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Mood, anxiety, and perceived quality of life in adults with epilepsy and intellectual disability

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Objective: Depression and anxiety symptoms are common among patients with epilepsy, but are relatively under-researched in patients with both epilepsy and intellectual disability (ID). The aim was to investigate whether epilepsy and ID characteristics are associated with mood, anxiety, and quality of life.

Materials and Methods: Adult patients with epilepsy and ID who rely on tertiary epilepsy care were included (N = 189). Mood, anxiety, and quality of life were assessed by standardized questionnaires. Epilepsy and ID characteristics were retrieved from patient charts or determined by psychometric instruments.

Results: Elevated levels of depressive and anxiety symptoms were present in 21.7% and 12.7%, respectively. Anxiety was significantly associated with a focal epilepsy type and ID domain discrepancy (substantial difference between two domains of adaptive behavior), but was negatively related to seizure frequency and drug load of mood-stabilizing antiepileptic drugs. Depressive symptoms were not significantly related to epilepsy characteristics, but a severe ID and ID domain discrepancy was associated with more depressive symptoms. Quality of life was significantly worse in those with multiple seizure types and ID domain discrepancy.

Conclusion: Whereas anxiety and quality of life are associated with individual epilepsy characteristics, this could not be confirmed for depressive symptoms in patients with epilepsy and ID, despite its high prevalence.

KEYWORDS
anxiety disorder, depression, developmental disability, mental health, seizures

1 | INTRODUCTION

Both depression and anxiety disorders are relatively common psychiatric disorders in patients with epilepsy. Pooled prevalence rates in this population are estimated at 22.9% and 20.2%,[1] which is much higher when compared to the prevalence of depression and anxiety disorders worldwide (4.4% and 3.6%).[2] Although epilepsy relatively often co-occurs with intellectual disability (ID),[3] literature on the presence of mood disorders among patients with both epilepsy and ID is scarce. Knowledge of this relationship is important as it might influence quality of life in these patients.

Depressive and anxiety symptoms can be associated with epilepsy for multiple reasons. They may have the same underlying neurobiological aetiology[4] or result from epilepsy due to seizure-related or psychosocial factors, such as increased dependence, experienced stigma, and poor seizure control.[5,6] Results from a systematic review indicate that having an epilepsy diagnosis is associated with an increase of depressive symptoms in adults with ID and that a severe

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form of epilepsy might be a risk factor for psychiatric disorders.[7] More specifically, Espie et al[8] concluded that psychiatric symptoms were most strongly related to epilepsy characteristics, such as seizure frequency and severity.

Both depressive and anxiety symptoms can have a negative influence on daily functioning and quality of life in this population that is already known for their complex needs.[9] For example, in a study among 142 adults with epilepsy and mild ID, it was found that psychological distress and seizure frequency were predictors of (health-related) quality of life.[10]

The primary aim of the present study is to investigate whether epilepsy and ID characteristics are associated with depressive symptoms and anxiety in adults with both epilepsy and ID. Our secondary aim is to describe associations between epilepsy and quality of life in a subset of adults with mild ID.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study had a cross-sectional design and was part of the TRIANGLE study (The Relation between epilepsy, ID, And Neuropsychiatric comorbidities in a Group of patients in Long-term care for Epilepsy), which was conducted among in- and outpatients who rely on tertiary epilepsy care facilities of Kempenhaeghe, The Netherlands. TRIANGLE is approved by the medical-ethical committee of Kempenhaeghe (No. 15.01), and the medical-ethical committee of Erasmus University medical center concluded that the rules laid down in the Medical Research Involving Human Subjects Act do not apply to this study (MEC-2016-408).

Inclusion criteria were as follows: (a) age ≥ 18 years, (b) diagnosis of epilepsy according to the clinical definition by the ILAE,[11] and (c) diagnosis of ID according to DSM-5[12] or current adaptive functioning at level of ID as evaluated by the individual's psychologist.

