

Quality of Life and Its Determinants in Adult Drug Refractory Epilepsy Patients Who Were Not Candidates for Epilepsy Surgery: A Correlational Study

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Background and Purpose: This study was performed to elucidate quality of life (QOL) and its determinants in adult drug refractory epilepsy (DRE) patients who were not candidates for epilepsy surgery.

Methods: A correlational study was performed at the center of excellence, epilepsy between July 2014 to June 2016. All consecutive DRE patients who were not candidates for epilepsy surgery were enrolled. The outcomes were QOL, assessed using the quality of life inventory in epilepsy-31 items (QOLIE-31) inventory and the correlation of QOL with epilepsy-related variables like seizure severity and frequency. We also compared current QOL with QOL during the pre-surgical evaluation to strengthen our study outcome.

Results: A total of 129 adult patients were enrolled over two years. The mean age was 26.5 ± 6.7 years and male : female ratio was 3 : 1. The mean age at epilepsy onset was 9.6 ± 6.6 years and mean duration of epilepsy was 14.9 ± 7.5 years. There was lower seizure frequency than during pre-surgical evaluation in 37.2% of patients, while in 62.8% the seizure frequency remained the same or was higher. Nine (6.98%) patients became seizure free. In comparison to QOL status during the pre-surgical evaluation, there was statistically significant worsening of QOL in all domains ($p < 0.01$). Seizure severity significantly correlated with almost all QOL domains ($p \leq 0.01$), while seizure frequency significantly correlated with only the single domain of overall QOL ($p = 0.03$).

Conclusions: The QOL of DRE patients who were not candidates for epilepsy surgery worsened relative to the QOL during the pre-surgical evaluation period. Seizure severity significantly correlated with QOL, but seizure frequency did not. (2018;8:81-86)

Key words: Quality of life, Drug refractory epilepsy, Epilepsy surgery

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Introduction

Drug refractory epilepsy (DRE) is defined¹ as the "failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drugs schedules (whether as mono-therapies or in combination) to achieve sustained seizure freedom". These patients have the option of epilepsy surgery with seizure freedom achieved in^{2,3} 27-46% of cases of extra-temporal, 44-66% of cases of temporal lobe epilepsy, with subsequent improvement in quality of life (QOL).⁴

After pre-surgical evaluation, some patients were found to be ineligible for epilepsy surgery. Very few studies⁵⁻⁷ have assessed the QOL in this group of non-surgical DRE patients. Epilepsy-related vari-

ables that determine QOL in these patients has not yet been systematically studied. With a lack of knowledge and evidence regarding the future course of epilepsy and associated QOL, it is very difficult to provide an informed prognosis⁸ to these patients during communication of non-surgical decisions. At the same time, further management and investigation is labour intensive.^{9,10}

Therefore, we planned this study with the aim of studying QOL of these non-surgical DRE patients during follow-up to elucidate which epilepsy-related variables correlated with their QOL.

Methods

After approval from the institutional ethics committee, we designed a 2-year correlational study from July 2014 to June 2016 at an apex tertiary care hospital and epilepsy surgery center. During their scheduled outpatient department visits, we enrolled consecutive DRE patients who were not candidates for epilepsy surgery. We included all patients who were aged 18 years or more, had undergone pre-surgical evaluations at our institute more than 2 year back. Patients were excluded if they had significant comorbidity, intellectual decline, or did not provide consent. Those patients who did not undergo surgery due to a lack of consent for invasive pre-surgical evaluation, lack of consent for epilepsy surgery even though cleared for surgery, or unable to afford of epilepsy surgery/complete pre-surgical evaluation were also excluded from the analysis. We recorded data related to socio-demographic details including age, sex, occupation, and marital status. Epilepsy-related variables including age at onset (age when first seizure noticed) and duration of epilepsy in years (defined as current age minus age at onset) were recorded. Seizure frequency per month during the pre-surgical evaluation (when patient was admitted to an epilepsy monitoring unit) was extracted from the epilepsy surgery database. Data related to risk factors of epilepsy including history of perinatal hypoxia, febrile seizure, head trauma, and nervous system infection were also extracted from epilepsy surgery database and reconfirmed during out patient department visits. Current seizure frequency per month was recorded from a seizure diary (if available) using the average number of seizures per month in the last 6 months. In those patients who were not maintaining a diary, approximate seizure frequency per month was calculated from the daily frequency to frequency per week for the last 6 months. For perceived change in seizure frequency, patients were simply asked one question regarding change in current seizure frequency in comparison to frequency during the pre-surgical evaluation. There were two potential responses, decreased frequency or not decreased (i.e., the same or increased frequency). Seizure severity was assessed using the national hospital seizure severity scale (NHS3). Seizure freedom was defined as no clinical seizures in the last year with antiepileptic drug treatment. Data related to the results of various pre-surgical investigations including video electroencephalography in the epilepsy monitoring unit, magnetic resonance imaging of brain, single-photon emission computed tomography, positron emission tomography scan of the brain, magnetoencephalography, and reasons of non-clearance for epilepsy surgery

were extracted from the epilepsy surgery database. After obtaining informed consent, patients were asked to fill out a disease-specific QOL proforma. The quality of life inventory in epilepsy 31-items (QOLIE 31) was used to record current quality of life.

