Epilepsy & Behavior 144 (2023) 109253

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical relevance of interictal dysphoric disorder and its impact on quality of life in drug-resistant epilepsy

E. Monteagudo-Gimeno [a,b,*], R. Sánchez-González [c,d], J. Raduà-Castaño [e,f,g,h,i], L. Fortea-González [e,g,j], T. Boget-Llucià [e,j,k], M. Carreño-Martínez [e,j,k], A. Donaire-Pedraza [e,j,k], N. Bargalló-Alabart [e,k], X. Setoain-Perego [e,j,k,l], J. Rumià-Arboix [j,k], A. Bulbena-Vilarrasa [a,c], L. Pintor-Pérez [e,j,m]

[a] Department of Psychiatry and Forensic Medicine, School of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[b] Benito Menni Mental HealthCare Complex, Sant Boi de Llobregat, Barcelona, Spain
[c] Department of Psychiatry, Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain
[d] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[e] Biomedical Research Institute August Pi i Sunyer (IDIBAPS), Hospital Clinic of Barcelona, Barcelona, Spain
[f] FIDMAG Research Foundation, Sant Boi de Llobregat, Barcelona, Spain
[g] Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[h] Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[i] Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[j] Clinical Institute of Neurosciences, Hospital Clinic of Barcelona, Barcelona, Spain
[k] Epilepsy Unit, Neurology Department, Hospital Clinic of Barcelona, Barcelona, Spain
[l] Biomedical Imaging Group, Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain
[m] Consultation-Liaison Service, Department of Psychiatry, Institut de Neurociències. Universitat de Barcelona, Hospital Clínic i Provincial de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 3 March 2023
Revised 28 April 2023
Accepted 28 April 2023
Available online 14 May 2023

Keywords:
Drug-Resistant Epilepsy
Psychopathology
Interictal Dysphoric Disorder

ABSTRACT

Objective: This study aims to assess the prevalence of Interictal Dysphoric Disorder (IDD) in drug-resistant epilepsy (DRE) and to describe its clinical and psychopathological profile, including personality, as well as its impact on quality of life (QOL).
Method: A retrospective cross-sectional study from an Epilepsy Unit from January 2007 to December 2017. All patients were diagnosed with DRE. Patients underwent a battery of tests (HADS, SCL-90R, PDQ-4+, QOLIE-31) and a psychiatrist assessed the presence of Axis-I disorders and IDD. Statistical procedures were carried out using R-4.0.1 software.
Results: A total of 282 patients were included. A statistically significant association was found between IDD and mood and anxiety disorders ($p < 0.001$ and $p < 0.05$ respectively), and between IDD and higher scores in all HADS and SCL-90-R items compared to subjects without IDD ($p < 0.001$). A statistically significant association was also found between IDD and obsessive–compulsive, borderline and depressive personality disorder ($p < 0.05$). Scores in all QOLIE-31 items except for 'medication effects' were significantly lower in subjects with IDD compared with subjects without IDD ($p < 0.001$).
Conclusions: In DRE, IDD subjects show differences in the psychopathological profile and QOL scores compared to subjects without a diagnosis of IDD. An early diagnosis of IDD could facilitate prompt interventions which might positively impact QOL.

Abbreviations: DRE, Drug-resistant epilepsy; HADS, Hospital Anxiety and Depression Scale; IDD, Interictal Dysphoric Disorder; ILAE, International League Against Epilepsy; PD, Psychiatric disorder; PDQ-4+, Personality Diagnostic Questionnaire-4+; QOL, Quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; QOLIET, QOLIE-31overall score; SCID-IV, Structured Clinical Interview for DSM-IV; SCL-90R, Symptom Checklist-90-R questionnaire.

* Corresponding author at: Department of Psychiatry and Legal Medicine, School of Medicine, Universitat Autònoma de Barcelona, Edifici M 08193 Bellaterra, Cerdanyola del Vallès, Spain.

