected global atrophy and one patient with unspecific white matter lesions). Thirteen of the 28 patients took AEDs (with four patients taking two different AEDs and one patient taking three AEDs, see also Table 1).

Table 1
Sociodemographic and clinical characteristics of the PWE and PNES patients.

	PWE (n = 120)	Patients with PNES (n = 28)	Statistics
Sex	57 ♀, 63 ♂	16 ♀, 12 ♂	$\chi^2 = 0.854$, p = .405
Mean Age (SD)	35.42 (13.86)	34.89 (12.11)	t = 1.84, p = .854
Mean years of school education (SD)	10.23 (1.52)	9.22 (1.0)	t = 4.19, p < .001
Mean age of seizure onset (SD)	16.96 (12.51)	26.96 (11.55)	t = −3.86, p < .001
Mean duration of epilepsy/PNES (M, SD)	18.44 (14.35)	7.93 (6.21)	t = 3.79, p < .001
Mean number of AEDs (SD)	2.19 (0.98)	0.68 (.86)	t = 7.51, p < .001
Seizure frequency, % (n)			
Daily	21.7 (26)	10.7 (3)	
Weekly	34.2 (41)	50.0 (14)	
Monthly	21.7 (26)	28.6 (8)	
Yearly	16.7 (20)	10.7 (3)	
None within the last year	5.8 (7)	0	

Table 2
Percentages and frequencies of psychiatric disorders in the PWE and the PNES patients. PNES patients more often had at least one current psychiatric diagnosis and at least one anxiety disorder ($\chi^2 > 5.47$, p < .022). The number of patients who suffered from at least one mood disorder did not differ significantly between groups ($\chi^2 = 0.61$, p = .458).

	PWE (n = 120) % (n)	PNES patients (n = 28) % (n)
At least 1 diagnosis	43.3 (52)	67.9 (19)
At least 1 affective disorder	21.7 (26)	28.6 (8)
Major depressive episode	5.0 (6)	17.9 (5)
Recurrent depressive disorder (with recent episode)	9.2 (11)	10.7 (3)
Dysthymia	7.5 (9)	0
Bipolar disorder	0	0
At least 1 anxiety disorder	30.8 (37)	64.3 (18)
Social phobia	9.2 (11)	10.7 (3)
Specific phobia	2.5 (3)	7.1 (2)
Panic disorder alone	0.8 (1)	0
Agoraphobia alone	5.0 (6)	14.3 (4)
Panic disorder with agoraphobia	3.3 (4)	21.4 (6)
Generalized anxiety disorder	4.2 (5)	10.7 (3)
Obsessive-compulsive disorder	2.5 (3)	3.6 (1)
Posttraumatic stress disorder	9.2 (11)	32.1 (9)
Adjustment disorder	5.8 (8)	3.6 (1)
Substance dependence	1.7 (2)	3.6 (1)
Eating disorder	0.8 (1)	0
Psychotic episode	3.3 (4)	0

2.2. Methods

All patients filled in a package of clinical questionnaires containing the IDDI and the psychopathology questionnaires summarized below. Afterwards, the patients underwent a structured clinical interview (see below). All patients gave written informed consent before participation. The study protocol was approved by the Ethics Committee of Bielefeld University (EK2010018).