2.2 | Instruments and procedure

2.2.1 | Mood and anxiety

Mood and anxiety were assessed using the Dutch version of the Anxiety, Depression and Mood Scale (ADAMS),[13,14] a by-proxy observational questionnaire that is specifically developed for people with ID. The ADAMS consists of 28 items which had to be rated by one professional caregiver on a 4-point scale, ranging from never/no problem to often/severe problem. The Dutch translation of the ADAMS consists of a four-factor structure: depressive mood, anxiety, social avoidance, and other problems. The validity and reliability of this structure was investigated in two Dutch samples, one sample older than 50 years of age (N = 198) and one adult sample below 50 years of age (N = 975),[13,15] and was found to be fair to good. Higher scores on (sub) scales are indicative of more anxiety or negative mood. The subscale "other problems" and "social avoidance" were excluded from the analyses, because of the scope of the article and the substantive variability within the subscale.

In addition, information regarding the daily use of psychotropic medication and the history of psychiatric disorders were retrieved from the medical records.

2.2.2 | Quality of life

The self-reported quality of life was assessed by using the ID Quality of Life questionnaire (IDQOL-16).[16] This is a 16-item self-report questionnaire developed for people with a mild ID. Each (written) item is illustrated by pictograms and smileys in order to further clarify the question and response categories, which are based on a 5-point Likert scale varying from very unpleasant to very pleasant. The items correspond to three domains of quality of life: psychological function, social functioning, and satisfaction about daily living. The IDQOL-16 was only administered among subjects with a mild level of ID, if administration of the test was judged feasible by the subject's psychologist (ie, if the subject was likely to have sufficient verbal comprehension). In previous studies, the IDQOL-16 domains were found to have fair to good internal consistency.[17,18]

2.2.3 | Epilepsy characteristics

Epilepsy characteristics were retrieved from the subject's medical records and included the age at onset, epilepsy type, number of seizure types, number of seizures in the past year, the use and types of antiepileptic drugs, and the etiology of epilepsy. The diagnosis of epilepsy was classified by a specialized neurologist. Seizures were recorded by the nursing staff. Non-epileptic events, such as psychogenic non-epileptic seizures, were excluded. The epilepsy type and etiology were classified according to the most recent classification system by the International League Against Epilepsy (ILAE).[19]

As a measure for drug load of anti epileptic drugs (AEDs) with mood-stabilizing properties, that is, carbamazepine, valproic acid, and lamotrigine, the prescribed daily dose vs defined daily dose (PDD/DDD) ratio was calculated.[20] This was also calculated for benzodiazepines that were prescribed as AED, that is, clobazam, clonazepam, diazepam, and dipotassium clorazepate. The DDDs were retrieved from the database of the WHO[21] Collaborating Centre for Drug Statistics Methodology.

2.2.4 | Intellectual disability

Regarding the ID, we examined the overall level of ID and the presence of an ID domain discrepancy. The level of ID was based on the three domains of adaptive deficits as described in DSM-5: the conceptual, social, and practical domain. Each domain was assessed separately using standardized instruments, and the results were converted into a classification of mild, moderate, severe, or profound deficits. An ID profile was considered as discrepant when there was a substantial intra-individual difference between two DSM-5 domains, indicating that one domain is considerably

more or less deficient than the other two. For more information regarding the assessment of level of ID and domain discrepancy, see Van Ool et al.[22]

2.3 | Analyses

Descriptive statistics were calculated for the subscales of the ADAMS as well as Pearson's correlation coefficients between subscales. Also, the most reported items and the number of subjects having a score above the clinical cutoff for depressive symptoms (≥14) or anxiety (≥10) were calculated.[23]

Separate linear regression analyses were performed to examine direct associations between each epilepsy and ID characteristic and ADAMS subscale scores. Subsequently, multiple hierarchical regression analyses were performed in which predictors were added to the model in three steps. In the first step, demographic variables (age and sex) and the use of psychotropic drugs were entered; in the second step, level of ID and the presence of an ID discrepancy were added and in the final model, the epilepsy characteristics were added. Model statistics as well as predictor statistics were examined. Associations between predictors and quality of life were assessed using Pearson's correlation analyses and independent samples *t* tests (or non-parametric alternatives if the variables do not meet the normality assumption). Results were considered significant if $P < 0.05$. All analyses were conducted in IBM SPSS Statistics version 24.

3 | RESULTS

3.1 | Sample characteristics

A total of 240 patients were invited for the study, of whom 189 provided consent for the study (inclusion rate: 78.8%). The consent was provided by individuals and/or their legal guardian when appropriate. Participants were significantly younger than the 51 non-participants (mean difference = 6.04 years, $P = 0.015$) and were using psychotropic medication more often (41.8% vs 14.0%, respectively, $P < 0.001$). Individuals who participated did not differ from non-participants with respect to level of ID or gender. Twenty-four subjects (12.7%) with a mild ID had completed the quality of life questionnaire.