E-mail addresses: emonteagudo.hbmenni@hospitalarias.es (E. Monteagudo-Gimeno), rsanchezgonzalez@psmar.cat (R. Sánchez-González), radua@recerca.clinic.cat (J. Raduà-Castaño), lfortea@recerca.clinic.cat (L. Fortea-González), tboget@clinic.cat (T. Boget-Llucià), mcarreno@clinic.cat (M. Carreño-Martínez), jdonaire@clinic.cat (A. Donaire-Pedraza), bargallo@clinic.cat (N. Bargalló-Alabart), setoain@clinic.cat (X. Setoain-Perego), jrumia@clinic.cat (J. Rumià-Arboix), antoni.bulbena@uab.cat (A. Bulbena-Vilarrasa), lpintor@clinic.cat (L. Pintor-Pérez).

https://doi.org/10.1016/j.yebeh.2023.109253
1525-5050/

1. Introduction

Epilepsy is a major health problem as studies point to an estimated prevalence rate of 6.38 per 1,000 persons [1]. Drug-resistant epilepsy (DRE) accounts for around 30% of patients with epilepsy [2,3] and implies most of the burden of epilepsy in the population as a result of psychological dysfunction, social stigmatization, cognitive deficits, reduced quality of life, increased risk of mortality and presence of comorbid illnesses [4,5].

Among comorbidities, special focus must be placed on Interictal Dysphoric Disorder (IDD), the concept of which primarily derives from Kraepelin and Bleuler's observations of patients with untreated epilepsy [6,7]. The term IDD was latterly coined by Blumer and described as a pleomorphic affective disorder that appears in epilepsy and is characterized by labile depressive symptoms (depressive mood, anergia, pain, insomnia), labile affective symptoms (fear, anxiety), and the specific symptoms euphoria and paroxysmal irritability [8]. These symptoms occur intermittently, without external triggers, and have a duration that may last from a few hours up to two days, with a rapid beginning and end. The pharmacological treatment for IDD includes antiepileptic drugs, antidepressants, and, sometimes, low doses of neuroleptics.

Despite the high variability in epidemiological data, the actual prevalence of IDD is expected to be high and it is thought to be present to a higher extent in DRE [9] – some authors even consider it the key psychiatric syndrome associated with epilepsy [10].

There is a small body of evidence that describes an existing relationship between IDD, clinical aspects, and quality of life (QOL) in patients with epilepsy [11–13], suggesting that IDD is associated with the presence of psychiatric disorders, depressive episodes, and lower QOL. Moreover, no studies have attempted to define or quantify psychiatric symptoms in DRE, such as depression, anxiety, or personality traits, amongst others, and there are no investigations on QOL in this specific group of patients with DRE and IDD. Also, psychiatric symptoms in epilepsy are often difficult to classify into any of the standardized diagnostic systems, as they might not meet full diagnostic criteria. This can lead to underdiagnosis and undertreatment, and thus lower quality of life, as psychiatric symptoms have been proven to be the strongest predictors of QOL in DRE [14].

The current study aimed to assess the occurrence of IDD in DRE and to describe its clinical and psychopathological profile, including personality, as well as its impact on QOL in DRE.

2. Material and methods

We carried out a retrospective cross-sectional study of patients with DRE from an Epilepsy Unit at *University Hospital Clínic de Barcelona* from January 2007 to December 2017.

2.1. Patients

Adult subjects with DRE that had been admitted to an Epilepsy Unit between January 2007 and December 2017 were enrolled in the study. All patients were considered to have DRE according to the definition of the International League Against Epilepsy (ILAE), which defines DRE as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [15]. Patients were excluded according to the following criteria: diagnosis of mental retardation, primary sensory or motor impairment altering test performance, non-Spanish speakers, and those who had undergone prior intracranial surgery.

The study was approved by the Human Research Ethics Committee of *University Hospital Clínic de Barcelona*. All patients were recruited upon written consent.

2.2. Assessment

During the subjects' admission to the Epilepsy Unit, they were evaluated by neurologists, psychiatrists, and neuropsychologists. They all underwent video-encephalography monitoring and comprehensive neuropsychological testing. Sociodemographic information (age, gender, education level, employment) and epilepsy characteristics (frequency of seizures, age of onset, frequency, duration, focus, AEDs, neuroimaging) were extracted from clinical records.

2.2.1. Psychiatric assessment

Axis-I disorders were assessed by a psychiatrist following the Structured Clinical Interview for DSM-IV (SCID-IV) [16]. Disorders were grouped into four clusters: mood disorders, anxiety disorders, psychotic disorders, and other disorders.

Anxiety and depressive symptoms were assessed using the Spanish version of the Hospital Anxiety and Depression Scale (HADS) [17]. This scale was designed to measure anxiety and depressive symptoms in non-psychiatric populations during the week prior to the evaluation, to facilitate the detection and management of mood and anxiety disorders [18] and has been established as an efficient screening instrument in people with epilepsy [19]. It consists of 14 multiple-choice items divided into anxiety and depression subscales. The items are scored from 0 to 3 and the final score ranges from 0 to 21.

