

Original Article

Gender differences in quality of life and psychiatric comorbidities among persons with juvenile myoclonic epilepsy: A single-center cross-sectional study

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ABSTRACT

Objectives: Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized/genetic epilepsy syndrome. Gender differences are known in clinical presentation, with a well-identified female predilection. We aimed to study gender-based differences in quality of life (QoL) and psychiatric comorbidities among persons with JME.

Materials and Methods: This was a cross-sectional study conducted at a teaching hospital in Delhi, India. Persons above 11 years of age with JME diagnosed according to the International League Against Epilepsy criteria established in 2001 were enrolled. QoL assessment was made using Quality of Life in Epilepsy Inventory-Adolescents-48 (QOLIE-AD-48) and Patient-Weighted Quality of Life in Epilepsy Inventory 31 (QOLIE-31-P) for adolescent and adult patients, respectively. For the assessment of psychiatric comorbidities, participants were administered the Mini-International Neuropsychiatric Interview (M.I.N.I.). Participants who tested positive for psychiatric comorbidities on M.I.N.I. subsequently underwent the Diagnostic and Statistical Manual-5 categorization.

Results: We enrolled 50 patients with JME. Eighteen (36%) were male and 32 (64%) were female patients. The median age of males at study enrollment was 23.5 (range 15–38) years. The median age of females was 22 (16–48) years. The median QOLIE-31-P score among males was 68.31 (37.13–91.82) and for females was 66.9 (31.7–99.1). The median overall QoL score for males was 65 (25–87.5), which qualified as “fair” QoL. For females, the median overall QoL score was 62.5 (10–87.5) which also qualified as “fair” QoL. No significant difference was noted between genders in QoL ($P = 0.723$). Among males, 55.5% had psychiatric comorbidity. Of these, two had mild depression and eight had anxiety. Among female patients, 34.4% had comorbid psychiatric issues; 6 had anxiety and 5 had depression. No significant difference was noted between genders ($P = 0.9136$).

Conclusion: Persons with JME do not have gender-stratified differences in terms of psychiatric comorbidities and QoL despite differences in exposure to antiseizure medications and other gender-related factors. All persons with JME should be screened for psychiatric comorbidities, specifically anxiety, and depression.

Keywords: Depression, Anxiety, QOLIE-31-P, Gender

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized/genetic epilepsy syndrome. Gender differences are known in clinical presentation, with a well-identified female predilection.^[1] Gender differences are also known to impact seizure-related prognosis. Female patients with JME with absence seizures and stress-related precipitants tend to have the highest prevalence of drug refractoriness.^[2] The female gender may also be associated with several negative disease-based outcomes.^[3] Women with JME have a higher prevalence of absence seizures,^[4] later response to antiseizure medications (ASMs), and worse

seizure control. Electroencephalographic (EEG) changes have also been reported, with women having more prolonged EEG epileptiform discharge runs and eye closure sensitivity.^[3]

Gender-specific psychosocial outcomes are known for epilepsy in general. Women with epilepsy display more anxiety, lower employment, and greater divorce rates compared to men with epilepsy.^[5] Persons with JME may suffer from poorer social cognition, disadvantageous social traits including cognitive impulsivity,^[6] and unfavorable social outcomes.^[7] Poorer quality of life (QoL) may be associated with the presence of psychiatric comorbidities.^[8] Comorbid psychiatric disorders occur in 37–51% of persons with JME, and are known to

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negatively impact QoL.^[9-13] Moreover, nearly 35% of JME may be refractory, with psychiatric comorbidities being one of the variables that may contribute to refractoriness.^[14] Most studies on QoL and psychiatric comorbidities in JME do not address gender differences. This is an important issue for several reasons: Women in the reproductive age group with JME are generally not prescribed valproate,^[5,15] which is the drug of choice and is associated with better disease-based outcomes. Instead, levetiracetam and benzodiazepines are preferred for women. Levetiracetam itself may contribute to psychiatric and behavioral issues in 10–15% of adult patients, occasionally leading to discontinuation of the drug.^[16]

Recognizing this gap in the literature, we aimed to study gender-based differences in QoL and psychiatric comorbidities among persons with JME.

MATERIALS AND METHODS

Study setting

This was a cross-sectional study conducted at a government-sponsored teaching hospital in Delhi, India. The study was conducted over 18 months (June 2019–December 2020). Patients were recruited from the neurology outpatient and epilepsy clinics. The study was approved by the institutional ethics committee. Written informed consent was obtained from the participants or their legal representatives, in case of minors.