The sample comprised 58.7% males and had a mean age of 47.9 years (SD = 15.6; range 18.3-85.9 years). The majority of subjects resided in residential facilities (76.2%); the others lived in community settings. The level of ID was mild in 20.1%, moderate in 30.7%, severe in 29.1%, and profound in 20.1%, and an ID domain discrepancy was present in 32.8%. Clinical characteristics are described in Table 1. The descriptive statistics of the ADAMS subscales are presented in Table 2. Elevated levels of depressive and anxiety symptoms were present in 21.7% and 12.7%, respectively. The subscales were moderately to highly correlated (Pearson *r* varying from 0.426 to 0.571, all *P*-values <0.001). The ADAMS items that were reported most frequently were tense (74.1%), does not relax (70.9%), fatigued (64.6%), distracted (63.4%), and lacked energy (63.4%).

TABLE 1 Clinical characteristics of the study sample (N = 189)

Characteristics	Values
Age at onset of epilepsy (years)	*Mdn* = 2.0, *IQR* = 0-5.5, range 0-53
Infancy (<1 y)	32.8%
Childhood (1-12 y)	54.0%
Adolescence (12-18 y)	10.1%.
Adulthood (18+ y)	3.2%
Epilepsy type[a]	
Generalized only	10.6%
Focal only	41.3%
Both generalized and focal	44.4%
Missing/unknown	3.7%
Number of seizure types (semiology)[a]	*Mdn* = 3.0, *IQR* = 1-4, range 0-8
Seizure frequency (last year)	*Mdn* = 70.0, *IQR* = 11.5-153.0, range 0-1206
Seizure-free	12.7%
Yearly	12.2%
Monthly	19.6%
Weekly	43.9%
Daily	11.6%
Etiology of epilepsy[a]	
Structural	28.6%
Genetic	20.1%
Infectious	6.3%
Metabolic	1.1%
Unknown	43.9%
Daily use of antiepileptic drugs	*Mdn* = 3.0, *IQR* = 2.5-4.0, range 0-6
Daily use of psychotropic drugs	41.8%
Psychiatric classification (DSM-IV)	20.6%

ID, intellectual disability.
[a]Based on ILAE 2017 criteria.[19]

TABLE 2 Descriptive statistics of the ADAMS subscales (N = 189)

	M	SD	Range	Above clinical cutoff[a]
Depressive symptoms	9.99	7.04	0-34	21.7%
Anxiety	4.73	3.73	0-15	12.7%

[a]Based on cutoff values provided by Hermans et al.[23]

Reliability analyses on the ADAMS subscales showed fair to good internal consistency for the study population (Cronbach's $\alpha = 0.795$-0.850). Regarding the IDQOL, the psychological domain had a good internal consistency ($\alpha = 0.83$). The domains social functioning and satisfaction about daily living had, however, insufficient

internal consistency (α = 0.50 and α = 0.58, respectively) and were therefore excluded from the analyses.

3.2 | Associations between epilepsy, ID, and mood and anxiety

Results of the linear regression analyses predicting depressive symptoms, anxiety, and social avoidance are presented in Table 3. The models yielded different results per outcome measure. For both depressive symptoms and anxiety, adding ID characteristics (severity of ID and presence of ID domain discrepancy) resulted in a significant increase in explained variance (R^2 change = 0.053, P = 0.004 and R^2 change = 0.033, P = 0.026, respectively). The introduction of epilepsy characteristics (ie, number of seizure types, seizure frequency, epilepsy type, drug load of mood-stabilizing AED and of benzodiazepine AED, and use of rescue medication) in the final model did not yield a significant increase in explained variance of depressive symptoms, but did for anxiety (R^2 change = 0.034, P = 0.301, and R^2 change = 0.087, P = 0.002, respectively). Hence, the final models explained 20.0% of the variance in depressive symptoms (F = 3.86, P < 0.001) and 31.0% of the variance in anxiety scores (F = 6.95, P < 0.001).