Psychological distress was ascertained by the Spanish version of the Symptom Checklist-90-R questionnaire (SCL-90R) [20]. This scale assesses symptoms over the previous week, and it is comprised of 90 items, rated 0 to 4, divided into nine primary symptom scales including somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. It provides three indexes: the Global Severity Index, which measures overall mental distress, the Positive Symptom Total Score, which considers the total number of symptoms independent of their severity, and the Positive Symptom Distress Index, which indicates the measure of the intensity of symptoms perceived by patients. Higher scores indicate higher psychological distress.

Personality was assessed using the Spanish version of the Personality Diagnostic Questionnaire-4+ (PDQ-4+) [21,22]. It is a self-report questionnaire developed for the evaluation of personality disorders based on DSM-IV criteria. It is made up of a total of 99 items distributed throughout 12 subscales where items are answered using a yes/no format. It assesses ten specific personality disorders (Paranoid, Schizoid, Schizotypal, Antisocial, Borderline, Histrionic, Narcissistic, Avoidant, Dependent, and Obsessive-Compulsive) along with two personality disorders proposed in the DSM-IV Appendix B (Negativistic (Passive-Aggressive) and Depressive). It has demonstrated satisfactory psychometric reliability [23–25].

The presence of an Interictal Dysphoric Disorder was evaluated according to the diagnostic criteria established by Blumer [10] following the questions incorporated into the Seizure Questionnaire. These require at least three of eight main symptoms -depressive mood, anergia, pain, insomnia, fear, anxiety, euphoria, or paroxysmal irritability- of moderate or serious severity, leading to moderate or severe limitation. The symptoms must have been present in the previous 12 months.

2.2.2. Quality of life assessment

Quality of life was evaluated using the Spanish version of the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), which evaluates patients' subjective feelings towards their quality of life in various aspects related to epilepsy [26,27]. It consists of seven multi-item subscales that assess the Overall Quality of Life (QOL), energy/fatigue (EF), emotional well-being (EWB), social functioning (SF), cognition (COG), medication effects (ME) and seizure worry (SW). Each subscale has an item measuring the level of subjective distress of that particular subscale. The overall score ranges from 1 to 100. Higher scores indicate higher quality of life. An overall score (QOLIET) results from a weighted average of the multi-item scale scores.

2.3. Data analysis

We compared whether patients with IDD differed from patients without IDD in the following variables: the presence of a psychiatric disorder (PD) diagnosis according to SCID-IV, three HAD variables, sixteen PDQ variables, thirteen SCL-90R variables, and eight QOLIE-31 variables. To conduct these comparisons, we used chi-squared tests for categorical variables (e.g., PD diagnosis) and t-tests for numeric variables (e.g., HADA score). To correct for multiple comparisons, we applied Bonferroni correction within each scale. Corrected P values < 0.05 were regarded as statistically significant. All statistical procedures were carried out using R-4.0.1 software.

3. Results

3.1. Sociodemographic and clinical characteristics

A total number of 282 patients met the inclusion criteria. From the total sample, 98 patients had a diagnosis of IDD (34.8%), while 184 (65.2%) did not. Sociodemographic and clinical characteristics, along with differences between groups are summarized in Table 1. The only statistically significant difference found among both groups is marital status.

3.2. Psychopathological profile

3.2.1. SCID-IV

As previously stated, 98 patients had a diagnosis of IDD (34.8%), 70 (71.4%) of which were diagnosed with a psychiatric disorder (PD) according to SCID-IV, in contrast to 44 (23.9%) subjects in the group without IDD being diagnosed with a PD (p-value < 0.0 01), suggesting a higher prevalence of any psychiatric comorbidity in IDD patients with an odds ratio (OR) of 7.88. Patients with IDD were also more likely to have a diagnosis of mood or anxiety disorder. See results in Table 2.

3.2.2. HADS

In the analysis of the association between depressive and anxious symptoms and IDD, statistically significant differences were found in all HADS items. Scores in all HADS items were higher in subjects with IDD compared with subjects without IDD. See results in Table 3.

3.2.3. SCL-90-R

In the analysis of the association between different psychiatric symptoms and the presence of IDD diagnosis, scores in all the items of SCL-90-R were statistically significantly higher in subjects with IDD compared with subjects without IDD. See results in Table 3.

3.2.4. PDQ

In the analysis of the association between different personality traits and the presence of IDD diagnosis, scores in the overall cluster C group, and the subgroups obsessive–compulsive, borderline and depressive personality disorder were statistically significantly higher in IDD patients compared with non-IDD patients. See results in Table 3.

