



Patient and caregiver quality of life in psychogenic non-epileptic seizures compared to epileptic seizures



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ABSTRACT

Purpose: Little is known about the effect of psychogenic non epileptic seizures (PNES) to caregiver quality of life (QOL), particularly as it compares to epileptic seizures (ES). We sought to characterize this effect and identify its determinants.

Methods: The study population comprised of 126 ES and 33 PNES patients who underwent video EEG monitoring along with 48 and 18 caregivers respectively who accompanied them to their investigations. Patients completed questionnaires providing demographic, disease-related, cognitive, psychiatric, sleep and QOL information on admission, prior to their diagnosis being clarified. Their caregivers completed questionnaires providing demographic, disease burden and generic QOL information. Paraclinical data were also gathered. Regression analysis was used to identify patient and caregiver related determinants of patient and caregiver QOL.

Results: QOL scores were significantly worse for PNES than ES patients and were mainly linked to depression levels. PNES and ES caregivers had comparable demographic characteristics and QOL scores. ES caregiver QOL was better in employed caregivers with lower burden scores for the physical component summary (PCS) and worse in female caregivers of depressed patients with higher burden scores for the mental component summary (MCS). Caregiver burden score was the strongest correlate of PNES caregiver MCS QOL score.

Conclusion: Caregiver QOL in PNES does not differ from caregiver QOL in ES, while patient QOL is worse in PNES. Caregiver burden emerges as a consistent correlate of caregiver QOL both in ES and PNES. These findings advocate for consideration of caregiver burden and QOL in PNES in clinical practice and for future research paradigms.

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1. Introduction

Clinical behavior in psychogenic nonepileptic seizures (PNES) resembles epileptic seizures (ES) without an electrographic correlate and has a strong psychological basis.¹ PNES constitute 10–30% of referrals to epilepsy specialists,^{2,3} with their prevalence in the general population being estimated at 2–33 per 100,000,³ generating a significant public health problem with an estimated lifetime cost per patient cohort year in the US ranging from \$110 to 920 million.⁴

In addition to the society, PNES take a significant toll on the individual patient. Quality of life (QOL) in patients with PNES has been consistently shown to be worse than in patients with epileptic seizures (ES).⁵ Despite their significant impact on their bearers, our understanding of PNES pathophysiology is limited and hence optimal approach to management remains elusive.⁶ A number of interventions have been proposed, which are not limited to pharmacotherapy, cognitive-behavioral therapy, psychodynamic, psychotherapy, hypnosis and group therapy.⁷ These treatments predominantly target the patient,⁸ typically use seizure frequency as the primary endpoint,⁶ have limited generalizability⁹ and have yielded overall poor outcomes.^{10,11}

More recently, LaFrance et al. elegantly explored the role of family dysfunction as a potential contributor to poorer QOL in patients with PNES and subsequently, as a potential foothold for

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intervention.¹² QOL was examined from the patient but not from the caregiver perspective. The primary aims of this study are (i) to characterize caregiver QOL in PNES and (ii) to identify which patient and caregiver related factors determine it. As a secondary aim, we use a comparison group of patients/caregivers with ES and attempt to ascertain how patient and caregiver characteristics, QOL scores and QOL determinants differ between the two populations. We subsequently discuss clinical and research repercussions of our findings.

2. Methods

2.1. Participants

The study was approved by the institutional review boards of the participating hospitals. This cross-sectional study was conducted between September 2009 and June 2011 at Massachusetts General Hospital (MGH) and Boston University Medical Center (BUMC). Adult patients admitted electively to Epilepsy monitoring units at in those two sites for continuous video-EEG monitoring were asked to participate by completing a series of questionnaires and undergoing bed-side cognitive evaluation. Patients who were non English speakers or unable to read and write due to mental handicap were excluded. Caregivers who accompanied them were also asked to complete questionnaires. Caregiver was defined as the family member who was primarily responsible for providing every-day care for the patient. After monitoring was completed, patients were classified as ES vs PNES based on video-EEG criteria. Only patient with documented ES (80 at MGH and 46 at BUMC) and PNES (31 at MGH and 2 at BUMC) along with their respective caregivers (48 for ES and 18 for PNES, all at MGH) were included in the analysis, while patients with other non-epileptic seizures (e.g. cardiac arrhythmias, sleep or movement disorders, etc.), mixed disorder or unclear diagnosis were excluded along with their caregivers.