Essentially, having a more severe level of ID and the presence of an ID domain discrepancy were significantly associated with more depressive symptoms (P = 0.013 and P = 0.004, respectively). Anxiety levels were also significantly associated with the presence of an ID domain discrepancy (P = 0.010), but not with the level of ID. Regarding epilepsy, none of the epilepsy characteristics were related to depressive symptoms. Anxiety levels were, however, significantly higher in subjects with focal epilepsy (P = 0.034). Lower levels of anxiety were significantly associated with a high drug load of mood-stabilizing AEDs (carbamazepine, valproic acid, and lamotrigine) and a high seizure frequency (P = 0.009 and P = 0.006, respectively). See Figure 1 for an overview of statistically significant predictors.

Post hoc regression analyses were performed to investigate which ID domains were particularly low in case of high levels of mood and anxiety. Results of these analyses indicated that depressive symptoms were significantly higher when having a discrepancy at the expense of the practical domain (B = 3.42, SE = 1.54, P = 0.028), anxiety levels were mostly linked to a discrepancy at the expense of the social domain (B = 1.18, SE = 0.68, P = 0.086), and there was significantly more social avoidance when having a discrepancy at the expense of the social domain (B = 1.57, SE = 0.74, P = 0.035).

3.3 | Self-reported quality of life

Spearman's rank correlation analyses were performed to investigate the associations between the IDQOL's subscale psychological

TABLE 3 Linear regression analyses predicting affective outcomes

	Unadjusted analyses			Adjusted analyses		
	B (SE)	*β*	*P*	*B* (SE)	*β*	*P*
Depressive symptoms						
Number of seizure types	0.14 (0.27)	0.04	0.596	−0.42 (0.38)	−0.11	0.270
Seizure frequency	0.19 (0.03)	0.05	0.531	0.03 (0.04)	0.08	0.884
Focal epilepsy	0.22 (1.67)	0.10	0.198	2.23 (1.58)	−0.10	0.160
Drug load mood-stabilizing AED	−0.91 (0.71)	−0.09	0.205	−0.59 (0.70)	−0.06	0.399
Drug load benzodiazepine AED	0.42 (0.81)	0.04	0.607	0.44 (0.80)	0.04	0.552
Use of rescue medication	−0.05 (0.05)	−0.06	0.379	−0.08 (0.06)	−0.10	0.183
ID discrepancy	2.79 (1.07)	0.19	0.010*	3.25 (1.13)	0.22	0.004**
Level ID (severe/profound)	0.43 (1.03)	0.03	0.673	3.05 (1.22)	0.22	0.013*
Anxiety						
Number of seizure types	−0.04 (0.14)	−0.02	0.803	0.09 (0.19)	0.04	0.653
Seizure frequency	−0.03 (0.02)	−0.15	0.035*	−0.05 (0.02)	−0.23	0.006**
Focal epilepsy	1.74 (0.88)	0.15	0.050*	1.67 (0.78)	0.14	0.034*
Drug load mood-stabilizing AED	−0.73 (0.38)	−0.14	0.053	−0.91 (0.35)	−0.17	0.009**
Drug load benzodiazepine AED	−0.06 (0.43)	−0.01	0.898	0.22 (0.40)	0.04	0.546
Use of rescue medication	−0.03 (0.03)	−0.08	0.254	−0.01 (0.3)	−0.02	0.788
ID discrepancy	1.82 (0.56)	0.23	0.001**	1.45 (0.56)	0.18	0.010**
Level ID (severe/profound)	−0.72 (0.54)	−0.10	0.187	0.47 (0.60)	0.06	0.435

AEDs, antiepileptic drugs; B, beta; ID, intellectual disability; SE, standard error; β, standardized beta.
The adjusted multivariate models also included age, gender, and use of psychotropic drugs as predictors.
*P < 0.05.
**P < 0.01.