3.3. Quality of life

In the analysis of the association between QOL and IDD, scores in all items of QOLIE-31 except for "medication effects" were statistically significantly lower in subjects with IDD compared with subjects without IDD. Results from the total sample of the evaluation of the quality of life using QOLIE-31 are shown in Table 4.

4. Discussion

The main finding of our study is that DRE subjects with IDD show differences in the clinical and psychopathological profiles compared to subjects without a diagnosis of IDD, and these differences have a relevant impact on QOL, showing lower QOL scores in IDD in comparison with subjects without IDD.

Firstly, from the scarce previous studies that have estimated the prevalence of IDD in epilepsy (without distinction between DRE and not DRE), most results have ranged from 17% to 21.3% [9,12,13,28]. The fact that we have observed a higher occurrence might be explained by the consideration that our sample was composed only of subjects with DRE. De Araujo *et al.* [9] estimated a prevalence of 18.4% in a sample of DRE. However, it must be noted that they did not perform a diagnosis of IDD if participants met diagnostic criteria for an Axis I disorder according to DSM, which we believe may have contributed to the discrepancy among prevalences. In our sample, one-third of patients with DRE had a diagnosis of IDD, which we consider to be high. Given our results, the presence of IDD should always be considered by physicians when attending patients with DRE, in an attempt to reduce its misdiagnose and possible undertreatment.

Furthermore, it has been suggested that psychiatric symptomatology in epilepsy does not find a place in the current standardized classificatory systems [29]. However, we aimed to evaluate the association between IDD and PD, in order to characterize the disorders that are most frequently associated with IDD in DRE. Previous studies in epilepsy have found high comorbidity of IDD with other psychiatric disorders, especially mood and anxiety disorders [12,28,30], while some have even encouraged future research to validate whether IDD is nosologically independent of other psychiatric conditions. Nonetheless, no investigations are assessing the presence of IDD and other PD in DRE. We report an association between IDD and resistant epilepsy and PD, as more than two-thirds of subjects with IDD from our sample (71.4%) had at least one psychiatric diagnosis, indicating that patients with DRE and IDD are at a higher risk of suffering from comorbid PDs, in particular anxiety or mood disorders. Previous studies have stated that psychiatric comorbidities are underrecognized and go untreated in patients with epilepsy [31]. Given the high comorbidity found in our study, one of the key points when assessing these patients should be recognizing comorbid psychopathology.

Whether existing psychiatric classificatory systems are adequate or not in epilepsy, a greater understanding of the psychopathology in these subjects through psychometric scales could also contribute to improving clinical practice in this specific subgroup of patients. We assessed anxiety and depressive symptoms using HADS and found statistically significant differences between patients with IDD and without IDD, where the group with

Table 1
Sociodemographic and neurological characteristics.

	Whole sample group (N = 282)			IDD group (N = 98)			No IDD group (N = 184)			Difference (p-value)
	%	Mean	sd	%	Mean	sd	%	Mean	sd	
Sociodemographic										
Age		38.15	11.93		39.17	12.26		37.6	11.75	0.3
Gender										0.5322
Women	55.7			59.2			53.8			
Men	44.3			40.8			46.2			
Education						−1			−1	0.753
Primary	42.2			43.9			41.3			
Secondary	42.5			38.8			44			
Tertiary	14.9			16.3			14.3			
No data	0.7			0.5			1			
Occupation										0.3838
Inactive	37.6			41.8			35.3			
Housewife/student	16.7			18.4			15.8			
Active	45.4			38.8			48.9			
No data	0.3			1			0			
Marital status										
Married	53.5			62.2			48.9			**0.0239****
Divorced/widowed	10.3			13.3			8.7			
Single	35.1			23.5			41.3			
No data	1			1			1			
Neurological										
Etiology										0.4959
Idiopathic	63.8			66.3			59.2			
Secondary	36.2			33.7			40.8			
Type of seizures										0.587
Focal onset	69.5			73.5			67.4			
Generalized onset	24.8			22.4			26.1			
No data	5.7			4.1			6.5			
Locus										0.3836
Temporal	48.2			50			47.3			
Extratemporal	22			16.3			25			
Unestablished	18.1			19.4			17.4			
No data	11.7			14.3			10.3			
Hemisphere										0.2285
Right	37.9			40.8			36.4			
Left	37.3			29.6			41.3			
Bilateral	7.4			6.1			8.1			
Unknown	4.3			7.1			2.7			
No data	13.1			16.3			11.4			
Number of seizures per month										0.7543
<1	5			6.1			4.3			
1–5	40.4			37.8			41.8			
>5	53.5			55.1			52.7			

**Statistically significant difference in marital status between patients with and without IDD.

Table 2
Association of SCID-IV and IDD diagnoses.