2.2. Questionnaires and procedures

Participating patients completed questionnaires providing demographic (age, gender, race, religion, employment, education, living situation and marital status) and epilepsy related (age of disease onset, disease duration, average number of seizures/spells per month in the past year, number of AED, compliance) information. Additional information collected was gleaned from medical records review. Anxiety and depression levels were measured using the Beck anxiety¹³ and Beck depression¹⁴ inventory respectively. Both have been extensively used previously in research for ES¹⁵ and PNES.¹² Sleep quality was assessed by completing the Epworth sleeping scale¹⁶ and the sleep apnea section of the sleep disorder questionnaire (SDQ-SA).¹⁷ While not specific to patients with epilepsy, the Epworth sleeping scale has been widely used to assess sleepiness in a host of diseases including epilepsy.¹⁸ The SDQ-SA has also been commonly applied to the epilepsy population.¹⁹ Quality of life was evaluated by completing the QOLIE-31 instrument. QOLIE-31 is one of the most commonly applied QOL instruments in epilepsy with good reliability and validity.²⁰ It has been previously used for evaluation of QOL in PNES, given the shared concerns by both groups of patients, both in this abbreviated form²¹ as well as in its original version (QOLIE-89).¹⁰ Cognitive evaluation was performed by a neurologist via administration of the Montreal cognitive assessment (MoCA) test.²² This is a brief screening tool that has been shown to be superior to the commonly used mini-mental status examination for the detection of mild cognitive impairment in the epilepsy population.²³ All these evaluations took place on the day of the admission under electrographic guidance to ensure the absence of subclinical electrographic seizure activity affecting

some of the responses. At the time of the testing, the patients were maintained on their home AED(s) and had not been yet sleep deprived with the intent that their answers would be representative of their baseline state in the ambulatory setting. They were also not aware yet of the final EMU diagnosis.

Caregivers accompanying the patients also completed questionnaires prior to establishing the final EMU diagnosis. The questionnaires included several demographic information (age, gender, race, religion, employment, education, marital status, cohabitation and time spent for patient care in hours per week). The latter was loosely defined as the time devoted to everyday activities where caregiver participation was indispensable including AED provision, outpatient and emergency department visits and driving for any patient-related activity. Given the lack of a disease specific questionnaire to assess their burden, the Zarit caregiver burden inventory was used instead. This is a 22-item inventory derived from the original 29-item inventory.²⁴ It is the most widely used standardized, validated scale to assess caregiver burden, administered previously in various neurological disorders, including epilepsy.^{25,26} Caregiver health-related quality of life was assessed by administering the second version of the SF-36 generic questionnaire (SF36v2).²⁷ This is a generic QOL instrument that assesses eight health concepts. Scores standardized to norms and weighted averages are used to create a summary physical component summary (PCS) and a mental component summary (MCS) composed by the first and last four of the aforementioned health concepts respectively. Scores are standardized to norm and this allows direct comparison among different populations²⁷; thus it has established precedence in epilepsy caregiver research. Various paraclinical (laboratory, electroencephalographic and radiologic) data were collected as part of standard of care. Routine AED levels were drawn on admission prior to initiation of gradual withdrawal. For patients on more than one AED, they were deemed to be suprathreshold, therapeutic or subtherapeutic on their regimen depending on the level of the majority of drugs in their regimen. EEG data pertained to the initial recording during the completion of the questionnaires (normal, slow, epileptiform) including the maximal posterior dominant rhythm at the time of completion and the final EMU report for classification to the ES vs PNES category. Radiological data included findings of the last patient's brain magnetic resonance imaging (normal vs abnormal) obtained before, during or right after this monitoring.

For a detailed description of the questionnaires used both for patients and caregivers, please refer to the [Appendix](#).

2.3. Analysis

Summary scores were created for all the aforementioned variables and descriptive statistics were used. Univariate comparisons for demographic variables between the ES and PNES patients and between the ES and PNES caregivers was performed using *t*-test (or non-parametric equivalent) for continuous variables respectively and Chi-square test for categorical variables. The outcome variable of interest was QOLIE-31 score for ES and PNES patients and SF-36v2 (PCS and MCS separately) scores for ES and PNES caregivers. For QOL of ES and PNES patients, only patient related characteristics were used as covariates. For QOL of ES and PNES caregivers, both patient and caregiver related characteristics were used as covariates. Univariate associations between the outcomes of interest and their potential determinants were explored by using *t*-test or one-way ANOVA for categorical variables and Pearson correlation for continuous variables. Statistical significance was set at 0.05. Those variables identified as statistically significant in the univariate analysis were subsequently fitted in a multivariate linear regression model in order to conduct an adjusted evaluation of QOL determinants.

When the number of events limited the ability to adjust for confounders (e.g. QOL predictors for PNES caregivers), the results of the univariate analysis were emphasized instead. Statistical analysis was performed in SAS (North Carolina).