Study participants

Persons above 11 years of age, with JME, were diagnosed according to the International League Against Epilepsy criteria established in 2001. As per this criteria, patients with JME should have: Age at onset between 12 and 18 years, normal neurological examination and intellectual abilities, myoclonic jerk as the predominant seizure type, often with generalized tonic-clonic seizures (GTCS) on awakening, and less often, with absence seizures, seizures often precipitated by sleep deprivation, alcohol, fatigue, and stress, well controlled with valproate/other ASMs, interictal EEG showing irregular, rapid, 4–6 Hz spike-wave and polyspike-wave discharges occurring in bursts commonly after awakening, without close correlation between EEG spikes and jerks.

Patients were excluded if they had an intelligence quotient score <70, other chronic medical conditions such as chronic liver or renal disease, recent (<6 weeks) traumatic brain injury, patients with stroke/neurological deficits, patients with a history of meningoencephalitis, or with history of alcohol or drug abuse.

Assessment

Patients enrolled in the study underwent comprehensive history-taking and detailed examination. Details were

obtained pertaining to the duration of epilepsy, age at seizure onset, semiology, seizure type and frequency, family history, and details of ASMs. As per our departmental protocol, all patients undergo 40 min of awake and sleep EEG on a 24-channel EEG machine and magnetic resonance imaging brain to rule out any structural lesion. QoL assessment was made using Quality of Life in Epilepsy Inventory-Adolescents-48 (QOLIE-AD-48) and Patient-Weighted Quality of Life in Epilepsy Inventory 31 (QOLIE-31-P) for adolescent and adult patients, respectively. QOLIE-AD-48 is administered in adolescents ≤17 years of age.^[17] It contains 48 items in eight subscales: epilepsy impact (12 items), memory, concentration (10 items), attitude toward epilepsy (four items), physical functioning (five items), stigma (six items), social support (four items), school behavior (four items), and health perception (three items). Higher total scores indicate better QoL.

QOLIE-31-P is applied to patients >18 years of age.^[18] It contains 30 items divided into seven subscale domains: seizure worry (5 items), emotional well-being (5 items), energy/fatigue (4 items), cognitive functioning (6 items), medication effects (3 items), overall QoL (2 items), and social functioning (5 items). Each domain is scored by calculating the mean score of responses in each domain. The raw scores are converted to “0–100.” Higher scores indicate better QoL. QoL is further defined as “poor” if the score is between 0 and 49, “fair,” if it is between 50 and 74, and “good,” if it is between 75 and 100. Total and subscale scores are calculated according to the QOLIE-31-P scoring manual.

For the assessment of psychiatric comorbidities, participants were administered Mini-International Neuropsychiatric Interview (M.I.N.I.) version 7.0.2, which is a widely used psychiatric instrument for diagnosis.^[19] It requires yes/no answers. Participants who tested positive for psychiatric comorbidities on M.I.N.I. underwent Diagnostic and Statistical Manual-5 (DSM-5) categorization.^[20]

Statistical analysis

Data were entered into a Microsoft Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences version 21.0.

Categorical variables were presented as frequency (percentage). Continuous variables were represented as median (range). Quantitative variables were compared using an independent t-test. Continuous variables were compared using Chi-square test/Fisher's exact test.

The association between clinical and sociodemographic data with psychiatric evaluation and QoL in epilepsy was evaluated using logistic regression analysis. A $P < 0.05$ was considered statistically significant.

RESULTS

We enrolled 50 patients with JME. Eighteen (36%) were male and 32 (64%) were female patients [Table 1]. The median age of males at study enrollment was 23.5 (range 15–38) years. The median age of females was 22 (16–48) years. The median age at onset in males was 15 (11–19) years and in females was 15.5 (12–22) years. The median duration of illness was 9 (2–37) years among males and 7 (0.5–26) years among females. Most patients had a combination of myoclonic seizures and GTCS. 30% ($n = 6$) of male patients had 1–2 GTCS/year, 30% had more frequent and 30% had less frequent GTCS. 12.5% of female patients had 1–2 GTCS/year. The remainder had not had GTCS after the onset of the disease. Only one patient provided a history of absence seizures. Among males, 50% were on monotherapy (valproate or levetiracetam), whereas 65.6% (21/32) of female patients were on monotherapy with levetiracetam. Suboptimal seizure control was observed in 65.6% of females and 50% of males ($P = 0.2790$).

The median QOLIE-31-P score among males was 68.31 (37.13–91.82) and for females was 66.9 (31.7–99.1) [Table 2]. The median overall QoL score for males was 65 (25–87.5), which qualified as “fair” QoL. For females, the median overall QoL score was 62.5 (10–87.5) which also qualified as “fair” QoL. No significant difference was noted between genders in QoL ($P = 0.723$).