	Whole sample (N = 282)	IDD (N = 98)	No IDD (N = 184)	Difference	Odds Ratio	95% Confidence Interval
SCID diagnoses	N (%)	N (%)	N (%)	p-value		
Mood Disorder	64 (22.7)	46 (46.9)	18 (9.8)	**<0.001**	8.40	4.34–16.88
Anxiety Disorder	54 (19.1)	28 (28.6)	26 (14.1)	**0.017**	2.48	1.30–4.76
Psychosis Disorder	10 (3.5)	6 (6.1)	4 (2.2)	0.285	2.97	0.68–14.58
Other disorders	4 (1.4)	3 (3.1)	1 (0.5)	0.411	5.83	0.46–309.31
Any Disorder	114 (40.4)	70 (71.4)	44 (23.9)	**<0.001**	7.88	4.42–14.41

Estimates in boldface are statistically significant ($p < 0.05$).

IDD showed higher scores in the anxiety and depression subscales, as well as in the total scale. Previous literature has shown that DRE is significantly associated with anxious and depressive symptoms, which are in turn associated with impaired QOL [32], but no studies have addressed these symptoms in IDD with resistant epilepsy.

Continuing with this approach, psychological distress was evaluated with SCL-90-R, which has not been used in precedent literature in the assessment of patients with DRE and IDD. We found that subjects with IDD scored significantly higher in all subscales compared to those without a diagnosis of IDD. As mentioned in the introduction, IDD is characterized by eight main symptoms: depressive mood, anergia, pain, insomnia, fear, anxiety, euphoria, and paroxysmal irritability [8]. However, our results show significant differences in symptoms addressed in SCL-90-R that are not included in the main assessment established for IDD, such as obsessive-compulsiveness, interpersonal sensitivity, paranoid

Table 3
Psychopathological characteristics.

	Whole sample (N = 282)		IDD (N = 98)		No IDD (N = 184)		Difference
	Mean	Std	Mean	Std	Mean	Std	p-value
HADS							
Anxiety	7.5	4.27	10.04	4.18	6.15	3.66	**<0.001**
Depression	5.12	4.07	7.5	4.49	3.87	3.19	**<0.001**
Total score	12.62	7.42	17.57	7.58	10.01	5.86	**<0.001**
SCL-90-R							
Anxiety	1.16	0.79	1.59	0.82	0.93	0.67	**<0.001**
Depression	1.45	0.89	1.96	0.90	1.17	0.76	**<0.001**
Hostility	0.95	0.76	1.25	0.90	0.79	0.62	**<0.001**
Interpersonal sensitivity	1.20	0.77	1.52	0.82	1.03	0.68	**<0.001**
Obsessive-compulsiveness	1.76	0.89	2.18	0.91	1.53	0.79	**<0.001**
Paranoid ideation	1.12	0.83	1.45	0.97	0.94	0.69	**<0.001**
Phobic anxiety	0.90	0.91	1.29	1.02	0.69	0.77	**<0.001**
Psychoticism	0.77	0.63	1.04	0.68	0.63	0.55	**<0.001**
Somatization	1.23	0.84	1.62	0.94	1.02	0.70	**<0.001**
Additional items	1.24	0.80	1.60	0.84	1.04	0.71	**<0.001**
Global severity index	1.21	0.68	1.59	0.74	1.00	0.55	**<0.001**
Positive symptom distress index	2.02	0.54	2.26	0.56	1.89	0.49	**<0.001**
Total score	50.74	19.80	60.47	17.73	45.47	18.88	**<0.001**
PDQ							
Paranoid	38.39	25.93	42.68	28.62	36.07	24.14	1
Schizoid	30.42	21.33	30.62	21.70	30.32	21.21	1
Schizotypal	30.68	21.27	33.40	24.29	29.20	19.37	1
Antisocial	13.69	16.17	16.22	19.47	12.32	13.94	1
Borderline	32.30	21.94	39.46	23.03	28.42	20.38	**<0.001**
Histrionic	29.40	17.74	32.79	18.99	27.56	16.81	0.693
Narcissistic	23.92	18.63	22.62	18.03	24.63	18.98	1
Avoidant	39.62	25.76	43.42	25.77	37.56	25.61	1
Dependent	26.07	24.15	31.82	24.22	22.96	23.62	0.152
Obsessive-compulsive	44.42	21.70	50.42	22.32	41.17	20.72	**0.047**
Depressive	50.19	28.04	61.14	26.79	44.26	26.97	**<0.001**
Negativistic	34.45	21.58	36.58	22.11	33.30	21.27	1
Cluster A	33.73	18.37	36.38	20.75	32.3	16.85	1
Cluster B	25.12	14.02	27.96	15.54	23.58	12.92	0.565
Cluster C	36.42	18.12	41.71	18.01	33.56	17.58	**0.023**
Total	32.51	14.98	36.41	15.84	30.4	14.1	0.091

Std: standard deviation.