Instruments

The NHS3¹¹ has seven seizure-related factors and reported as a score from one to 27 with a higher score reflective of greater severity. A seizure severity score was recorded for each seizure type. We used a time frame of "the past 6 months" for seizure severity measurements. We used the seizure with the highest seizure severity score for analysis if patient had multiple seizure types. The scale was administered during an interview with the patient and a witness during their OPD visit.

The QOLIE-31¹² is an epilepsy-specific questionnaire to assess QOL of adult patients. The QOLIE-31 contains 31 items and seven quality of life domains including seizure worry, overall quality of life (overall QOL), emotional wellbeing, energy/fatigue, cognition, medication effects, social function, and one total QOL score (overall score). The raw values of the QOLIE-31 are converted to a score ranging 0-100. Higher values reflect better QOL, but there is no cutoff value distinguishing good and poor quality of life. We used the validated version of the QOLIE-31 after obtaining permission from authors. The questionnaire was filled during the scheduled OPD visit in the epilepsy clinic's waiting area. Each patient completed questionnaire two times more than one month apart. The better of the two QOL responses was taken for analysis. We routinely used the QOLIE-31 to record QOL during the pre-surgical evaluation.

The QOLIE 31 scale has no cut-off value distinguishing good and poor QOL. At our center, all patients who underwent pre-surgical evaluation also underwent QOL evaluation during pre-surgical evaluation using the same QOLIE 31 scale. Data related to QOL during the pre-surgical evaluation were stored in the epilepsy database. Therefore, we planned to compare current QOL with QOL during the pre-surgical evaluation of same patients as a historical control to strengthen our study. QOL during the pre-surgical evaluation was extracted from epilepsy database.

Statistical analysis

Statistical analysis was performed using STATA 12.0 (Stata Corp. LP, College Station, TX, USA). The outcomes were current quality of life and the comparison of current QOL with QOL during pre-surgical evaluation. The other outcome was the correlation between epi-

Table 1. Baseline characteristics of adult drug refractory epilepsy patients who were not candidates for epileptic surgery

Baseline variable	Value (n = 129)
Age (years)	26.5 ± 6.7
Gender	
Male	96 (74.4)
Female	33 (25.6)
Occupation	
Student	57 (44.3)
Employed	39 (30.3)
Unemployed	33 (25.4)
Marital status	
Married	21 (16.3)
Unmarried	108 (83.7)
Perinatal hypoxia	15 (11.6)
Febrile seizure	21 (16.3)
Others	15 (11.6)
Localization	
Temporal	54 (41.9)
Extra-temporal	75 (58.1)
Age at onset (years)	9.6 ± 6.6
Duration of epilepsy (years)	14.9 ± 7.5
Duration after pre-surgical evaluation (years)	3.8 ± 1.4
Seizure severity score	9.2 ± 6.5
Seizure frequency per month	12 (2-60)
Change in seizure frequency	
Decreased	48 (37.21)
Not decreased (same or increased)	81 (62.79)
Seizure free patients	9 (6.98)
Number of antiepileptic drugs	4 (3-4)

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).

lepsy-related variables, including seizure severity, seizure frequency, age at onset of epilepsy, duration of epilepsy, and perceived change in seizure frequency with the status of various current QOL domains. For correlational analyses, the non-parametric Spearman correlation test was used for continuous variables, and the non-parametric Wilcoxon rank-sum test and parametric *t*-test were used for categorical variables. *p*-values at level of less than 0.05 were considered significant.

Results

Baseline characteristics

A total of 129 adult patients were enrolled over a 2-year period from 2014 to 2016. Socio-demographic and epilepsy-related baseline characteristics are shown in Table 1. The mean age of subjects was 26.5 ± 6.7 years and the male to female ratio was 3 : 1. The mean duration after pre-surgical evaluation was 3.8 ± 1.4 years. In these patients, only 30.3% were employed and 83.7% were unmarried.

