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► To cite this version:

Marion Gagny, Louise Grenevald, Wissam El-Hage, Jan Chrusciel, Stéphane Sanchez, et al.. Explanatory factors of quality of life in psychogenic non-epileptic seizure. *Seizure - European Journal of Epilepsy*, 2021, 84, pp.6-13. 10.1016/j.seizure.2020.10.028 . hal-03492924

HAL Id: hal-03492924

<https://hal.science/hal-03492924>

Submitted on 15 Dec 2022

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Explanatory Factors of Quality of Life in Psychogenic Non-Epileptic Seizure

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Declarations of interest: none

Key Words: PNES, quality of life, prognosis, mental health consultation, psychiatric comorbidity

Number of text pages: 9

Number of words: 3915

Number of references: 45

Number of figures: 1

Number of tables: 3

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ABSTRACT:

Objective: Previous studies showed that patients with Psychogenic Non-Epileptic Seizures (PNES) have poor quality of life (QoL). This study explored the explicative factors of the QoL at the time of diagnosis and monitored changes over the two years of follow-up.

Methods: We evaluated 107 participants with a diagnosis of Psychogenic Non-Epileptic Seizure (PNES), every 6 months for 24 months. Quality of life (QoL) was evaluated using the QOLIE-31 and SF-36 scales (respectively specific and generic scales of QoL). Positive evolution of QoL was defined by the increase in the score of overall QoL using QOLIE-31 sub-scale from baseline to the last interview of the patient. We also collected for each patient data on psychiatric dimensions (childhood abuse, history of traumatic events, post-traumatic stress disorder (PTSD), depression, anxiety, alexithymia, and dissociation), clinical evolution of seizures and the number of mental health consultations.

Results: According to the QOLIE-31 and the SF-36, depression ($p \leq 0.001$), anxiety ($p < 0.001$), alexithymia ($p \leq 0.001$), and dissociation ($p \leq 0.004$) were related to QoL at the time of the diagnosis. According to SF-36 (mental and physical), PTSD was also significantly associated with QoL ($p < 0.05$). The number of seizures or the co-occurrence of epilepsy did not influence QoL. Positive evolution of QoL was linked to the number of consultations for mental health issues ($p = 0.02$).

Significance: Post-traumatic dimensions (PTSD, dissociation), alexithymia and psychiatric comorbidities (depression and anxiety disorders) seem to alter QoL in people with PNES. The current study suggests that mental health care improves QoL of patients with PNES.

HIGHLIGHTS:

- Depression, anxiety, and alexithymia corresponded with worse QoL.
- The number of seizures or the cooccurrence of epilepsy does not influence the initial QoL.
- Persons with a history of trauma (emotional abuse in childhood, PTSD, and dissociation) had lower QoL.
- The number of mental health consultations is linked with an improvement of the QoL over time.
- Therapy is one of the keys to improve QoL of patients with PNES.

1. INTRODUCTION

Psychogenic non-epileptic seizures (PNES) are experiences of paroxysmal episodes with varying combinations of motor, sensory, emotional signs and impairment of consciousness [1]. This semiology looks very close to an epileptic seizure [2]. The PNES diagnosis is confirmed by the absence of an ictal cerebral electrical activity on video-EEG, which is the gold-standard examination [1]. This is a chronic disorder relatively unfamiliar to the medical community [3]. Psychological origin is suspected and PNES are classified into conversive disorders as convulsions in functional neurological symptoms according to the DSM-5 (Diagnostic and Statistical Manual of Mental Health 5th Revision) [4]. In ICD-11 (International Classification of Disease 11th Revision), it is recognised as an acute dissociation disorder with neurological symptoms [6].

Prevalence of PNES is estimated at 33/100,000, and the incidence at 4.9/100,000/year [7]. These seizures are found in one in five patients with a diagnosis of treatment resistant epilepsy [8,9]. Durant et al. found that fewer than 40% of newly diagnosed adults became seizure-free within 5 years after diagnosis [10]. PNES can lead to poor outcome and significant functional handicap [10]. Studies have shown that quality of life (QoL) of patients with PNES is lower than those with epilepsy [11–13]. A previous study showed that interpersonal factors (avoidance coping strategy or unsupportive family environment) and psychological factors (depression, anxiety, and dissociation tendencies) were responsible of a drop of the QoL in patients with PNES [14]. According to Boesten et al., PNES patients with a history of trauma have a lower QoL than others [15]. Identifying prognostic factors of the QoL could be a way to help patients to better live with their issue and perhaps act on these levers to deviate the trajectory of the disease in terms of QoL. Whereas a majority of studies about PNES has been cross-sectional, this study has a longitudinal design over two years of follow-up.

Its purpose was to identify explicative factors of QoL in patients with PNES at the time of diagnosis and to seek factors linked to the positive evolution of the QoL during follow up.