3. Results

3.1. Patient and caregiver characteristics

ES and PNES patient characteristics are detailed in Table 1a. The mean age of the patients was 38 years while the mean age for the caregivers was approximately 42 years. Consistent with previous

studies, PNES patients were more likely to be female (approximately 79% vs 59% in the ES cohort, $p = 0.03$). On the other hand, ES patients typically had an earlier disease onset (24 vs 35 years of age, $p = 0.0005$) and a longer disease duration (15 vs 7 years, $p = 0.0001$). Despite experiencing more events per month (6 vs 3, $p = 0.009$), PNES patients were on average on fewer AED (1 vs 2, $p < 0.0001$). As expected, PNES patients had a faster posterior dominant rhythm on their EEG (9.96 vs 9.4 Hz, $p = 0.01$) and fewer EEG abnormalities (88% with a normal EEG vs 46% in the ES cohort, $p < 0.0001$). Similarly, MRI was abnormal only in 36% of PNES patients, typically due to nonspecific white matter disease, as opposed to 69% of ES patients ($p < 0.0006$). In accord to existing

Table 1
Subject characteristics.

a: Patient characteristics			
	Epilepsy patients N=126	PNES patients N=33	p Value
<i>Demographic characteristics</i>			
Age (mean ± SD)	38.20 ± 13.48	41.84 ± 11.44	0.15 ^a
Gender (n, % female)	74 (58.73%)	26 (78.79%)	0.03 ^b
Race (n, % caucasian)	103 (83.74%)	29 (87.88%)	0.55 ^b
Religion (n, % Christian)	75 (75%)	20 (64.52%)	0.25 ^b
Employment (n, % employed)	68 (55.74%)	15 (46.88%)	0.37 ^b
Education (n, % some college and beyond)	85 (75.89%)	27 (87.10%)	0.18 ^b
Living situation (n, % living with family or others)	101 (85.59%)	27 (81.82%)	0.59 ^b
Marital status (n, % married)	51 (40.78%)	19 (57.58%)	0.07 ^b
<i>Epilepsy characteristics</i>			
Age of onset of epilepsy (mean ± SD)	23.84 ± 16.42	34.78 ± 12.98	0.0005 ^a
Duration of epilepsy (mean ± SD)	14.80 ± 13.54	7.12 ± 8.24	0.0001 ^a
Number of seizures/spells per month (median, IQR)	3 (1–8)	6 (3–25)	0.007 ^c
Number of AED (median, IQR)	2 (1–3)	1 (1–2)	<0.0001 ^c
Compliance (n, % compliant)	95 (77.87%)	21 (77.78%)	0.87 ^b
<i>Paraclinical characteristics</i>			
AEDs level			
Normal	66 (70.21%)	15 (88.24%)	0.25 ^b
Low	20 (21.28%)	2 (11.76%)	
High	8 (8.51%)	0 (0%)	
EEG posterior dominant rhythm (mean ± SD)	9.40 ± 1.13	9.96 ± 1.17	0.01 ^a
EEG findings			
Slowing	21 (16.94%)	4 (12.12%)	<0.0001 ^b
Interictal spikes	46 (37.10%)	0 (0%)	
Normal	57 (45.97%)	29 (87.88%)	
MRI findings (n, % abnormal)	83 (69.17%)	11 (35.48%)	<0.0006 ^b
<i>Neuropsychological and sleep characteristics</i>			
Montreal cognitive assessment score (MoCA) (median, IQR)	25.32 ± 3.49	25.62 ± 3.40	0.65 ^a
Beck depression inventory (mean ± SD)	13.25 ± 12.09	19 ± 11.55	0.01 ^a
Beck anxiety inventory (mean ± SD)	15.64 ± 13.34	22.96 ± 17.17	0.01 ^a
Epworth sleepiness scale (mean ± SD)	8.71 ± 4.58	7.77 ± 6.41	0.44 ^a
Sleep disordered questionnaire for sleep apnea (SDQ-SA)	24.31 ± 7.63	27.75 ± 7.57	0.03 ^a
b: Caregiver characteristics			
	Caregivers ES N=48	Caregivers PNES N=18	p Value
<i>Demographic characteristics</i>			
Age (mean ± SD)	46.18 ± 13.20	47.44 ± 9.67	0.71 ^a
Gender (n, % female)	33 (68.75%)	9 (50%)	0.15 ^b
Race (n, % caucasian)	45 (93.75%)	17 (94.44%)	0.91 ^b
Religion (n, % Christian)	36 (75%)	14 (77.78%)	0.81 ^b
<i>Relationship to patient (n, %)</i>			
Spouse/partner	28 (58.34%)	14 (77.77%)	0.13 ^b
Parent/sibling	18 (37.50%)	3 (16.66%)	
Other	2 (4.17%)	1 (5.55%)	
Employment (n, % employed)	34 (70.83%)	13 (72.22%)	0.91 ^b
Education (n, % some college and beyond)	39 (81.25%)	12 (66.67%)	0.20 ^b
Marital status (n, % married)	38 (79.17%)	15 (83.33%)	0.70 ^b
Cohabitation with patient (n, %)	43 (89.58%)	15 (83.33%)	0.48 ^b
Time spent for patient care (hours) per week (mean ± SD)	11.43 ± 21.22	19.78 ± 25.14	0.20 ^a