Regarding epileptic risk factors, a history of perinatal hypoxia was present in 11.6%, febrile seizure in 16.3%, and other risk factors including head trauma, nervous system infections, and family history in 11.6%. Mean age at epilepsy onset was 9.6 ± 6.6 years and mean duration of epilepsy was 14.9 ± 7.5 years. Mean NHS3 score was 9.2 ± 6.5 (range, 0-21) and median (interquartile range) seizure frequency was 12 (2-60) per month. Only 14 patients (10.8%) had maintained a proper seizure diary. There was decreased seizure frequency relative to that in the pre-surgical evaluation period in 37.2%, including seizure-free patients, while in 62.8% seizure frequency remained the same or increased. Only nine patients (6.98%) reported seizure freedom. The median number of anti epileptic drugs

Table 2. Quality of life among adult epilepsy patients currently, during pre-surgical evaluation, and in comparison

QOLIE-31 QOL domains	Pre-surgical evaluation QOL status	Current QOL status	Difference between two means	<i>p</i> -value
Seizure worry	57.1 ± 26.3	41.2 ± 20.1	15.9	< 0.01
Overall QOL	50.8 ± 20.6	38.0 ± 9.3	12.8	< 0.01
Emotional wellbeing	55.7 ± 13.2	41.4 ± 12.4	14.3	< 0.01
Energy/fatigue	51.6 ± 13.4	46.9 ± 11.7	4.7	< 0.03
Cognition	51.4 ± 25.4	45.1 ± 16.7	6.3	< 0.02
Medication side effects	57.2 ± 21.0	46.0 ± 14.2	11.2	< 0.01
Social function	53.9 ± 30.0	40.6 ± 19.4	13.3	< 0.01
Overall score	54.1 ± 19.3	42.7 ± 15.7	11.4	< 0.01

QOLIE-31, quality of life inventory in epilepsy-31 items; QOL, quality of life.

(AED) being taken by them was four (3-4) (Table 1).

Reasons for non-clearance for epilepsy surgery

We recruited drug refractory patients who were not candidates for epilepsy surgery after pre-surgical evaluation. Various causes of non-clearance for epilepsy surgery were extracted from the pre-surgical database. These were multifocal epileptic zones in 20.6%, epileptic zone in eloquent cortex in 10.5%, diffuse abnormality in 16.8%, lack of consent for invasive pre-surgical evaluation in 15.5%, lack of consent due to inability to afford treatment in 23.4%, lack of consent for surgery 4.2%, and other causes like discordant imaging and electro-encephalographic locus in 5.0% or normal imaging/no focus in 3.2%.

QOL in DRE patients

QOL in adult epilepsy patients was measured using the QOLIE-31 scale and reported as the mean score of seven QOL domains and overall score (Table 2). In comparison to QOL status during the pre-surgical evaluation, there is a statistically significant ($p < 0.01$) worsening of QOL in all seven domains. The greatest worsening was in the seizure worry domain while the energy/fatigue and cognition domains were affected least. Out of the seven domains, five domains exhibited not only statistically significant worsening but more than ten points of worsening in the mean score.

Determinants of quality of life

Epilepsy-related independent variables including age at onset, duration of epilepsy, seizure severity (NHS3 total score), current seizure frequency, and change in seizure frequency (decreased and not de-

creased) were evaluated for their correlation with individual QOL domains and total QOL score (Table 3). In these patients, age at onset was most strongly correlated with social function ($p = 0.02$), while duration of epilepsy significantly correlated with the cognition domain, social domain, and overall score ($p = 0.01$). Seizure severity significantly correlated with all QOL domains ($p \leq 0.01$) except medication effects ($p = 0.34$). Seizure frequency significantly correlated with only the overall QOL ($p = 0.03$), while perceived change in seizure frequency significantly correlated with overall QOL, social function ($p \leq 0.01$), emotional wellbeing ($p = 0.02$), and overall score ($p = 0.03$).

Discussion

This study was performed with the aim of evaluating the QOL of DRE patients who were not candidates for epilepsy surgery. The results suggest that the QOL of these patients worsened with time in all domains, relative to QOL during pre-surgical evaluation. This is the main strength of this study where we not only measured the current QOL but also compared it with QOL during pre-surgical evaluation.