2. METHODS

a) Population

This study used the data collected from the prospective multicentric trial EDUQ-CPNE study from January 2014 to July 2019, in 4 French neurologic departments of university hospitals (Dijon, Nancy, Reims, and Tours). The aim of the study was the evaluation of psychopathological dimensions and quality of life, prospectively every 6 months over 24 months of PNES patients. All participants gave their written informed consent (Agreement of the French Ethics Committee: 2012-A01580-43).

For the present study, the inclusion criteria were subjects over 18 years of age who have experienced at least 3 months of seizures. The diagnosis of PNES has been confirmed by video-EEG. For each participant, the recruitment was performed by a neurologist and a psychiatrist or a neuropsychologist with expertise in epilepsy and PNES. For all subjects, the diagnosis announcement was made according to the standardized and validated protocol by trained practitioners [16].

b) Collection data

The data were collected by a neurologist, a psychiatrist, or a neuropsychologist during systematic interviews at inclusion, and follow-up visits at 6, 12, 18 and 24 months. Standardized evaluation and validated scales were filled out for every interview. Detailed of the scales used is referred in supplemental material untitled “Psychometrics measures of scales used in this study”.

a. Quality of life data:

We evaluated the QoL every 6 months using two validated scales, one generic (SF-36) and one specific (QOLIE-31). We defined initial QoL as the quality of life at the time of diagnosis before initiating psychological care. We used the general score of physical and mental QoL according to the SF-36 which is the most commonly used scale [17]. We used the French version of the quality of life in epilepsy inventory (QOLIE-31) which has been showed to satisfied the established psychometric criteria for validity and reliability [18]. This scale initially design for epileptic population has been adapted to CNEP patients replacing the word “crisis” by “seizures”. Only one of the seven dimensions: the “overall QoL” was take into account in this study.. Scores of the QOLIE-31 are reported as a percentage of the maximum score, with higher scores indicating a better QoL [19].

Future QoL was assessed with the evolution of the score of the overall quality of life measured by the QOLIE-31.. The positive evolution of QoL was defined by the positive difference at the last intended interview and at the inclusion.

b. Sociodemographic data:

We collected the age at inclusion, sex, the number of years of education, active or non-active professional status, marital status, intelligence quotient (IQ) value (IQ was assessed using the WAIS III: Wechsler Adult Intelligence Scale third version) of the patient.

c. Clinical PNES data:

We collected the co-occurrence of epilepsy, the duration of the illness since the beginning of the PNES (years) and the delay of diagnosis (months). We collected the number of seizures that occurred in the 6 months prior to the interview, using a seizure calendar that was delivered to patients at every follow-up interview. Patients and their families were instructed on the way to completed it. The evolution percentage of the number of seizures was defined by the difference between the number of seizures at the last interview and at the inclusion reduced in percentage.

d. Psychopathologic data:

Level of depression was assessed by Montgomery-Åsberg Depression Rating Scale (MADRS), which defined depression for scores greater than or equal to 15 out of 60 [20]. Anxiety level was assessed using Hamilton Anxiety Rating Scale (HAM-A). Scores below 17 out of 56 indicate mild anxiety, between 18 and 24 mild to moderate severity and between 25 and 30 moderate to severe anxiety and greater than 31 severe anxiety [21]. Alexithymia was measured according to the Toronto Alexithymia Scale (TAS) [22]. Below 51, there is no

alexithymia, between 52 to 60, alexithymia is possible, and alexithymia is certain for score above 60. We assessed the dissociation tendency using the Dissociative Experience Scale (DES) [23]. It evaluates the frequency of different experiences of dissociation. When the score is greater than or equal to 25%, the diagnosis of a dissociative disorder is likely.

e. Traumatic data:

Trauma history in childhood was explored through the Childhood Trauma Questionnaire (CTQ), which investigates forms of sexual, physical, and emotional abuse or neglect in childhood. Through detailed questioning, we also screened for a traumatic sexual, psychological/emotional, and physical events that have occurred in adulthood. The list of traumatic life events from the Clinician Administered PTSD Scale (CAPS-4) was used to explore the trauma lifetime. Post-traumatic stress disorder (PTSD) was diagnosed using the DSM-IV criteria. The history of traumatic event was categorized by the time of occurrence: childhood trauma, adulthood trauma and lifetime trauma (traumatic event occurring both in childhood and adulthood).

f. Mental health care consultations

After the diagnosis, the patients were referred to a psychological follow-up either to the nearest community mental health consultation centre or to a private psychiatrist/psychologist. They were addressed for routine mental health care. Clinicians had varying levels of experience and knowledge of PNES, reflecting current real-life practice. A leaflet was sent to the mental health caregivers to inform them about PNES and the therapeutic possibilities to ensure a minimum knowledge of the disorder.

The number of mental health consultations for each patient was collected through cross-referenced data from both mental health caregivers and patients. This data was collected by calling the mental health structures designated at inclusion by the patients and who were informed of the study. The aim of the call was to find out whether the patient initiated a care program, the number of attended consultations and if the caregiver received the leaflet. At the same time, patients were also contacted by phone to enquire if they started another program in a different structure.

c) Statistical analysis

Continuous variables were presented with means and standard deviations (SD) or with medians and the interquartile range.