SD, standard deviation; IQR, inter-quartile range; AEDs, antiepileptic drugs; EMU, epilepsy monitoring unit; EEG, electroencephalogram; TLE, temporal lobe epilepsy; IGE, idiopathic generalized epilepsy; MRI, magnetic resonance imaging; SF36v2, short form 36 health survey.

Higher score is better for MoCA and worse for Beck depression and anxiety inventories as well as for the Epworth sleepiness scale and the SDQ-SA.

^a t-test.

^b Chi-square test.

^c Wilcoxon rank-sum test (Mann–Whitney U test).

Table 2
Comparison of QOL scores.

a: Subscores of ES vs PNES patients			
	Epilepsy patients N=126	PNES patients N=33	p Value
<i>Quality of life characteristics (QOLIE-31)</i>			
Seizure worry	43.36 ± 27.93	42.58 ± 32.58	0.89 ^a
Overall quality of life	57.90 ± 21.62	48.95 ± 19.89	0.03 ^a
Emotional wellbeing	61.03 ± 21.31	53.76 ± 23.21	0.08 ^a
Energy/fatigue	43.02 ± 22.69	40.84 ± 21.34	0.61 ^a
Cognitive functioning	50.54 ± 25.64	41.28 ± 25.94	0.06 ^a
Medication effects	44.35 ± 28.28	44.01 ± 30.67	0.95 ^a
Social functioning	46.87 ± 28.40	32.99 ± 21.48	0.009 ^a
Overall score	51.31 ± 18.29	43.41 ± 16.35	0.02 ^a
b: Subscores of ES vs PNES caregivers			
	Caregivers ES N=48	Caregivers PNES N=18	p Value
<i>Quality of life characteristics (SF36v2)</i>			
Physical component scale (PCS) (mean ± SD)	53.91 ± 8.86	51.70 ± 8.58	0.37 ^a
Mental component scale (MCS) (mean ± SD)	45.51 ± 11.31	41.23 ± 12.88	0.20 ^a
<i>Burden characteristics</i>			
Zarit burden inventory (mean ± SD)	20.02 ± 14.47	23.27 ± 13.53	0.41 ^a

Higher score is better for all subscales of QOLIE-31.

Higher score is better for SF36v2 scales and worse for Zarit burden inventory.

^a *t*-test.

literature, PNES patients scored higher both in the depression (mean BDI score 19 vs 13, $p = 0.01$) and anxiety (mean BAI score 23 vs 16, $p = 0.01$) inventories. Interestingly, a higher score was also seen in the PNES cohort in the sleep apnea component of the SDQ (28 vs 24, $p = 0.03$).

ES and PNES caregivers were comparable in all socio-demographic categories. The majority were around 47 years of age, Caucasians, with some college education, employed, married and cohabitants with the patients. These findings are depicted in Table 1b.

3.2. Comparison of QOL scores of patients with ES and PNES

Consistent with previous literature, the overall QOL score of PNES patients was inferior to that of ES patients (43 vs 53, $p = 0.02$). Certain subscales of the QOLIE-31 inventory such as overall quality of life ($p = 0.03$) and social functioning ($p = 0.009$) also reached statistical significance of similar directionality, while others such as emotional well-being ($p = 0.08$) and cognitive functioning ($p = 0.06$) approximated statistical significance (Table 2a).

3.3. Comparison of QOL scores of caregivers with ES and PNES

As illustrated in Table 2b, the physical component summary score of the SF36v2 QOL questionnaire was approximately 54 for ES caregivers and 52 for PNES caregivers. Their respective mental component summary scores for the two cohorts were 46 and 51,

respectively. These differences did not attain statistical significance. The Zarit burden interview score was on average 20 for ES caregivers and 23 for PNES caregivers; again a non-significant statistical difference.