Table 4
Quality of life characteristics.

	Whole sample (N = 282)		IDD (N = 98)		No IDD (N = 184)		Difference
	Mean	Std.	Mean	Std.	Mean	Std.	p-value
QOLIE-31							
Cognition	45.91	10.75	41.20	10.01	48.35	10.33	**<0.001**
Energy/Fatigue	49.61	9.10	45.48	8.60	51.76	8.62	**<0.001**
Emotional well-being	44.80	10.29	39.99	9.13	47.30	9.99	**<0.001**
Medication effects	46.22	9.45	44.23	9.67	47.27	9.18	0.112
Overall quality of life	44.37	9.82	41.16	9.55	46.04	9.56	**<0.001**
Social functioning	43.11	9.33	39.85	8.62	44.81	9.26	**<0.001**
Seizure worry	43.63	10.08	39.90	8.97	45.57	10.10	**<0.001**
Total score	43.13	10.06	37.64	9.08	46.03	9.34	**<0.001**

Std: standard deviation.

ideation, and psychoticism. To our knowledge, no previous research has investigated these symptoms in IDD. These results possibly support the pleomorphic nature of IDD, which along with the intermittent duration of its symptoms might favor its frequent failure to meet criteria for standardized diagnostic systems. We believe that this broad range of symptoms has an impact on QOL and could be considered a predictor of lower QOL [14]. Therefore, the identification and management of not only anxious and depressive symptoms, but a wider range of psychiatric symptoms, should become a crucial issue when attending to these patients.

Moreover, research on how epilepsy can affect neural circuits mediating personality has shown that seizures may lead to the development of maladaptive personality traits [33,34]. The presence of abnormal personality profiles in patients with epilepsy is high, being more severe in DRE [35]. An interictal personality has been described [36], formerly known as Gastaut-Geschwind Syndrome and frequently found in temporal lobe epilepsy, but there is limited investigation on further personality traits on IDD. Suda *et al* [12] found no association between IDD and antisocial personality disorder assessed with the Mini-International Neuropsychi-

atric Interview [37] but did not assess other personality disorders and the sample was not DRE specific. We evaluated all personality disorders using PDQ-4+ and found an association between IDD and Borderline Personality Disorder, Obsessive-Compulsive Personality Disorder, and Depressive Personality Disorder. As personality disorders could influence the ability to treat underlying epilepsy [34], identifying different personality profiles should be of concern, paying specific attention to Borderline, Obsessive-Compulsive, and Depressive personality disorders when treating patients with IDD in DRE, according to our results. Also, personality has been found to play an important role in adjusting to epilepsy, so its assessment is also relevant in the recognition of patients at risk of poorer QOL [38].

Although an extensive literature has examined the impact of epilepsy in QOL, there are relatively few studies investigating the impact of IDD on QOL, none of them being performed on patients with DRE. On one hand, investigations have aimed to relate DRE to impaired QOL [39], highlighting psychiatric symptoms as predominant determinants of QOL [32,40,41]. On the other hand and as aforementioned, patients with IDD have significantly lower QOL [12,13]. Our findings suggest the presence of a strong negative impact of IDD in resistant epilepsy on QOL, in comparison to DRE without IDD. We found differences among all the subscales examined by QOLIE-31 except for "medication effects". Among these subscales, we find energy/fatigue emotional well-being, cognition, seizure worry, and social functioning, all of which might be accompanied by distress at a psychopathological level. Thus, addressing not only psychiatric comorbidity but specifically IDD is likely to become a beneficial intervention in this group of patients, raising the possibility of novel therapeutic approaches aiming to improve impaired QOL in these subjects.