Variables associated with Quality of Life (QOLIE-31 score) at the beginning of follow-up were investigated by univariate linear regression analysis. To eliminate confounding, a multiple linear regression was performed to explain the variations in QOLIE-31 according to selected predictors. The predictors included in the analysis were selected according to their clinical relevance based on expert review.

In the model explaining the baseline QOLIE31 score, regression diagnostics did not show problematic correlations between variables. The highest correlation coefficient was observed between the MADRS score and the HAMA anxiety scale ($r=0.63$). The Variance Inflation Factor (VIF) for these variables were 2.1 and 2.5 respectively, indicating that this correlation

was not likely to cause estimation problems. Residuals of the linear model did not show significant deviations from normality (Shapiro-Wilke test: $p=0.63$).

The characteristics related to a positive evolution of quality of life were investigated using a multivariable logistic regression analysis. Missing values in the multivariable models were treated with multiple imputation, with $m=100$ imputations. P values <0.05 were considered statistically significant. The analysis was performed using R version 3.5.2 (www.R-project.org).

3. RESULTS

a) Population:

Among the 107 patients at inclusion, there was 75.7% of women ($n=81$). The mean age was 33.7 years (range 18-58 years), and 22.4% ($n=24$) had an Intellectual Quotient (IQ) under or equal to 70, which defines them as having an intellectual disability. On average, patients have 11.3 years of education after their first year of elementary school. At the time of the diagnosis, 37.4% ($n=40$) were employed, 83.2% ($n=89$) had experienced at least one traumatic event in their life. At baseline, patients had an average of 130.3 seizures over 6 months (>20 per month).

Not all patients followed the 24 months protocol: 17.8% patients attended only the initial interview, 8.4% stopped after 6 months, 9.3% after 12 months, and 9.3% after 18 months. Finally, 55.1% ($n=59$) patients completed the 24 months follow-up protocol.

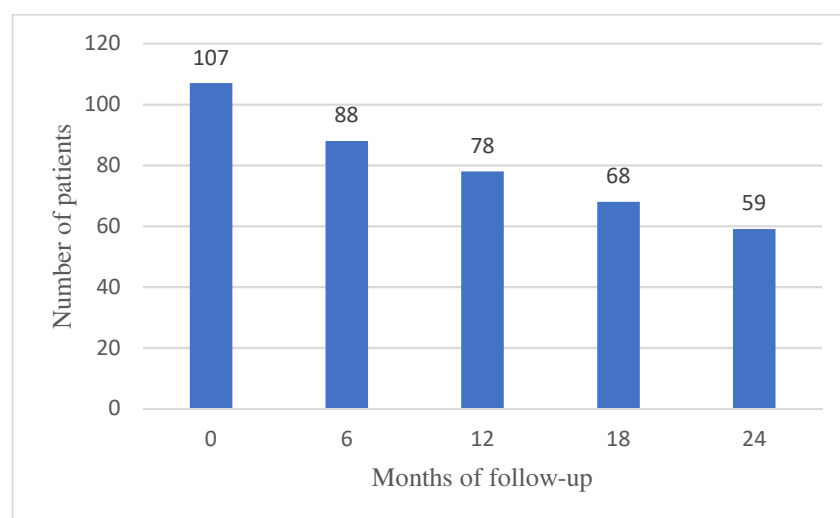


Figure 1. Evolution of the number of patients during follow-up.

b) Explanatory factors of quality of life at the time of diagnosis

- Sociodemographic data:

According to our findings, the quality of life of patients with PNES was not influenced by the sex at the time of diagnosis.

We found a significant correlation between age at diagnosis and poorer QoL using physical SF-36 ($p=0.001$), but not according to QOLIE-31 or mental SF-36. We found a statistical positive association between the QoL and the IQ value according the physical SF-36 ($p=0.038$) (Table 1).

In multivariate analysis, the association between poorer QoL and age at diagnosis ($p=0.023$), and better QoL and IQ value ($p=0.002$) persisted according to physical SF-36. The older the person was at the time of PNES diagnosis, the poorer the QoL. While, the higher the IQ the better the QoL (Table 2).

- Clinical PNES data:

We found no significant association between the number of seizures in the past 6 months and the QoL at the time of diagnosis. Having co-occurred epilepsy did not influence the QoL.

- Psychopathological data:

Regardless the scales of quality of life (“overall QoL” dimension of QOLIE-31 and mental and physical SF-36) used: significant association is found between QoL and depression using MADRS score ($p\leq 0.001$), anxiety according to HAM-A score ($p<0.001$), dissociation using DES score ($p\leq 0.005$) and alexithymia score ($p\leq 0.001$) (Table 1).