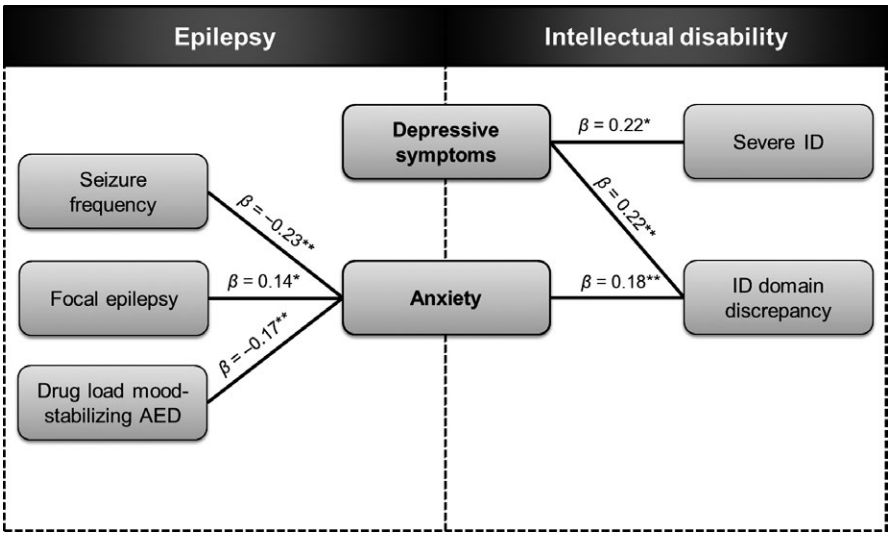

FIGURE 1 Overview of factors significantly associated with depressive symptoms and anxiety

functioning and number of seizure types, seizure frequency, and the PDD/DDD ratio of mood-stabilizing AEDs (see Table 4). There was a strong, negative association between the number of seizure types and the reported quality of life with respect to psychological functioning (ρ = −0.551, P = 0.005). Although not statistically significant, there was a clinically relevant association with a medium effect between quality of life and seizure frequency (ρ = −0.349, P = 0.094) and PDD/DDD ratio of mood-stabilizing AEDs (ρ = 0.312, P = 0.138), with a higher frequency related to a poorer quality of life and a higher drug load of mood-stabilizing AEDs related to a better quality of life. In addition, subjects who had an ID domain discrepancy reported a significant poorer quality of life than subjects without a discrepancy (difference in medians = 3.0, P = 0.020). There was no association between seizure type and quality of life. Also, correlation analyses between ADAMS subscales and IDQOL psychological functioning yielded no significant associations (Spearman's rho varying from −0.224 to −0.016, all P values >0.05).

TABLE 4 Associations between epilepsy characteristics and quality of life (N = 24 patients with mild ID)

	Quality of life—psychological functioning	*P*
Number of seizure types	Spearman *r* = −0.551	0.005**
Seizure frequency	Spearman *r* = −0.349	0.094
PDD/DDD ratio mood AEDs	Spearman *r* = 0.312	0.138
Both focal and generalized epilepsy		0.423
Yes	Mdn = 20.5, IQR = 19.0-24.3	
No (only focal)	Mdn = 20.0, IQR = 18.0-22.0	
ID discrepancy		0.020*
Yes	Mdn = 22.0, IQR = 19.0-23.0	
No	Mdn = 19.0, IQR = 11.5-20.0	

*P < 0.05.
**P < 0.01.

4 | DISCUSSION

Depressive and anxiety symptoms are a clinically relevant and important issue among patients with epilepsy and ID, as 21.7% and 12.7% of them show evidence for elevated levels of depressive or anxiety symptoms. This rate of depressive symptoms is in line with the pooled prevalence of depression estimated at 22.9% for patients with epilepsy in general.[1] However, the results of our study suggest that the prevalence of anxiety is less pronounced in patients with both epilepsy and ID in our study as compared to the pooled prevalence of anxiety disorders (20.2%) in the general population of patients with epilepsy.[1] Besides the findings and hypothesis written below, this might also be due to measurement aspects of our study. For example, we only used the ADAMS, a by-proxy observational questionnaire, which is not available in the general population.

The associations between epilepsy and ID characteristics in relation to mood and anxiety were different per affective outcome. Epilepsy was significantly associated with anxiety in both positive as well as negative directions. While adjusting for demographics and other predictors, higher levels of anxiety were associated with having a focal epilepsy type. Although we did not have information about the localization of the epilepsies in our sample, the link between focal epilepsy and anxiety has also been described in previous studies[24,25] and might be explained by the involvement of temporal brain structures in many patients with epilepsy and anxiety.[26,27] In addition, focal epilepsies (in other structures) may include focal seizures without impaired awareness of which the conscious experience—and not understanding this experience—might be more frightening for someone with ID or lead to a fear of injury.