3.4. QOL determinants in ES and PNES patients

In the adjusted analysis (Table 3a and b), male gender ($\beta = 9.29$, $p = 0.0011$), employed status ($\beta = 5.68$, $p = 0.0371$), smaller AED number ($\beta = -5.6$, $p = 0.0004$), lower anxiety level ($\beta = -0.56$, $p < 0.0001$) and lower sleep apnea complaints ($\beta = -0.58$, $p = 0.0006$) were associated with higher QOL scores for the ES patients (Adjusted R^2 : 0.52). On the other hand, for the PNES population, the only determinant of better QOL was lower depression scores ($\beta = -0.85$, $p = 0.0025$) (Adjusted $R^2 = 0.55$).

3.5. QOL determinants in ES and PNES caregivers

The physical component summary (PCS) score of ES caregiver QOL was mostly determined by the caregiver employment status and the burden associated with patient care, with employed caregivers ($\beta = 5.59$, $p = 0.0376$) with lower burden scores ($\beta = -0.16$, $p = 0.0435$) enjoying a better quality of life (Adjusted $R^2 = 0.25$). The mental component summary (MCS) score of caregiver QOL was better for male caregivers ($\beta = 8.42$, $p = 0.0036$) who cared for less depressed patients ($\beta = -0.32$, $p = 0.0418$) and experienced lower burden scores ($\beta = -0.36$, $p = 0.0006$) (Adjusted $R^2 = 0.43$).

Table 3
QOL determinants for patients^a.

a: QOL determinants for ES patients			
Variable	Beta coefficient	Standard error	p Value
Patient male gender	9.29080	2.76918	0.001
Patient employed	5.68276	2.68688	0.03
Number of AEDs	-5.60662	1.51196	0.0004
Patient Beck anxiety inventory score	-0.56245	0.11754	<0.0001
Patient SDQ-sleep apnea score	-0.58948	0.16705	0.0006
b: QOL determinants for PNES patients ^b			
Variable	Beta coefficient	Standard error	p Value
Patient Beck depression inventory score	-0.85819	0.25680	0.002

^a Higher score is worse for Beck anxiety inventory and SDQ-SA.

^b Higher score is worse for Beck depression inventory.

Table 4
QOL determinants for caregivers.

a: QOL determinants for ES caregivers ^a			
Variable	Beta coefficient	Standard error	p Value
<i>Quality of life-physical component score (PCS)</i>			
Caregiver employed	5.59881	2.60389	0.03
Caregiver Zarit burden interview score	−0.16902	0.08107	0.04
<i>Quality of life-mental component score (MCS)</i>			
Patient Beck depression inventory score	−0.32197	0.15325	0.04
Caregiver male gender	8.42970	2.73260	0.003
Caregiver Zarit burden interview score	−0.36883	0.09852	0.0006
b: QOL determinants for PNES caregivers ^b			
Variable	Pearson correlation coefficient		p Value
<i>Quality of life-physical component score (PCS)</i>			
None	–		–
<i>Quality of life-mental component score (MCS)</i>			
Patient posterior dominant rhythm	0.55		0.03
Caregiver age	0.49		0.04
Caregiver Zarit burden interview score	−0.73		0.0009

^a Higher score is worse for Zarit burden and Beck depression inventories.

^b Higher score is worse for Zarit burden inventory. Multivariate analysis was limited by the modest number of available PNES caregivers.

Multivariate analysis of PNES caregiver QOL predictors was limited by the modest number of PNES caregivers. In the univariate analysis, no statistically significant predictor of PNES caregiver QOL PCS score was identified. On the other hand, the MCS score of PNES caregiver QOL was again dependent on the burden associated with patient care ($r = -0.73$, $p = 0.0009$), the age of the caregiver ($r = 0.49$, $p = 0.04$) and patient posterior dominant rhythm ($r = 0.55$, $p = 0.03$). From those three factors, only the burden associated with patient care ($\beta = -0.60$, $p = 0.01$) sustained in a subsequent multivariate regression model (not shown).

These results are summarized in Table 4a and b.

4. Discussion

This study yields two novel findings and corroborates two previously reported observations. The novel findings are that (i) caregiver QOL scores in PNES are comparable to those in ES and that (ii) they are consistently dependent on caregiver burden. The two attested observations are that (i) that patient QOL in PNES is worse than in ES and that (ii) they are both dependent on psychopathology more than disease characteristics.