This study has limitations. Firstly, it is an observational study and lacks a control group. Results should not be generalized as it is a monocentric study. Moreover, the type and duration of AED treatment were not controlled. AEDs have psychotropic effects that might result in psychopathological manifestations, being difficult to differentiate from symptoms secondary to epilepsy itself. Despite using the Seizure Questionnaire to assess IDD, the Interictal Dysphoric Disorder Inventory [42] could have brought greater consistency to the objective assessment of IDD. Finally, subjects diagnosed with different types of epilepsy were included in the study which may lead to certain heterogeneity. However, we controlled for types of epilepsy (idiopathic/secondary), types of seizures, hemispheres, and locus.

5. Conclusions

We believe our findings have relevant implications for clinical practice as well as research. Our results indicate that the prevalence of IDD in DRE is particularly high and that psychiatric symptoms are determinant in this subgroup of patients when compared to patients without IDD. These results may guide clinicians to a better understanding of the psychiatric comorbidity in DRE, particularly in those patients presenting with IDD, as it must be noticed that despite depressive and anxious symptoms are the most frequently evaluated in IDD, a broader range of psychiatric symptoms (including personality) should be considered, which all contribute to an impaired QOL. Furthermore, many symptoms of IDD might be easily managed with antidepressants and sometimes neuroleptics.

Therefore, and especially in case of inability to achieve seizure freedom, we encourage clinicians to include interventions focused on assessing the presence of IDD as well as addressing accompanying psychiatric symptoms as they are likely to improve QOL.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon C-S, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies (Neurology (2017) 88 (296-303) DOI: 10.1212/WNL.0000000000003509). Neurology 2017;89(6):642.
[2] Kwan P, Brodie MJ. Early Identification of Refractory Epilepsy. N Engl J Med 2000;342(5):314–9.
[3] Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia 2018;59(12):2179–93.
[4] Monteagudo-Gimeno E, Sánchez-González R, Rodríguez-Urrutia A, Fonseca-Casals F, Pérez-Sola V, Bulbena-Vilarrasa A, et al. Relationship between cognition and psychopathology in drug-resistant epilepsy: A systematic review. *Eur J Psychiat* 2020:109–19.
[5] Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N, et al. The consequences of refractory epilepsy and its treatment. Epilepsy Behav 2014;37:59–70.
[6] Kraepelin E, Diefendorf A. Clinical psychiatry (1907). Delmar: N.Y. Sch. Facsimiles Repr; 1981.
[7] Bleuler E. Textbook of psychiatry. South Med J 1924;17(8):pp.
[8] Blumer D. Dysphoric disorders and paroxysmal affects: recognition and treatment of epilepsy-related psychiatric disorders. Harv Rev Psychiatry 2000;8(1):8–17.
[9] de Araújo Filho GM, Tarifa B, Santos RE, de Oliveira Dias AL, Ulliano JRL, Marques LHN. Clinical and sociodemographic variables associated with interictal dysphoric disorder and interictal personality in patients with drug-resistant temporal lobe epilepsy: A controlled study. Epilepsy Behav 2017;69:100–3.
[10] Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. Epilepsy Behav 2004;5(6):826–40.
[11] do Nascimento PPG, Oliva CH, Ribeiro Franco CM, Mazetto L, Yamashiro AS, de Araújo Filho GM, et al. Transtorno disfórico interictal: Uma comorbidade psiquiátrica frequente entre pacientes com epilepsia acompanhados em dois serviços terciários. Arq Neuropsiquiatr 2013;71(11):852–5.
[12] Suda T, Tatsuzawa Y, Mogi T, Yoshino A. Interictal dysphoric disorder in patients with localization-related epilepsy: Diagnostic relationships with DSM-IV psychiatric disorders and the impact of psychosocial burden. EpilepsyBehav 2016;54:142–7.
[13] Tedrus G, de Lima Silva R. Cognitive and clinical variables associated with interictal dysphoric disorder in patients with epilepsy. Epilepsy Behav 2018;82:175–8.
[14] Johnstone B, Malpas CB, Velakoulis D, Kwan P, O'Brien TJ. Psychiatric symptoms are the strongest predictors of quality of life in patients with drug-resistant epilepsy or psychogenic nonepileptic seizures. Epilepsy Behav 2021;117.
[15] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2009;51(6):1069–77.
[16] First MB, Spitzer RL, Gibbon M. Structured Clinical Interview for DSM-IV Axis I Disorders - clinician version (SCID-IV). Washington DC and London, England: American Psychiatry Association Press, Inc; 1997 (Spanish version, Masson SA, 1999).
[17] Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. Gen Hosp Psychiatry 2003;25(4):277–83.
[18] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361–70.
[19] De Oliveira GN, Lessa JMK, Gonçalves AP, Portela EJ, Sander JW, Teixeira AL. Screening for depression in people with epilepsy: Comparative study among Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Hospital Anxiety and Depression Scale Depression Subscale (HADS-D), and Beck Depression Inventory (BDI). EpilepsyBehav 2014;34:50–4.
[20] González de Rivera J, De las Cuevas C, Rodríguez M, Rodríguez F. Cuestionario de 90 síntomas SCL-90-R de Derogatis Adaptación española. TEA Ediciones. Madrid: TEA Ediciones; 2002.
[21] Hyler SE, Rieder RO, Williams JBW, Spitzer RL, Hendler J, Lyons M. The Personality Diagnostic Questionnaire: Development and preliminary results. J Pers Disord 1988;2(3):229–37.
[22] Calvo Piñero N, Caseras Vives X, Gutiérrez Ponde de León F, Torrubia Beltri R. Adaptación española del Personality Diagnostic Questionnaire-4+ (PDQ-4+). Actas Españolas Psiquiatr 2002;30(1):7–13.
[23] Calvo N, Gutiérrez F, Casas M. Concordancia diagnóstica entre el Personality Diagnostic Questionnaire-4+ (PDQ-4+) y su Escala de Signifi cacaón Clínica. Psicothema 2013;25(4):427–32.