Like other studies,⁵⁻⁷ the overall results suggest that this drug refractory, non-operated group of epilepsy patients had poor QOL despite continued pharmacological treatment. The results suggest that these patients are not only more worried about their seizures but also worried about the long-term side effects of the drugs on their body. They felt that their social function is restricted because of their uncontrolled epilepsy. All these adverse circumstances made them emotionally weaker. These results are in contrast to those of previous studies in which patients' QOL was poor but they were not worried

Table 3. Correlation between QOL domains and epilepsy-related variables

QOLIE-31 domain	Age at onset of epilepsy	Duration of epilepsy	Seizure severity	Seizure frequency	Perceived change in seizure frequency
Seizure worry	0.15 (0.35)	-0.28 (0.06)	-0.65* (< 0.01)	-0.10 (0.54)	0.21
Overall QOL	0.31* (0.04)	-0.24 (0.12)	-0.67* (< 0.01)	-0.33* (0.03)	< 0.01
Emotional wellbeing	0.02 (0.92)	-0.25 (0.10)	-0.40* (0.01)	-0.15 (0.34)	0.02
Energy/fatigue	0.32* (0.04)	-0.16 (0.32)	-0.41* (0.01)	-0.24 (0.13)	0.20
Cognition	0.27 (0.09)	-0.37* (0.01)	-0.55* (< 0.01)	-0.15 (0.34)	0.13
Medication side effects	-0.09 (0.58)	-0.30* (0.04)	-0.15 (0.34)	0.11 (0.47)	0.89
Social function	0.36* (0.02)	-0.39* (0.01)	-0.68* (< 0.01)	-0.18 (0.26)	< 0.01
Overall score	0.33* (0.03)	-0.42* (0.01)	-0.69* (< 0.01)	-0.24 (0.13)	0.03

QOL, quality of life; QOLIE-31, quality of life inventory in epilepsy- 31 items.

*Spearman correlation coefficient, rho (p -value), perceived change in frequency variable, only p -value of t -test result.

about seizures or the adverse effects of medications. A possible explanation is that no prior studies made a comparison with QOL during the pre-surgical evaluation. Second, in this study patients felt themselves to be more energetic and cognitively less affected compared to the level during the pre-surgical evaluation.

We also studied various epilepsy-related variables that determine QOL in these patients. In adult DRE patients, seizure severity was the most important modifiable factor to improve QOL, as with increasing seizure severity, patients' worry about their epilepsy also increased. Patients with severe seizures were more likely to have poor cognition and lack energy. They felt emotionally disturbed and more socially restricted. Therefore, we speculate that to improve the QOL of these patients, seizure severity should be controlled. An early age of onset of epilepsy correlated with poor social function and poor overall QOL, while a long duration of epilepsy correlated with poor social function, worsening of cognition, and more medication-related adverse effects. Only a single QOL domain correlated with absolute seizure frequency, overall QOL, but two domains including overall QOL and social function, along with overall score correlated with perceived change in seizure frequency. Like previous studies,^{6,7,13,14} in our study more QOL domains correlated with perceived change in frequency rather than absolute seizure frequency. Therefore, we speculate that QOL has determinants other than epilepsy-related variables, which we did not measure in this study. This contradiction of absolute frequency and perceived change in frequency may be due to several possible reasons like a high frequency of seizures in patients who are not used to maintaining a seizure diary; therefore they estimated their seizure frequency. Another but more important explanation is that they perceive a decrease or increase in seizure frequency according to their emotional well-being, social function, and overall QOL and not merely on the basis of the absolute number of seizures. Even though about 37% of patients perceived a decrease in seizure frequency, including 7% of patients reporting being seizure free, the mean scores of all QOL domains worsened and were poorly determined by absolute seizure frequency while they moderately correlated with the perceived change in seizure frequency.

Therefore, the QOL of DRE patients was not only worsened, but at the same time was very difficult to determine based on only epilepsy-related variables except seizure severity. It is not over-speculative to state that there is not only an urgent need for new AEDs as well as interventions for these patients, but also outcome assessments in trials should be holistic and account for improvements in QOL and not mere reduction in seizure frequency. Therapeutic inter-

ventions should target the determinants of QOL including those that are directly epilepsy related, as well as indirectly related, such as psychological factors.

Meanwhile these patients require social, occupational, and psychological support as well as legal help regarding disability benefits from health policy makers and recommendations from the national epilepsy governing body.

Our study has limitations. The study subjects were enrolled at a tertiary care hospital and therefore may have more severe disease; thus, the determinants may vary from a typical community population of DRE patients. This was a correlational study and involved the assessment of the association of the analyzed variables with a single point in time across the cohort of patients. A longitudinal study might allow for examination of the variables that were associated with change in QOL over time and/or as the effects of a specific intervention. We did not evaluate depression or other psychiatric co-morbidities as a co-determinant of QOL domains with epilepsy-related variables. Regardless, this study still has the power to highlight the current knowledge gap and suggest directions for future research.

The QOL of DRE patients who were not candidates of epilepsy surgery worsened during follow-up relative to QOL during pre-surgical evaluation. Seizure severity has significant correlation with most QOL factors but seizure frequency did not.

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