4.1. Patient and caregiver characteristics

Our ES and PNES populations were both remarkably similar to previous comparison studies.¹² Replicating previous literature, patients with PNES had later disease onset^{5,28} and a shorter disease duration prior to being diagnosed of approximately 7 years.²⁹ Also, PNES patients were more likely to be female,^{12,30} with higher spell frequency^{5,12} and on fewer AEDs.⁵ They had higher levels of depression and anxiety.^{5,12,31} The higher index of sleep apnea symptomatology is intriguing and may be an outcome of the higher body mass index in PNES patients compared to ES observed in other studies.³² Other investigators have also shown poorer quality of sleep in PNES than ES.³³ Consistent with previous reports,⁵ electroencephalographic and radiological abnormalities were less prevalent in PNES patients compared to the ES cohort, but not negligible. Past investigations also mentioned EEG abnormalities in about 9% of PNES patients³⁴ and MRI abnormalities in approximately 23–27% of patients.¹⁰ No additional differences were seen in demographic variables, AED compliance and levels. Mirroring previous research, no neurocognitive differences were

seen between ES and PNES patients, a finding possibly representing poor effort during assessment.³⁵

4.2. Comparison of QOL scores of patients with ES and PNES

Patient QOL scores have been consistently found to be lower in PNES, irrespective whether seizure-directed (e.g. QOLIE-31¹² or QOLIE-89³⁶) or generic questionnaires (SF36³⁷) were applied. Our absolute values for both populations were also similar to former studies using the same instrument in the inpatient³⁸ and outpatient¹² setting, in the US¹² and the UK,³⁸ advocating for generalizability of our results.

4.3. Comparison of QOL scores of caregivers with ES and PNES

Our caregiver QOL scores are difficult to compare with the existing literature. We could only identify caregiver studies on ES patients. Most have focused on the pediatric population. In the adult population, the majority has been performed in the outpatient setting and outside the US. In particular, similar to our study, a Dutch outpatient study identified a trend of decreased mental component of QOL in caregivers of refractory ES patients.³⁹ In Brazil, Westphal-Guitti et al. compared 50 adolescent and adult patients with juvenile myoclonic epilepsy (JME) and another 50 with temporal lobe epilepsy (TLE) along with their caregivers.²⁶ Mild-moderate caregiver burden, averaging 22 for JME and 30 for TLE in the Zarit scale was identified. For JME patients that burden correlated with poorer emotional, social and physical domains of the caregivers' quality of life measured with SF-36, while for TLE patients the emotional component was primarily affected.²⁶ Another study of 65 patient-caregiver pairs from Hong Kong identified below average scores on the quality of life measure applied and severe levels of depression and anxiety in 14% and 22% of caregivers respectively.⁴⁰ In agreement with the Brazilian²⁶ and the Dutch studies,³⁹ we also recognized heavier impact in the mental component of caregiver QOL.

4.4. QOL determinants in ES and PNES patients

Depression and anxiety are the most common psychiatric comorbidities in ES patients.⁴¹ Similar to our study, they have been more closely associated with poorer quality of life than

demographic and epilepsy variables.^{5,42–45} Beyond psychopathology, we identified poorer QOL in female ES patients. That is in accord with some literature⁴⁶ but at odds with other.⁴⁷ Employed patients had higher scores, an observation made also elsewhere.^{48,49} That comes as no surprise since employment, independence and worries related to driving are major concerns patients with advanced epilepsy in the Western world⁵⁰ and unemployment is one of the major contributors to epilepsy stigma.⁵¹ We also noticed poorer QOL in ES patients on polypharmacy, an association also reported before,⁴⁹ irrespective of the generation of AED used.⁵² Finally, sleep disturbance was also a contributor to worse QOL, a statement made in previous investigations where sleep questionnaires were incorporated.^{46,53,54}

Along similar lines, PNES commonly occur in the setting of various psychiatric comorbidities, among which depression, anxiety and personality disorders are the most prevalent.⁵⁵ In PNES patients depression has been also repeatedly related to poorer QOL, irrespective of frequency of events^{12,56}; a finding reinforced by the current study.

4.5. QOL determinants in ES and PNES caregivers

Determinants of caregiver QOL in ES have been rarely sought in the past. In the current study, we identified caregiver unemployment and higher caregiver burden as the main determinants of the physical component summary of caregiver QOL. Higher caregiver burden determined also poorer mental component summary score, along with patient depression levels and female gender. In partial agreement with our findings, caregiver self-perceived burden of care and coping style were deemed to be more reliable indicators of caregiver QOL,³⁹ while no specific patient or disease characteristic appeared to drive caregiver QOL.³⁹ The gender association was previously noted in a study of 257 caregivers escorting patients to outpatient clinics in Sudan where lower QOL scores were also found for caregivers who were children of the patients and had lower education attainment.⁵⁷ Contrary to our findings, seizure severity and age at onset negatively correlated with psychosocial adjustment of caregivers; on the other hand, perceived support level had a positive impact in their well-being and quality of life.⁴⁰ The variability of potential contributors to caregiver burden and QOL reported in the literature highlights cultural differences, the diverse nature of epilepsy, and the pleomorphic research methodology applied.