In a multivariate analysis of the same variables, only MADRS was still significantly associated with poorer QoL using QOLIE-31 (-0.863 , CI $[-1.382 - -0.345]$, $p=0.001$) and mental SF-36 (-0.639 , CI $[-1.127 - -0.152]$, $p=0.011$). Mental and Physical SF-36 showed significant association with anxiety using HAM-A (respectively -0.783 , CI $[-1.358 - -0.208]$, $p=0.008$ and -1.012 , CI $[-1.56 - -0.463]$, $p<0.001$) (Table 2).

- Traumatic data:

Using SF-36, we found a significant association between diagnosis of PTSD (mental SF-36: $p=0.003$, physical SF-36: $p=0.037$) and poorer QoL. Negative correlation was found between QoL and emotional abuse ($p=0.006$) using the mental SF-36, but not in physical dimension. This means that the more emotional abuse there is, the worse the QoL is. No relation was found using “overall QoL” dimension of QOLIE-31 for traumatic data. There was no statistical association between the QoL and the period of life when the trauma occurred.

	“Overall QoL” dimension of QOLIE-31		Mental SF-36		Physical SF-36	
Variable	β (CI 95%)	p value	β (CI 95%)	p value	β (CI 95%)	p value
<u>Sociodemographic</u>						

Age at inclusion	-0.096 (-0.428 - 0.236)	0.566	-0.287 (-0.66 - 0.085)	0.129	-0.572 (-0.888 - -0.256)	0.001
Sex	3.107 (-6.377 - 12.591)	0.517	0.762 (-10.002 - 11.525)	0.889	-4.936 (-14.452 - 4.579)	0.306
IQ (WAIS-IV)	0.061 (-0.195 - 0.318)	0.637	-0.029 (-0.345 - 0.287)	0.854	0.285 (0.016 - 0.553)	0.038
<u>Clinical</u>						
Number of seizures among 6 months	0.005 (-0.006 - 0.016)	0.344	0.006 (-0.006 - 0.018)	0.321	0.002 (-0.009 - 0.013)	0.763
Associated epilepsy	4.244 (-4.286 - 12.773)	0.326	-0.929 (-10.633 - 8.776)	0.85	2.186 (-6.427 - 10.8)	0.616
<u>Psychopathological</u>						
MADRS	-1 (-1.356 - -0.644)	<0.001	-1.413 (-1.781 - -1.044)	<0.001	-0.692 (-1.077 - -0.307)	0.001
HAM-A	-0.755 (-1.157 - -0.353)	<0.001	-1.514 (-1.9 - -1.129)	<0.001	-1.055 (-1.434 - -0.676)	<0.001
DES	-0.423 (-0.708 - -0.137)	0.004	-0.776 (-1.077 - -0.474)	<0.001	-0.447 (-0.733 - -0.161)	0.002
TAS	-0.627 (-0.969 - -0.285)	<0.001	-0.977 (-1.342 - -0.612)	<0.001	-0.598 (-0.944 - -0.251)	0.001
<u>Traumatic</u>						
PTSD	-5.915 (-14.264 - 2.434)	0.163	-13.838 (-22.86 - -4.815)	0.003	-8.774 (-17.019 - -0.528)	0.037
Childhood trauma	-2.177 (-15.803 - 11.448)	0.752	-6.752 (-22.173 - 8.669)	0.387	2.597 (-11.17 - 16.365)	0.709
Adulthood trauma	-11.95 (-28.511 - 4.611)	0.155	-11.082 (-29.825 - 7.66)	0.244	-11.67 (-28.403 - 5.064)	0.17
Lifetime trauma	-4.489 (-16.69 - 7.713)	0.467	-8.945 (-22.754 - 4.864)	0.202	-2.752 (-15.081 - 9.577)	0.659
Emotional abuse (CTQ)	-0.436 (-1.106 - 0.233)	0.199	-1.071 (-1.825 - -0.317)	0.006	-0.003 (-0.698 - 0.691)	0.993
Sexual abuse (childhood)	-0.1 (-8.995 - 8.795)	0.982	-5.017 (-15.058 - 5.025)	0.324	-2.885 (-11.829 - 6.06)	0.524
Sexual abuse (adulthood)	10.674 (-7.555 - 28.902)	0.248	-2.712 (-23.291 - 17.867)	0.794	11.989 (-6.342 - 30.32)	0.197
Sexual abuse (lifetime)	-1.588 (-18.62 - 15.444)	0.854	-10.042 (-29.27 - 9.186)	0.303	-8.361 (-25.488 - 8.767)	0.335

IQ: Intellectual quotient by WAIS: Wechsler Adult Intelligence Scale; QOLI-31: Quality of Life in Epilepsy Inventory ; SF-36: The Short Form (36) Health Survey; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; DES: Dissociative Experiences Scale; TAS: Toronto Alexithymia Scale ; CTQ : Childhood Trauma Questionnaire ; PTSD: Post-traumatic stress disorder according DSM-IV.

Table 1. Associated factors of quality of life at inclusion (univariate analysis).