Among males, 55.5% (10/18) suffered from psychiatric comorbidity [Table 3]. Of these, two had mild depression and eight had anxiety (7 had mild and 1 had moderate anxiety). Among female patients, 34.4% had comorbid psychiatric issues; 6 had anxiety (4 had mild and 2 had moderate anxiety) and 5 had depression (mild). No significant difference was noted between genders in terms of psychiatric comorbidities ($P = 0.9136$). No association could be determined between QoL and features such as the presence of psychiatric comorbidities, age at onset, epilepsy duration, seizure control monotherapy/polytherapy, or sociodemographic features (age, gender, educational status, socio-economic status, religion, occupation, and marital status). No association could be determined between the presence of psychiatric comorbidities and features such as age at onset, epilepsy duration, monotherapy/polytherapy, or sociodemographic features (age, gender, educational status, socio-economic status, religion, occupation, and marital status).

Subgroup analysis of QOLIE-AD-48 was conducted among patients below 17 years of age (one male, three females). For the male patient, the score was 54.9 and the average score for females was 61.5.

DISCUSSION

In this cross-sectional study, no significant gender differences in persons with JME in terms of QoL and psychiatric

Table 1: Demographic and clinical features of patients enrolled in the study ($n=50$).

Feature	Female	Male	P value
Number (%)	32 (64)	18 (36)	
Age at enrollment (years)	22 (15–48)	23.5 (15–52)	0.2796
Age at onset (years)	15.5 (12–22)	15 (12–20)	0.5178
Duration of disease (years)	7 (0.5–26)	9 (2–37)	0.1321
Education			
Postgraduate	3 (9.4)	-	-
Graduate	9 (28.1)	13 (72.2)	0.0025
High school	17 (53.1)	3 (16.7)	0.0115
Did not complete school	3 (9.4)	2 (11.1)	-
Employment			
Student	13 (40.6)	7 (38.8)	0.9043
Homemaker/not employed	11 (34.4)	1 (5.6)	0.0220
Employed	8 (25)	10 (55.6)	0.0307
Marital status			
Married	11 (34.3)	4 (22.2)	0.3680
Type of seizure			
GTCS	31 (96.9)	17 (94.4)	
Myoclonus	32 (100)	17 (94.4)	
Absence	-	1 (5.6)	
ASM therapy			
Monotherapy	21 (65.6)	9 (50)	0.2790
Two ASMs	9 (28.2)	5 (27.8)	0.4323
Three ASMs	2 (6.3)	4 (22.2)	0.0952
ASM drugs			
Valproate	8 (25)	11 (61.1)	0.0116
Levetiracetam	23	11 (61.1)	0.4335
Clobazam	9 (28.1)	5 (27.8)	0.9790
Lamotrigine	-	1 (5.6)	-
Topiramate	1 (3.1)	-	-
Phenobarbitone	1 (3.1)	-	-
Phenytoin	4 (12.5)	-	-
Seizure frequency			
>2 GTCS/year	-	4 (22.2)	
1–2 GTCS/year	4 (12.5)	12 (66.7)	
MJ 1–2/month, no GTCS for the past 2 years	28 (87.5)	2 (11.1)	
Recurrent GTCS/MJ	1 (3.1)	-	
No GTCS, no MJ	-	-	
Seizure control			
Suboptimal	21 (65.6)	9 (50)	0.2790

ASM: Antiseizure medication, GTCS: Generalized tonic-clonic seizure, MJ: Myoclonic jerk, $P < 0.05$

comorbidities were observed. This is the first study to examine gender-related concerns in persons with JME in terms of psychiatric comorbidities and QoL.

Limited data exist on QoL and its determinants in JME. In a retrospective study among 33 patients with JME (21 females) who were followed for more than 20 years, early and long-term seizure freedom was associated with better QoL

Table 2: Gender-stratified QoL assessment among persons with JME.

QOLIE-31-P	Female	Male	P value
Emotional well-being	71 (8–100)	73.5 (8–96)	0.9908
Social functioning	66 (28–100)	67 (32–100)	0.4549
Energy/fatigue	65 (10–100)	75 (20–100)	0.3849
Cognitive functioning	65 (7.5–100)	64.4 (11.8–100)	0.6819
Seizure worry	50 (0–85)	44.3 (0–100)	0.3248
Medication effects	44.4 (0–77.7)	52.7 (0–100)	0.5240
Overall QoL	62.5 (10–87.5)	65 (25–87.5)	0.2331
Overall QOLIE-31-P score	66.9 (31.7–99.1)	68.3 (37.1–91.8)	0.9908

QoL: Quality of life, JME: Juvenile myoclonic epilepsy, QOLIE-31-P: Patient-Weighted Quality of Life in Epilepsy Inventory-31

Table 3: Gender-stratified psychiatric comorbidities among persons with JME.