It is difficult to consider the clinical implications of the correlates of caregiver QOL in PNES that were found in the current study, given the lack of previous studies on this topic. The strongest correlation we identified was between higher caregiver burden score and worse mental component summary score of caregiver QOL. Family dysfunction is known to impact QOL in ES patients a reciprocal way.⁵⁸ Family dysfunction is prominent both in ES and PNES and plays a predictive role to patient QOL.¹² It is possible that family dysfunction may be related to increased caregiver burden, which would help to account for the association with caregiver QOL that was found in our study. However, such a suggestion is speculative given that lack of an objective measure of family dysfunction.

4.6. Advantages and limitations

There are certain advantages to our study. The focus was on adult patients, where most of the literature is sparse. They could complete the surveys independently, which prevented potential bias inevitably incurred by proxy-reports in the pediatric caregiver literature.⁵⁹ The participants completed their questionnaires prior to their diagnosis was clarified by spell characterization with

video-EEG monitoring. That increased the equipoise among them and facilitated more unbiased answers. The patients recruited were classified reliably to ES vs PNES with inpatient video-EEG monitoring, excluding equivocal cases. We monitored and minimized factors that may have interfered with patient's testing such as seizures or commonly applied procedures in the EMU (e.g., antiepileptic medication withdrawal or sleep deprivation). Cross-reference with medical records provided an additional checkpoint for accuracy. The data collected were thorough and covered most of the parameters reported to be associated with health-related QOL in epilepsy, including para-clinical data such as AED levels, an understudied field previously. Contrary to previous studies investigating family dysfunction¹² that utilized the patient as the informant, we had direct reporting of burden and QOL from the caregiver. Thus, multiple patient- and caregiver-related factors were taken into account when assessing QOL. Moreover, our data were representative of both ES and PNES cohorts of patients.^{5,12} Finally, a comparison group of ES patients and caregivers was available to provide direct comparison.

On the other hand, there are limitations to acknowledge. The self-reporting nature of the study bears a risk of recall bias. Yet, self-report scales are widely-used, cost-effective methods both for diagnostic assessment and for outcome evaluation, albeit admittedly not as exhaustive and objective as standardized cognitive and psychiatric interviews or physiologic sleep recording procedures. The modest sample size of caregiver participants may have underpowered us for the detection of additional associations and jeopardized the stability of a multiple regression analysis model, limiting our related analysis to univariate correlations. Despite the extensive evaluation of several variables, other patient-related parameters (e.g. structured clinical interviews for DSM-IV axis disorders or detailed psychiatric history for PNES patients, such as information on personality disorders) and particularly other caregiver-related aspects (e.g. social support, financial information, medical and psychiatric comorbidities, etc.) that may have been significant determinants of patient and caregiver QOL were not directly addressed. They partially constitute however components of the Zarit burden inventory used. The cross-sectional nature of the study prevented further insight into the evolution of these associations longitudinally as well as inference of causation. We aspire though to gather follow up data on our participants to examine the effect of establishing a diagnosis through long-term video-EEG monitoring on their QOL. Not all patients were accompanied by caregivers and not all caregivers participated in the study, suggesting possibly that those willing to participate may not be fully representative of the caregiver population and thus creating a response bias. Similarly, the study population may limit generalizability, particularly to certain PNES populations not or under-represented in our study (e.g. children,⁶⁰ veterans,⁶¹ male⁶² and elderly⁶³ patients). Our participants were patients and caregivers recruited in the EMU. While this allowed rigorous classification of their seizures and QOL determinants, it may have skewed the results to a more severely afflicted patient-caregiver group generating a selection bias that jeopardizes generalizability of our findings to the community. However, our patient cohort characteristics have been validated from previous inpatient and outpatient studies as mentioned previously. Even if intractability was overrepresented in our study, refractory population is expected to be the target population that would mostly benefit from social interventions.