	“Overall QoL” dimension of QOLIE-31		Mental SF-36		Physical SF-36	
Variable	β (XI 95%)	p value	β (XI 95%)	p value	β (XI 95%)	p value
<u>Sociodemographic</u>						
Age at inclusion	-0.079 (-0.491 - 0.334)	0.706	-0.031 (-0.419 - 0.357)	0.876	-0.429 (-0.797 - -0.06)	0.023
Sex	9.11 (-2.085 - 20.306)	0.109	0.006 (-10.543 - 10.556)	0.999	5.068 (-4.87 - 15.005)	0.313
IQ (WAIS-IV)	0.068 (-0.285 - 0.421)	0.700	-0.14 (-0.463 - 0.184)	0.392	0.475 (0.177 - 0.773)	0.002
<u>Clinical</u>						
Number of seizures among 6 months	0.003 (-0.008 - 0.014)	0.635	0.002 (-0.008 - 0.012)	0.665	-0.007 (-0.016 - 0.003)	0.169
Associated epilepsy	3.18 (-5.579 - 11.94)	0.472	-3.843 (-12.075 - 4.389)	0.356	4.09 (-3.607 - 11.786)	0.294
<u>Psychopathological</u>						
MADRS	-0.863 (-1.382 - -0.345)	0.001	-0.639 (-1.127 - -0.152)	0.011	-0.029 (-0.497 - 0.44)	0.903
HAM-A	-0.056 (-0.669 - 0.556)	0.855	-0.783 (-1.358 - -0.208)	0.008	-1.012 (-1.56 - -0.463)	<0.001
DES	-0.151 (-0.484 - 0.183)	0.372	-0.31 (-0.623 - 0.004)	0.053	-0.249 (-0.547 - 0.05)	0.101
TAS	-0.272 (-0.745 - 0.202)	0.257	-0.34 (-0.782 - 0.102)	0.130	-0.01 (-0.431 - 0.412)	0.964
<u>Traumatic</u>						
PTSD	3.967 (-5.662 - 13.596)	0.415	-1.564 (-10.641 - 7.513)	0.733	4.269 (-4.39 - 12.928)	0.330
Childhood trauma	2.907 (-12.615 - 18.43)	0.711	10.933 (-3.639 - 25.505)	0.139	7.255 (-6.852 - 21.363)	0.309
Adulthood trauma	-11.451 (-27.912 - 5.011)	0.170	-3.864 (-19.444 - 11.715)	0.623	-9.996 (-25.007 - 5.016)	0.189
Lifetime trauma	-0.527 (-14.853 - 13.799)	0.942	8.604 (-4.871 - 22.079)	0.208	2.261 (-10.716 - 15.238)	0.730
Emotional abuse (CTQ)	0.307 (-0.526 - 1.139)	0.466	-0.306 (-1.07 - 0.459)	0.429	0.685 (-0.039 - 1.409)	0.063
Sexual abuse (childhood)	-1.285 (-11.588 - 9.019)	0.805	-2.012 (-11.621 - 7.598)	0.678	-7.662 (-16.762 - 1.438)	0.098
Sexual abuse (adulthood)	7.089 (-11.005 - 25.184)	0.438	-7.384 (-24.449 - 9.68)	0.392	8.569 (-7.818 - 24.957)	0.301
Sexual abuse	1.871	0.838	-2.269	0.790	-8.342	0.311

(lifetime)	(-16.268 - 20.01)	(-19.15 - 14.613)	(-24.626 - 7.942)
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IQ: Intellectual quotient by WAIS: Wechsler Adult Intelligence Scale; QOLI-31: Quality of Life in Epilepsy Inventory ; SF-36: The Short Form (36) Health Survey; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; DES: Dissociative Experiences Scale; TAS: Toronto Alexithymia Scale ; CTQ : Childhood Trauma Questionnaire ; PTSD: Post-traumatic stress disorder according DSM-IV.

Table 2. Associated factors of quality of life at inclusion (multivariate analysis, multiple imputation, m=100).

c) Factors influencing positively the evolution of the QoL according to QOLIE-31

A total of 88 patients among the 107 included patients attended at least two follow-up interviews. A majority (n=53, 60%) improved their QoL according to the score “overall quality of life” of QOLIE-31. The mean of the positive QoL evolution was 27.7 and the median 26.2 (SD=18.2; Q1=12.5; Q4=82.5) (Table 3).

- Sociodemographic data:

The sex, the family and professional status did not show any significant association with the positive evolution of the QoL during the two years follow-up.

- Clinical PNES data:

We found no statistical association of the evolution of the QoL with the number of seizures at the beginning of the follow-up, the duration of the disease or the delay of diagnosis.

- Psychopathological data:

We found no statistical influence of the depression using MADRS, anxiety using HAM-A, alexithymia using TAS and dissociation using DES on the evolution of the QoL.

- Traumatic data:

According to our findings, the evolution of the QoL was not significantly associated with PTSD, neither with history of emotional nor sexual abuse in childhood.

- Mental health follow-up

We found a significant association between the number of mental health consultations and the positive evolution of QoL (p=0,02). The more mental health consultations the subject received, the greater the QoL appeared with a multivariate Odds Ratio at 1.041 (CI 95%, 1.006 - 1.076) per additional consultation.