Comorbidity	Female (n=32)	Male (n=18)	P-value
Present	11 (34.4)	10 (55.6)	
Depression	5 (15.6)	2 (11.2)	0.6588
Anxiety	6 (18.8)	8 (44.4)	0.0520
None	21 (65.6)	8 (44.4)	0.1452

JME: Juvenile myoclonic epilepsy

(odds ratio 2.25).^[21] The presence of more severe epilepsy, side effects from ASMs, the presence of depression, and sleep disruptions negatively impacted QoL. Another study, which assessed 30 patients with JME, explored the impact of psychiatric comorbidities on QoL, using the QoL in Epilepsy Inventory-89 (QOLIE-89). JME patients who had mood disorders scored lower on the attention/concentration subscale and negatively affected QoL.^[9] In another large study from India with 165 patients with JME, the presence of psychiatric comorbidities was associated with a lower overall QOLIE-31 score (55.84 ± 13.07 vs. 68.70 ± 11.23 , $P < 0.001$) and lower social function score (80.95 ± 19.22 vs. 91.09 ± 14.74 , $P < 0.001$).^[10] Similar to the latter study, most persons with JME in our study had “fair” QoL, although we did not observe a correlation between the presence of psychiatric comorbidity or seizure control. Gender-stratified QoL has not been explored in these studies.

In terms of psychiatric comorbidities, the burden in JME is substantial. The prevalence of psychiatric comorbidities ranges from 37% to 51%.^[11-13] In a study from India, 46.6% of persons with JME had psychiatric disorders.^[10] In this study, females constituted 38.6% of the cohort. Similar to our study, 16.3% of the patients in this study had depressive disorder, and 30.3% had anxiety, which is similar to our cohort (28% had anxiety overall). This is also similar to another study by de Araujo Filho and Yacubian.^[22] However, the proportion of male patients with JME was much higher (44%) in our study compared to female patients, which trended toward statistical significance. This is an interesting finding that urges assessment in larger studies.

The profile of psychiatric comorbidities among persons with JME has also been observed to differ among those who harbor anxiety compared to those who have comorbid depression. In a study by Somayajula *et al.*, depression was more prevalent among older persons (above 35 years of age) with JME, and a strong correlation was observed between marriage and depression.^[10] We did not observe such a difference, which may be due to the small number of patients who were married in our cohort, and the younger age group. Only one patient in each of the groups based on gender was above the age of 35 years.

Only one patient provided a history of absence seizures, suggesting that this seizure type was likely to be underrecognized in our cohort. As per historical cohorts, 20–40% of patients with JME have absence seizures.

Expectedly, a significantly higher proportion of male patients were on valproate treatment compared to female patients in our cohort. Valproate has well-established dose-dependent teratogenic effects and is avoided in women of childbearing potential.^[23] However, valproate has better efficacy in JME compared to alternative drugs. This is also reflected in our observation that a higher proportion of women in our cohort continued to have seizures compared to men, although this difference was not statistically significant. Lamotrigine (<325 mg/day) may also be used as an alternative drug in this subgroup,^[24] but it was highly underutilized in our cohort. This could partly be because levetiracetam, valproate, phenytoin, and clobazam are provided by our institute, whereas lamotrigine is not available, explaining the bias in prescription from our center. Of the 25% of women who were on valproate from our center, only two had completed the family. These observations indicate the challenges of managing JME among patients of childbearing potential. A prescription of valproate in this population should be at the lowest possible dose and after an informed discussion with the patient regarding risks and benefits.^[23]

The implication of gender on seizure-related prognosis remains uncertain, with conflicting reports in the literature. In a meta-analysis by Stevelink *et al.*, gender was not a

determinant of refractoriness in JME.^[14] Even long-term prognosis in terms of seizure control and freedom may not differ between male and female patients.^[25] Our study did not find a significant difference in terms of seizure control among male and female patients with JME.

The strengths of this study were a comprehensive assessment of psychiatric comorbidities, first by the M.I.N.I screening questionnaire and then confirmation based on DSM-5 criteria. A detailed QoL assessment was performed using QOLIE-31-P and QOLIE-48-AD scores. This is the first study to assess gender differences in QoL and psychiatric comorbidities in JME.

The limitations include a small number of patients enrolled, which was mainly due to the study being conducted during the COVID-19 pandemic, which restricted recruitment. We did not assess the relationship between seizure-related outcomes and QoL in terms of gender, which is also an interesting question to consider.

CONCLUSION

Persons with JME do not have gender-stratified differences in terms of psychiatric comorbidities and QoL despite differences in exposure to ASMs and other gender-related factors. Both female and male persons with JME should be screened for psychiatric comorbidities, specifically anxiety, and depression, and also assessed for differences in neuropsychological profiles and determinants of such differences, if any. Studies with a larger number of patients are required to assess determinants of QoL among persons with JME.

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Declaration of patient consent

The authors certify that they have obtained all appropriate consent.

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Conflicts of interest

There are no conflicts of interest.

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