4.7. Significance and future outlook

The findings of this study may have both clinical and research repercussions. PNES is a heterogeneous disorder^{6,7,64,65} where complex interactions of genetic, environmental and psychosocial

parameters take place.⁷ Hence a comprehensive approach integrating the dynamics, the needs and the impact on the family is required.¹² In clinical practice, physicians should consider incorporating the caregiver into their assessment and treatment plan in an effort to eventually improve the patient's QOL. That is corroborated by the results of a recent meta-analysis of 148 studies examining the association between social relationships and mortality risk showing a 50% increased likelihood of survival for participants with better social support.⁶⁶ It is particularly significant in PNES where families have been occasionally seen to restore the patients' identities as epileptics reinforcing abnormal illness behavior and need for AED, even after an EMU diagnosis of PNES has been established.⁶⁷ Caregiver counseling and education, evaluation and treatment of evolving caregiver psychopathology, and tailored individualized and/or group multidisciplinary interventions to provide physical, emotional, social and financial support to the caregiver may allow the caregiver to proceed with life relatively unencumbered. This may in turn translate to QOL improvement for the patient. Previous studies on caregivers of patients with dementia have corroborated that potential.⁶⁸ Further, advocacy groups should include caregiver feelings and needs into their agenda and expert opinion panel reviews as well as national clinical guidelines should further emphasize caregiver QOL as one of the core quality measures in the evaluation and management of PNES.⁶⁹ In the research realm, the focus of investigation should expand to incorporate the family well-being. Our findings suggest associations that warrant further examination in future studies. Specific QOL measures need to be created and validated for caregivers of PNES patients and incorporated into future medication and intervention related clinical trials, in addition to the so far prevailing focus on freedom of spells.¹⁰ Similarly, caregiver parameters may be incorporated to proposed research avenues such as nonlinear methods application and international databases development in an effort to address the heterogeneity of the PNES population.⁷⁰ There is need for rigorous research in this understudied field and funding agencies should consider this important issue.

5. Conclusion

In addition to corroborating that patient QOL is worse in ES vs PNES patients, we were also able to show that caregiver QOL in PNES is comparable to that in ES. Caregiver burden emerges as a consistent determinant of caregiver QOL both in ES and PNES. These important and unique study findings emphasize the need for further evaluation of the caregiver burden and quality of life in PNES and for their consideration in future intervention trials and research endeavors.

Conflict of interest

None of the authors has any conflict of interest to disclose related to this project.

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Appendix. Questionnaires details

Beck anxiety¹³ and Beck depression¹⁴ inventory: These are 21-item inventories that assess the presence and degree of affective,

cognitive, motivational and psychomotor components. Each item is scored 0–3 and the aggregate score is 0–63. Higher scores depict higher levels of psychopathology (Depression: 1–10: normal, 11–16: mild depression, 17–20: borderline depression, 21–30: moderate depression, 31–40: severe depression, >41: extreme depression; Anxiety: 0–21: very low anxiety, 22–35 moderate anxiety and >36 high anxiety).

Epworth sleeping scale¹⁶: This is a brief questionnaire rating the chances that they would doze off or fall asleep when in eight different situations commonly encountered in daily life. A score of 0–3 is given to each situation and the aggregate score is 0–24. Higher scores are suggestive of higher sleepiness level (a cut-off of >10 is generally interpreted as daytime sleepiness).

Sleep disorder questionnaire-sleep apnea scale (SDQ-SA)¹⁷: A score equal or more than 36 for men and 32 for women is considered to have approximately 80% sensitivity and specificity for polysomnogram-proven sleep apnea [17].

Quality of life in epilepsy 31 (QOLIE-31)²⁰: The 31-item self-administered questionnaire has seven subscales: seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive function, medication effects and social functioning. A score ranging from 1–100 is obtained from each subscale with higher scores indicating better quality of life.

Montreal cognitive assessment (MoCA)²²: This test assesses multiple cognitive functions (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation) and an aggregate score of 0–30 is created. Higher scores are associated with better cognitive state (a cut-off of <26 is considered abnormal).

Zarit caregiver burden inventory²⁴: This is a 22-item inventory derived from the original 29-item inventory. The 22 items evaluate the effect of disease on the caregiver's quality of life, psychological suffering, financial difficulty, shame, guilt and difficulty in social and family relationships. Scores range from 0 to 88 with higher scores indicating higher burden (<20: little or no burden, 21–40: mild to moderate burden, 41–60: moderate to severe burden, 61–88: severe burden).

SF-36 generic questionnaire-version 2 (SF36v2)²⁷: This is a generic QOL instrument that assesses eight health concepts (physical functioning, role limitation caused by physical problems, bodily pain, general health perception, vitality, social functioning, role limitation caused by emotional problems, mental health). Scores standardized to norms and weighted averages are used to create a summary physical component summary (PCS) and a mental component summary (MCS) composed by the first and last four of the aforementioned health concepts respectively. All health dimension scores are standardized to normal by employing a linear transformation of data originally scores on a 0–100 scale. Norm-based scores have a mean of 50 and a standard deviation of 10 in the general US population. Therefore, any score <50 for any health dimension and component scale falls below the general population mean and each point represents 1/10th of a standard deviation.

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