Variable	Odds Ratio (OR) (CI 95%)	p value
<u>Sociodemographic</u>		
Sex	0.552 (0.191 – 1.556)	0.26
Family status	0.421 (0.146 - 1.209)	0.11
Professional status	2.207 (0.725 - 6.726)	0.16
<u>Clinical</u>		
Number of seizures among 6 months at inclusion	1.001 (0.999 – 1.005)	0.37
Duration of disease (years)	1.008 (0.925 - 1.097)	0.86
Diagnosis delay (month)	0.999 (0.991 - 1.007)	0.81
Number of psychological counselling during follow-up	1.041 (1.006 - 1.076)	0.02
<u>Psychopathological</u>		
MADRS	1.034 (0.973 – 1.103)	0.29
HAM-A	0.980 (0.919 – 1.044)	0.53
DES	1.009 (0.972 – 1.051)	0.65
TAS	1.001 (0.950 – 1.054)	0.95
<u>Traumatic</u>		
PTSD	0.714 (0.264 – 1.891)	0.5
Emotional abuse (CTQ)	1.181 (0.431 - 3.235)	0.74
Sexual abuse (CTQ)	1.261 (0.436 - 3.644)	0.66

QOLI-31: Quality of Life in Epilepsy Inventory; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; DES: Dissociative Experiences Scale; TAS: Toronto Alexithymia Scale ; CTQ : Childhood Trauma Questionnaire ; PTSD: Post-traumatic stress disorder according to DSM-IV.

Table 3. Factors influencing positively QoL (overall QoL using QOLIE-31) (multivariate analysis).

4. DISCUSSION

Explanatory factors of quality of life at the time of diagnosis:

Our study confirms that psychological dimensions, such as depression, anxiety, alexithymia, and traumatic dimension such as dissociation and PTSD, explain at least partially the low QoL at the time of the diagnosis on patients with PNES compared to PNES patients without those issues. We did not find a link with the frequency of seizures.

These results are consistent with previously published studies. Healthy population is also sensitive to the impact of psychological comorbidities on QoL [24]. In nonspecific population referring to primary care offices, the impact of psychological comorbidities on QoL is also found [25,26]. The study of Brenes recruited 919 incoming patients from 2 university-affiliated primary care offices [25]. It showed that depression and anxiety symptoms significantly impair work functioning, social functioning, and alter all domains of QoL in its

population. Spitzer et al. had the same conclusion and found that mood disorders affect all domain of QoL (using SF-20, generic scale of QoL) whereas others types of mental disorders such as anxiety affected only selected domains [26]. Diprose et al. found rates of psychiatric comorbidities (particularly depression, anxiety, personality disorder and PTSD) ranging from 53% to 100% in patients with PNES, which is higher than in patients with epilepsy [27]. Even compared with mild-major depression disorder, PNES patients show an over-representation of depression, anxiety, alexithymia, and somatoform dissociation [28]. Due to their high frequency in PNES, it is important to assess the impact of mental health disorder on health and functioning. Rawling et al. reported a greater predictive power of psychological distress on QoL of patients with PNES than seizure frequency or demographics data [29]. In this study, 45 subjects with PNES and 62 patients with epilepsy were recruited from outpatient neurology clinics in a hospital in United Kingdom and from membership-led organizations for individuals who experience seizures. According to the study, patients with PNES who reported lower QoL, had higher scores on measures of depression and anxiety, and considered their condition as more threatening than patients with epilepsy. Jones et al. conducted a systematic review across 14 articles including 538 individuals with PNES [14]. Their results also stated that interpersonal and psychological factors, such as depression, anxiety, and dissociation, were negatively correlated with QoL in PNES. Beyond the direct consequences of PNES, our results recall the responsibility of psychological comorbidities in the alteration of patients functioning. The added consequences of depression and anxiety must be treated as a priority to improve the QoL of the patients with PNES.

Alexithymia is also linked to a lower QoL compared to patients without alexithymia in univariate analysis with each QoL measurement tool in our study. This relationship was also found in previous studies. Wolf et al. showed that alexithymia impacts QoL in both epilepsy and PNES [11]. Alexithymia is the difficulty in analysing, recognizing and verbally describing emotional state [30]. The majority of PNES explanatory models or of somatoform disorders involves the alteration of emotion regulation (28). Alexithymic individuals present a cognitive limitation to understand and regulate their emotions, that can lead them to focus on the body sensations accompanying intense emotions [32]. This misattribution of emotional states as physical phenomena could increase the tendency to exhibit somatic symptoms without an identifiable organic lesion to avoid painful or unendurable emotion [33]. Koelen et al. examined the association between two insecure attachment strategies (deactivation or hyperactivation strategies) and two types of alexithymia in a sample of 128 patients with somatoform disorders [30]. They distinguished two types of alexithymia: cognitive alexithymia (inability to differentiate or verbalize emotions, difficulty to identify distinct emotions) and affective alexithymia which refers to a reduced ability to experience emotional feelings and a diminished fantasy life. They showed that alexithymia affects interpersonal functioning by impairing the capacities to feel empathy or to take the perspective of others and by altering the understanding of social causality. Martino et al. hypothesized that anxiety status may lead to develop alexithymia [28]. Alexithymia seems to be an interesting therapeutic target for patients with PNES. The understanding, acceptance and verbalization of emotional states might reduce the tendency to express emotional distress through somatoform symptoms and probably improve QoL.