Lower levels of anxiety were associated with a high drug load of mood-stabilizing AEDs. Most probably, this is due to the combination of the use of both multiple AEDs and the therapeutic properties of the described mood-stabilizing AEDs. Remarkably, anxiety appeared to be also related to a higher seizure frequency, even when the use of benzodiazepines as AED (daily or as rescue medication) was taken into account. This is in contrast with recent findings by

Dehn et al[28] who demonstrated that a higher seizure frequency was significantly correlated with anxiety in patients with difficult-to-treat epilepsy (but without cognitive impairments) admitted to an epilepsy center. This difference might be explained by the fact that all our patients are living at a tertiary epilepsy center and that their seizure frequency is higher than in the study by Dehn et al[28] it could be hypothesized that the patients are therefore more habituated to having seizures and to its consequences in daily life. Also, professional caregivers who are specialized in epilepsy are always in close proximity and provide care and attention to patients who have seizures. Such environmental factors were beyond the scope of this study, but should be included in future research.

Despite a relative high number of patients having elevated levels of depressive symptoms, none of the epilepsy characteristics were found to be significantly related. This seems to conflict with some studies on epilepsy and depression in patients without ID, suggesting that depression is associated with epilepsy-related characteristics.[28,29] However, a review study by Hoppe and Elger concluded that the overall evidence is weak if stress-related epilepsy factors, such as social stigma, are taken into account.[30] A social stigma might be less prominent in this sample, as the majority of patients live together with other patients with epilepsy and are therefore less "distinguished" from other members of the society. Furthermore, knowledge about the pathogenic mechanisms in the relationships between epilepsy, depression, and anxiety has been increasing.[31] Future research is necessary to determine to what extent the underlying pathophysiology of epilepsy, depression, and anxiety applies to people with ID.

Irrespective of the epilepsy, this study demonstrated that ID characteristics were significantly associated with depressive and anxiety symptoms. With respect to the association between a more severe level of ID and depressive symptoms, it should be considered that the corresponding ADAMS subscale includes several somatic symptoms, such as fatigue and lack of energy. People with a more severe ID and epilepsy often are part of a frail population with multiple health problems,[32] which might imply an increased vulnerability in this subgroup. Individuals who had an ID domain discrepancy, indicating that one domain of adaptive functioning is considerably more or less deficient than the other(s), had significantly higher depressive and anxiety levels than those without. Especially, the practical and social abilities were more impaired in those with more depressive symptoms and anxiety, respectively. Although this concept of discrepancy requires further investigation, one could hypothesize that people with an ID domain discrepancy might be confronted with their (physical) limitations or are at risk of being overestimated by others, which may lead to feelings of frustration or stress.

Finally, despite the small subsample size, our findings confirm that a more severe epilepsy is associated with poorer quality of life regarding the domain of psychological functioning, which seems to emphasize the burden of epilepsy in their daily life. The quality of life was also significantly poorer in those with an ID domain discrepancy. There was, however, no direct association between the self-reported quality of life and the depressive and anxiety levels. This might be due to measurement aspects, such as the difference in informant (self-report vs report by proxy) and the time span (current situation vs past 6 months).

4.1 | Limitations

Of course, this cross-sectional study is not without limitations. The study describes a specific (highly complex) population, with a highly frequent use of psychotropic medication (41.8% of the 189 participants vs 14.0% of the 51 non-participants; $P < 0.001$).

Findings concerning QoL are based on a small subsample size of people with a mild ID, as the QoL self-report required a certain amount of verbal and cognitive abilities.

Comorbid psychiatric diagnosis such as autism or hyperkinetic disorders and etiological influences were beyond the scope of this present study. This will be part of future research in our centre, as we know that in general, they often are accompanied by a higher level of anxiety and depressive symptoms.

5 | CONCLUSIONS

To conclude, this study emphasizes the relevance of depressive and anxiety symptoms in patients with epilepsy and ID, although the representability of our sample is limited to patients with primarily severe epilepsy who rely on tertiary epilepsy care facilities. Whereas anxiety and perceived quality of life are associated with specific epilepsy characteristics, depressive symptoms were only related to ID characteristics. These aspects should be taken into consideration by professionals working with this vulnerable population, so that they can anticipate on such comorbidities and contribute to good clinical care.

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CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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