[24] Davison S, Leese M, Taylor PJ. Examination of the screening properties of the personality diagnostic questionnaire 4+ (PDQ-4+) in a prison population. J Pers Disord 2001;15(2):180–94.
[25] Fonseca-Pedrero E, Paino M, Lemos-Giráldez S, Muñiz J. Maladaptive personality traits in adolescence: Psychometric properties of the Personality Diagnostic Questionnaire-4+. Int J Clin Heal Psychol 2013;13(3):207–15.
[26] Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia 1998;39(1):81–8.
[27] Torres X, Arroyo S, Araya S, De Pablo J. The Spanish version of the Quality-of-Life in Epilepsy Inventory (QOLIE- 31): Translation, validity, and reliability. Epilepsia 1999;40(9):1299–304.
[28] Mula M, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, et al. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. Epilepsia 2008;49(4):650–6.
[29] Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE Commission on Psychobiology of Epilepsy. Epilepsy Behav 2007;10(3):349–53.
[30] Wiglusz MS, Landowski J, Cubała WJ. Interictal dysphoric disorder of epilepsy: A continuing diagnostic challenge. EpilepsyBehav 2019;95:34–8.
[31] Kanner AM. Obstacles in the treatment of common psychiatric comorbidities in patients with epilepsy: What is wrong with this picture? Epilepsy Behav 2019;98:291–2.
[32] Ridsdale L, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, et al. Characteristics associated with quality of life among people with drug-resistant epilepsy. J Neurol 2017;264(6):1174–84.
[33] Swinkels WAM, Duijsens IJ, Spinhoven P. Personality disorder traits in patients with epilepsy. Seizure 2003;12(8):587–94.
[34] Trimble M. Treatment issues for personality disorders in epilepsy. Epilepsia 2013;54:41–5.
[35] Novais F, Franco A, Loureiro S, Andrea M, Luísa Figueira M, Pimentel J, et al. Personality patterns of people with medically refractory epilepsy – Does the epileptogenic zone matter? EpilepsyBehav 2019;97:130–4.
[36] Waxman SG, Geschwind N. The interictal behavior syndrome of temporal lobe epilepsy. Arch Gen Psychiatry 1975;32(12):1580–6.
[37] Sheehan D, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10 – PubMed. J Clin Psychiatry 1998;59(Suppl 2).
[38] Rassart J, Luyckx K, Verdyck L, Mijnster T, Mark RE. Personality functioning in adults with refractory epilepsy and community adults: Implications for health-related quality of life. Epilepsy Res 2020;159.
[39] Akdemir V, Sut N, Guldiken B. Factors affecting the quality of life in drug-resistant epilepsy patients. Acta Neurol Belg 2016;116(4):513–8.
[40] Monteagudo Gimeno E, Sánchez-González R, Raduà-Castaño J, Fortea González L, Boget Llucià T, Carreño Martínez M, et al. Association between Depressive and Anxious Symptoms with Cognitive Function and Quality of Life in Drug-Resistant Epilepsy. SSRN Electron J 2022.
[41] Luoni C, Bisulli F, Paola Canevini M, De Sarro G, Fattore C, Andrea Galimberti C, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia 2011;52(12):2181–91.
[42] Mula M, Trimble MR. What Do We Know About Mood Disorders in Epilepsy? Psychiat Controvers Epilepsy 2008:49–66.