Furthermore, dissociation tendencies are related to the drop of QoL at the time of diagnosis according to ours results. We likewise found a significant negative correlation between PTSD diagnosis and QoL according to the mental and physical dimensions of SF-36. These results are consistent with the literature [15]. Dissociation cannot be considered having the same link

with PNES as others psychological comorbidities. The dissociation tendency seems to participate to the mechanism underlying PNES development and perpetuation. In another study, psychological trauma and dissociation have been identified as predominant risks factors for PNES development [8]. Thus, dissociation is a mechanism referring to a loss or altered integration of the continuity of the experience of the self [34]. This theory does not explain the disease development for all patients with PNES. According to Reuber et al., dissociation does not appear as an independent factor for all PNES' patients [35], and some seizures presented by patients with PNES might not be dissociative. According to this study, a subgroup of patients experienced an excessive inhibition of emotion which lead to seizure [36]. Dissociation is one of the defence mechanism that is typically used to alleviate anxiety deriving from traumatic events [37]. Studies showed that most of the patients with PNES have experienced traumatic events. According to Myers et al., patients with PNES report higher rates of traumas than patients suffering of intractable epilepsy [38]. Patients with PNES who experienced traumatic events, especially in childhood, show more dissociative experiences and more psychiatric comorbidities (depression and anxiety) than those without traumatic experiences [39,40]. Selkirk et al. also found that the clinical presentation of PNES among patients who reported sexual abuse was different than those who did not [41]. According to their study, PNES patients reporting sexual abuse were more likely to present "convulsive" seizures, more severe and with emotional triggers, prodromes or flashbacks than patients without sexual abuse experience. Because of its clinical and comorbidity outcomes which are known to have an impact on the QoL, it appears consistent that having a history of trauma lead to a severe drop of QoL. As a matter of fact, PNES patients with a history of trauma have a lower QoL than those without according to Boesten and al. [15]. Surprisingly, in our study, history of trauma (emotional or sexual) event or abuse does not show any significant association with the QoL. This might mean that the type of trauma does not have a determinant influence on QoL whereas the development of PTSD and high dissociation does.. We suggest that identifying high dissociation tendency and the development of constituted PTSD in patients with PNES is paramount. Psychotherapy focused on these conditions could improve QoL and reduce perceived functional impairment. Our results confirm the necessity for clinicians to keep in mind the possible negative impact of history of trauma on QoL of patients with PNES. It is always important to inform the patient that a traumatic history can be a vulnerability factor to PNES and thus offer the patient the possibility to evoke such a traumatic history at the time of follow-up.. But in some case, there is no stressful life events or history of trauma founded [5] and then clinicians need innovative approach to understand the development of PNES for those patients.

Factors influencing positively the evolution of the QoL according to QOLIE-31:

After identifying the factors that explain QoL at the time of diagnosis, we investigated whether these factors could be predictive of positive changes in patient QoL. Patients with PNES may present diagnostic acceptance difficulties and the idea of psychological care is often not easy for patients at first glance. A study related to this protocol showed that 64.9% did not follow the initial follow-up recommendations [42]. The two main reasons for stopping follow-up were the lack of interest and the sense of well-being according to this study [42]. In our study, only 55.1% of the patients completed the 24 months follow-up protocol.

In our study, we determined the evolution of the QoL by the difference between the overall QoL score of the QOLIE-31 at the last interview intended by the patient and at the beginning

of the follow-up. We did not consider the fact that patients partially or totally attended the interviews. The only variable that is significantly associated with positive evolution of QoL is the number of mental health consultations during follow-up. According to the literature, cognitive-behavioural therapy (CBT) is the most successful in PNES treatment. Most authors have used seizure frequency as the variable to define the improvement in the disease. LaFrance et al. reported a 50% reduction in seizure frequency as well as seizure cessation in more than 50% of patients with PNES who used CBT [43]. They also found significant improvement on QoL, family functioning and psychological functioning in a short-term treatment. Another study of Myers et al. confirmed that prolonged exposure therapy, which is a cognitive-behavioural approach, is effective in reducing the seizure frequency and improve psychological symptoms for patients with a dual diagnosis of PNES and PTSD [44]. As we have seen, previous studies in their secondary outcomes have shown a positive impact of psychotherapy on the QoL in PNES. Our findings show that even with non-specific psychotherapy, QoL improves. We suggest that the mental health follow-up might be a path to improve the subjective impression of illness and to reduce the alteration of the QoL for patients with high rates of psychological comorbidities or history of traumatic events. Studies showed that non-specific psychotherapy may lead to reduce psychiatric symptoms, accelerate natural healing processes, and improve life functioning in multiple psychiatric disorders such as depression, anxiety or PTSD [45,46]. As there is no single mechanism that leads to a disorder, a treatment might work for multiple reasons and patients in the same treatment could respond for different reasons [47]. In our study, patients with the lower QoL are those with higher scores on scales related to different psychological comorbidities. We did not analyse the evolution of the scores of the different comorbidities during the follow-up. Further studies should explore if the link between the improvement of the QoL and the number of mental health consultations might be due to rather the effectiveness of psychotherapy on comorbidities or on PNES. In our study 18 of the 85 patients have an IQ <70 (21,17%). Learning disabilities constitute vulnerability and predisposing factors for PNES as shown by Duncan et al. [50,51]. Indeed they showed that in their population of PNES patients, 8.6% had learning disabilities. Patients with those issues were more likely men, with associated epilepsy, their seizures often triggered by social circumstances [51]. In most studies, PNES patients with low IQ (<70) are often excluded. We chose not to exclude them from our sample because they represent for us a real subgroup of PNES patients.

In our study, according to Physical SF-36, older age at diagnosis is associated with lower QoL and higher IQ is correlated with better QoL. In the same way, Reuber et al. suggested that patients with greater educational attainments and younger onset of PNES have better outcomes regarding seizure frequency and individual dependence [48]. Our results suggest that age at diagnosis and IQ influence clinical factors of seizures and functional dimension. We did not find any significant influence of demographic data such as family, or professional status, neither of the psychopathological comorbidities (depression, anxiety, traumatic history, and alexithymia), the duration of the disease or the diagnosis delay on the evolution of the QoL. Another study found relevant that the delay of diagnosis is related with a drop of QoL [8]. This might mean that the delay of diagnosis has an impact on the QoL at the time of the diagnosis because of medical and therapeutic wandering during an average delay of 5 to 7 years before the PNES has been identified [8] but it does not seem to have any prognostic value for the evolution of QoL over time.

A strength of our study is the use of two different scales to evaluate QoL whereas many studies only focus on one. Most of them used QOLIE-31, as others only used SF-36 [28]. SF-

36 is a generic tool suitable for general population [49] whereas QOLIE-31 is a QoL measurement tool specific to epilepsy and has been adapted to population suffering from PNES [19]. Because of these specificities, it seems interesting to explore both scales. In our study 18 of the 85 patients have an IQ <70 (21,17%). Learning disabilities constitute vulnerability and predisposing factors for PNES as shown by Duncan et al. [50,51]. Indeed they showed that in their population of PNES patients, 8.6% had learning disabilities. Patients with those issues were more likely men, with associated epilepsy, their seizures often triggered by social circumstances [51]. In most studies, PNES patients with low IQ (<70) are often excluded. We chose not to exclude them from our sample because they represent for us a real subgroup of PNES patients. One limitation of our report lies in the small sample size. Additionally, we used the number of mental health consultations without knowing the orientation of the proposed therapy (medication, CBT, or other psychological therapy). Thus, there is a great disparity among caregivers, some specifically trained in psychotrauma or dissociative disorders, others not. This allows us to be representative of the current mental health care available in the territory. Another limitation lies on the fact that outcomes such as the number of seizures and the history of traumatic events were self-reported. We try to limit this issue by providing a seizure calendar to each patient and by working with professionals sensible to the search of traumatic events. The QoL is a complex data for exploitation during studies because it is multidimensional. The choice to include the positive evolution of the score of the QoL on the only “overall quality of life” dimension of QOLIE-31 is arbitrary in the absence of formalized recommendations in the literature, in the context of this exploratory study. The sensitivity of the QOL and its multiple dimensions might have been the most limiting factor in highlighting a possible association between history of trauma and QoL. Moreover, we do not study the evolution of SF36 score during the follow-up, and it would have been interesting to take into account the evolution of these two scores, are they moving in the same direction or in opposite directions? Moreover, the fact that all the patients were not followed over the same duration is also a source of bias but was intended to get closer to the follow-up in real life.

5. CONCLUSION

This study finds that QoL at the time of diagnosis is mainly associated with psychiatric comorbidities (depression, anxiety, alexithymia, and dissociation). The detection of dissociation and past traumatic events is relevant to predict the risk of lower functioning. A mental health follow-up appears to be the principal factor to improve the QoL over time. This study suggests, as in others studies [40], that there is an important heterogeneity of profiles among PNES patients. Research should focus on identifying subgroups of patients and studying their specific explanatory factors of QoL, their specificities and needs to adapt treatment accordingly. The different therapies used have to be studied to determine their mechanisms, their effectiveness and to adapt the care to the specificities of patients with PNES.

ACKNOWLEDGEMENTS

Protocol PHRC EDUQ _CPNE

ETHICAL PUBLICATION STATEMENT

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.

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